

The ANTs Longitudinal Cortical Thickness Pipeline

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Abstract

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

Introduction

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

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

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

¹<https://github.com/stnava/ANTs>

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

Methods and materials

Longitudinal ADNI imaging data

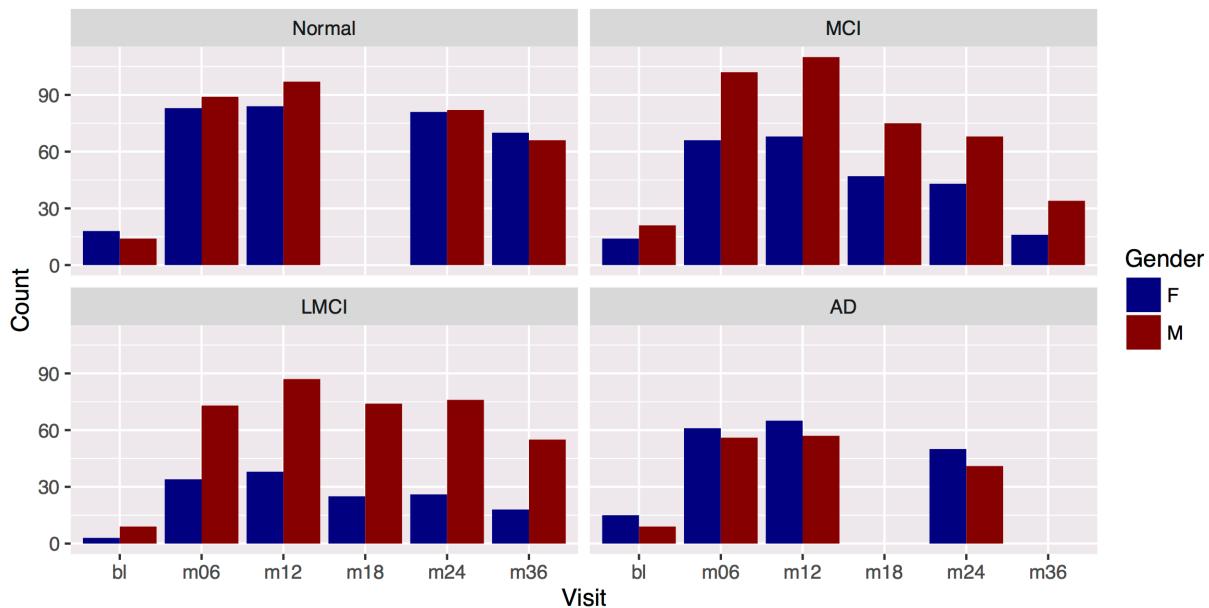


Figure 1: Demographic breakdown of the number of ADNI subjects by diagnosis i.e., normal, mild cognitive impairment (MCI), late mild cognitive impairment (LMCI), and Alzheimer’s disease (AD). Within each panel we plot the number of subjects (by gender) per visit—baseline (“bl”) and n months (“mn”).

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

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

total, we included 186 elderly cognitive normals, 178 MCI subjects, 128 LMCI subjects, and 123 AD subjects. A further breakdown of demographic information is given in Figure X.

ANTs Cortical thickness estimation

Cross-sectional processing

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

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

ROI-based quantification is achieved through the use of the joint label fusion approach of [67] and the use of the MindBoggle-101 data labeled using the Desikan–Killiany–Tourville (DKT) protocol [68] consisting of 31 labels per hemisphere (cf Table 1). This pipeline has since been enhanced by the implementation [69] of a patch-based denoising algorithm [70] as an optional preprocessing step and multi-modal integration capabilities.

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

The resulting regional statistics (including cortical thickness, surface area [75], volumes, and Jacobian determinant values) are available online.² These include the corresponding FreeSurfer measurements which are also publicly available for research studies (e.g., [76]). Since publication this pipeline has been used in a number of cross-sectional studies (e.g., [77–79]).

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

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

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

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 can significantly reduce inter-subject measurement variability. The ANTs longitudinal cortical thickness pipeline extends the ANTs cortical thickness pipeline for longitudinal studies which takes into account various bias issues previously discussed in the literature [52, 56, 57]. Given N time-point T1-weighted MR images and a group template and prior probability maps (described below), the longitudinal pipeline consists of the following steps:

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

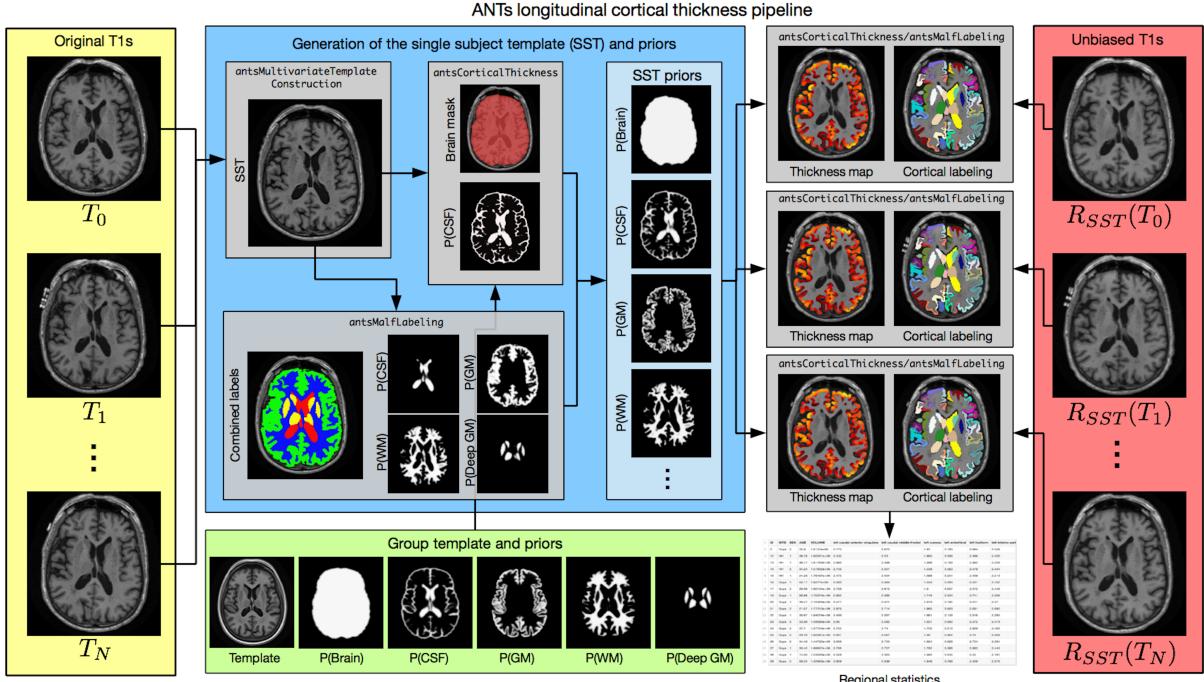


Figure 2: Diagrammatic illustration of the ANTs longitudinal cortical thickness pipeline for a single subject with N time points. From the N original T1-weighted images (left column, yellow panel) and the group template and priors (bottom row, green panel), the single-single subject template (SST) and auxiliary prior images are created (center, blue panel). These subject-specific template and other auxiliary images are used to generate the individual time-point cortical thickness maps. Optionally, one can rigidly transform the time-point images prior to segmentation and cortical thickness estimation (right column, red panel). For regional thickness values, regional labels can be propagated to each image using a given atlas set and cortical parcellation scheme.

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

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

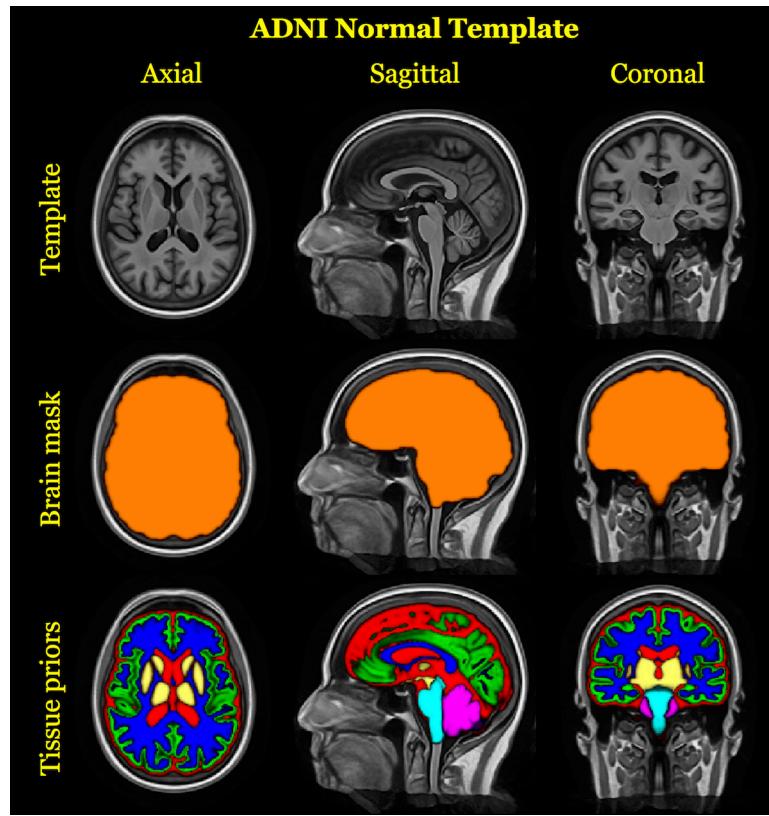


Figure 3: Top row: Canonical views of the template created from 52 normal subjects of the ADNI database. The prior probability mask for the whole brain (middle row) and the 6 tissue priors (bottom row) are used to “seed” each SST during longitudinal processing.

Single-subject template, brain mask, and tissue priors. Following the offline construction of the group template and prior probability images, each subject undergoes similar processing. First, an average shape and intensity single subject template (SST) is created from all time point images [55]. Subsequent processing segments the SST into six probabilistic tissues classes: cerebrospinal fluid (CSF), gray matter (GM), white

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

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

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

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

Statistical methods

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

As previously noted we observed yearly cortical thickness measurements from sixty-two separate regions of interest. To assess the above variance criterion while accounting for changes that may occur through the passage

of time, we used a hierarchical Bayesian model for parameter estimation. Let Y_{ij}^k denote the i^{th} individual's cortical thickness measurement corresponding to the k^{th} region of interest at measurement j . Under the Bayesian paradigm we utilized a model of the form

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

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

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

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

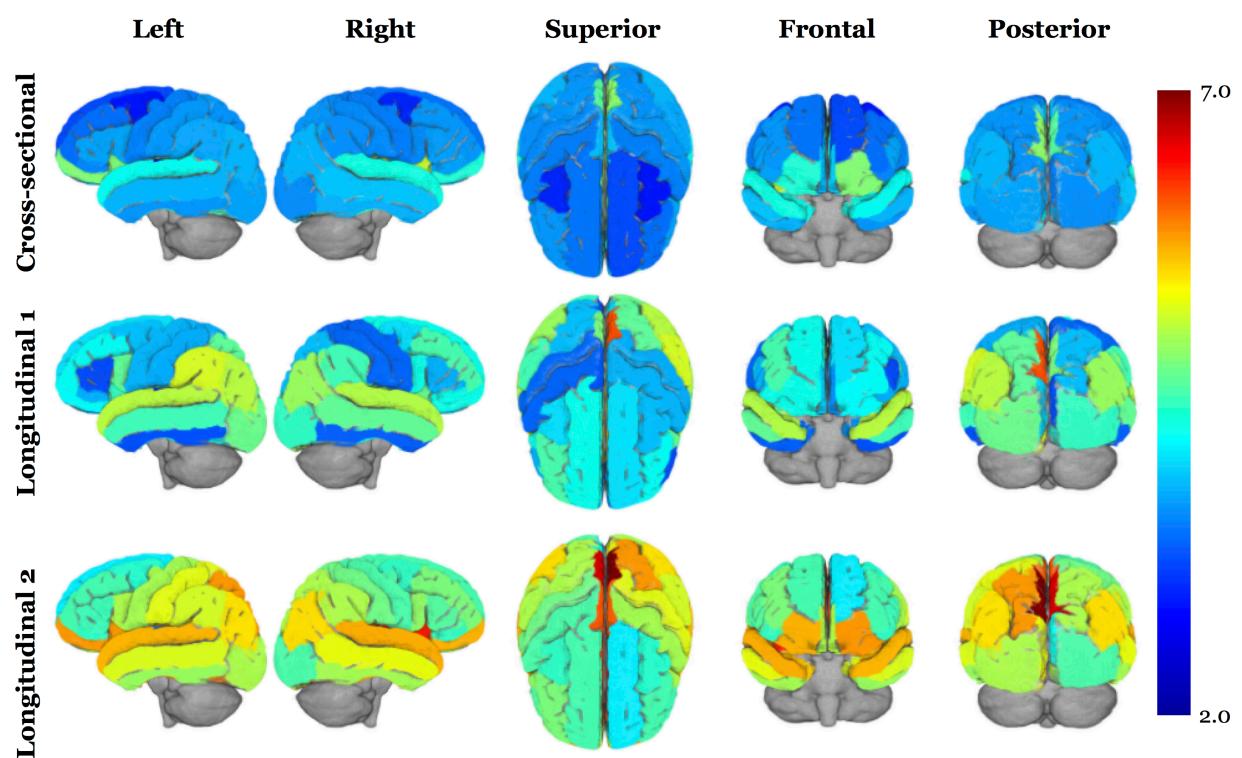


Figure 4: 3-D volumetric rendering of the normed difference of the longitudinal variance ratio minus the cross-sectional variance ratio specified for each of the 62 cortical regions.

References

1. Du, A.-T., Schuff, N., Kramer, J. H., Rosen, H. J., Gorno-Tempini, M. L., Rankin, K., Miller, B. L., and Weiner, M. W. “**Different Regional Patterns of Cortical Thinning in Alzheimer’s Disease and Frontotemporal Dementia**” *Brain* 130, no. Pt 4 (2007): 1159–66. doi:[10.1093/brain/awm016](https://doi.org/10.1093/brain/awm016)
2. Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., Grodstein, F., Wright, C. I., Blacker, D., Rosas, H. D., Sperling, R. A., Atri, A., Growdon, J. H., Hyman, B. T., Morris, J. C., Fischl, B., and Buckner, R. L. “**The Cortical Signature of Alzheimer’s Disease: Regionally Specific Cortical Thinning Relates to Symptom Severity in Very Mild to Mild AD Dementia and Is Detectable in Asymptomatic Amyloid-Positive Individuals**” *Cereb Cortex* 19, no. 3 (2009): 497–510. doi:[10.1093/cercor/bhn113](https://doi.org/10.1093/cercor/bhn113)
3. Jubault, T., Gagnon, J.-F., Karama, S., Ptito, A., Lafontaine, A.-L., Evans, A. C., and Monchi, O. “**Patterns of Cortical Thickness and Surface Area in Early Parkinson’s Disease**” *Neuroimage* 55, no. 2 (2011): 462–7. doi:[10.1016/j.neuroimage.2010.12.043](https://doi.org/10.1016/j.neuroimage.2010.12.043)
4. Thompson, P. M., Lee, A. D., Dutton, R. A., Geaga, J. A., Hayashi, K. M., Eckert, M. A., Bellugi, U., Galaburda, A. M., Korenberg, J. R., Mills, D. L., Toga, A. W., and Reiss, A. L. “**Abnormal Cortical Complexity and Thickness Profiles Mapped in Williams Syndrome**” *J Neurosci* 25, no. 16 (2005): 4146–58. doi:[10.1523/JNEUROSCI.0165-05.2005](https://doi.org/10.1523/JNEUROSCI.0165-05.2005)
5. Ramasamy, D. P., Benedict, R. H. B., Cox, J. L., Fritz, D., Abdelrahman, N., Hussein, S., Minagar, A., Dwyer, M. G., and Zivadinov, R. “**Extent of Cerebellum, Subcortical and Cortical Atrophy in Patients with MS: A Case-Control Study**” *J Neurol Sci* 282, no. 1-2 (2009): 47–54. doi:[10.1016/j.jns.2008.12.034](https://doi.org/10.1016/j.jns.2008.12.034)
6. Chung, M. K., Robbins, S. M., Dalton, K. M., Davidson, R. J., Alexander, A. L., and Evans, A. C. “**Cortical Thickness Analysis in Autism with Heat Kernel Smoothing**” *Neuroimage* 25, no. 4 (2005): 1256–65. doi:[10.1016/j.neuroimage.2004.12.052](https://doi.org/10.1016/j.neuroimage.2004.12.052)
7. Hardan, A. Y., Muddasani, S., Vemulapalli, M., Keshavan, M. S., and Minshew, N. J. “**An MRI Study of Increased Cortical Thickness in Autism**” *Am J Psychiatry* 163, no. 7 (2006): 1290–2. doi:[10.1176/appi.ajp.163.7.1290](https://doi.org/10.1176/appi.ajp.163.7.1290)
8. DaSilva, A. F. M., Granziera, C., Snyder, J., and Hadjikhani, N. “**Thickening in the Somatosensory Cortex of Patients with Migraine**” *Neurology* 69, no. 21 (2007): 1990–5. doi:[10.1212/01.wnl.0000291618.32247.2d](https://doi.org/10.1212/01.wnl.0000291618.32247.2d)
9. Kühn, S., Schubert, F., and Gallinat, J. “**Reduced Thickness of Medial Orbitofrontal Cortex in**

Smokers” *Biol Psychiatry* 68, no. 11 (2010): 1061–5. doi:[10.1016/j.biopsych.2010.08.004](https://doi.org/10.1016/j.biopsych.2010.08.004)

10. Fortier, C. B., Leritz, E. C., Salat, D. H., Venne, J. R., Maksimovskiy, A. L., Williams, V., Milberg, W. P., and McGlinchey, R. E. “**Reduced Cortical Thickness in Abstinent Alcoholics and Association with Alcoholic Behavior**” *Alcohol Clin Exp Res* 35, no. 12 (2011): 2193–201. doi:[10.1111/j.1530-0277.2011.01576.x](https://doi.org/10.1111/j.1530-0277.2011.01576.x)
11. Makris, N., Gasic, G. P., Kennedy, D. N., Hodge, S. M., Kaiser, J. R., Lee, M. J., Kim, B. W., Blood, A. J., Evins, A. E., Seidman, L. J., Iosifescu, D. V., Lee, S., Baxter, C., Perlis, R. H., Smoller, J. W., Fava, M., and Breiter, H. C. “**Cortical Thickness Abnormalities in Cocaine Addiction—a Reflection of Both Drug Use and a Pre-Existing Disposition to Drug Abuse?**” *Neuron* 60, no. 1 (2008): 174–88. doi:[10.1016/j.neuron.2008.08.011](https://doi.org/10.1016/j.neuron.2008.08.011)
12. Nesvåg, R., Lawyer, G., Varnäs, K., Fjell, A. M., Walhovd, K. B., Frigessi, A., Jönsson, E. G., and Agartz, I. “**Regional Thinning of the Cerebral Cortex in Schizophrenia: Effects of Diagnosis, Age and Antipsychotic Medication**” *Schizophr Res* 98, no. 1-3 (2008): 16–28. doi:[10.1016/j.schres.2007.09.015](https://doi.org/10.1016/j.schres.2007.09.015)
13. Lyoo, I. K., Sung, Y. H., Dager, S. R., Friedman, S. D., Lee, J.-Y., Kim, S. J., Kim, N., Dunner, D. L., and Renshaw, P. F. “**Regional Cerebral Cortical Thinning in Bipolar Disorder**” *Bipolar Disord* 8, no. 1 (2006): 65–74. doi:[10.1111/j.1399-5618.2006.00284.x](https://doi.org/10.1111/j.1399-5618.2006.00284.x)
14. Jacobus, J., Squeglia, L. M., Meruelo, A. D., Castro, N., Brumback, T., Giedd, J. N., and Tapert, S. F. “**Cortical Thickness in Adolescent Marijuana and Alcohol Users: A Three-Year Prospective Study from Adolescence to Young Adulthood**” *Dev Cogn Neurosci* 16, (2015): 101–9. doi:[10.1016/j.dcn.2015.04.006](https://doi.org/10.1016/j.dcn.2015.04.006)
15. Sowell, E. R., Kan, E., Yoshii, J., Thompson, P. M., Bansal, R., Xu, D., Toga, A. W., and Peterson, B. S. “**Thinning of Sensorimotor Cortices in Children with Tourette Syndrome**” *Nat Neurosci* 11, no. 6 (2008): 637–9. doi:[10.1038/nn.2121](https://doi.org/10.1038/nn.2121)
16. Wang, D., Shi, L., Chu, W. C. W., Burwell, R. G., Cheng, J. C. Y., and Ahuja, A. T. “**Abnormal Cerebral Cortical Thinning Pattern in Adolescent Girls with Idiopathic Scoliosis**” *Neuroimage* 59, no. 2 (2012): 935–42. doi:[10.1016/j.neuroimage.2011.07.097](https://doi.org/10.1016/j.neuroimage.2011.07.097)
17. Kumar, R., Yadav, S. K., Palomares, J. A., Park, B., Joshi, S. H., Ogren, J. A., Macey, P. M., Fonarow, G. C., Harper, R. M., and Woo, M. A. “**Reduced Regional Brain Cortical Thickness in Patients with Heart Failure**” *PLoS One* 10, no. 5 (2015): e0126595. doi:[10.1371/journal.pone.0126595](https://doi.org/10.1371/journal.pone.0126595)
18. Jiang, J., Zhu, W., Shi, F., Liu, Y., Li, J., Qin, W., Li, K., Yu, C., and Jiang, T. “**Thick Visual Cortex in**

the Early Blind” *J Neurosci* 29, no. 7 (2009): 2205–11. doi:[10.1523/JNEUROSCI.5451-08.2009](https://doi.org/10.1523/JNEUROSCI.5451-08.2009)

19. Frøkjær, J. B., Bouwense, S. A. W., Olesen, S. S., Lundager, F. H., Eskildsen, S. F., Goor, H. van, Wilder-Smith, O. H. G., and Drewes, A. M. **“Reduced Cortical Thickness of Brain Areas Involved in Pain Processing in Patients with Chronic Pancreatitis”** *Clin Gastroenterol Hepatol* 10, no. 4 (2012): 434–8.e1. doi:[10.1016/j.cgh.2011.11.024](https://doi.org/10.1016/j.cgh.2011.11.024)
20. Shin, Y.-W., Yoo, S. Y., Lee, J. K., Ha, T. H., Lee, K. J., Lee, J. M., Kim, I. Y., Kim, S. I., and Kwon, J. S. **“Cortical Thinning in Obsessive Compulsive Disorder”** *Hum Brain Mapp* 28, no. 11 (2007): 1128–35. doi:[10.1002/hbm.20338](https://doi.org/10.1002/hbm.20338)
21. Almeida Montes, L. G., Prado Alcántara, H., Martínez García, R. B., De La Torre, L. B., Avila Acosta, D., and Duarte, M. G. **“Brain Cortical Thickness in ADHD: Age, Sex, and Clinical Correlations”** *J Atten Disord* (2012): doi:[10.1177/1087054711434351](https://doi.org/10.1177/1087054711434351)
22. Raji, C. A., Ho, A. J., Parikshak, N. N., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., Leow, A. D., Toga, A. W., and Thompson, P. M. **“Brain Structure and Obesity”** *Hum Brain Mapp* 31, no. 3 (2010): 353–64. doi:[10.1002/hbm.20870](https://doi.org/10.1002/hbm.20870)
23. Peterson, B. S., Warner, V., Bansal, R., Zhu, H., Hao, X., Liu, J., Durkin, K., Adams, P. B., Wickramaratne, P., and Weissman, M. M. **“Cortical Thinning in Persons at Increased Familial Risk for Major Depression”** *Proc Natl Acad Sci U S A* 106, no. 15 (2009): 6273–8. doi:[10.1073/pnas.0805311106](https://doi.org/10.1073/pnas.0805311106)
24. Ballmaier, M., Sowell, E. R., Thompson, P. M., Kumar, A., Narr, K. L., Lavretsky, H., Welcome, S. E., DeLuca, H., and Toga, A. W. **“Mapping Brain Size and Cortical Gray Matter Changes in Elderly Depression”** *Biol Psychiatry* 55, no. 4 (2004): 382–9. doi:[10.1016/j.biopsych.2003.09.004](https://doi.org/10.1016/j.biopsych.2003.09.004)
25. Kochunov, P., Glahn, D. C., Lancaster, J., Thompson, P. M., Kochunov, V., Rogers, B., Fox, P., Blangero, J., and Williamson, D. E. **“Fractional Anisotropy of Cerebral White Matter and Thickness of Cortical Gray Matter Across the Lifespan”** *Neuroimage* 58, no. 1 (2011): 41–9. doi:[10.1016/j.neuroimage.2011.05.050](https://doi.org/10.1016/j.neuroimage.2011.05.050)
26. Luders, E., Narr, K. L., Thompson, P. M., Rex, D. E., Woods, R. P., Deluca, H., Jancke, L., and Toga, A. W. **“Gender Effects on Cortical Thickness and the Influence of Scaling”** *Hum Brain Mapp* 27, no. 4 (2006): 314–24. doi:[10.1002/hbm.20187](https://doi.org/10.1002/hbm.20187)
27. Luders, E., Sánchez, F. J., Tosun, D., Shattuck, D. W., Gaser, C., Vilain, E., and Toga, A. W. **“Increased Cortical Thickness in Male-to-Female Transsexualism”** *J Behav Brain Sci* 2, no. 3 (2012): 357–362.

doi:[10.4236/jbbs.2012.23040](https://doi.org/10.4236/jbbs.2012.23040)

28. Luders, E., Narr, K. L., Thompson, P. M., Rex, D. E., Jancke, L., and Toga, A. W. “**Hemispheric Asymmetries in Cortical Thickness**” *Cereb Cortex* 16, no. 8 (2006): 1232–8. doi:[10.1093/cercor/bhj064](https://doi.org/10.1093/cercor/bhj064)
29. Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., Evans, A., Rapoport, J., and Giedd, J. “**Intellectual Ability and Cortical Development in Children and Adolescents**” *Nature* 440, no. 7084 (2006): 676–9. doi:[10.1038/nature04513](https://doi.org/10.1038/nature04513)
30. Wei, G., Zhang, Y., Jiang, T., and Luo, J. “**Increased Cortical Thickness in Sports Experts: A Comparison of Diving Players with the Controls**” *PLoS One* 6, no. 2 (2011): e17112. doi:[10.1371/journal.pone.0017112](https://doi.org/10.1371/journal.pone.0017112)
31. Lazar, S. W., Kerr, C. E., Wasserman, R. H., Gray, J. R., Greve, D. N., Treadway, M. T., McGarvey, M., Quinn, B. T., Dusek, J. A., Benson, H., Rauch, S. L., Moore, C. I., and Fischl, B. “**Meditation Experience Is Associated with Increased Cortical Thickness**” *Neuroreport* 16, no. 17 (2005): 1893–7.
32. Bermudez, P., Lerch, J. P., Evans, A. C., and Zatorre, R. J. “**Neuroanatomical Correlates of Musicianship as Revealed by Cortical Thickness and Voxel-Based Morphometry**” *Cereb Cortex* 19, no. 7 (2009): 1583–96. doi:[10.1093/cercor/bhn196](https://doi.org/10.1093/cercor/bhn196)
33. Foster, N. E. V. and Zatorre, R. J. “**Cortical Structure Predicts Success in Performing Musical Transformation Judgments**” *Neuroimage* 53, no. 1 (2010): 26–36. doi:[10.1016/j.neuroimage.2010.06.042](https://doi.org/10.1016/j.neuroimage.2010.06.042)
34. Hudziak, J. J., Albaugh, M. D., Ducharme, S., Karama, S., Spottswood, M., Crehan, E., Evans, A. C., Botteron, K. N., and Brain Development Cooperative Group. “**Cortical Thickness Maturation and Duration of Music Training: Health-Promoting Activities Shape Brain Development**” *J Am Acad Child Adolesc Psychiatry* 53, no. 11 (2014): 1153–61, 1161.e1–2. doi:[10.1016/j.jaac.2014.06.015](https://doi.org/10.1016/j.jaac.2014.06.015)
35. Raine, A., Laufer, W. S., Yang, Y., Narr, K. L., Thompson, P., and Toga, A. W. “**Increased Executive Functioning, Attention, and Cortical Thickness in White-Collar Criminals**” *Hum Brain Mapp* (2011): doi:[10.1002/hbm.21415](https://doi.org/10.1002/hbm.21415)
36. Heim, C. M., Mayberg, H. S., Mletzko, T., Nemerooff, C. B., and Pruessner, J. C. “**Decreased Cortical Representation of Genital Somatosensory Field After Childhood Sexual Abuse**” *Am J Psychiatry* 170, no. 6 (2013): 616–23. doi:[10.1176/appi.ajp.2013.12070950](https://doi.org/10.1176/appi.ajp.2013.12070950)
37. Haier, R. J., Karama, S., Leyba, L., and Jung, R. E. “**MRI Assessment of Cortical Thickness and Functional Activity Changes in Adolescent Girls Following Three Months of Practice on a Visual-**

Spatial Task” *BMC Res Notes* 2, (2009): 174. doi:[10.1186/1756-0500-2-174](https://doi.org/10.1186/1756-0500-2-174)

38. MacDonald, D., Kabani, N., Avis, D., and Evans, A. C. “**Automated 3-D Extraction of Inner and Outer Surfaces of Cerebral Cortex from MRI**” *Neuroimage* 12, no. 3 (2000): 340–56. doi:[10.1006/nimg.1999.0534](https://doi.org/10.1006/nimg.1999.0534)
39. Magnotta, V. A., Andreasen, N. C., Schultz, S. K., Harris, G., Cizadlo, T., Heckel, D., Nopoulos, P., and Flaum, M. “**Quantitative in Vivo Measurement of Gyrification in the Human Brain: Changes Associated with Aging**” *Cereb Cortex* 9, no. 2 (1999): 151–60.
40. Kim, J. S., Singh, V., Lee, J. K., Lerch, J., Ad-Dab’bagh, Y., MacDonald, D., Lee, J. M., Kim, S. I., and Evans, A. C. “**Automated 3-D Extraction and Evaluation of the Inner and Outer Cortical Surfaces Using a Laplacian Map and Partial Volume Effect Classification**” *Neuroimage* 27, no. 1 (2005): 210–21. doi:[10.1016/j.neuroimage.2005.03.036](https://doi.org/10.1016/j.neuroimage.2005.03.036)
41. Zeng, X., Staib, L. H., Schultz, R. T., and Duncan, J. S. “**Segmentation and Measurement of the Cortex from 3-D MR Images Using Coupled-Surfaces Propagation**” *IEEE Trans Med Imaging* 18, no. 10 (1999): 927–37. doi:[10.1109/42.811276](https://doi.org/10.1109/42.811276)
42. Jones, S. E., Buchbinder, B. R., and Aharon, I. “**Three-Dimensional Mapping of Cortical Thickness Using Laplace’s Equation**” *Hum Brain Mapp* 11, no. 1 (2000): 12–32.
43. Das, S. R., Avants, B. B., Grossman, M., and Gee, J. C. “**Registration Based Cortical Thickness Measurement**” *Neuroimage* 45, no. 3 (2009): 867–79. doi:[10.1016/j.neuroimage.2008.12.016](https://doi.org/10.1016/j.neuroimage.2008.12.016)
44. Vachet, C., Hazlett, H. C., Niethammer, M., Oguz, I., Cates, J., Whitaker, R., Piven, J., and Styner, M. “**Group-Wise Automatic Mesh-Based Analysis of Cortical Thickness**” *SPIE medical imaging: Image processing* (2011):
45. Dale, A. M., Fischl, B., and Sereno, M. I. “**Cortical Surface-Based Analysis. I. Segmentation and Surface Reconstruction**” *Neuroimage* 9, no. 2 (1999): 179–94. doi:[10.1006/nimg.1998.0395](https://doi.org/10.1006/nimg.1998.0395)
46. Fischl, B., Sereno, M. I., and Dale, A. M. “**Cortical Surface-Based Analysis. II: Inflation, Flattening, and a Surface-Based Coordinate System**” *Neuroimage* 9, no. 2 (1999): 195–207. doi:[10.1006/nimg.1998.0396](https://doi.org/10.1006/nimg.1998.0396)
47. Fischl, B. and Dale, A. M. “**Measuring the Thickness of the Human Cerebral Cortex from Magnetic Resonance Images**” *Proc Natl Acad Sci USA* 97, no. 20 (2000): 11050–5. doi:[10.1073/pnas.200033797](https://doi.org/10.1073/pnas.200033797)
48. Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Kouwe, A. van der, Killiany, R.,

- Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., and Dale, A. M. “**Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain**” *Neuron* 33, no. 3 (2002): 341–55.
49. Fischl, B., Kouwe, A. van der, Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., Busa, E., Seidman, L. J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., and Dale, A. M. “**Automatically Parcellating the Human Cerebral Cortex**” *Cereb Cortex* 14, no. 1 (2004): 11–22.
50. Kraemer, H. C., Yesavage, J. A., Taylor, J. L., and Kupfer, D. “**How Can We Learn About Developmental Processes from Cross-Sectional Studies, or Can We?**” *Am J Psychiatry* 157, no. 2 (2000): 163–71. doi:[10.1176/appi.ajp.157.2.163](https://doi.org/10.1176/appi.ajp.157.2.163)
51. Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., Harvey, D., Jack, C. R., Jagust, W., Liu, E., Morris, J. C., Petersen, R. C., Saykin, A. J., Schmidt, M. E., Shaw, L., Siuciak, J. A., Soares, H., Toga, A. W., Trojanowski, J. Q., and, Alzheimer’s Disease Neuroimaging Initiative. “**The Alzheimer’s Disease Neuroimaging Initiative: A Review of Papers Published Since Its Inception.**” *Alzheimers Dement* 8, no. 1 Suppl (2012): S1–68.
52. Reuter, M. and Fischl, B. “**Avoiding Asymmetry-Induced Bias in Longitudinal Image Processing**” *Neuroimage* 57, no. 1 (2011): 19–21. doi:[10.1016/j.neuroimage.2011.02.076](https://doi.org/10.1016/j.neuroimage.2011.02.076)
53. Xue, Z., Shen, D., and Davatzikos, C. “**CLASSIC: Consistent Longitudinal Alignment and Segmentation for Serial Image Computing**” *Neuroimage* 30, no. 2 (2006): 388–99. doi:[10.1016/j.neuroimage.2005.09.054](https://doi.org/10.1016/j.neuroimage.2005.09.054)
54. Wang, L., Shi, F., Li, G., and Shen, D. “**4D Segmentation of Brain MR Images with Constrained Cortical Thickness Variation**” *PLoS One* 8, no. 7 (2013): e64207. doi:[10.1371/journal.pone.0064207](https://doi.org/10.1371/journal.pone.0064207)
55. Avants, B. B., Yushkevich, P., Pluta, J., Minkoff, D., Korczykowski, M., Detre, J., and Gee, J. C. “**The Optimal Template Effect in Hippocampus Studies of Diseased Populations**” *Neuroimage* 49, no. 3 (2010): 2457–66. doi:[10.1016/j.neuroimage.2009.09.062](https://doi.org/10.1016/j.neuroimage.2009.09.062)
56. Reuter, M., Schmansky, N. J., Rosas, H. D., and Fischl, B. “**Within-Subject Template Estimation for Unbiased Longitudinal Image Analysis**” *Neuroimage* 61, no. 4 (2012): 1402–18. doi:[10.1016/j.neuroimage.2012.02.084](https://doi.org/10.1016/j.neuroimage.2012.02.084)
57. Yushkevich, P. A., Avants, B. B., Das, S. R., Pluta, J., Altinay, M., Craige, C., and Alzheimer’s Disease Neuroimaging Initiative. “**Bias in Estimation of Hippocampal Atrophy Using Deformation-Based Morphometry Arises from Asymmetric Global Normalization: An Illustration in ADNI 3 T MRI**

Data” *Neuroimage* 50, no. 2 (2010): 434–45. doi:[10.1016/j.neuroimage.2009.12.007](https://doi.org/10.1016/j.neuroimage.2009.12.007)

58. Tustison, N. J., Cook, P. A., Klein, A., Song, G., Das, S. R., Duda, J. T., Kandel, B. M., Strien, N. van, Stone, J. R., Gee, J. C., and Avants, B. B. **“Large-Scale Evaluation of ANTs and FreeSurfer Cortical Thickness Measurements”** *Neuroimage* 99, (2014): 166–79. doi:[10.1016/j.neuroimage.2014.05.044](https://doi.org/10.1016/j.neuroimage.2014.05.044)
59. Fujishima, M., Maikusa, N., Nakamura, K., Nakatsuka, M., Matsuda, H., and Meguro, K. **“Mild Cognitive Impairment, Poor Episodic Memory, and Late-Life Depression Are Associated with Cerebral Cortical Thinning and Increased White Matter Hyperintensities”** *Front Aging Neurosci* 6, (2014): 306. doi:[10.3389/fnagi.2014.00306](https://doi.org/10.3389/fnagi.2014.00306)
60. Das, S. R., Mancuso, L., Olson, I. R., Arnold, S. E., and Wolk, D. A. **“Short-Term Memory Depends on Dissociable Medial Temporal Lobe Regions in Amnestic Mild Cognitive Impairment”** *Cereb Cortex* 26, no. 5 (2016): 2006–17. doi:[10.1093/cercor/bhv022](https://doi.org/10.1093/cercor/bhv022)
61. Olm, C. A., Kandel, B. M., Avants, B. B., Detre, J. A., Gee, J. C., Grossman, M., and McMillan, C. T. **“Arterial Spin Labeling Perfusion Predicts Longitudinal Decline in Semantic Variant Primary Progressive Aphasia”** *J Neurol* 263, no. 10 (2016): 1927–38. doi:[10.1007/s00415-016-8221-1](https://doi.org/10.1007/s00415-016-8221-1)
62. Mugler, J. P., 3rd and Brookeman, J. R. **“Three-Dimensional Magnetization-Prepared Rapid Gradient-Echo Imaging (3D MP RAGE)”** *Magn Reson Med* 15, no. 1 (1990): 152–7.
63. Jack, C. R., Jr, Bernstein, M. A., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P. J., L Whitwell, J., Ward, C., Dale, A. M., Felmlee, J. P., Gunter, J. L., Hill, D. L. G., Killiany, R., Schuff, N., Fox-Bosetti, S., Lin, C., Studholme, C., DeCarli, C. S., Krueger, G., Ward, H. A., Metzger, G. J., Scott, K. T., Mallozzi, R., Blezek, D., Levy, J., Debbins, J. P., Fleisher, A. S., Albert, M., Green, R., Bartzokis, G., Glover, G., Mugler, J., and Weiner, M. W. **“The Alzheimer’s Disease Neuroimaging Initiative (ADNI): MRI Methods”** *J Magn Reson Imaging* 27, no. 4 (2008): 685–91. doi:[10.1002/jmri.21049](https://doi.org/10.1002/jmri.21049)
64. Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., and Gee, J. C. **“N4ITK: Improved N3 Bias Correction”** *IEEE Trans Med Imaging* 29, no. 6 (2010): 1310–20. doi:[10.1109/TMI.2010.2046908](https://doi.org/10.1109/TMI.2010.2046908)
65. Avants, B. B., Klein, A., Tustison, N. J., Woo, J., and Gee, J. C. **“Evaluation of an Open-Access, Automated Brain Extraction Method on Multi-Site Multi-Disorder Data”** (2010):
66. Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., and Gee, J. C. **“An Open Source Multivariate Framework for n-Tissue Segmentation with Evaluation on Public Data”** *Neuroinformatics* 9, no. 4 (2011):

381–400. doi:[10.1007/s12021-011-9109-y](https://doi.org/10.1007/s12021-011-9109-y)

67. Wang, H., Suh, J. W., Das, S. R., Pluta, J. B., Craige, C., and Yushkevich, P. A. “**Multi-Atlas Segmentation with Joint Label Fusion**” *IEEE Trans Pattern Anal Mach Intell* 35, no. 3 (2013): 611–23. doi:[10.1109/TPAMI.2012.143](https://doi.org/10.1109/TPAMI.2012.143)
68. Klein, A. and Tourville, J. “**101 Labeled Brain Images and a Consistent Human Cortical Labeling Protocol**” *Front Neurosci* 6, (2012): 171. doi:[10.3389/fnins.2012.00171](https://doi.org/10.3389/fnins.2012.00171)
69. Tustison, N. J. and Herrera, J. M. “**Two Luis Miguel Fans Walk into a Bar in Nagoya —> (Yada, Yada, Yada) —> an ITK-Implementation of a Popular Patch-Based Denoising Filter**” *Insight Journal* (2016):
70. Manjón, J. V., Coupé, P., Martí-Bonmatí, L., Collins, D. L., and Robles, M. “**Adaptive Non-Local Means Denoising of MR Images with Spatially Varying Noise Levels**” *J Magn Reson Imaging* 31, no. 1 (2010): 192–203. doi:[10.1002/jmri.22003](https://doi.org/10.1002/jmri.22003)
71. Available at <http://brain-development.org/ixi-dataset/>
72. Landman, B. A., Huang, A. J., Gifford, A., Vikram, D. S., Lim, I. A. L., Farrell, J. A. D., Bogovic, J. A., Hua, J., Chen, M., Jarso, S., Smith, S. A., Joel, S., Mori, S., Pekar, J. J., Barker, P. B., Prince, J. L., and Zijl, P. C. M. van. “**Multi-Parametric Neuroimaging Reproducibility: A 3-T Resource Study**” *Neuroimage* 54, no. 4 (2011): 2854–66. doi:[10.1016/j.neuroimage.2010.11.047](https://doi.org/10.1016/j.neuroimage.2010.11.047)
73. Available at http://fcon_1000.projects.nitrc.org/indi/pro/nki.html
74. Available at <http://www.oasis-brains.org>
75. Lehmann, G. and Legland, D. “**Efficient N-Dimensional Surface Estimation Using Crofton Formula and Run-Length Encoding**” *Insight Journal* (2012):
76. Hasan, K. M., Mwangi, B., Cao, B., Keser, Z., Tustison, N. J., Kochunov, P., Frye, R. E., Savatic, M., and Soares, J. “**Entorhinal Cortex Thickness Across the Human Lifespan**” *J Neuroimaging* 26, no. 3 (2016): 278–82. doi:[10.1111/jon.12297](https://doi.org/10.1111/jon.12297)
77. Price, A. R., Bonner, M. F., Peele, J. E., and Grossman, M. “**Converging Evidence for the Neuroanatomic Basis of Combinatorial Semantics in the Angular Gyrus**” *J Neurosci* 35, no. 7 (2015): 3276–84. doi:[10.1523/JNEUROSCI.3446-14.2015](https://doi.org/10.1523/JNEUROSCI.3446-14.2015)
78. Wisse, L. E. M., Butala, N., Das, S. R., Davatzikos, C., Dickerson, B. C., Vaishnavi, S. N., Yushkevich, P. A., Wolk, D. A., and Alzheimer’s Disease Neuroimaging Initiative. “**Suspected Non-AD Pathology in Mild**

Cognitive Impairment” *Neurobiol Aging* 36, no. 12 (2015): 3152–62. doi:[10.1016/j.neurobiolaging.2015.08.029](https://doi.org/10.1016/j.neurobiolaging.2015.08.029)

79. Betancourt, L. M., Avants, B., Farah, M. J., Brodsky, N. L., Wu, J., Ashtari, M., and Hurt, H. “**Effect of Socioeconomic Status (SES) Disparity on Neural Development in Female African-American Infants at Age 1 Month**” *Dev Sci* (2015): doi:[10.1111/desc.12344](https://doi.org/10.1111/desc.12344)

80. Bartko, J. J. “**On Various Intraclass Correlation Reliability Coefficients.**” *Psychological bulletin* 83, no. 5 (1976): 762.

81. Carpenter, B., Gelman, A., Hoffman, M., Lee, D., Goodrich, B., Betancourt, M., Brubaker, M. A., Guo, J., Li, P., and Riddell, A. “**Stan: A Probabilistic Programming Language**” *J Stat Softw* (2016):