

# The ANTs longitudinal cortical thickness pipeline

Nicholas J. Tustison<sup>1,2</sup>, Andrew J. Holbrook<sup>3</sup>, Jared M. Roberts<sup>2</sup>, Brian B. Avants<sup>4</sup>, Philip A. Cook<sup>5</sup>, James R. Stone<sup>1</sup>, Daniel L. Gillen<sup>3</sup>, and Michael A. Yassa<sup>2</sup> for the Alzheimer's Disease Neuroimaging Initiative\*

<sup>1</sup>Department of Radiology and Medical Imaging, University of Virginia, Charlottesville, VA

<sup>2</sup>Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA

<sup>3</sup>Department of Statistics, University of California, Irvine, Irvine, CA

<sup>4</sup>Biogen, Cambridge, MA

<sup>5</sup>Department of Radiology, University of Pennsylvania, Philadelphia, PA

Corresponding author:

Nicholas J. Tustison

4173 Cardamon Circle

Corona, CA 92883

540-383-2719

[ntustison@virginia.edu](mailto:ntustison@virginia.edu)

---

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

## **Abstract**

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 longitudinal data processing. Issues of normalization reference coordinate systems and the potential for bias are discussed in [52]. Briefly, interpolation-induced artifacts can artificially inflate effect size. Orientation bias

In [53], 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.<sup>1</sup> In this previously published work we processed a cohort comprising four publicly available data sets totaling over 1200 subjects. We used the derived thickness measurements to predict common demographic outcomes (i.e., age, gender) which compared favorably with predictions based on the corresponding FreeSurfer quantities. This proposed ANTs-based pipeline has since been directed at a variety of neuroimaging topics including mild cognitive impairment and depression [54], short term memory in mild cognitive impairment [55], and aphasia [56].

In this work, we introduce the ANTs longitudinal cortical thickness pipeline and apply it to the entire ADNI1 data set.

---

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

## Materials and Methods

### Imaging

#### Cortical thickness

##### Single time point processing

In [53] 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 [53]):

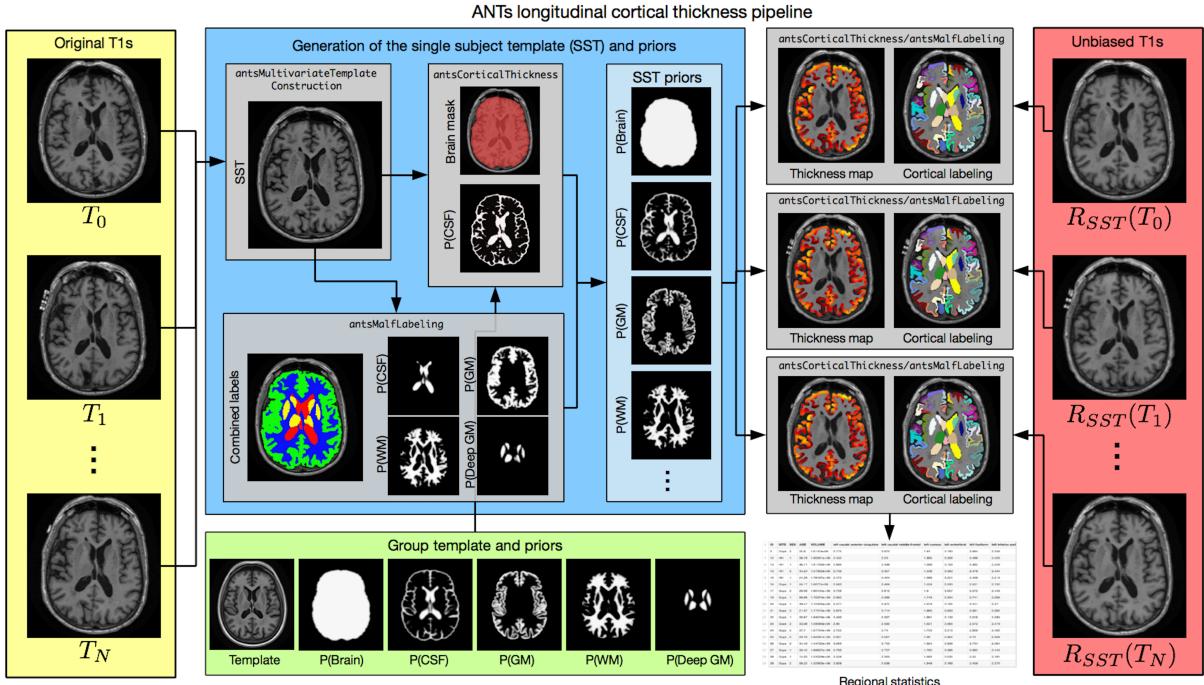
- N4 bias correction [57],
- brain extraction [58],
- Atropos six-tissue segmentation [59], and
- cortical thickness estimation [43]

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 [60] consisting of 31 labels per hemisphere (see Table 1). Consensus labelings in each subject were generated from the joint label fusion approach of [61]. 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 [62]. The resulting regional statistics (including cortical thickness, surface area [63], 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., [64]). Since publication, this pipeline has been used in a number of cross-sectional studies [65–67].

##### 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 [52]. Prior to the processing of any individual subjects a group template [71] 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 undergoes similar processing. First, an average shape and intensity single subject template (SST) is created from all time point images [71]. 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.



**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 [68] 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.

**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)	

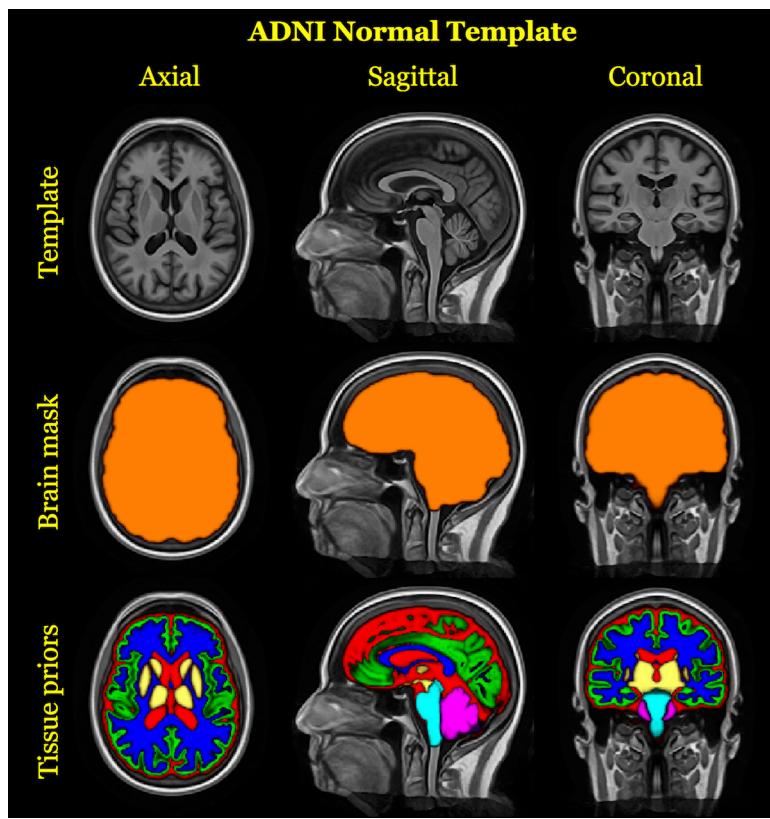
Each rigidly-aligned time point image is processed using the ANTs original pipeline and the SST template and template priors resulting in a brain extraction mask, six-tissue segmentation, and a cortical thickness map for each time point image. The cortical ROIs from the DKT atlases are propagated to 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 [60], a class-leading multi-atlas joint label fusion step [61] 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 [68, 72]

*ADNI normal template.*

*“Cooking” the template priors.*

*Pseudo-geodesic for large cohort labeling.*



**Figure 2:** The ADNI normal template

### 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

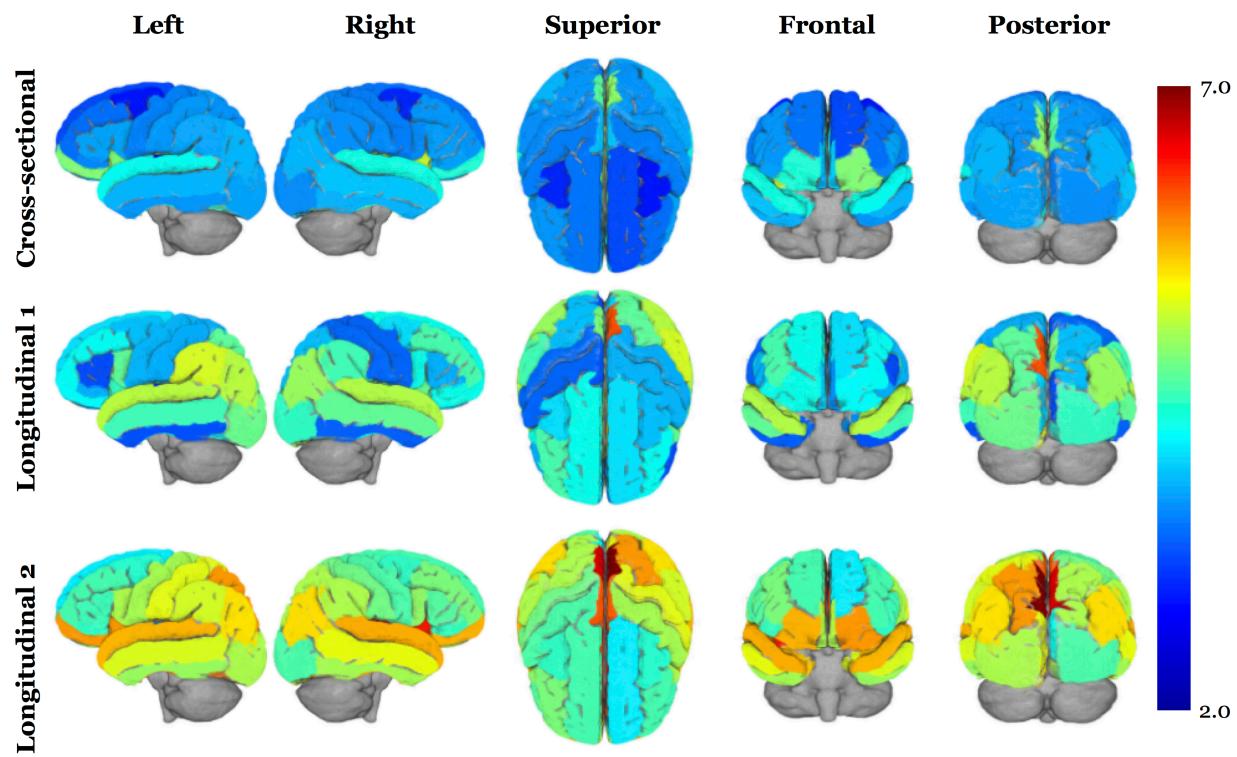
We used a simple statistical principle to compare performance between cross-sectional and longitudinal processing methods. We said that one method outperforms the other when it does a better job minimizing within-subject variability and maximizing between-subject variability in cortical thickness measurements. 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 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.  $\tau_k^2$  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 [73]. The posterior distribution of  $r^k$  was summarized via the posterior median. Where the posterior distributions were obtained using Stan probabilistic programming language [74].

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  $\delta^k$  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.



**Figure 3:** 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.

## **Results**

### **Discussion**

#### **Subsection 1**

And a sweet equation:

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

## 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., Nemeroff, 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 Gyration 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. 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)
53. 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)
54. 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)
55. 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)
56. 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)
57. 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)

58. 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):

59. 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)

60. 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)

61. 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)

62. 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)

63. Lehmann, G. and Legland, D. **“Efficient N-Dimensional Surface Estimation Using Crofton Formula and Run-Length Encoding”** *Insight Journal* (2012):

64. 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)

65. Price, A. R., Bonner, M. F., Peelle, 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)

66. 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)

67. 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)

68. Tustison, N. J., Avants, B. B., Cook, P. A., Kim, J., Whyte, J., Gee, J. C., and Stone, J. R. **“Logical Circularity in Voxel-Based Analysis: Normalization Strategy May Induce Statistical Bias”** *Hum Brain Mapp* 35, no. 3 (2014): 745–59. doi:[10.1002/hbm.22211](https://doi.org/10.1002/hbm.22211)

69. 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)

70. 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)

71. 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)
72. Avants, B. B., Duda, J. T., Kilroy, E., Krasileva, K., Jann, K., Kandel, B. T., Tustison, N. J., Yan, L., Jog, M., Smith, R., Wang, Y., Dapretto, M., and Wang, D. J. J. “**The Pediatric Template of Brain Perfusion**” *Sci Data* 2, (2015): 150003. doi:[10.1038/sdata.2015.3](https://doi.org/10.1038/sdata.2015.3)
73. Bartko, J. J. “**On Various Intraclass Correlation Reliability Coefficients.**” *Psychological bulletin* 83, no. 5 (1976): 762.
74. 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):