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2 ANTsX: A dynamic ecosystem for 3 quantitative biological and medical imaging

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22 Abstract

23 The Advanced Normalizations Tools ecosystem, known as ANTsX, consists of multiple open-
24 source software libraries which house top-performing algorithms used worldwide by scientific
25 and research communities for processing and analyzing biological and medical imaging data.
26 The base software library, ANTs, is built upon, and contributes to, the NIH-sponsored
27 Insight Toolkit. Founded in 2008 with the highly regarded Symmetric Normalization image
28 registration framework, the ANTs library has since grown to include additional functionality.
29 Recent enhancements include statistical, visualization, and deep learning capabilities through
30 interfacing with both the R statistical project (ANTsR) and Python (ANTsPy). Additionally,
31 the corresponding deep learning extensions ANTsRNet and ANTsPyNet (built on the popular
32 TensorFlow/Keras libraries) contain several popular network architectures and trained models
33 for specific applications. One such comprehensive application is a deep learning analog
34 for generating cortical thickness data from structural T1-weighted brain MRI, both cross-
35 sectionally and longitudinally. These pipelines significantly improve computational efficiency
36 and provide comparable-to-superior accuracy over multiple criteria relative to the existing
37 ANTs workflows and simultaneously illustrate the importance of the comprehensive ANTsX
38 approach as a framework for medical image analysis.

³⁹ **The ANTsX ecosystem: A brief overview**

⁴⁰ **Image registration origins**

⁴¹ The Advanced Normalization Tools (ANTs) is a state-of-the-art, open-source software toolkit
⁴² for image registration, segmentation, and other functionality for comprehensive biological and
⁴³ medical image analysis. Historically, ANTs is rooted in advanced image registration techniques
⁴⁴ which have been at the forefront of the field due to seminal contributions that date back to
⁴⁵ the original elastic matching method of Bajcsy and co-investigators^{1–3}. Various independent
⁴⁶ platforms have been used to evaluate ANTs tools since their early development. In a landmark
⁴⁷ paper⁴, the authors reported an extensive evaluation using multiple neuroimaging datasets
⁴⁸ analyzed by fourteen different registration tools, including the Symmetric Normalization
⁴⁹ (SyN) algorithm⁵, and found that “ART, SyN, IRTK, and SPM’s DARTEL Toolbox gave
⁵⁰ the best results according to overlap and distance measures, with ART and SyN delivering
⁵¹ the most consistently high accuracy across subjects and label sets.” Participation in other
⁵² independent competitions^{6,7} provided additional evidence of the utility of ANTs registration
⁵³ and other tools^{8–10}. Despite the extremely significant potential of deep learning for image
⁵⁴ registration algorithmic development¹¹, ANTs registration tools continue to find application
⁵⁵ in the various biomedical imaging research communities.

⁵⁶ **Current developments**

⁵⁷ Since its inception, though, ANTs has expanded significantly beyond its image registration
⁵⁸ origins. Other core contributions include template building¹², segmentation¹³, image pre-
⁵⁹ processing (e.g., bias correction¹⁴ and denoising¹⁵), joint label fusion^{16,17}, and brain cortical
⁶⁰ thickness estimation^{18,19} (cf Table 1). Additionally, ANTs has been integrated into multiple,
⁶¹ publicly available workflows such as fMRIprep²⁰ and the Spinal Cord Toolbox²¹. Frequently
⁶² used ANTs pipelines, such as cortical thickness estimation¹⁹, have been integrated into Docker
⁶³ containers and packaged as Brain Imaging Data Structure (BIDS)²² and FlyWheel applica-
⁶⁴ tions (i.e., “gears”). It has also been independently ported for various platforms including
⁶⁵ Neurodebian²³ (Debian OS), Neuroconductor²⁴ (the R statistical project), and Nipype²⁵

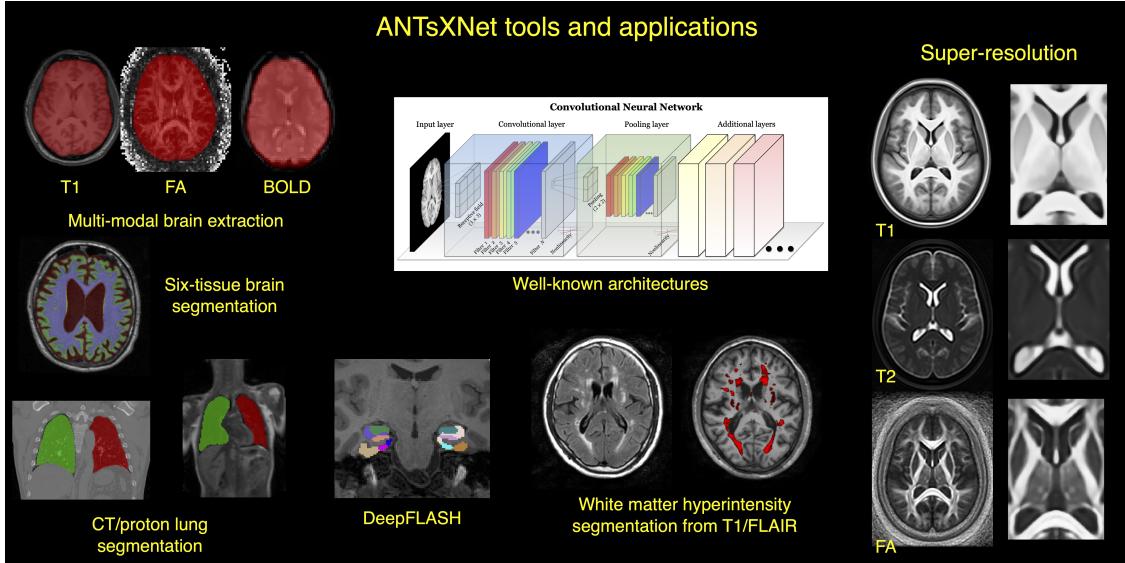


Figure 1: An illustration of the tools and applications available as part of the ANTsRNet and ANTsPyNet deep learning toolkits. Both libraries take advantage of ANTs functionality through their respective language interfaces—ANTsR (R) and ANTsPy (Python). Building on the Keras/TensorFlow language, both libraries standardize popular network architectures within the ANTs ecosystem and are cross-compatible. These networks are used to train models and weights for such applications as brain extraction which are then disseminated to the public.

66 (Python). Additionally, other widely used software, such as FreeSurfer²⁶, have incorporated
 67 well-performing and complementary ANTs components^{14,15} into their own libraries. According
 68 to GitHub, recent unique “clones” have averaged 34 per day with the total number of clones
 69 being approximately twice that many. 50 unique contributors to the ANTs library have made
 70 a total of over 4500 commits. Additional insights into usage can be viewed at the ANTs
 71 GitHub website.

72 Over the course of its development, ANTs has been extended to complementary frameworks
 73 resulting in the Python- and R-based ANTsPy and ANTsR toolkits, respectively. These
 74 ANTs-based packages interface with extremely popular, high-level, open-source programming
 75 platforms which have significantly increased the user base of ANTs. The rapidly rising
 76 popularity of deep learning motivated further recent enhancement of ANTs and its extensions.
 77 Despite the existence of an abundance of online innovation and code for deep learning
 78 algorithms, much of it is disorganized and lacks a uniformity in structure and external data
 79 interfaces which would facilitate greater uptake. With this in mind, ANTsR spawned the deep

Functionality	Citations
SyN registration ⁵	2616
bias field correction ¹⁶	2188
ANTs registration evaluation ⁶	2013
joint label fusion ¹⁸	669
template generation ¹⁴	423
cortical thickness: implementation ²⁰	321
MAP-MRF segmentation ¹⁵	319
ITK integration ¹²	250
cortical thickness: theory ¹⁹	180

Table 1: The significance of core ANTs tools in terms of their number of citations (from October 17, 2020).

80 learning ANTsRNet package²⁷ which is a growing Keras/TensorFlow-based library of popular
 81 deep learning architectures and applications specifically geared towards medical imaging.
 82 Analogously, ANTsPyNet is an additional ANTsX complement to ANTsPy. Both, which we
 83 collectively refer to as “ANTsXNet”, are co-developed so as to ensure cross-compatibility
 84 such that training performed in one library is readily accessible by the other library. In
 85 addition to a variety of popular network architectures (which are implemented in both 2-D
 86 and 3-D), ANTsXNet contains a host of functionality for medical image analysis that have
 87 been developed in-house and collected from other open-source projects. For example, an
 88 extremely popular ANTsXNet application is a multi-modal brain extraction tool that uses
 89 different variants of the popular U-net²⁸ architecture for segmenting the brain in multiple
 90 modalities. These modalities include conventional T1-weighted structural MRI as well as
 91 T2-weighted MRI, FLAIR, fractional anisotropy, and BOLD data. Demographic specialization
 92 also includes infant T1-weighted and/or T2-weighted MRI. Additionally, we have included
 93 other models and weights into our libraries such as a recent BrainAGE estimation model²⁹,
 94 based on > 14,000 individuals; HippMapp3r³⁰, a hippocampal segmentation tool; the winning
 95 entry of the MICCAI 2017 white matter hyperintensity segmentation competition³¹; MRI
 96 super resolution using deep back-projection networks³²; and NoBrainer, a T1-weighted brain
 97 extraction approach based on FreeSurfer (see Figure 1).

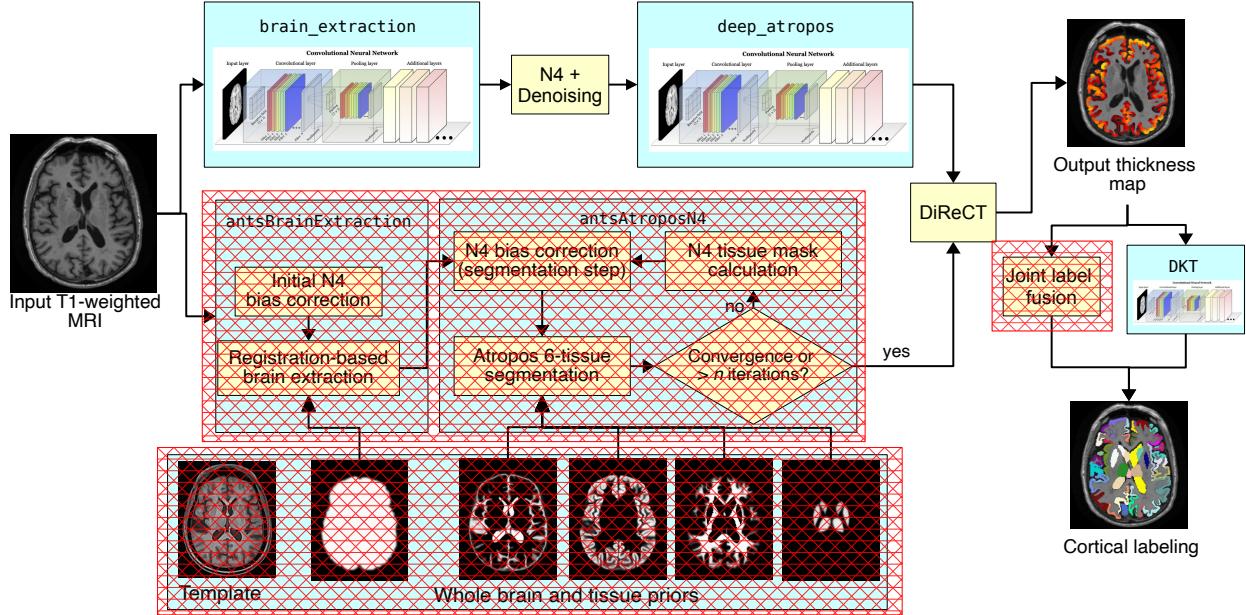


Figure 2: Illustration of the ANTsXNet cortical thickness pipeline and the relationship to its traditional ANTs analog. The hash-designated sections denote pipeline steps which have been obviated by the deep learning approach. These include template-based brain extraction, template-based n -tissue segmentation, and joint label fusion for cortical labeling. In our prior work, execution time of the thickness pipeline was dominated by registration. In the deep version of the pipeline, it is dominated by DiReCT. However, we note that registration and DiReCT execute much more quickly than in the past in part due to major improvements in the underlying ITK multi-threading strategy.

98 The ANTsXNet cortical thickness pipeline

99 The most recent ANTsX innovation involves the development of deep learning analogs of
100 our popular ANTs cortical thickness cross-sectional¹⁹ and longitudinal³³ pipelines within
101 the ANTsXNet framework. Figure 2, adapted from our previous work¹⁹, illustrates some of
102 the major changes associated with the single-subject, cross-sectional pipeline. The resulting
103 improvement in efficiency derives primarily from eliminating deformable image registration
104 from the pipeline—a step which has historically been used to propagate prior, population-
105 based information (e.g., tissue maps) to individual subjects for such tasks as brain extraction³⁴
106 and tissue segmentation¹³ which is now configured within the neural networks and trained
107 weights.

108 These structural MRI processing pipelines are currently available as open-source within the

¹⁰⁹ ANTsXNet libraries. Evaluations using both cross-sectional and longitudinal data are de-
¹¹⁰ scribed in subsequent sections and couched within the context of our previous publications^{19,33}.
¹¹¹ Related work has been recently reported by external groups^{35,36} and provides [a context for](#)
¹¹² comparison to motivate the utility of the ANTsX ecosystem.

¹¹³ Results

¹¹⁴ Cross-sectional performance evaluation

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)	

Table 2: The 31 cortical labels (per hemisphere) of the Desikan-Killiany-Tourville atlas. The ROI abbreviations from the R `brainGraph` package are given in parentheses and used in later figures.

¹¹⁵ Due to the absence of ground-truth, we utilize the evaluation strategy from our previous
¹¹⁶ work¹⁹ where we used cross-validation to build and compare age prediction models from
¹¹⁷ data derived from both the proposed ANTsXNet pipeline and the established ANTs pipeline.
¹¹⁸ Specifically, we use “age” as a well-known and widely-available demographic correlate of
¹¹⁹ cortical thickness³⁷ and quantify the predictive capabilities of corresponding random forest
¹²⁰ classifiers³⁸ of the form:

$$AGE \sim VOLUME + GENDER + \sum_{i=1}^{62} T(DKT_i) \quad (1)$$

121 with covariates *GENDER* and *VOLUME* (i.e., total intracranial volume). $T(DKT_i)$ is the
 122 average thickness value in the i^{th} Desikan-Killiany-Tourville (DKT) region³⁹ (cf Table 2).
 123 Root mean square error (RMSE) between the actual and predicted ages are the quantity
 124 used for comparative evaluation. As we have explained previously¹⁹, we find these evaluation
 125 measures to be much more useful than other commonly applied criteria as they are closer to
 126 assessing the actual utility of these thickness measurements as biomarkers for disease⁴⁰ or
 127 growth. In recent work³⁵ the authors employ correlation with FreeSurfer thickness values
 128 as the primary evaluation for assessing relative performance with ANTs cortical thickness¹⁹.
 129 This evaluation, unfortunately, is fundamentally flawed in that it is a prime example of a
 130 type of circularity analysis⁴¹ whereby data selection is driven by the same criteria used to
 131 evaluate performance. Specifically, the underlying DeepSCAN network used for the tissue
 132 segmentation step employs training based on FreeSurfer results which directly influences
 133 thickness values as thickness/segmentation are highly correlated and vary characteristically
 134 between software packages. Relative performance with ANTs thickness (which does not use
 135 FreeSurfer for training) is then assessed by determining correlations with FreeSurfer thickness
 136 values. Almost as problematic is their use of repeatability, which they confusingly label
 137 as “robustness,” as an additional ranking criterion. Repeatability evaluations should be
 138 contextualized within considerations such as the bias-variance tradeoff and quantified using
 139 relevant metrics, such as the intra-class correlation coefficient which takes into account both
 140 inter- and intra-observer variability.

141 In addition to the training data listed above, to ensure generalizability, we also compared
 142 performance using the SRPB data set⁴² comprising over 1600 participants from 12 sites. Note
 143 that we recognize that we are processing a portion of the evaluation data through certain
 144 components of the proposed deep learning-based pipeline that were used to train the same
 145 pipeline components. Although this does not provide evidence for generalizability (which is
 146 why we include the much larger SRPB data set), it is still interesting to examine the results

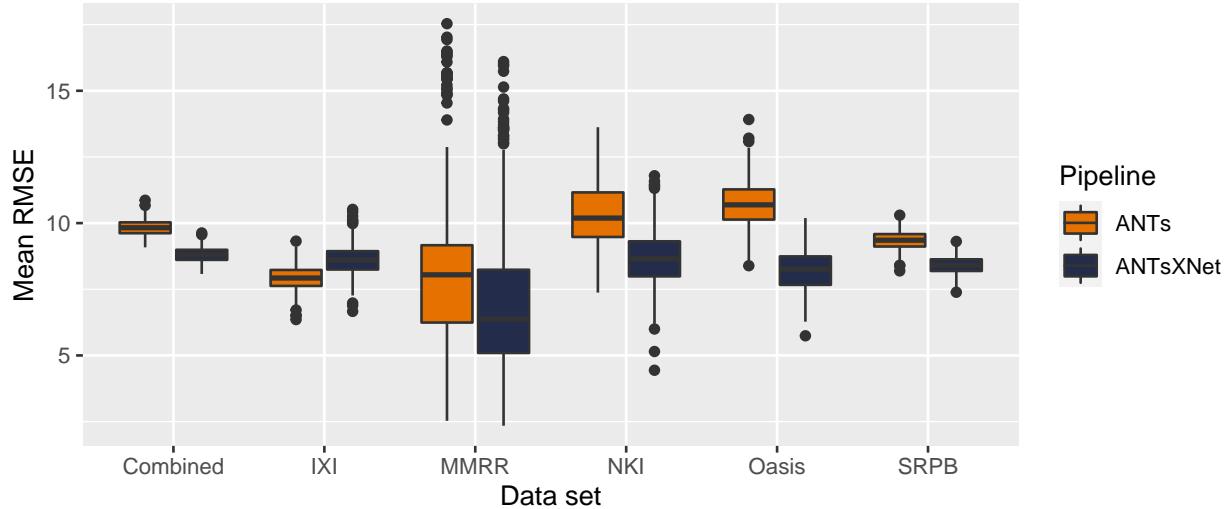


Figure 3: Distribution of mean RMSE values (500 permutations) for age prediction across the different data sets between the traditional ANTs and deep learning-based ANTsXNet pipelines. Total mean values are as follows: Combined—9.3 years (ANTs) and 8.2 years (ANTsXNet); IXI—7.9 years (ANTs) and 8.6 years (ANTsXNet); MMRR—7.9 years (ANTs) and 7.6 years (ANTsXNet); NKI—8.7 years (ANTs) and 7.9 years (ANTsXNet); OASIS—9.2 years (ANTs) and 8.0 years (ANTsXNet); and SRPB—9.2 years (ANTs) and 8.1 years (ANTsXNet).

147 since, in this case, the deep learning training can be considered a type of noise reduction on
 148 the final results. It should be noted that training did not use age prediction (or any other
 149 evaluation or related measure) as a criterion to be optimized during network model training
 150 (i.e., circular analysis⁴¹).

151 The results are shown in Figure 3 where we used cross-validation with 500 permutations
 152 per model per data set (including a “combined” set) and an 80/20 training/testing split.

153 The ANTsXNet deep learning pipeline outperformed the classical pipeline¹⁹ in terms of age
 154 prediction in all data sets except for IXI. This also includes the cross-validation iteration
 155 where all data sets were combined. Additionally, repeatability assessment on [the regional](#)
[cortical thickness values of the](#) MMRR data set yielded ICC values (“average random rater”)
 157 of 0.99 for both pipelines.

158 A comparative illustration of regional thickness measurements between the ANTs and
 159 ANTsXNet pipelines is provided in Figure 4 for three different ages spanning the lifespan.
 160 Linear models of the form

$$T(DKT_i) \sim GENDER + AGE \quad (2)$$

were created for each of the 62 DKT regions for each pipeline. These models were then used to predict thickness values for each gender at ages of 25 years, 50 years, and 75 years and subsequently plotted relative to the absolute maximum predicted thickness value (ANTs: right entorhinal cortex at 25 years, male). Although there appear to be systematic differences between specific regional predicted thickness values (e.g., $T(ENT)_{ANTs} > T(ENT)_{ANTsXNet}$, $T(pORB)_{ANTs} < T(pORB)_{ANTsXNet}$), a pairwise t-test evidenced no statistically significant difference between the predicted thickness values of the two pipelines.

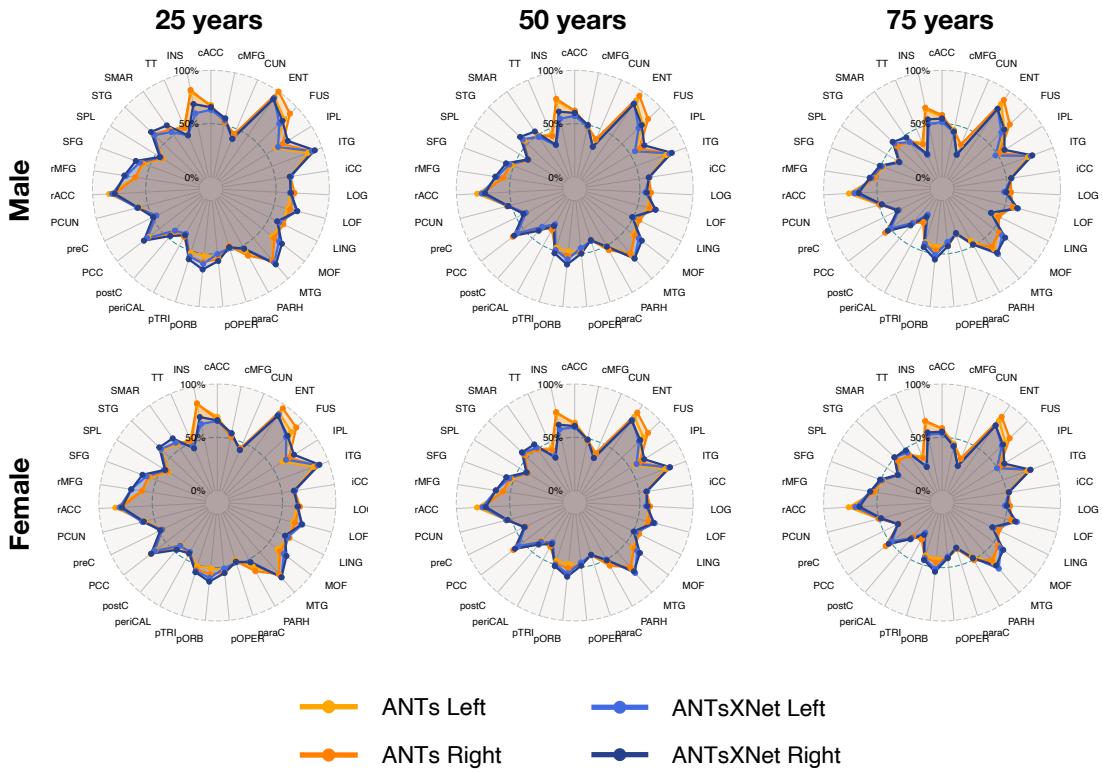
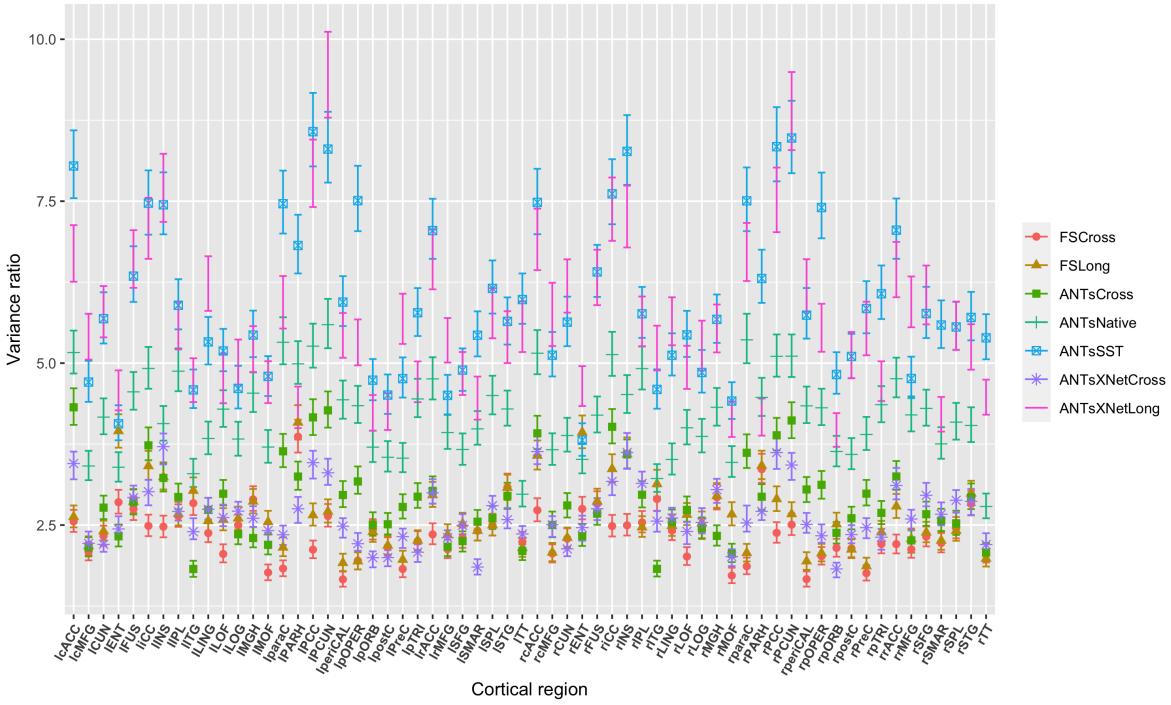
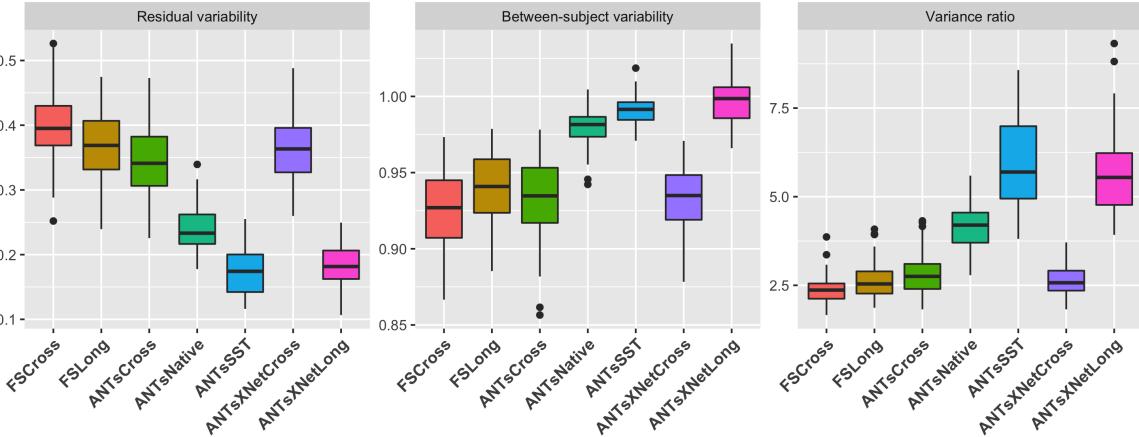


Figure 4: Radar plots enabling comparison of relative thickness values between the ANTs and ANTsXNet cortical thickness pipelines at three different ages sampling the life span. See Table 2 for region abbreviations.



(a)



(b)

Figure 5: Performance over longitudinal data as determined by the variance ratio. (a) Region-specific 95% confidence intervals of the variance ratio showing the superior performance of the longitudinally tailored ANTsX-based pipelines, including ANTsSST and ANTsXNetLong. (b) Residual variability, between subject, and variance ratio values per pipeline over all DKT regions.

168 Longitudinal performance evaluation

169 Given the excellent performance and superior computational efficiency of the proposed
 170 ANTsXNet pipeline for cross-sectional data, we evaluated its performance on longitudinal

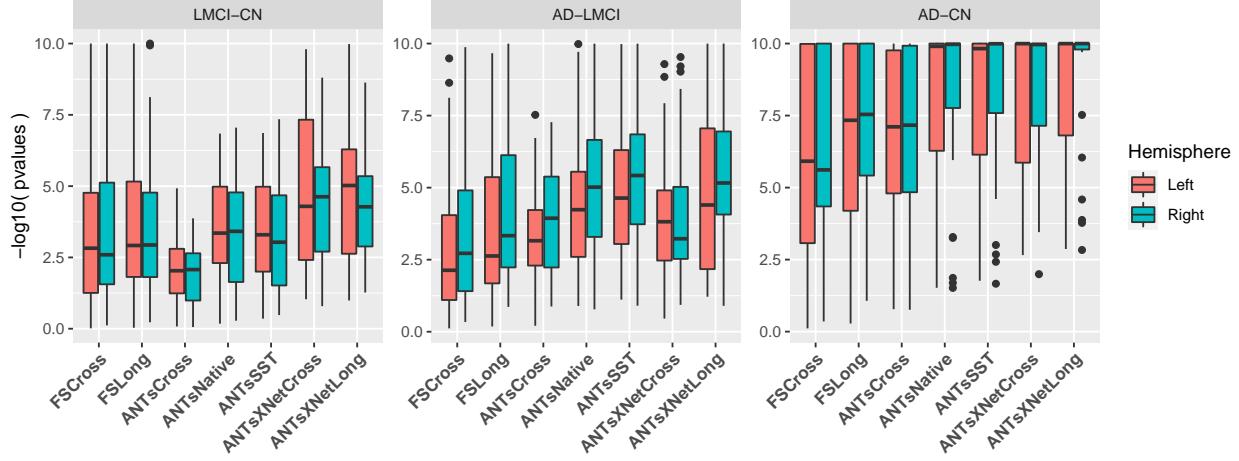


Figure 6: Measures for the supervised evaluation strategy where log p-values for diagnostic differentiation of LMCI-CN, AD-LMCI, and AD-CN subjects are plotted for all pipelines over all DKT regions.

171 data using the longitudinally-specific evaluation strategy and data we employed with the
 172 introduction of the longitudinal version of the ANTs cortical thickness pipeline³³. We also
 173 evaluated an ANTsXNet-based pipeline tailored specifically for longitudinal data. In this
 174 variant, an SST is generated and processed using the previously described ANTsXNet cross-
 175 sectional pipeline which yields tissue spatial priors. These spatial priors are used in our
 176 traditional brain segmentation approach¹³. The computational efficiency of this variant is
 177 also significantly improved, in part, due to the elimination of the costly SST prior generation
 178 which uses multiple registrations combined with joint label fusion¹⁷.

179 The ADNI-1 data used for our longitudinal performance evaluation³³ consists of over 600
 180 subjects (197 cognitive normals, 324 LMCI subjects, and 142 AD subjects) with one or
 181 more follow-up image acquisition sessions every 6 months (up to 36 months) for a total
 182 of over 2500 images. In addition to the ANTsXNet pipelines (“ANTsXNetCross” and
 183 “ANTsXNetLong”) for the current evaluation, our previous work included the FreeSurfer²⁶
 184 cross-sectional (“FSCross”) and longitudinal (“FSLong”) streams, the ANTs cross-sectional
 185 pipeline (“ANTsCross”) in addition to two longitudinal ANTs-based variants (“ANTsNative”
 186 and “ANTsSST”). Two evaluation measurements, one unsupervised and one supervised, were
 187 used to assess comparative performance between all seven pipelines. We add the results of

¹⁸⁸ the ANTsXNet pipeline cross-sectional and longitudinal evaluations in relation to these other
¹⁸⁹ pipelines to provide a comprehensive overview of relative performance.

First, linear mixed-effects (LME)⁴³ modeling was used to quantify between-subject and residual variabilities, the ratio of which provides an estimate of the effectiveness of a given biomarker for distinguishing between subpopulations. In order to assess this criteria while accounting for changes that may occur through the passage of time, we used the following Bayesian LME model:

$$\begin{aligned} Y_{ij}^k &\sim N(\alpha_i^k + \beta_i^k t_{ij}, \sigma_k^2) \\ \alpha_i^k &\sim N(\alpha_0^k, \tau_k^2) \quad \beta_i^k \sim N(\beta_0^k, \rho_k^2) \\ \alpha_0^k, \beta_0^k &\sim N(0, 10) \quad \sigma_k, \tau_k, \rho_k \sim \text{Cauchy}^+(0, 5) \end{aligned} \quad (3)$$

where Y_{ij}^k denotes the i^{th} individual's cortical thickness measurement corresponding to the k^{th} region of interest at the time point indexed by j and specification of variance priors to half-Cauchy distributions reflects commonly accepted best practice in the context of hierarchical models⁴⁴. The ratio of interest, r^k , per region of the between-subject variability, τ_k , and residual variability, σ_k is

$$r^k = \frac{\tau_k}{\sigma_k}, k = 1, \dots, 62 \quad (4)$$

¹⁹⁰ where the posterior distribution of r_k was summarized via the posterior median.

Second, the supervised evaluation employed Tukey post-hoc analyses with false discovery rate (FDR) adjustment to test the significance of the LMCI-CN, AD-LMCI, and AD-CN diagnostic contrasts. This is provided by the following LME model

$$\begin{aligned} \Delta Y &\sim Y_{bl} + AGE_{bl} + ICV_{bl} + APOE_{bl} + GENDER + DIAGNOSIS_{bl} \\ &+ VISIT : DIAGNOSIS_{bl} + (1|ID) + (1|SITE). \end{aligned} \quad (5)$$

¹⁹¹ Here, ΔY is the change in thickness of the k^{th} DKT region from baseline (bl) thickness

¹⁹² Y_{bl} with random intercepts for both the individual subject (*ID*) and the acquisition site.
¹⁹³ The subject-specific covariates *AGE*, *APOE* status, *GENDER*, *DIAGNOSIS*, *ICV*, and
¹⁹⁴ *VISIT* were taken directly from the ADNIMERGE package.

¹⁹⁵ Results for all pipelines with respect to the longitudinal evaluation criteria are shown in
¹⁹⁶ Figures 5 and 6. Figure 5(a) provides the 95% confidence intervals of the variance ratio for
¹⁹⁷ all 62 regions of the DKT cortical labeling where ANTsSST consistently performs best with
¹⁹⁸ ANTsXNetLong also performing well. These quantities are summarized in Figure 5(b). The
¹⁹⁹ second evaluation criteria compares diagnostic differentiation via LMEs. Log p-values are
²⁰⁰ provided in Figure 6 which demonstrate excellent LMCI-CN and AD-CN differentiation for
²⁰¹ both deep learning pipelines.

²⁰² Discussion

²⁰³ The ANTsX software ecosystem provides a comprehensive framework for quantitative biological
²⁰⁴ and medical imaging. Although ANTs, the original core of ANTsX, is still at the forefront
²⁰⁵ of image registration technology, it has moved significantly beyond its image registration
²⁰⁶ origins. This expansion is not confined to technical contributions (of which there are many)
²⁰⁷ but also consists of facilitating access to a wide range of users who can use ANTsX tools
²⁰⁸ (whether through bash, Python, or R scripting) to construct tailored pipelines for their own
²⁰⁹ studies or to take advantage of our pre-fabricated pipelines. And given the open-source
²¹⁰ nature of the ANTsX software, usage is not limited, for example, to non-commercial use—a
²¹¹ common constraint characteristic of other packages such as the FMRIB Software Library
²¹² (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Licence>).

²¹³ One of our most widely used pipelines is the estimation of cortical thickness from neuroimaging.
²¹⁴ This is understandable given the widespread usage of regional cortical thickness as a
²¹⁵ biomarker for developmental or pathological trajectories of the brain. In this work, we used
²¹⁶ this well-vetted ANTs tool to provide training data for producing alternative variants which
²¹⁷ leverage deep learning for improved computational efficiency and also provides superior performance
²¹⁸ with respect to previously proposed evaluation measures for both cross-sectional¹⁹ and

²¹⁹ longitudinal scenarios³³. In addition to providing the tools which generated the original training
²²⁰ data for the proposed ANTsXNet pipeline, the ANTsX ecosystem provides a full-featured
²²¹ platform for the additional steps such as preprocessing (ANTsR/ANTsPy); data augmentation
²²² (ANTsR/ANTsPy); network construction and training (ANTsRNet/ANTsPyNet); and
²²³ visualization and statistical analysis of the results (ANTsR/ANTsPy).

²²⁴ It is the comprehensiveness of ANTsX that provides several advantages over much of the
²²⁵ deep learning work that is currently taking place in medical imaging. In other words, various
²²⁶ steps in the deep learning training processing (e.g., data augmentation, preprocessing) can all
²²⁷ be performed within the same ecosystem where such important details as header information
²²⁸ for image geometry are treated the same. In contrast, related work³⁵ described and evaluated
²²⁹ a similar thickness measurement pipeline. However, due to the lack of a complete processing
²³⁰ and analysis framework, training data was generated using the FreeSurfer stream, deep
²³¹ learning-based brain segmentation employed DeepSCAN⁴⁵ (in-house software), and cortical
²³² thickness estimation¹⁸ was generated using the ANTs toolkit. The interested researcher must
²³³ ensure the consistency of the input/output interface between packages (a task for which the
²³⁴ Nipype development team is quite familiar.)

²³⁵ Although potentially advantageous in terms of such issues as computational efficiency and
²³⁶ other performance measures, there are a number of limitations associated with the ANTsXNet
²³⁷ pipeline that should be mentioned both to guide potential users and possibly motivate future
²³⁸ related research. As is the case with many deep learning models, usage is restricted based on
²³⁹ training data. For example, much of the publicly available brain data has been anonymized
²⁴⁰ through various defacing protocols. That is certainly the case with the training data used for
²⁴¹ the ANTsXNet pipeline which has consequences specific to the brain extraction step which
²⁴² could lead to poor performance. We are currently aware of this issue and have provided
²⁴³ a temporary workaround while simultaneously resuming training on whole head data to
²⁴⁴ mitigate this issue. Related, although the ANTsXNet pipeline performs relatively well as
²⁴⁵ assessed across lifespan data, performance might be hampered for specific age ranges (e.g.,
²⁴⁶ neonates), whereas the traditional ANTs cortical thickness pipeline is more flexible and might
²⁴⁷ provide better age-targeted performance. This is the subject of ongoing research. Additionally,

248 application of the ANTsXNet pipeline would be limited with high-resolution acquisitions.
249 Due to the heavy memory requirements associated with deep learning training, the utility of
250 any resolution greater than 1 mm isotropic would not be leveraged by the existing pipeline.
251 However, there is a potential pipeline variation (akin to the longitudinal variant) that would
252 be worth exploring where Deep Atropos is used only to provide the priors for a subsequent
253 traditional Atropos segmentation on high-resolution data.

254 In terms of additional future work, the recent surge and utility of deep learning in medical
255 image analysis has significantly guided the areas of active ANTsX development. As demon-
256 strated in this work with our widely used cortical thickness pipelines, there are many potential
257 benefits of deep learning analogs to existing ANTs tools as well as the development of new
258 ones. Performance is mostly comparable-to-superior relative to existing pipelines depending
259 on the evaluation metric. Specifically, the ANTsXNet cross-sectional pipeline does well for
260 the age prediction performance framework and in terms of the ICC. Additionally, this pipeline
261 performs relatively well for longitudinal ADNI data for disease differentiation but not so
262 much in terms of the generic variance ratio criterion. However, for such longitudinal-specific
263 studies, the ANTsXNet longitudinal variant performs well for both performance measures.
264 We see possible additional longitudinal extensions incorporating subject ID and months as
265 additional network inputs.

266 Methods

267 The original ANTs cortical thickness pipeline

268 The original ANTs cortical thickness pipeline¹⁹ consists of the following steps:

- 269 • preprocessing: denoising¹⁵ and bias correction⁴⁶;
- 270 • brain extraction³⁴;
- 271 • brain segmentation with spatial tissue priors¹³ comprising the
- 272 – cerebrospinal fluid (CSF),
- 273 – gray matter (GM),

- 274 – white matter (WM),
275 – deep gray matter,
276 – cerebellum, and
277 – brain stem; and
- 278 • cortical thickness estimation¹⁸.

279 Our recent longitudinal variant³³ incorporates an additional step involving the construction
280 of a single subject template (SST)¹² coupled with the generation of tissue spatial priors of
281 the SST for use with the processing of the individual time points as described above.

282 Although the resulting thickness maps are conducive to voxel-based⁴⁷ and related analyses⁴⁸,
283 here we employ the well-known Desikan-Killiany-Tourville (DKT)³⁹ labeling protocol (31
284 labels per hemisphere) to parcellate the cortex for averaging thickness values regionally (cf
285 Table 2). This allows us to 1) be consistent in our evaluation strategy for comparison with
286 our previous work^{19,33} and 2) leverage an additional deep learning-based substitution within
287 the proposed pipeline.

288 Overview of cortical thickness via ANTsXNet

289 The entire analysis/evaluation framework, from preprocessing to statistical analysis, is made
290 possible through the ANTsX ecosystem and simplified through the open-source R and
291 Python platforms. Preprocessing, image registration, and cortical thickness estimation are
292 all available through the ANTsPy and ANTsR libraries whereas the deep learning steps are
293 performed through networks constructed and trained via ANTsRNet/ANTsPyNet with data
294 augmentation strategies and other utilities built from ANTsR/ANTsPy functionality.

295 The brain extraction, brain segmentation, and DKT parcellation deep learning components
296 were trained using data derived from our previous work¹⁹. Specifically, the IXI⁴⁹, MMRR⁵⁰,
297 NKI⁵¹, and OASIS⁵² data sets, and the corresponding derived data, comprising over 1200
298 subjects from age 4 to 94, were used for network training. Brain extraction employs a
299 traditional 3-D U-net network²⁸ with whole brain, template-based data augmentation²⁷
300 whereas brain segmentation and DKT parcellation are processed via 3-D U-net networks with

301 attention gating⁵³ on image octant-based batches. Additional network architecture details
 302 are given below. We emphasize that a single model (as opposed to ensemble approaches
 303 where multiple models are used to produce the final solution³¹) was created for each of these
 304 steps and was used for all the experiments described below.

305 Implementation

306 Software, average DKT regional thickness values for all data sets, and the scripts to perform
 307 both the analysis and obtain thickness values for a single subject (cross-sectionally or
 308 longitudinally) are provided as open-source. Specifically, all the ANTsX libraries are hosted
 309 on GitHub (<https://github.com/ANTsX>). The cross-sectional data and analysis code are
 310 available as .csv files and R scripts at the GitHub repository dedicated to this paper (<https://github.com/ntustison/PaperANTsX>) whereas the longitudinal data and evaluation scripts
 311 are organized with the repository associated with our previous work³³ (<https://github.com/ntustison/CrossLong>).

```

314
315 import ants
316 import antspynet
317
318 # ANTsPy/ANTsPyNet processing for subject IXI002-Guys-0828-T1
319 t1_file = "IXI002-Guys-0828-T1.nii.gz"
320 t1 = ants.image_read(t1_file)
321
322 # Atropos six-tissue segmentation
323 atropos = antspynet.deep_atropos(t1, do_preprocessing=True, verbose=True)
324
325 # Kelly Kapowski cortical thickness (combine Atropos WM and deep GM)
326 kk_segmentation = atropos['segmentation_image']
327 kk_segmentation[kk_segmentation == 4] = 3
328 kk_gray_matter = atropos['probability_images'][2]
329 kk_white_matter = atropos['probability_images'][3] + atropos['probability_images'][4]
330 kk = ants.kelly_kapowski(s=kk_segmentation, g=kk_gray_matter, w=kk_white_matter,
331                           its=45, r=0.025, m=1.5, x=0, verbose=1)
332
333 # Desikan-Killiany-Tourville labeling
334 dkt = antspynet.desikan_killiany_tourville_labeling(t1, do_preprocessing=True, verbose=True)
335
336 # DKT label propagation throughout the cortex
337 dkt_cortical_mask = ants.threshold_image(dkt, 1000, 3000, 1, 0)
338 dkt = dkt_cortical_mask * dkt
339 kk_mask = ants.threshold_image(kk, 0, 0, 0, 1)
340 dkt_propagated = ants.iMath(kk_mask, "PropagateLabelsThroughMask", kk_mask * dkt)
341
342 # Get average regional thickness values
343 kkRegionalStats = ants.label_stats(kk, dkt_propagated)

```

Listing 1: ANTsPy/ANTsPyNet command calls for a single IXI subject in the evaluation study for the cross-sectional pipeline.

345 In Listing 1, we show the ANTsPy/ANTsPyNet code snippet for cross-sectional processing
346 a single subject which starts with reading the T1-weighted MRI input image, through the
347 generation of the Atropos-style six-tissue segmentation and probability images, applica-
348 tion of `ants.kelly_kapowski` (i.e., DiReCT), DKT cortical parcellation, subsequent label
349 propagation through the cortex, and, finally, regional cortical thickness tabulation. The
350 cross-sectional and longitudinal pipelines are encapsulated in the ANTsPyNet functions
351 `antspynet.cortical_thickness` and `antspynet.longitudinal_cortical_thickness`, re-
352 spectively. Note that there are precise, line-by-line R-based analogs available through
353 ANTsR/ANTsRNet.

354 Both the `ants.deep_atropos` and `antspynet.desikan_killiany_tourville_labeling`
355 functions perform brain extraction using the `antspynet.brain_extraction` function. Inter-
356 nally, `antspynet.brain_extraction` contains the requisite code to build the network and
357 assign the appropriate hyperparameters. The model weights are automatically downloaded
358 from the online hosting site <https://figshare.com> (see the function `get_pretrained_network`
359 in ANTsPyNet or `getPretrainedNetwork` in ANTsRNet for links to all models and weights)
360 and loaded to the constructed network. `antspynet.brain_extraction` performs a quick
361 translation transformation to a specific template (also downloaded automatically) using the
362 centers of intensity mass, a common alignment initialization strategy. This is to ensure
363 proper gross orientation. Following brain extraction, preprocessing for the other two deep
364 learning components includes `ants.denoise_image` and `ants.n4_bias_correction` and an
365 affine-based reorientation to a version of the MNI template⁵⁴.

366 We recognize the presence of some redundancy due to the repeated application of certain
367 preprocessing steps. Thus, each function has a `do_preprocessing` option to eliminate this
368 redundancy for knowledgeable users but, for simplicity in presentation purposes, we do not
369 provide this modified pipeline here. Although it should be noted that the time difference is
370 minimal considering the longer time required by `ants.kelly_kapowski`. `ants.deep_atropos`
371 returns the segmentation image as well as the posterior probability maps for each tissue
372 type listed previously. `antspynet.desikan_killiany_tourville_labeling` returns only
373 the segmentation label image which includes not only the 62 cortical labels but the remaining

374 labels as well. The label numbers and corresponding structure names are given in the program
375 description/help. Because the DKT parcellation will, in general, not exactly coincide with
376 the non-zero voxels of the resulting cortical thickness maps, we perform a label propagation
377 step to ensure the entire cortex, and only the non-zero thickness values in the cortex, are
378 included in the tabulated regional values.

379 As mentioned previously, the longitudinal version, `antspynet.longitudinal_cortical_thickness`,
380 adds an SST generation step which can either be provided as a program input or it can
381 be constructed from spatial normalization of all time points to a specified template.
382 `ants.deep_atropos` is applied to the SST yielding spatial tissues priors which are then used
383 as input to `ants.atropos` for each time point. `ants.kelly_kapowski` is applied to the
384 result to generate the desired cortical thickness maps.

385 Computational time on a CPU-only platform is approximately 1 hour primarily due to
386 `ants.kelly_kapowski` processing. Other preprocessing steps, i.e., bias correction and de-
387 noising, are on the order of a couple minutes. This total time should be compared with 4 – 5
388 hours using the traditional pipeline employing the `quick` registration option or 10 – 15 hours
389 with the more comprehensive registration parameters employed). As mentioned previously,
390 elimination of the registration-based propagation of prior probability images to individual
391 subjects is the principal source of reduced computational time. For ROI-based analyses, this
392 is in addition to the elimination of the optional generation of a population-specific template.
393 Additionally, the use of `antspynet.desikan_killiany_tourville_labeling`, for cortical
394 labeling (which completes in less than five minutes) eliminates the need for joint label fusion
395 which requires multiple pairwise registrations for each subject in addition to the fusion
396 algorithm itself.

397 Training details

398 Training differed slightly between models and so we provide details for each of these com-
399 ponents below. For all training, we used ANTsRNet scripts and custom batch generators.
400 Although the network construction and other functionality is available in both ANTsPyNet
401 and ANTsRNet (as is model weights compatibility), we have not written such custom batch

402 generators for the former (although this is on our to-do list). In terms of hardware, all
403 training was done on a DGX (GPUs: 4X Tesla V100, system memory: 256 GB LRDIMM
404 DDR4).

405 **T1-weighted brain extraction.** A whole-image 3-D U-net model²⁸ was used in conjunction
406 with multiple training sessions employing a Dice loss function followed by categorical cross
407 entropy. Training data was derived from the same multi-site data described previously
408 processed through our registration-based approach³⁴. A center-of-mass-based transformation
409 to a standard template was used to standardize such parameters as orientation and voxel size.
410 However, to account for possible different header orientations of input data, a template-based
411 data augmentation scheme was used²⁷ whereby forward and inverse transforms are used
412 to randomly warp batch images between members of the training population (followed by
413 reorientation to the standard template). A digital random coin flipping for possible histogram
414 matching⁵⁵ between source and target images further increased data augmentation. The
415 output of the network is a probabilistic mask of the brain. [The architecture consists of](#)
416 [four encoding/decoding layers with eight filters at the base layer which doubled every layer.](#)
417 Although not detailed here, training for brain extraction in other modalities was performed
418 similarly.

419 **Deep Atropos.** Dealing with 3-D data presents unique barriers for training that are often
420 unique to medical imaging. Various strategies are employed such as minimizing the number
421 of layers and/or the number of filters at the base layer of the U-net architecture (as we
422 do for brain extraction). However, we found this to be too limiting for capturing certain
423 brain structures such as the cortex. 2-D and 2.5-D approaches are often used with varying
424 levels of success but we also found better performance using full 3-D information. This led
425 us to try randomly selected 3-D patches of various sizes. However, for both the six-tissue
426 segmentations and DKT parcellations, we found that an octant-based patch strategy yielded
427 the desired results. Specifically, after a brain extracted affine normalization to the MNI
428 template, the normalized image is cropped to a size of [160, 190, 160]. Overlapping octant
429 patches of size [112, 112, 112] were extracted from each image and trained using a batch size
430 of 12 such octant patches with weighted categorical cross entropy as the loss function. [The](#)

⁴³¹ architecture consists of four encoding/decoding layers with 16 filters at the base layer which
⁴³² doubled every layer.

⁴³³ As we point out in our earlier work¹⁹, obtaining proper brain segmentation is perhaps the
⁴³⁴ most critical step to estimating thickness values that have the greatest utility as a potential
⁴³⁵ biomarker. In fact, the first and last authors (NT and BA, respectively) spent much time
⁴³⁶ during the original ANTs pipeline development¹⁹ trying to get the segmentation correct which
⁴³⁷ required manually looking at many images and manually adjusting where necessary. This
⁴³⁸ fine-tuning is often omitted or not considered when other groups^{35,56,57} use components of our
⁴³⁹ cortical thickness pipeline which can be potentially problematic⁵⁸. Fine-tuning for this partic-
⁴⁴⁰ ular workflow was also performed between the first and last authors using manual variation of
⁴⁴¹ the weights in the weighted categorical cross entropy. Specifically, the weights of each tissue
⁴⁴² type were altered in order to produce segmentations which most resemble the traditional
⁴⁴³ Atropos segmentations. Ultimately, we settled on a weight vector of (0.05, 1.5, 1, 3, 4, 3, 3) for
⁴⁴⁴ the CSF, GM, WM, Deep GM, brain stem, and cerebellum, respectively. Other hyperparam-
⁴⁴⁵ eters can be directly inferred from explicit specification in the actual code. As mentioned
⁴⁴⁶ previously, training data was derived from application of the ANTs Atropos segmentation¹³
⁴⁴⁷ during the course of our previous work¹⁹. Data augmentation included small affine and
⁴⁴⁸ deformable perturbations using `antspynet.randomly_transform_image_data` and random
⁴⁴⁹ contralateral flips.

⁴⁵⁰ **Desikan-Killiany-Tourville parcellation.** Preprocessing for the DKT parcellation train-
⁴⁵¹ ing was similar to the Deep Atropos training. However, the number of labels and the
⁴⁵² complexity of the parcellation required deviation from other training steps. First, labeling
⁴⁵³ was split into an inner set and an outer set. Subsequent training was performed separately
⁴⁵⁴ for both of these sets. For the cortical labels, a set of corresponding input prior probability
⁴⁵⁵ maps were constructed from the training data (and are also available and automatically
⁴⁵⁶ downloaded, when needed, from <https://figshare.com>). Training occurred over multiple
⁴⁵⁷ sessions where, initially, categorical cross entropy was used and then subsequently refined
⁴⁵⁸ using a Dice loss function. Whole-brain training was performed on a brain-cropped template
⁴⁵⁹ size of [96, 112, 96]. Inner label training was performed similarly to our brain extraction

460 training where the number of layers at the base layer was reduced to eight. Training also
461 occurred over multiple sessions where, initially, categorical cross entropy was used and then
462 subsequently refined using a Dice loss function. Other hyperparameters can be directly
463 inferred from explicit specification in the actual code. Training data was derived from
464 application of joint label fusion¹⁶ during the course of our previous work¹⁹. When call-
465 ing `antspynet.desikan_killiany_tourville_labeling`, inner labels are estimated first
466 followed by the outer, cortical labels.

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497 **References**

- 498 1. Bajcsy, R. & Broit, C. Matching of deformed images. in *Sixth International Conference on*
499 *Pattern Recognition (ICPR'82)* 351–353 (1982).
- 500 2. Bajcsy, R. & Kovacic, S. Multiresolution elastic matching. *Computer Vision, Graphics,*
501 *and Image Processing* **46**, 1–21 (1989).
- 502 3. Gee, J., Sundaram, T., Hasegawa, I., Uematsu, H. & Hatabu, H. Characterization of
503 regional pulmonary mechanics from serial magnetic resonance imaging data. *Acad Radiol* **10**,
504 1147–52 (2003).
- 505 4. Klein, A. *et al.* Evaluation of 14 nonlinear deformation algorithms applied to human brain
506 MRI registration. *Neuroimage* **46**, 786–802 (2009).
- 507 5. Avants, B. B., Epstein, C. L., Grossman, M. & Gee, J. C. Symmetric diffeomorphic
508 image registration with cross-correlation: Evaluating automated labeling of elderly and
509 neurodegenerative brain. *Med Image Anal* **12**, 26–41 (2008).
- 510 6. Murphy, K. *et al.* Evaluation of registration methods on thoracic CT: The EMPIRE10
511 challenge. *IEEE Trans Med Imaging* **30**, 1901–20 (2011).
- 512 7. Menze, B., Reyes, M. & Van Leemput, K. The multimodal brain tumor image segmentation
513 benchmark (BRATS). *IEEE Trans Med Imaging* (2014) doi:[10.1109/TMI.2014.2377694](https://doi.org/10.1109/TMI.2014.2377694).
- 514 8. Balakrishnan, G., Zhao, A., Sabuncu, M. R., Guttag, J. & Dalca, A. V. VoxelMorph: A
515 learning framework for deformable medical image registration. *IEEE Trans Med Imaging*
516 (2019) doi:[10.1109/TMI.2019.2897538](https://doi.org/10.1109/TMI.2019.2897538).
- 517 9. Vos, B. D. de *et al.* A deep learning framework for unsupervised affine and deformable
518 image registration. *Med Image Anal* **52**, 128–143 (2019).
- 519 10. Fu, Y. *et al.* DeepReg: A deep learning toolkit for medical image registration. *Journal of*
520 *Open Source Software* **5**, 2705 (2020).

- 521 11. Tustison, N. J., Avants, B. B. & Gee, J. C. Learning image-based spatial transformations
522 via convolutional neural networks: A review. *Magn Reson Imaging* **64**, 142–153 (2019).
- 523 12. Avants, B. B. *et al.* The optimal template effect in hippocampus studies of diseased
524 populations. *Neuroimage* **49**, 2457–66 (2010).
- 525 13. Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A. & Gee, J. C. An open source multivariate
526 framework for n -tissue segmentation with evaluation on public data. *Neuroinformatics* **9**,
527 381–400 (2011).
- 528 14. Tustison, N. J. & Gee, J. C. N4ITK: Nick’s N3 ITK implementation for MRI bias field
529 correction. *The Insight Journal* (2009).
- 530 15. Manjón, J. V., Coupé, P., Martí-Bonmatí, L., Collins, D. L. & Robles, M. Adaptive
531 non-local means denoising of MR images with spatially varying noise levels. *J Magn Reson*
532 *Imaging* **31**, 192–203 (2010).
- 533 16. Wang, H. & Yushkevich, P. A. Multi-atlas segmentation with joint label fusion and
534 corrective learning—an open source implementation. *Front Neuroinform* **7**, 27 (2013).
- 535 17. Wang, H. *et al.* Multi-atlas segmentation with joint label fusion. *IEEE Trans Pattern*
536 *Anal Mach Intell* **35**, 611–23 (2013).
- 537 18. Das, S. R., Avants, B. B., Grossman, M. & Gee, J. C. Registration based cortical thickness
538 measurement. *Neuroimage* **45**, 867–79 (2009).
- 539 19. Tustison, N. J. *et al.* Large-scale evaluation of ANTs and FreeSurfer cortical thickness
540 measurements. *Neuroimage* **99**, 166–79 (2014).
- 541 20. Esteban, O. *et al.* FMRIprep: A robust preprocessing pipeline for functional MRI. *Nat*
542 *Methods* **16**, 111–116 (2019).
- 543 21. De Leener, B. *et al.* SCT: Spinal cord toolbox, an open-source software for processing
544 spinal cord MRI data. *Neuroimage* **145**, 24–43 (2017).

- 545 22. Gorgolewski, K. J. *et al.* The brain imaging data structure, a format for organizing and
546 describing outputs of neuroimaging experiments. *Sci Data* **3**, 160044 (2016).
- 547 23. Halchenko, Y. O. & Hanke, M. Open is not enough. Let's take the next step: An
548 integrated, community-driven computing platform for neuroscience. *Front Neuroinform* **6**, 22
549 (2012).
- 550 24. Muschelli, J. *et al.* Neuroconductor: An R platform for medical imaging analysis.
551 *Biostatistics* **20**, 218–239 (2019).
- 552 25. Gorgolewski, K. *et al.* Nipype: A flexible, lightweight and extensible neuroimaging data
553 processing framework in python. *Front Neuroinform* **5**, 13 (2011).
- 554 26. Fischl, B. FreeSurfer. *Neuroimage* **62**, 774–81 (2012).
- 555 27. Tustison, N. J. *et al.* Convolutional neural networks with template-based data augmenta-
556 tion for functional lung image quantification. *Acad Radiol* **26**, 412–423 (2019).
- 557 28. Falk, T. *et al.* U-net: Deep learning for cell counting, detection, and morphometry. *Nat
558 Methods* **16**, 67–70 (2019).
- 559 29. Bashyam, V. M. *et al.* MRI signatures of brain age and disease over the lifespan based
560 on a deep brain network and 14,468 individuals worldwide. *Brain* **143**, 2312–2324 (2020).
- 561 30. Goubran, M. *et al.* Hippocampal segmentation for brains with extensive atrophy using
562 three-dimensional convolutional neural networks. *Hum Brain Mapp* **41**, 291–308 (2020).
- 563 31. Li, H. *et al.* Fully convolutional network ensembles for white matter hyperintensities
564 segmentation in mr images. *Neuroimage* **183**, 650–665 (2018).
- 565 32. Haris, M., Shakhnarovich, G. & Ukita, N. Deep back-projection networks for super-
566 resolution. in *2018 IEEE/CVF Conference on Computer Vision and Pattern Recognition*
567 1664–1673 (2018). doi:[10.1109/CVPR.2018.00179](https://doi.org/10.1109/CVPR.2018.00179).
- 568 33. Tustison, N. J. *et al.* Longitudinal mapping of cortical thickness measurements: An

⁵⁶⁹ Alzheimer's Disease Neuroimaging Initiative-based evaluation study. *J Alzheimers Dis* (2019)
⁵⁷⁰ doi:[10.3233/JAD-190283](https://doi.org/10.3233/JAD-190283).

⁵⁷¹ 34. Avants, B. B., Klein, A., Tustison, N. J., Woo, J. & Gee, J. C. Evaluation of open-access,
⁵⁷² automated brain extraction methods on multi-site multi-disorder data. in *16th annual meeting*
⁵⁷³ *for the organization of human brain mapping* (2010).

⁵⁷⁴ 35. Rebsamen, M., Rummel, C., Reyes, M., Wiest, R. & McKinley, R. Direct cortical
⁵⁷⁵ thickness estimation using deep learning-based anatomy segmentation and cortex parcellation.
⁵⁷⁶ *Hum Brain Mapp* (2020) doi:[10.1002/hbm.25159](https://doi.org/10.1002/hbm.25159).

⁵⁷⁷ 36. Henschel, L. *et al.* FastSurfer - a fast and accurate deep learning based neuroimaging
⁵⁷⁸ pipeline. *Neuroimage* **219**, 117012 (2020).

⁵⁷⁹ 37. Lemaitre, H. *et al.* Normal age-related brain morphometric changes: Nonuniformity
⁵⁸⁰ across cortical thickness, surface area and gray matter volume? *Neurobiol Aging* **33**, 617.e1–9
⁵⁸¹ (2012).

⁵⁸² 38. Breiman, L. Random forests. *Machine Learning* **45**, 5–32 (2001).

⁵⁸³ 39. Klein, A. & Tourville, J. 101 labeled brain images and a consistent human cortical
⁵⁸⁴ labeling protocol. *Front Neurosci* **6**, 171 (2012).

⁵⁸⁵ 40. Holbrook, A. J. *et al.* Anterolateral entorhinal cortex thickness as a new biomarker for
⁵⁸⁶ early detection of Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment &*
⁵⁸⁷ *Disease Monitoring* **12**, e12068 (2020).

⁵⁸⁸ 41. Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F. & Baker, C. I. Circular analysis
⁵⁸⁹ in systems neuroscience: The dangers of double dipping. *Nat Neurosci* **12**, 535–40 (2009).

⁵⁹⁰ 42. <https://bigr-resource.atr.jp/srpbs1600/>.

⁵⁹¹ 43. Verbeke, G. Linear mixed models for longitudinal data. in *Linear mixed models in practice*
⁵⁹² 63–153 (Springer, 1997).

- 593 44. Gelman, A. & others. Prior distributions for variance parameters in hierarchical models
594 (comment on article by Browne and Draper). *Bayesian analysis* **1**, 515–534 (2006).
- 595 45. McKinley, R. *et al.* Few-shot brain segmentation from weakly labeled data with deep
596 heteroscedastic multi-task networks. *CoRR* **abs/1904.02436**, (2019).
- 597 46. Tustison, N. J. *et al.* N4ITK: Improved N3 bias correction. *IEEE Trans Med Imaging*
598 **29**, 1310–20 (2010).
- 599 47. Ashburner, J. & Friston, K. J. Voxel-based morphometry—the methods. *Neuroimage* **11**,
600 805–21 (2000).
- 601 48. Avants, B. *et al.* Eigenanatomy improves detection power for longitudinal cortical change.
602 *Med Image Comput Comput Assist Interv* **15**, 206–13 (2012).
- 603 49. <https://brain-development.org/ixi-dataset/>.
- 604 50. Landman, B. A. *et al.* Multi-parametric neuroimaging reproducibility: A 3-T resource
605 study. *Neuroimage* **54**, 2854–66 (2011).
- 606 51. http://fcon_1000.projects.nitrc.org/indi/pro/nki.html.
- 607 52. <https://www.oasis-brains.org>.
- 608 53. Schlemper, J. *et al.* Attention gated networks: Learning to leverage salient regions in
609 medical images. *Med Image Anal* **53**, 197–207 (2019).
- 610 54. Fonov, V. S., Evans, A. C., McKinstry, R. C., Almlí, C. & Collins, D. L. Unbiased
611 nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*
612 **S102**, (2009).
- 613 55. Nyúl, L. G. & Udupa, J. K. On standardizing the MR image intensity scale. *Magn Reson*
614 *Med* **42**, 1072–81 (1999).
- 615 56. Clarkson, M. J. *et al.* A comparison of voxel and surface based cortical thickness
616 estimation methods. *Neuroimage* **57**, 856–65 (2011).

- 617 57. Schwarz, C. G. *et al.* A large-scale comparison of cortical thickness and volume methods
618 for measuring alzheimer's disease severity. *Neuroimage Clin* **11**, 802–812 (2016).
- 619 58. Tustison, N. J. *et al.* Instrumentation bias in the use and evaluation of scientific software:
620 Recommendations for reproducible practices in the computational sciences. *Front Neurosci*
621 **7**, 162 (2013).

622 **Author contributions**

- 623 • Conception and design N.T., A.H., M.Y., J.S., B.A.
- 624 • Analysis and interpretation N.T., A.H., D.G., M.Y., J.S. B.A.
- 625 • Creation of new software N.T., P.C., H.J., J.M., G.D., J.D., S.D., N.C., J.G., B.A.
- 626 • Drafting of manuscript N.T., A.H., P.C., H.J., J.M., G.D., J.G., B.A.

627 **Competing interests**

628 The authors declare no competing interests.