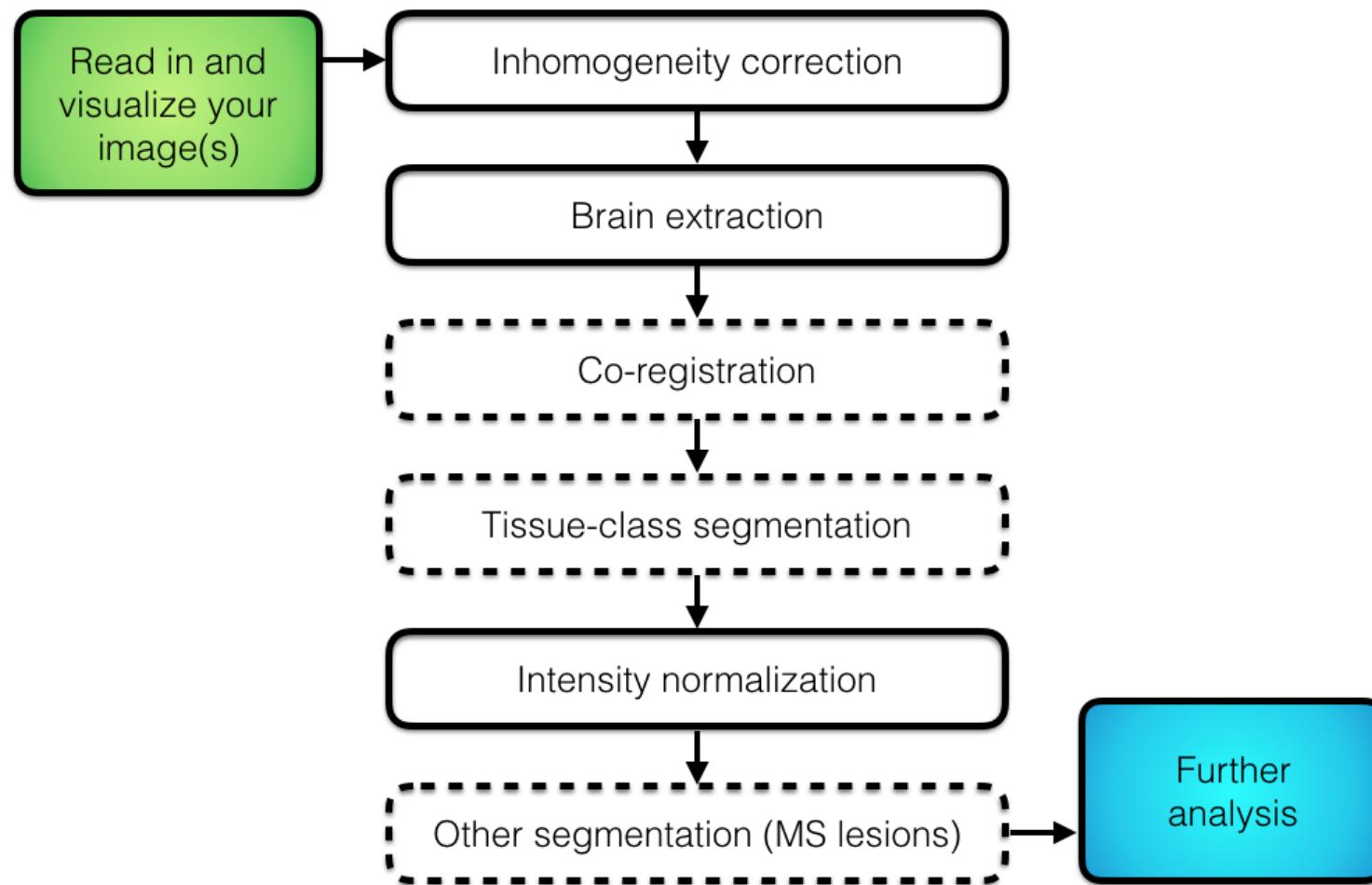


Image Harmonization

Overall Pipeline



Motivation

- Multi-site imaging studies are becoming increasingly common.
- Combining imaging data across sites introduces non-biological sources of variation that arise from the use of different scanner hardware and acquisition protocols.
 - E.g., field strength, manufacturer, subject positioning
- **Scanner effects** or **site effects** are similar to **batch effects** in the genomics literature
 - Known to affect measurement of regional volumes, cortical thickness, voxel-based morphometry, ...
 - More generally, structural, functional, diffusion tensor, and other types of images and features extracted from them may exhibit scanner effects

Motivation

- Need to eliminate or account for scanner effects in downstream statistical analyses
 - Most critical if sites or scanners are imbalanced with respect to other variables such as age, sex, race, clinical status
 - Simply including scanner as a confounding variable may not work well (Rao et al. 2017)
- Several methods for estimating and removing unwanted sources of variation due to site/scanner have been adapted to neuroimaging data.
- In this tutorial we will use ComBat (Johnson, Li, and Rabinovic 2007; Fortin et al. 2018) to harmonize cortical thicknesses from the ADNI data.
 - ComBat has been shown to effectively reduce scanner-to-scanner variability while preserving biological associations.

ADNI Cortical Thickness Data

- The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a multi-million dollar study funded by public and private sources.
 - National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and non-profit organizations.
- The goals of the ADNI are to better understand progression from normal aging to mild cognitive impairment (MCI) and early Alzheimer's disease (AD) and determine effective biomarkers for disease diagnosis, monitoring, and treatment development.
- We estimated cortical thicknesses from a subset of initial subject visits (N=156)
 - Mix of male/female and healthy controls, MCI, and AD diagnoses at baseline
- Our subset consists of images acquired from scanners at 14 different sites
 - Mix of field strength, manufacturer, and model

ADNI Data Access

<http://adni.loni.usc.edu/data-samples/access-data/>

Cortical Thickness

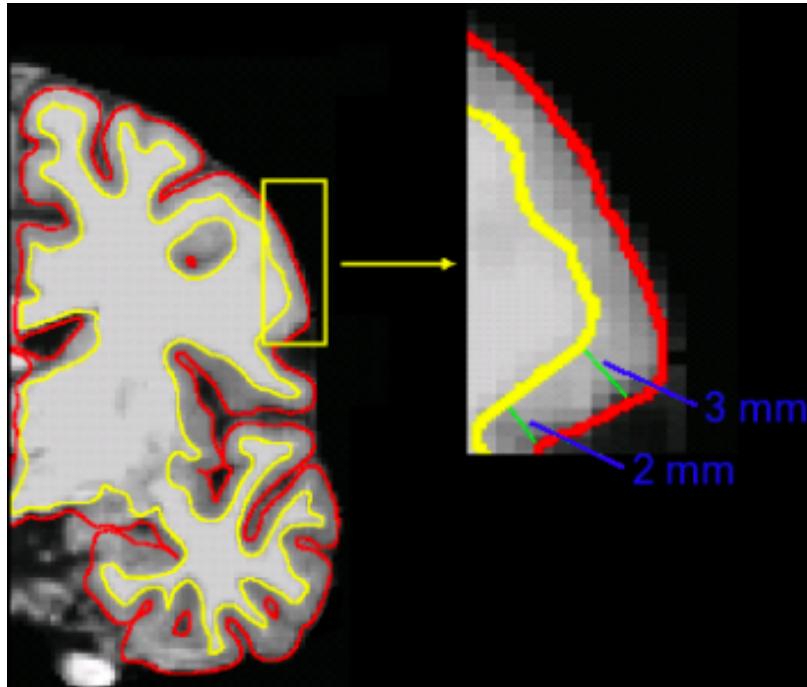
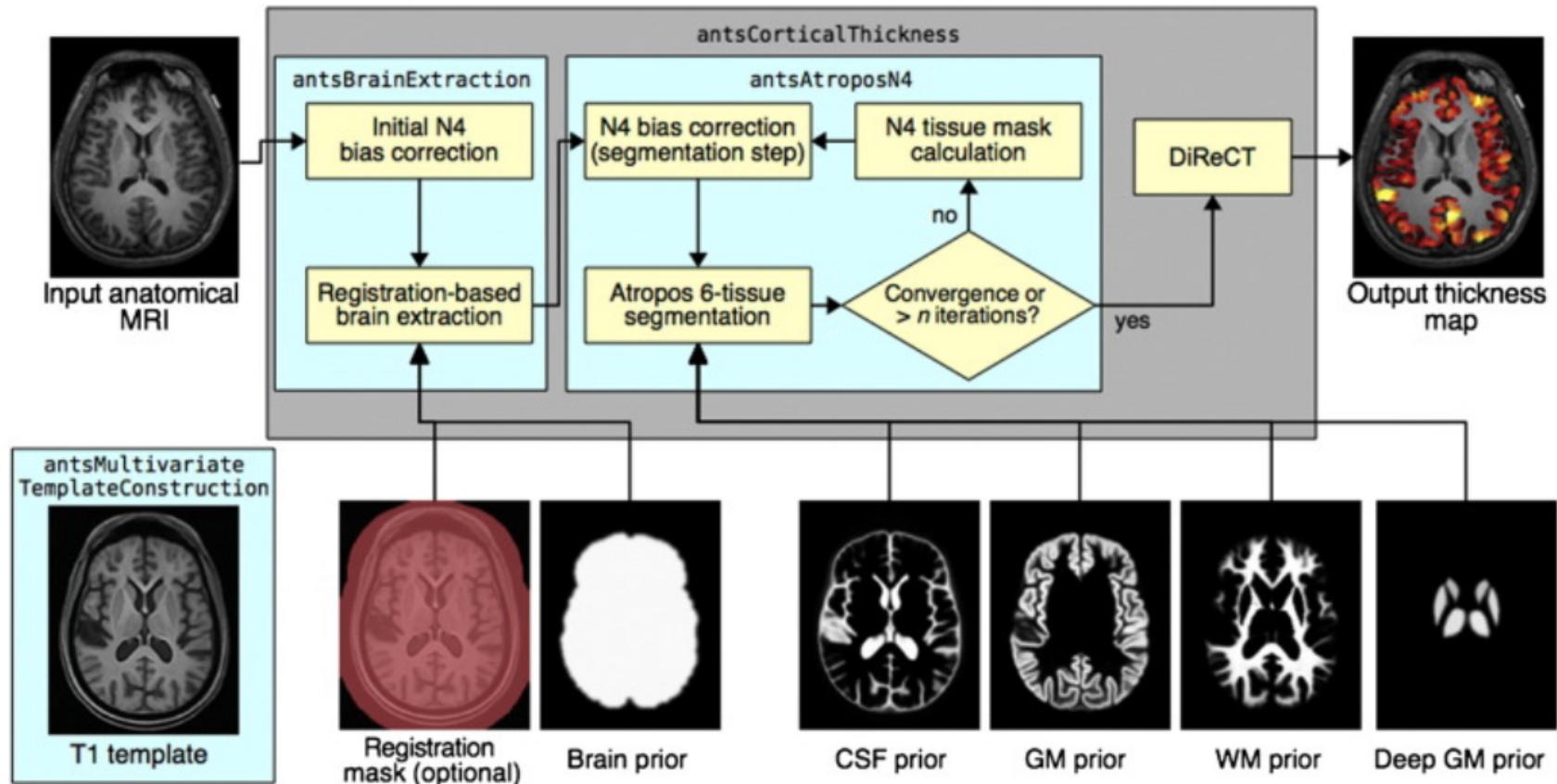


Image taken from <http://www.martinos.org/neurorecovery/technology.htm>

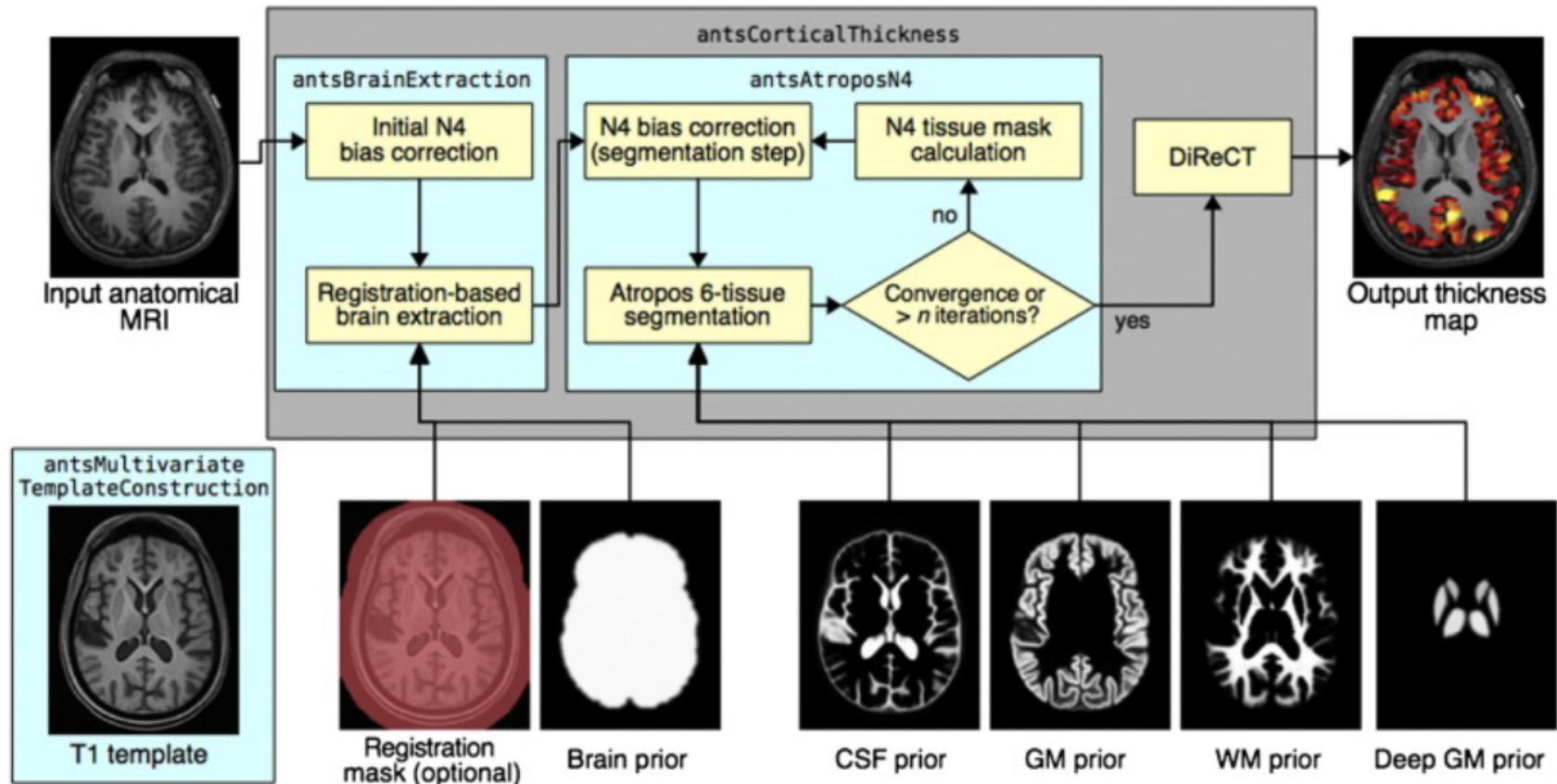
- There are several different ways to measure cortical thickness
- General idea is to measure perpendicular from the white/gray matter boundary to the pial surface
- Cortical thickness is an important imaging-based biomarker for numerous psychological and neurodegenerative diseases: Alzheimer's and other dementias, Schizophrenia, MS, addiction, ...

ANTs Cortical Thickness Pipeline (antsCorticalThickness.sh)



- Template: publicly available vs. “cooking” one based on your data
- DiReCT: Diffeomorphic Registration based CT measurement (Das et al. 2009)

ANTs Cortical Thickness Pipeline (antsCorticalThickness.sh)

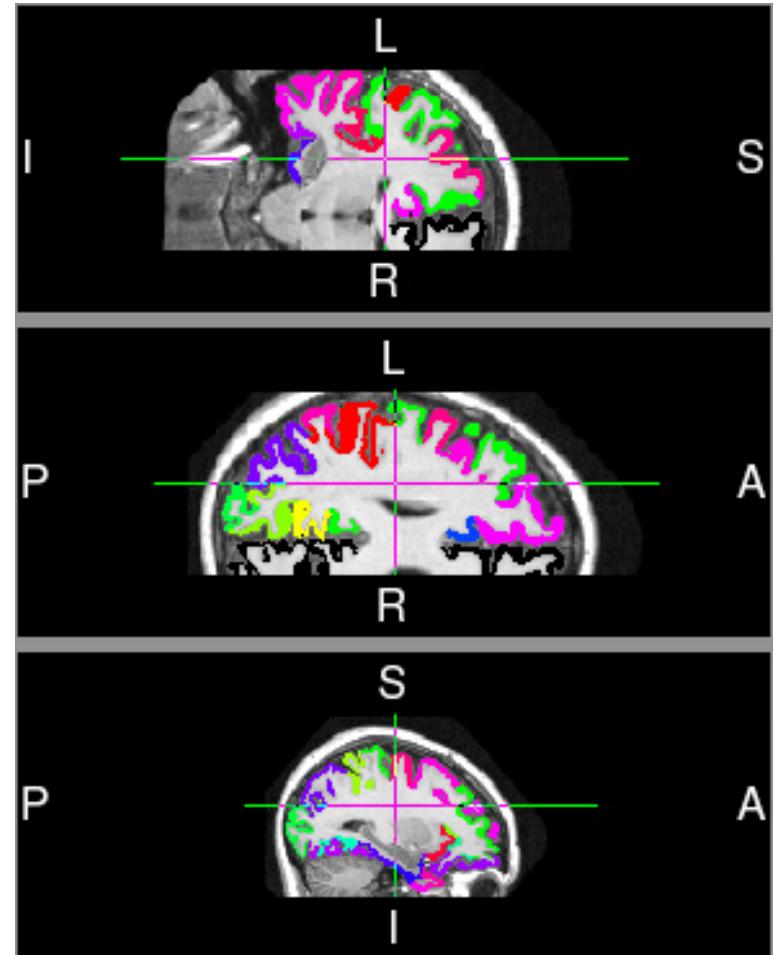


- With tissue priors and N4 corrected T1 from atropos, can use cort_thickness in extrantsr package

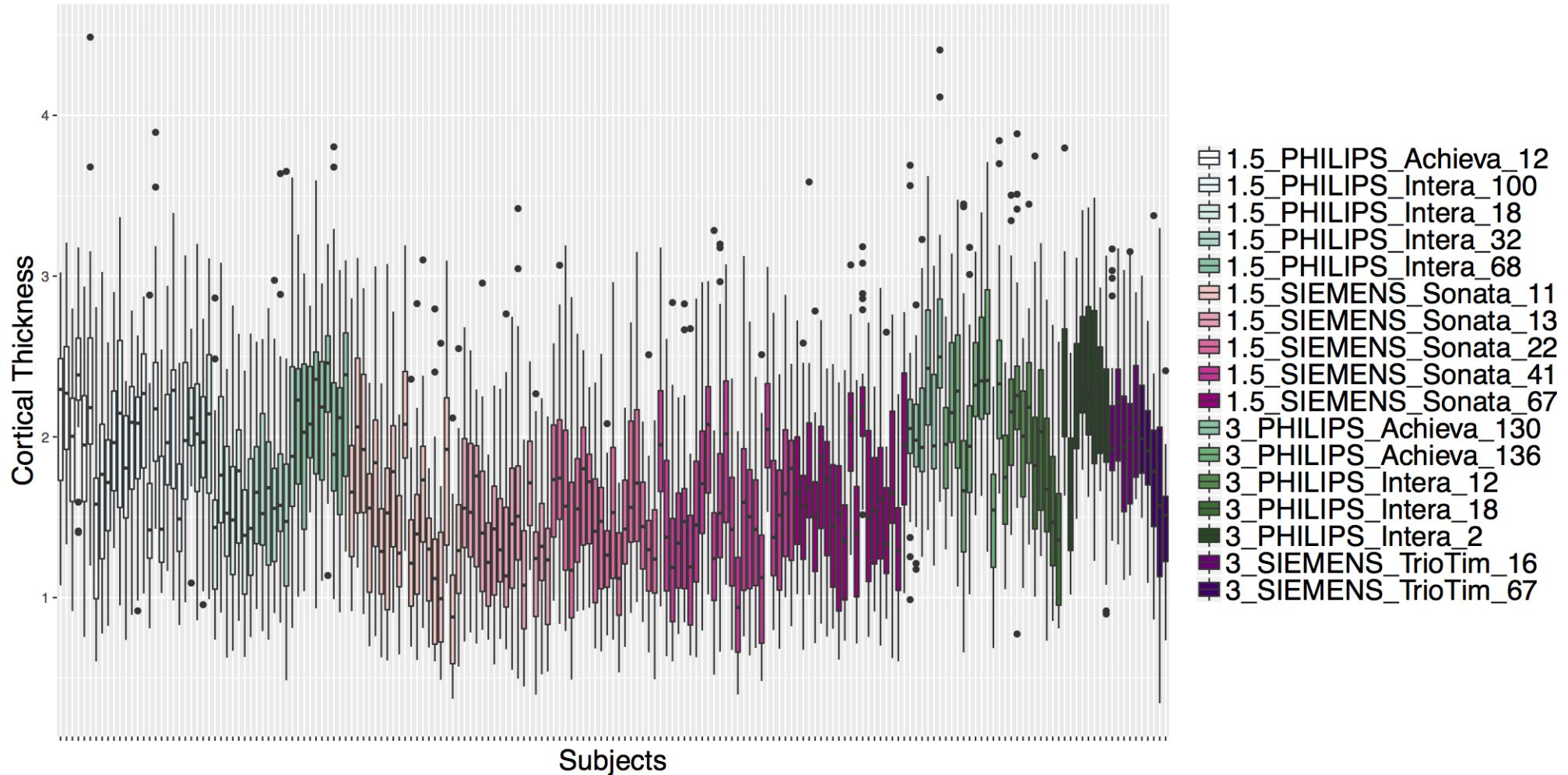
Cortical Thickness Regions

- Multi-atlas label fusion applied using 20 OASIS template T1s manually labeled with the Desikan-Killiany-Tourville (DKT) cortical labeling protocol (www.mindboggle.info).

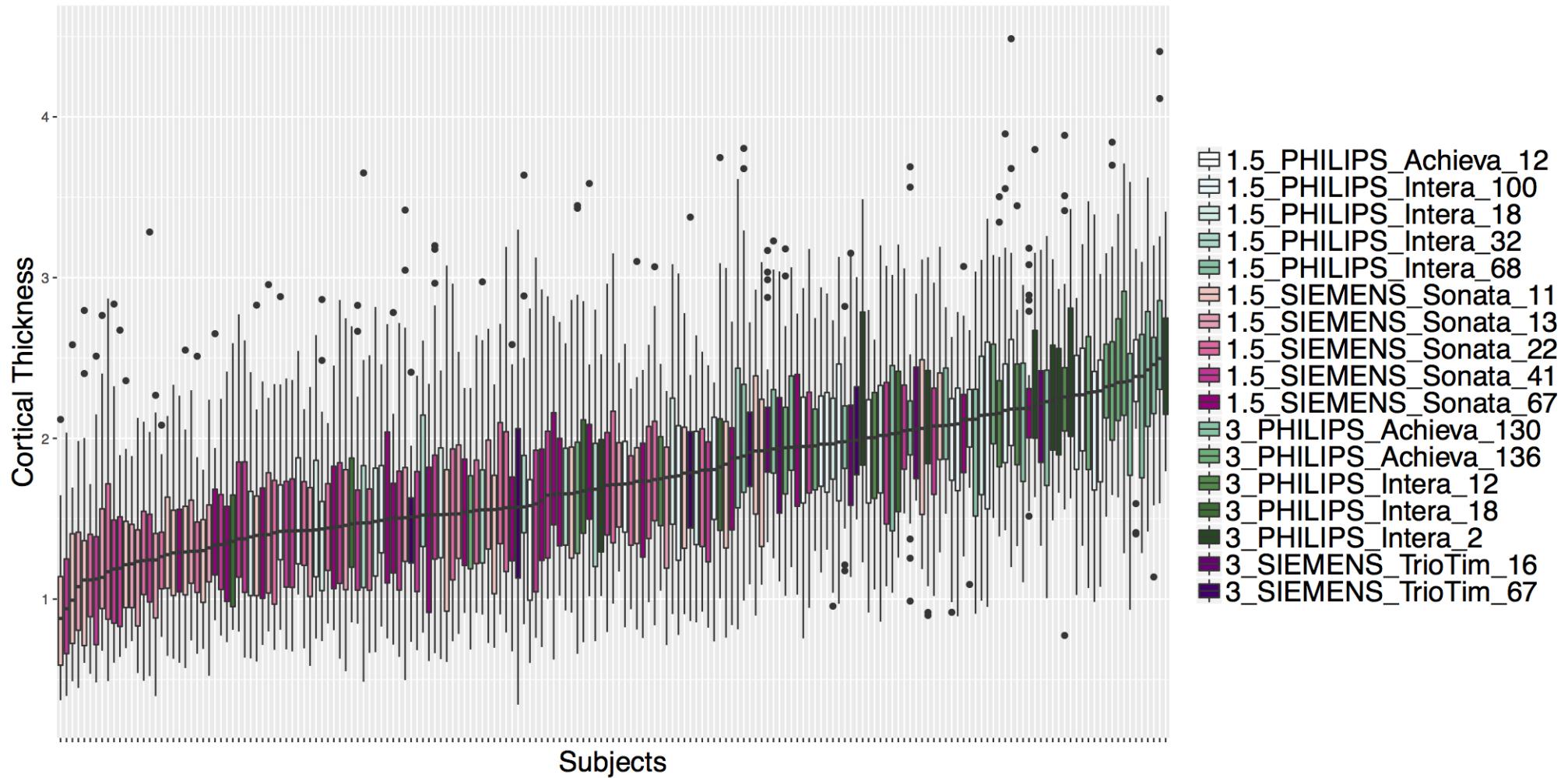
label	roi
1 X1002	"left caudal anterior cingulate"
2 X1003	"left caudal middle frontal"
3 X1005	"left cuneus"
4 X1008	"left inferior parietal"
5 X1017	"left paracentral"
6 X1022	"left postcentral"
7 X1023	"left posterior cingulate"
8 X1024	"left precentral"
9 X1025	"left precuneus"
10 X1027	"left rostral middle frontal"
11 X1028	"left superior frontal"
12 X1029	"left superior parietal"
13 X1030	"left superior temporal"
14 X1031	"left supramarginal"
15 X1035	"left insula"



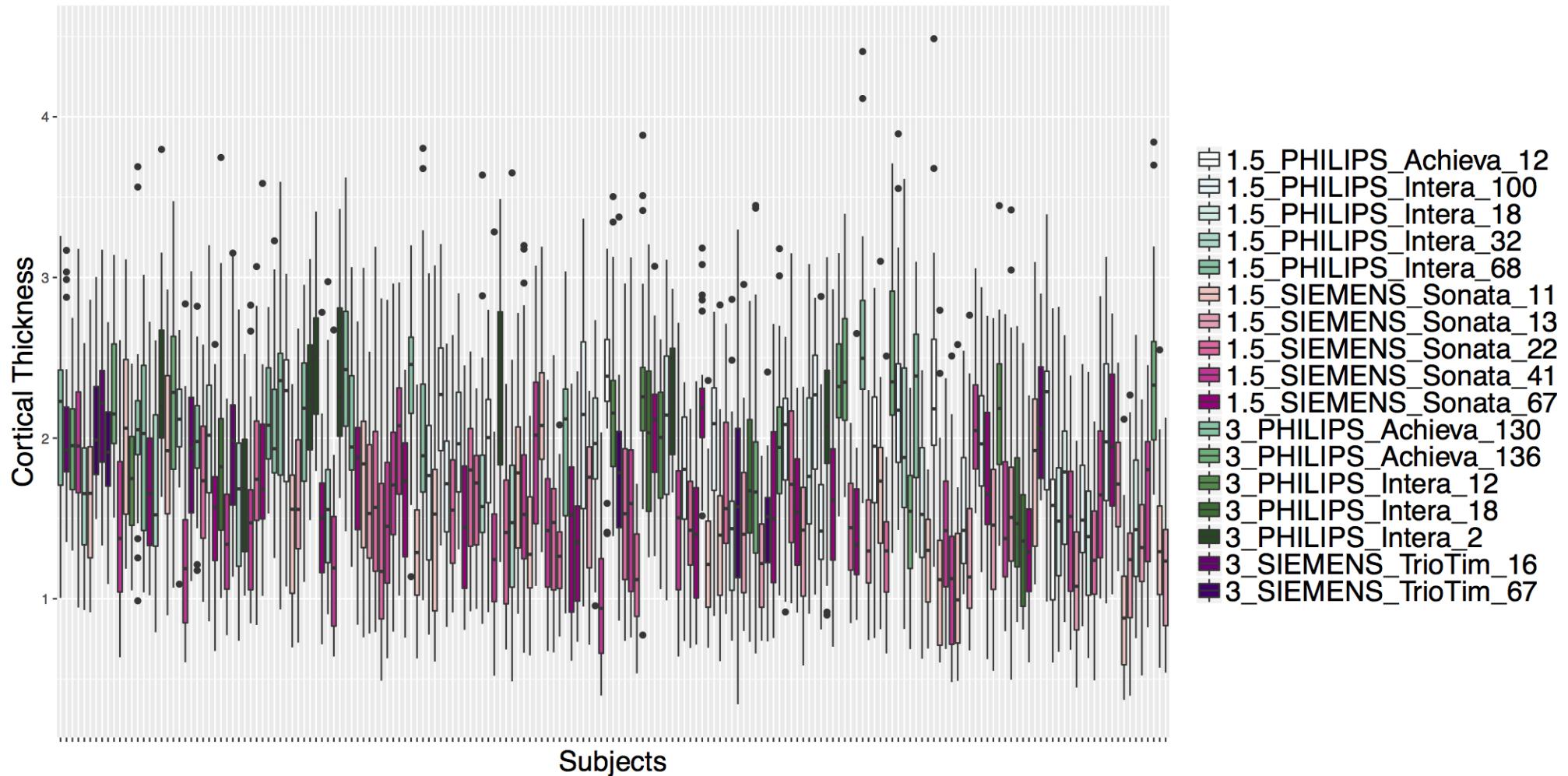
ADNI Cortical Thickness Data



ADNI Cortical Thickness Data

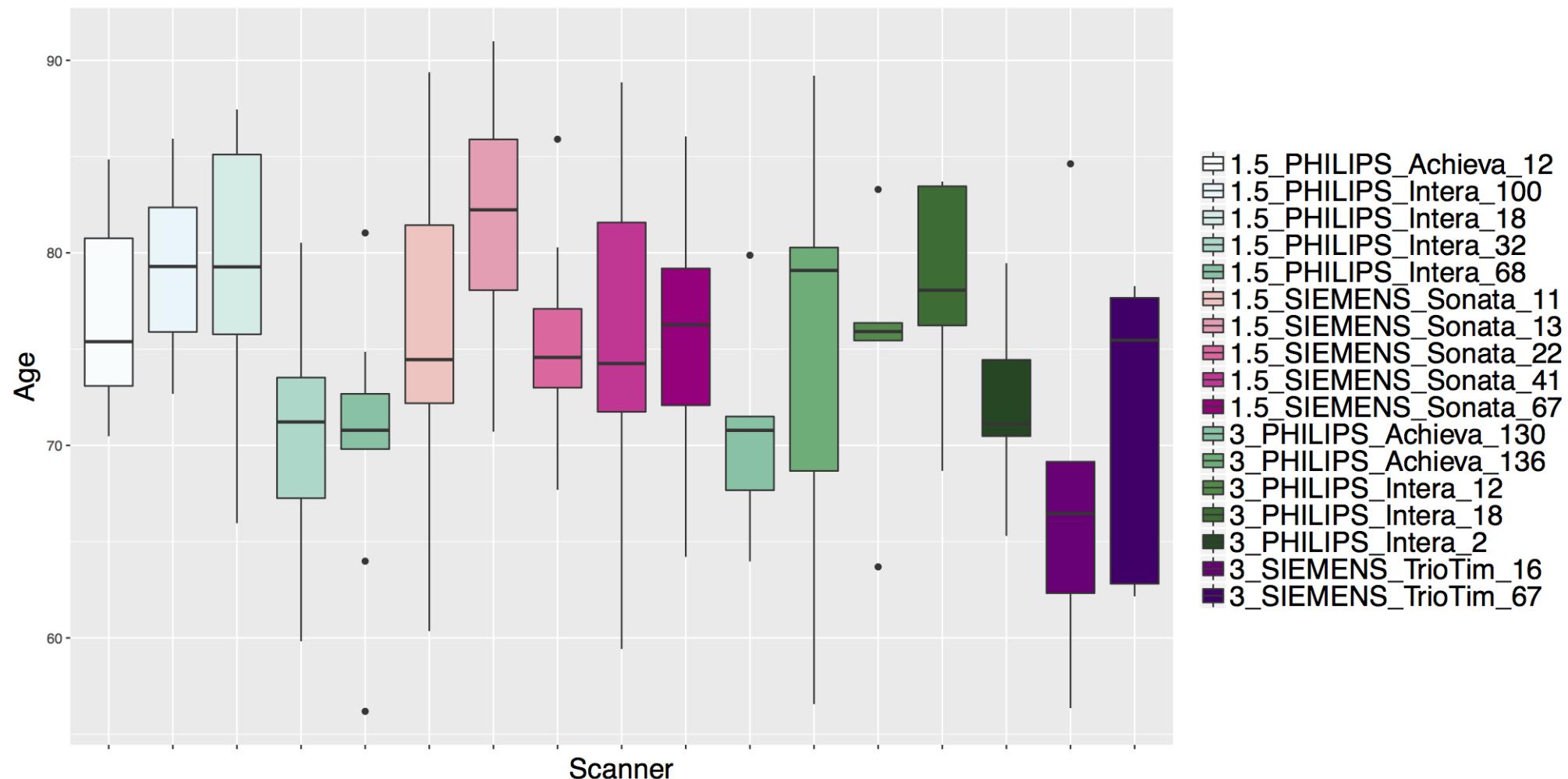


ADNI Cortical Thickness Data



ADNI Cortical Thickness Data

- Scanner is often confounded with biological covariates of interest.



ComBat Model

- ComBat (Johnson, Li, and Rabinovic 2007; Fortin et al. 2018) assumes the imaging feature measurements can be modeled as a linear combination of the biological variables and the scanner effects with an error term that includes a multiplicative scanner-specific scaling factor: $y_{i,j,v} = \alpha_v + X_{Ti,j}\beta_v + Z_{Ti,j}\theta_v + \delta_{j,v}\epsilon_{i,j,v}$
 - $y_{i,j,v}$ is average cortical thickness in ROI v from subject i , scanner j
 - $X_{Ti,j}$ is a vector of fixed covariates for subject i scanned on scanner j
 - α_v, β_v are the intercept and slope vector of covariates for measurement v
 - $Z_{Ti,j}$ is a vector that indicates which scanner subject i was imaged on
 - θ_v is the vector of additive scanner effects
 - $\delta_{j,v}$ is the multiplicative effect of scanner j on measurement v
 - $E(\epsilon_{i,j,v}) = 0$

ComBat Harmonization

- Substituting $\gamma_{j,v}$ for $Z_{Ti,j}\theta_v$ we have: $y_{i,j,v} = \alpha_v + X_{Ti,j}\beta_v + \gamma_{j,v} + \delta_{j,v}\epsilon_{i,j,v}$
- ComBat uses empirical Bayes estimation to improve quality of scanner-specific parameter estimates when sample sizes are small
 - Let $\gamma_{*j,v}$ and $\delta_{*j,v}$ denote the EB estimates of $\gamma_{j,v}$ and $\delta_{j,v}$, respectively.
- Then, the ComBat-harmonized cortical thicknesses are defined as
$$y_{\text{ComBati},j,v} = y_{i,j,v} - \hat{\alpha}_v - X_{Ti,j}\hat{\beta}_v - \gamma_{*j,v}\delta_{*j,v} + \hat{\alpha}_v + X_{Ti,j}\hat{\beta}_v$$

Applying ComBat

- Need utils.R and combat.R from <https://github.com/Jfortin1/ComBatHarmonization>

```
source('utils.R')
source('combat.R')
```

- The model matrix should contain covariates of biological interest.

```
modelData = read.csv('modelData.csv')
head(modelData)
```

	subject	age	sex	dx	scanner
1	002_S_0413	76.4329	F	Normal	3_PHILIPS_Intera_2
2	002_S_0559	79.4658	M	Normal	3_PHILIPS_Intera_2
3	002_S_0729	65.2986	F	MCI	3_PHILIPS_Intera_2
4	002_S_0816	70.9534	M	AD	3_PHILIPS_Intera_2
5	002_S_0954	69.5041	F	MCI	3_PHILIPS_Intera_2
6	002_S_1018	70.8055	F	AD	3_PHILIPS_Intera_2

- We will include age, sex, and diagnosis.

```
mod = model.matrix(~age+factor(sex)+factor(dx), data=modelData)
```

Applying ComBat

- Let's read in the cortical thickness data.

```
ctData = read.csv('imageData.csv')
head(ctData) [,1:10]
```

	subject	X1002	X1003	X1005	X1008	X1017	X1022
1	002_S_0413	2.349515	1.957340	1.6771022	2.929418	1.893073	1.733991
2	002_S_0559	2.814481	1.768518	0.9173002	2.297948	1.612640	2.071636
3	002_S_0729	2.788202	2.108902	1.6343228	3.154604	2.219242	1.984391
4	002_S_0816	2.753477	2.168249	1.7955870	2.880065	1.973897	2.042263
5	002_S_0954	2.523273	1.664635	1.0189855	2.077749	1.236037	1.468252
6	002_S_1018	2.596688	2.216399	1.9206076	2.424231	1.744081	1.800574
		X1023	X1024	X1025			
1		2.365209	1.968747	2.474627			
2		2.606214	1.838712	2.345573			
3		2.578613	1.782150	2.055732			
4		2.188748	1.990839	2.992091			
5		1.329828	1.468782	1.623318			
6		2.165901	1.947617	2.611285			

Applying ComBat

- The imaging data needs to be in a separate matrix where rows are features and columns are subjects.
- Let's remove the subject column and transpose the ctData object.

```
img = t(ctData[,-1])
head(img) [,1:10]
```

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]
X1002	2.349515	2.8144805	2.788202	2.753477	2.523273	2.596688	1.833424
X1003	1.957340	1.7685180	2.108902	2.168249	1.664635	2.216399	1.696198
X1005	1.677102	0.9173002	1.634323	1.795587	1.018986	1.920608	1.228951
X1008	2.929418	2.2979484	3.154604	2.880065	2.077749	2.424231	2.712218
X1017	1.893073	1.6126404	2.219242	1.973897	1.236037	1.744081	1.760396
X1022	1.733991	2.0716363	1.984391	2.042263	1.468252	1.800574	1.712189
	[,8]	[,9]	[,10]				
X1002	2.960386	3.191757	1.6549346				
X1003	2.220978	2.294089	1.1845660				
X1005	1.638375	1.760091	0.6901224				
X1008	2.727885	2.280574	1.2541459				
X1017	2.105533	1.890207	1.0815922				
X1022	2.095173	1.480126	0.8755437				

Applying ComBat

- Given a model matrix, scanner information, and image data matrix, ComBat just requires a single line of code:

```
harmonized = combat(dat=img, batch=modelData$scanner, mod=mod)
```

```
[combat] Performing ComBat with empirical Bayes  
[combat] Found 17 batches  
[combat] Adjusting for 4 covariate(s) or covariate level(s)  
[combat] Standardizing Data across features  
[combat] Fitting L/S model and finding priors  
[combat] Finding parametric adjustments  
[combat] Adjusting the Data
```

- 4 covariates: age, sex (2-level factor), and diagnosis (3-level factor).
- The combat() function returns a list.

ComBat Harmonized Data

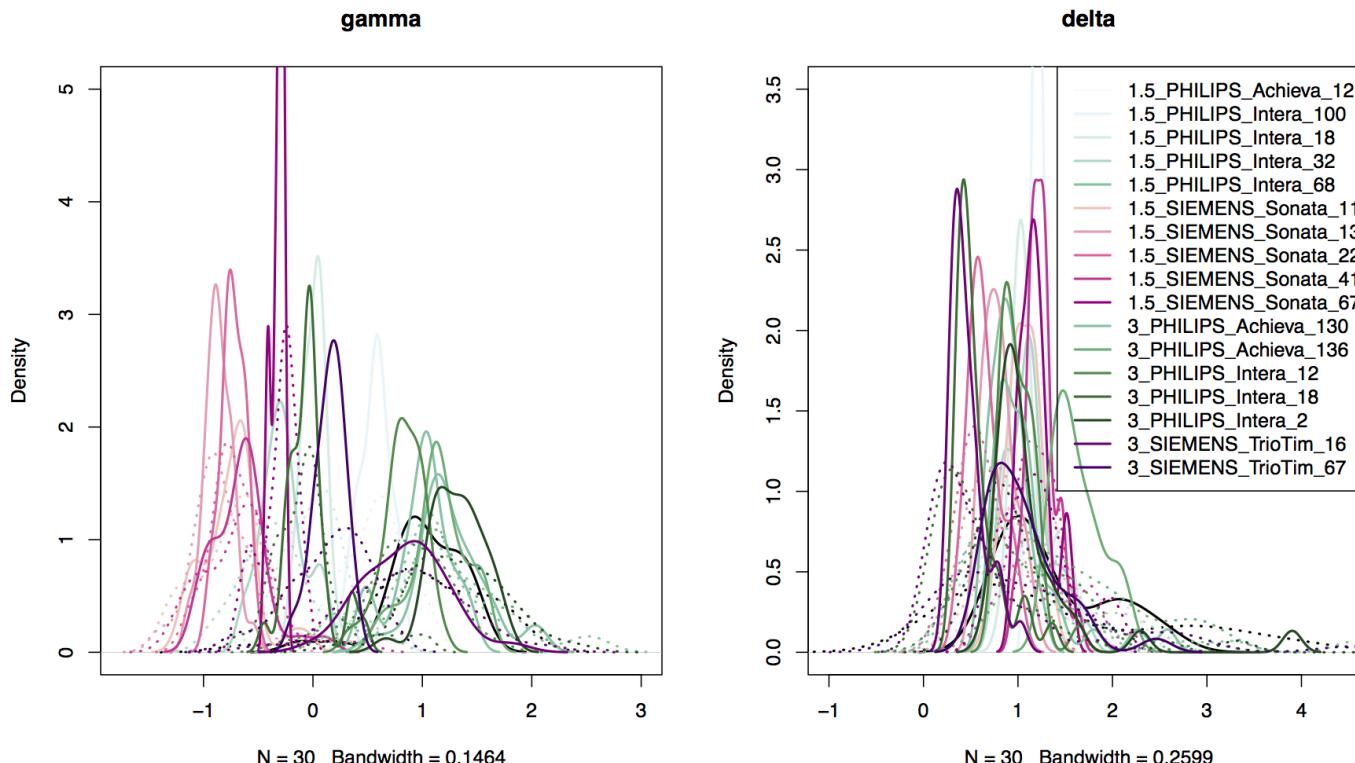
- The `combat()` function returns a list.
- Harmonized data are returned as a matrix with the same dimensions as the image data input (rows are features, columns are subjects).

```
head(harmonized$dat.combat) [,1:10]
```

```
      [,1]      [,2]      [,3]      [,4]      [,5]      [,6]      [,7]
X1002 2.076337 2.5552595 2.525369 2.495758 2.2556688 2.331964 1.5558972
X1003 1.635520 1.4235185 1.805149 1.870055 1.3177142 1.929260 1.3508204
X1005 1.293296 0.6417266 1.256812 1.403631 0.7206567 1.502427 0.9123136
X1008 2.302387 1.6780318 2.524931 2.252803 1.4591354 1.801200 2.0869015
X1017 1.465025 1.1773251 1.797372 1.547696 0.7929384 1.314142 1.3274822
X1022 1.247649 1.6198378 1.528395 1.594847 0.9498901 1.333454 1.2174725
      [,8]      [,9]      [,10]
X1002 2.699030 3.152924 1.7187182
X1003 1.922145 2.437532 1.4111655
X1005 1.260755 1.965677 0.8954355
X1008 2.103707 2.521345 1.4713336
X1017 1.682005 2.106027 1.3144201
X1022 1.650527 1.808523 1.1827775
```

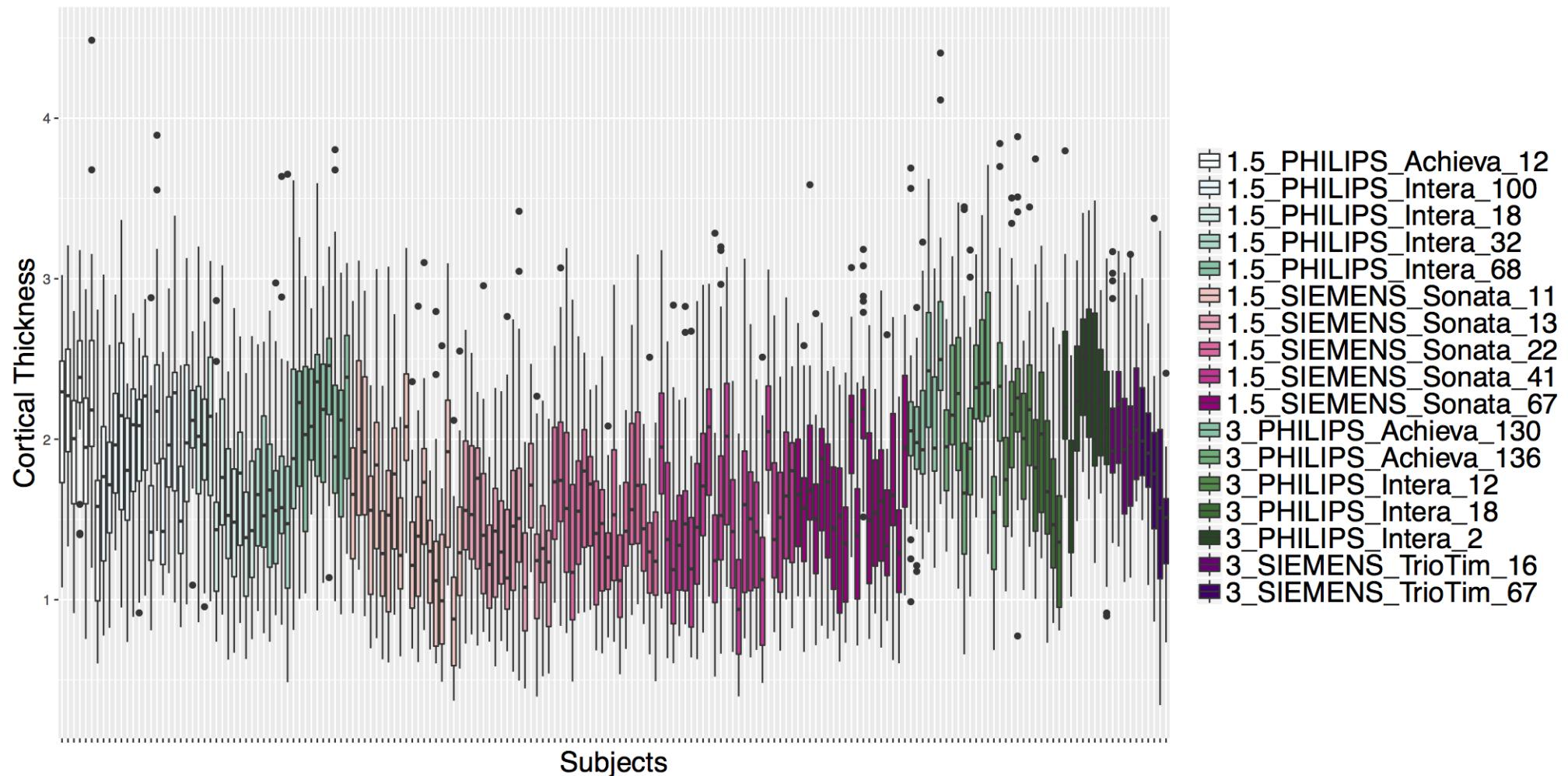
ComBat Priors

- Compare prior distributions to EB estimated parameter distributions
 - Location: `harmonized$gamma.hat` versus `harmonized$gamma.star`
 - Scale: `harmonized$delta.hat` versus `harmonized$delta.star`



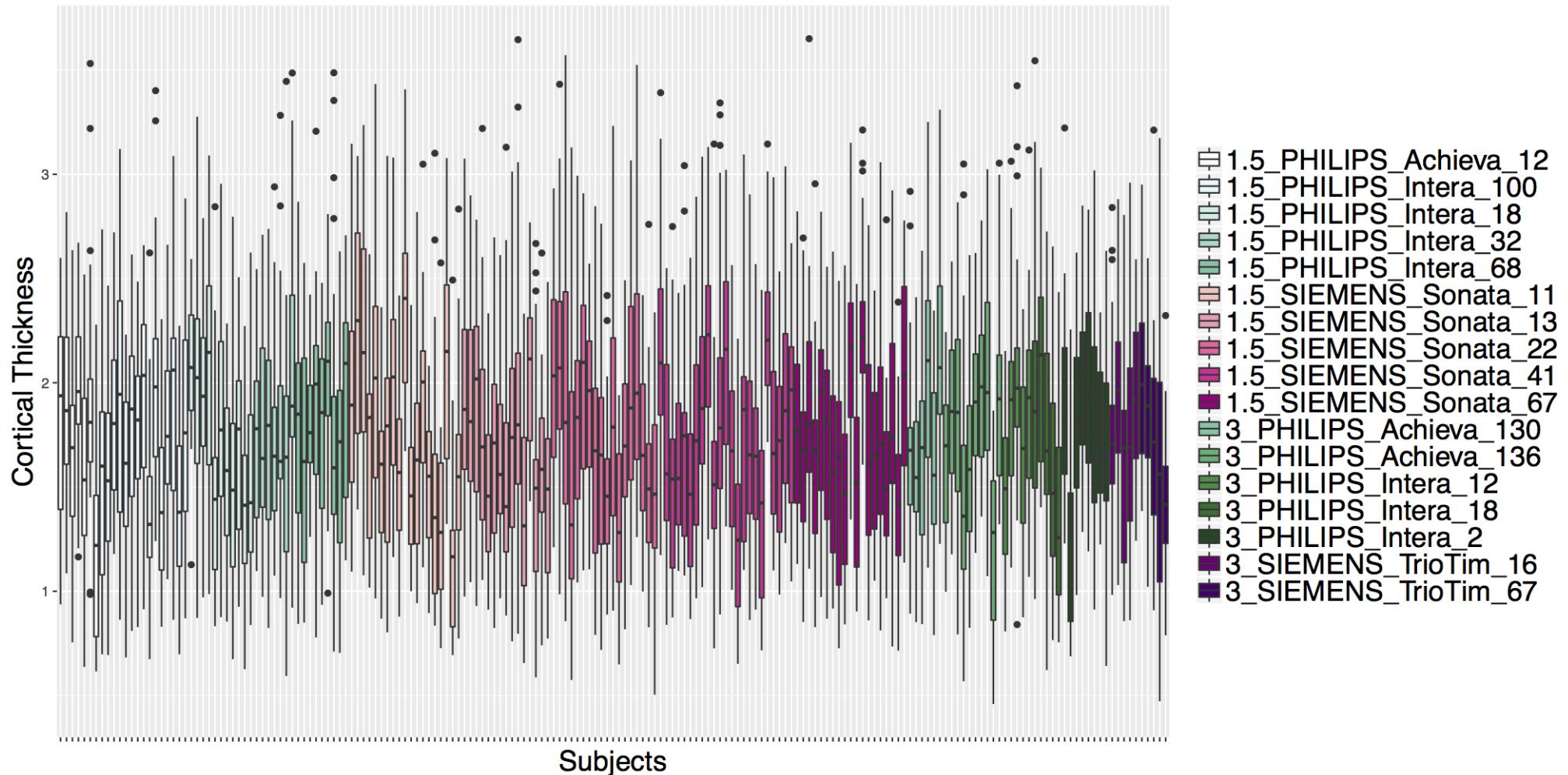
ADNI Cortical Thickness Data

- Before ComBat



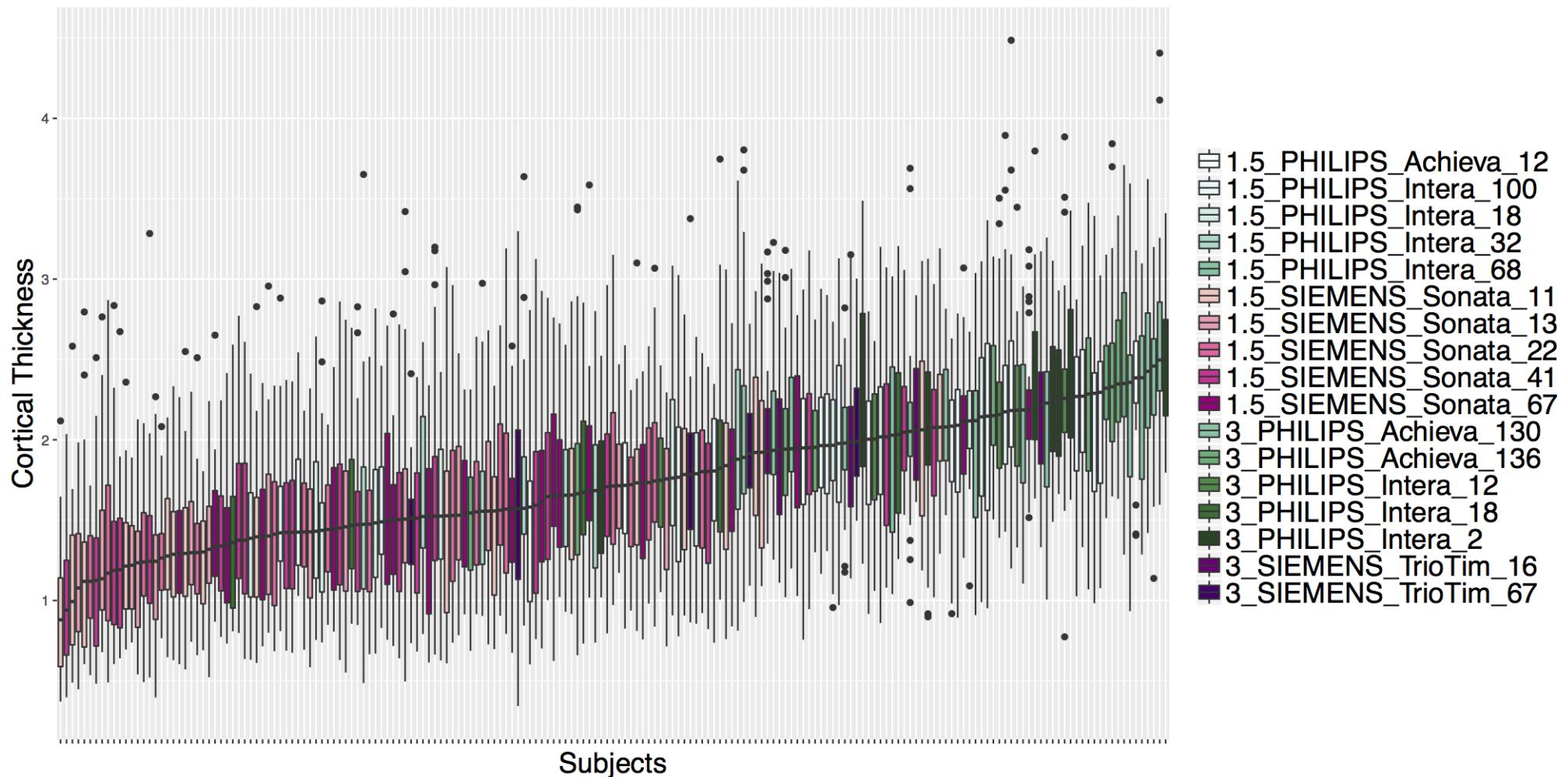
ADNI Cortical Thickness Data

- After ComBat



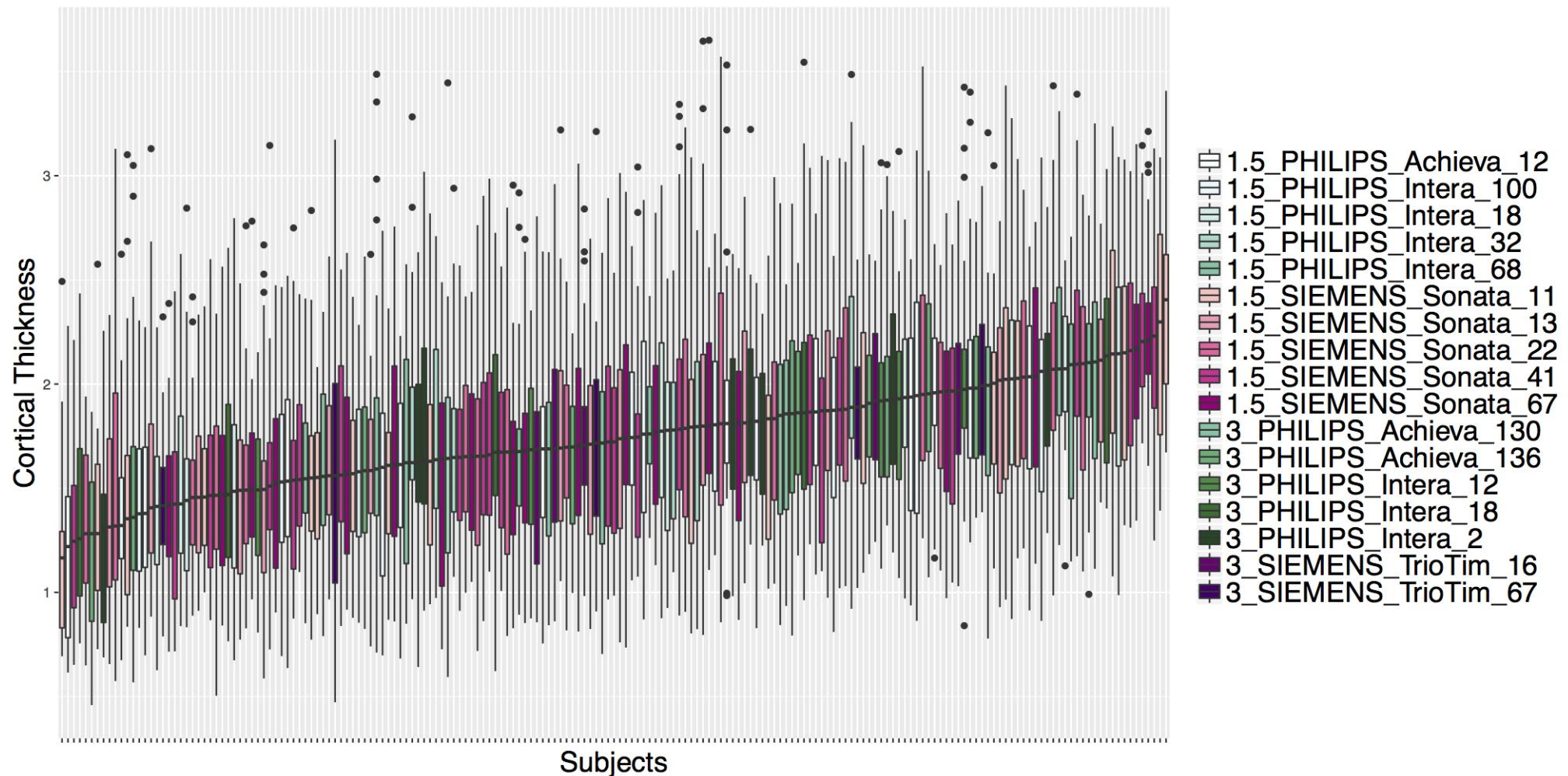
ADNI Cortical Thickness Data

- Before ComBat



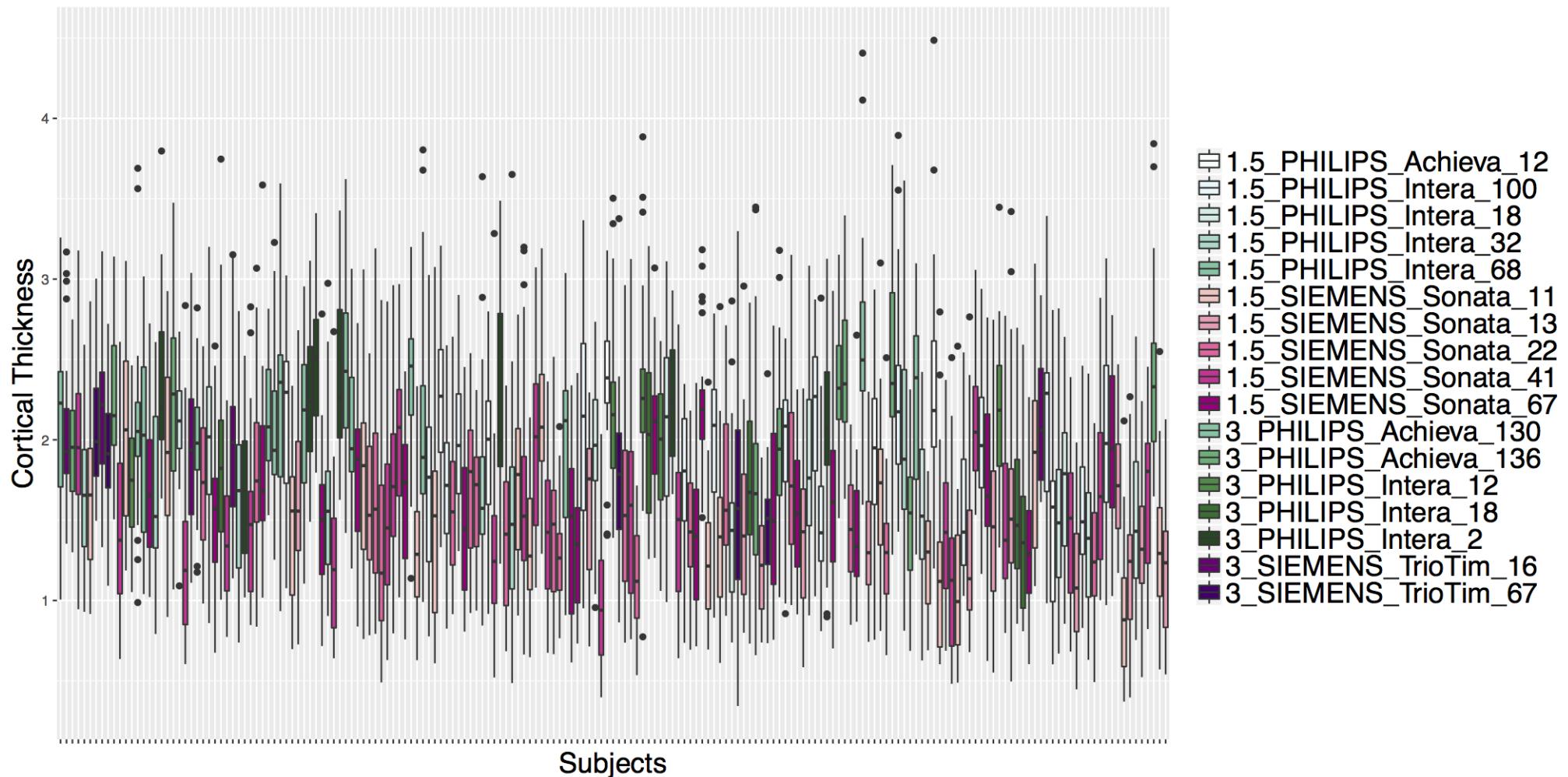
ADNI Cortical Thickness Data

- After ComBat



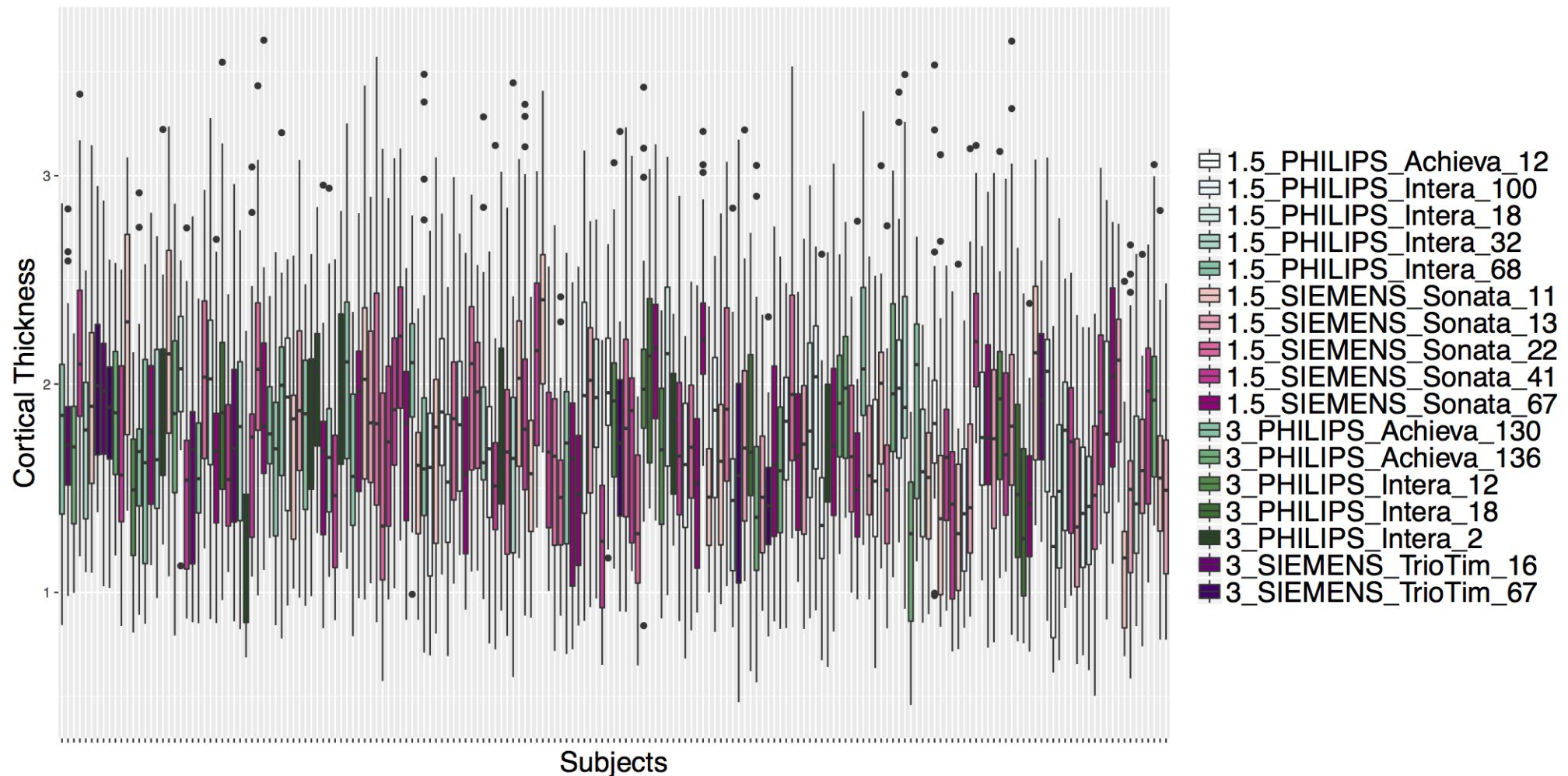
ADNI Cortical Thickness Data

- Before ComBat



ADNI Cortical Thickness Data

- After ComBat



Example: Test for Site Effects Before ComBat

```
modelData$sex = factor(modelData$sex)
modelData$dx = factor(modelData$dx)
modelData$scanner = factor(modelData$scanner)

preComBat = left_join(modelData, ctData, by='subject')
preRInsula = lm(X2035 ~ age + sex + dx + scanner, data=preComBat)
summary(aov(preRInsula))
```

	Df	Sum Sq	Mean Sq	F value	Pr (>F)	
age	1	3.14	3.1389	14.240	0.000224	***
sex	1	0.03	0.0322	0.146	0.702615	
dx	2	2.20	1.0984	4.983	0.007914	**
scanner	16	19.27	1.2042	5.463	2.9e-09	***
Residuals	166	36.59	0.2204			

Signif. codes:	0	'****'	0.001	'**'	0.01	'*'
					0.05	'..'
					0.1	' '
						1

Example: Test for Site Effects After ComBat

```
harmonizedData = as.data.frame(t(harmonized$dat.combat))  
harmonizedData$subject = ctData$subject  
  
postComBat = left_join(modelData, harmonizedData, by='subject')  
postRInsula = lm(X2035 ~ age + sex + dx + scanner, data=postComBat)  
summary(aov(postRInsula))
```

	Df	Sum Sq	Mean Sq	F value	Pr (>F)
age	1	0.86	0.8644	4.467	0.03605 *
sex	1	0.40	0.4000	2.067	0.15239
dx	2	2.13	1.0648	5.502	0.00486 **
scanner	16	0.74	0.0463	0.239	0.99900
Residuals	166	32.12	0.1935		

Signif. codes: 0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1					

Conclusions

- Data harmonization is an important step in any image analysis that combines data from different sites and/or scanners.
- ComBat has been successfully applied to DTI and cortical thickness data to remove scanner effects while preserving biological associations of interest (Fortin et al. 2017, 2018).
 - ComBat code is located at <https://github.com/Jfortin1/ComBatHarmonization>
 - Available in R and MATLAB
- To obtain valid statistical inference in downstream analyses, uncertainty in ComBat harmonization should be considered

Website

http://johnmuschelli.com/imaging_in_r

References

- Das, Sandhitsu R, Brian B Avants, Murray Grossman, and James C Gee. 2009. "Registration Based Cortical Thickness Measurement." 45 (3). Elsevier:867–79.
- Fortin, Jean-Philippe, Nicholas Cullen, Yvette I Sheline, Warren D Taylor, Irem Aselcioglu, Philip A Cook, Phil Adams, et al. 2018. "Harmonization of Cortical Thickness Measurements Across Scanners and Sites." 167. Elsevier:104–20.
- Fortin, Jean-Philippe, Drew Parker, Birkan Tunc, Takanori Watanabe, Mark A Elliott, Kosha Ruparel, David R Roalf, et al. 2017. "Harmonization of Multi-Site Diffusion Tensor Imaging Data." 161. Elsevier:149–70.
- Johnson, W Evan, Cheng Li, and Ariel Rabinovic. 2007. "Adjusting Batch Effects in Microarray Expression Data Using Empirical Bayes Methods." 8 (1). Oxford University Press:118–27.