PENNSIVE

MRI Harmonization

Russell (Taki) Shinohara
Penn Statistical Imaging and Visualization Center
Department of Biostatistics, Epidemiology, and Informatics
University of Pennsylvania

Disclosures

- Dr. Shinohara receives grant funding from the National Institutes of Health, and previously has been funded by the National Multiple Sclerosis Society.
- Dr. Shinohara receives consulting income from Octave Bioscience and compensation for statistical reviewing from the American Medical Association. The work being presented is unrelated to these activities.

MRI Data Are Susceptible to Scanner Effects

Inter-Scanner MRI Biases

- While the data we work with are processed to produce *quantitative* measurements, they are dependent on **acquisition equipment** and **processing pipeline**.
- In particular, inter-scanner differences are known to be quite large, even in simple **volumetric studies** – this has been attributed to differences across scanner manufacturers as well as imaging protocols.

HUMAN BRAIN MAPPING Open Access

Research Article | Free Access

Reliability of brain volumes from multicenter MRI acquisition: A calibration study

Hugo G. Schnack, Neeltje E.M. van Haren, Hilleke E. Hulshoff Pol, Marco Picchioni, Matthias Weisbrod, Heinrich Sauer, Tyrone Cannon, Matti Huttunen, Robin Murray, René S. Kahn

First published:03 June 2004 | https://doi.org/10.1002/hbm.20040 | Citations: 57

HUMAN BRAIN MAPPING Open Access

Research Article | Free Access

Mapping reliability in multicenter MRI: Voxel-based morphometry and cortical thickness

Hugo G. Schnack, Neeltje E.M. van Haren, Rachel M. Brouwer, G. Caroline M. van Baal, Marco Picchioni, Matthias Weisbrod, Heinrich Sauer, Tyrone D. Cannon, Matti Huttunen, Claude Lepage, D. Louis Collins, Alan Evans, Robin M. Murray, René S. Kahn, Hilleke E. Hulshoff Pol
... See fewer authors

First published:16 November 2010 | https://doi.org/10.1002/hbm.20991 | Citations: 48

HUMAN BRAIN MAPPING Open Access

Research Article | Free Access

Reliability of neuroanatomical measurements in a multisite longitudinal study of youth at risk for psychosis

Tyrone D. Cannon, Frank Sun, Sarah Jacobson McEwen, Xenophon Papademetris, George He, Theo G.M. van Erp, Aron Jacobson, Carrie E. Bearden, Elaine Walker, Xiaoping Hu, Lei Zhou, Larry J. Seidman, Heidi W. Thermenos, Barbara Cornblatt, Doreen M. Olvet, Diana Perkins, Aysenil Belger, Kristin Cadenhead, Ming Tsuang, Heline Mirzakhanian, Jean Addington, Richard Frayne, Scott W. Woods, Thomas H. McGlashan, R. Todd Constable, Maolin Qiu, Daniel H. Mathalon, Paul Thompson, Arthur W. Toga ... See fewer authors

First published:24 August 2013 | https://doi.org/10.1002/hbm.22338 | Citations: 30

ELSEVIER NeuroImage
Volume 83, December 2013, Pages 472-484

Brain morphometry reproducibility in multi-center 3 T MRI studies: A comparison of cross-sectional and longitudinal segmentations

Jorge Jovicich [a,1], Moira Marizzoni [b,1], Roser Sala-Llonch [c], Beatriz Bosch [q], David Bartrés-Faz [c], Jennifer Arnold [d], Jens Benninghoff [d], Jens Wiltfang [d], Luca Roccatagliata [e,f], Flavio Nobili [g], Tilman Hensch [h], Anja Tränkner [h], Peter Schönknecht [h], Melanie Leroy [i], Renaud Lopes [r], Régis Bordet [i], Valérie Chanoine [j], Jean-Philippe Ranjeva [j] ... Giovanni B. Frisoni [b]

ELSEVIER NeuroImage
Volume 46, Issue 1, 15 May 2009, Pages 177-192

MRI-derived measurements of human subcortical, ventricular and intracranial brain volumes: Reliability effects of scan sessions, acquisition sequences, data analyses, scanner upgrade, scanner vendors and field strengths

Jorge Jovicich [a], Silvester Czanner [b], Xiao Han [c], David Salat [d,e], Andre van der Kouwe [d,e], Brian Quinn [d,e], Jenni Pacheco [d,e], Marilyn Albert [h], Ronald Killiany [i], Deborah Blacker [g], Paul Maguire [j], Diana Rosas [d,e,f], Nikos Makris [d,e,k], Randy Gollub [d,e], Anders Dale [l], Bradford C. Dickerson [d,f,g,m,1], Bruce Fischl [d,e,n,1]

(See also Badhwar et al., 2020; Byrge et al., 2022; Cai et al., 2021; Han et al., 2006; Shinohara et al., 2017; Takao et al., 2014, 2011, and many more)

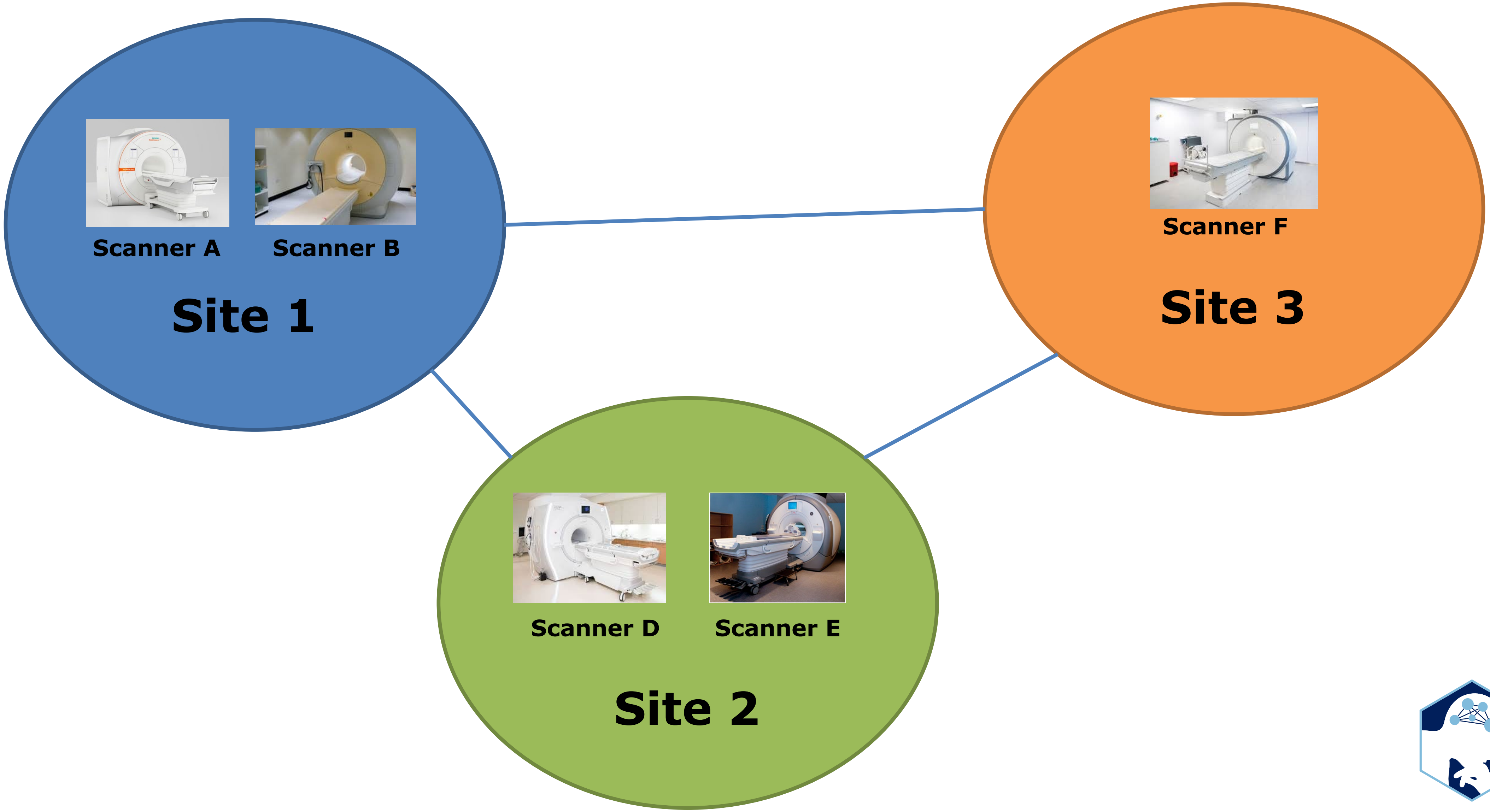
Large-Scale Imaging often Requires Collaboration

ADNI
Alzheimer's Disease
Neuroimaging Initiative

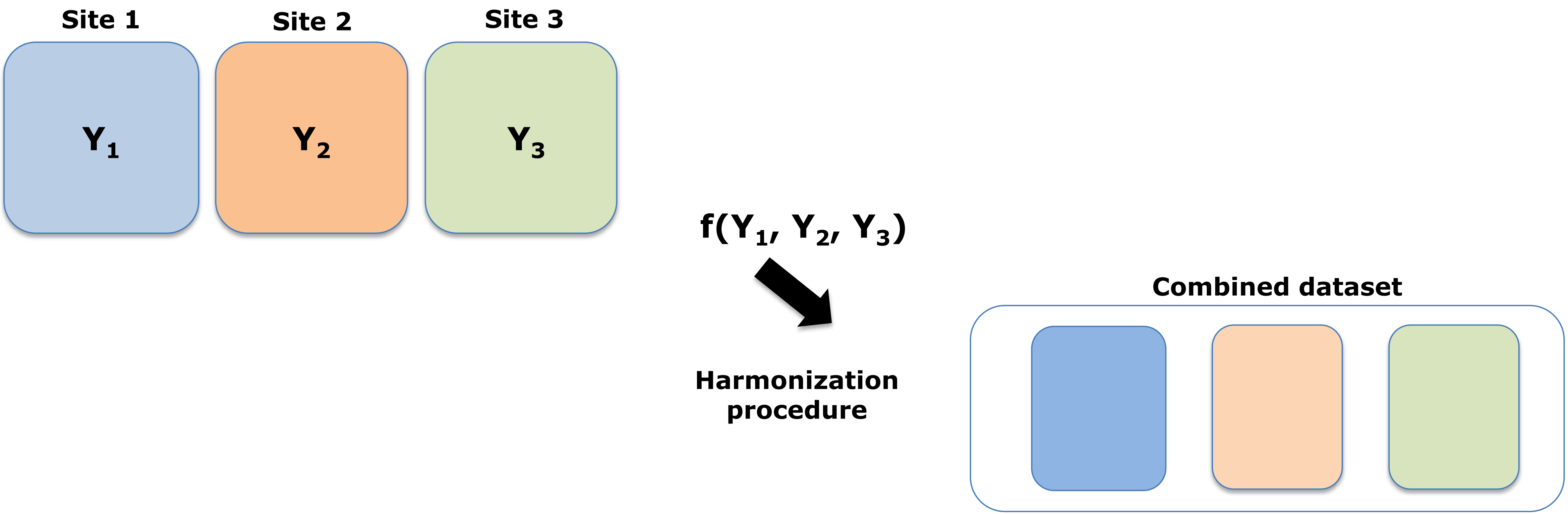
Adolescent Brain Cognitive Development®
Teen Brains. Today's Science. Brighter Future.

biobank uk
Improving the health of future generations

Multi-Center Imaging Networks



Harmonization of Multi-Site MRI Data



Overview of Harmonization Methods

How has our field been doing this?

- Regression adjustment
  - Simply include a dummy variable for scanner in subsequent analyses to address mean shifts.

- Other calibration techniques that include scaling
  - Example:

Neuroimage. 2016 Jul 1;134:281-294. doi: 10.1016/j.neuroimage.2016.03.051. Epub 2016 Apr 1.

Power estimation for non-standardized multisite studies.

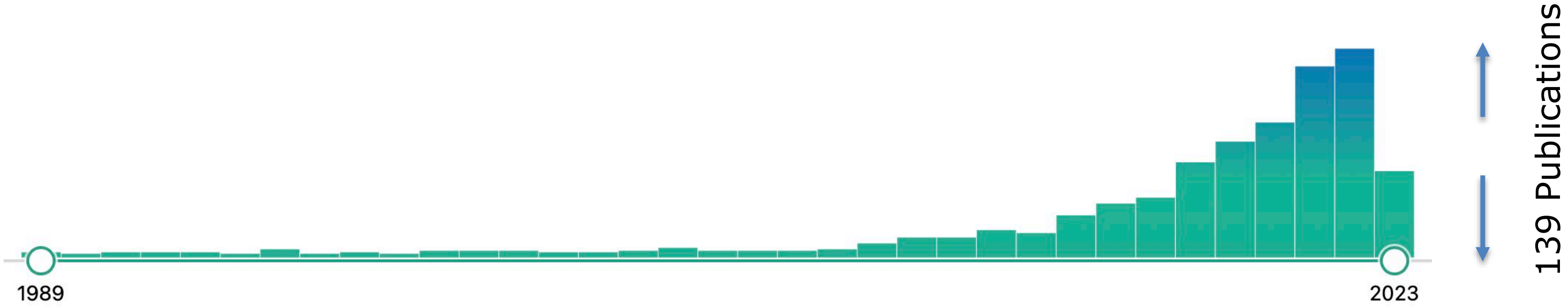
Keshavan A[1], Paul F[2], Beyer MK[3], Zhu AH[4], Papinutto N[5], Shinohara RT[6], Stern W[7], Amann M[8], Bakshi R[9], Bischof A[10], Carriero A[11], Comabella M[12], Crane JC[13], D'Alfonso S[14], Demaerel P[15], Dubois B[16], Filippi M[17], Fleischer V[18], Fontaine B[19], Gaetano L[20], Goris A[21], Graetz C[22], Gröger A[23], Groppa S[24], Hafler DA[25], Harbo HF[26], Hemmer B[27], Jordan K[28], Kappos L[29], Kirkish G[30], Llufriu S[31], Magon S[32], Martinelli-Boneschi F[33], McCauley JL[34], Montalban X[35], Mühlau M[36], Pelletier D[37], Pattany PM[38], Pericak-Vance M[39], Cournu-Rebeix I[40], Rocca MA[41], Rovira A[42], Schlaeger R[43], Saiz A[44], Sprenger T[45], Stecco A[46], Uitdehaag BMJ[47], Villoslada P[48], Wattjes MP[49], Weiner H[50], Wuerfel J[51], Zimmer C[52], Zipp F[53]; International Multiple Sclerosis Genetics Consortium. Electronic address: AIVINSON@PARTNERS.ORG[54], Hauser SL[55], Oksenberg JR[56], Henry RG[57].

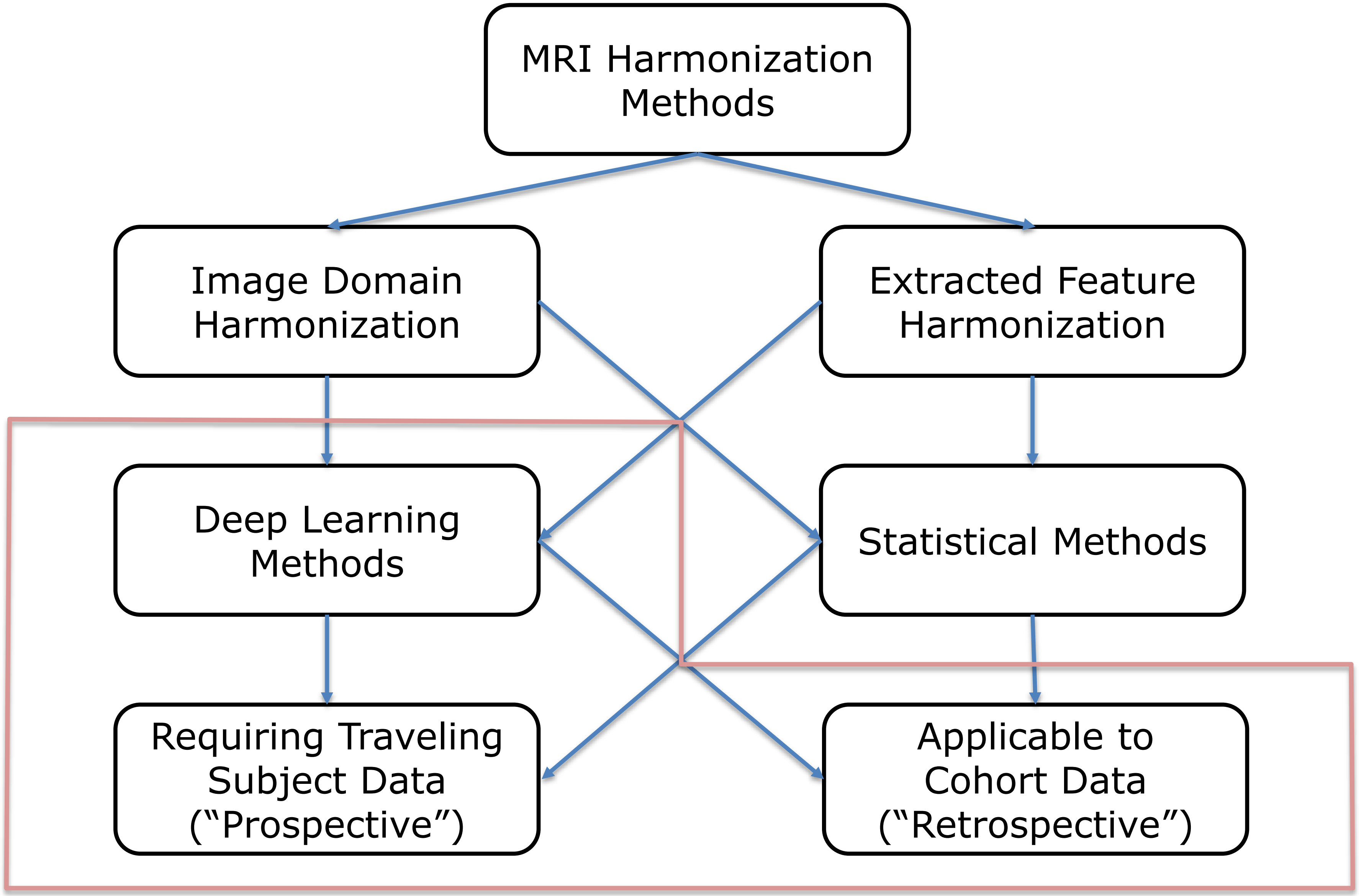
- But these methods don’t consider a key factor:

we make multiple measurements when we assess the brain

MRI Harmonization Is of Increasing Interest

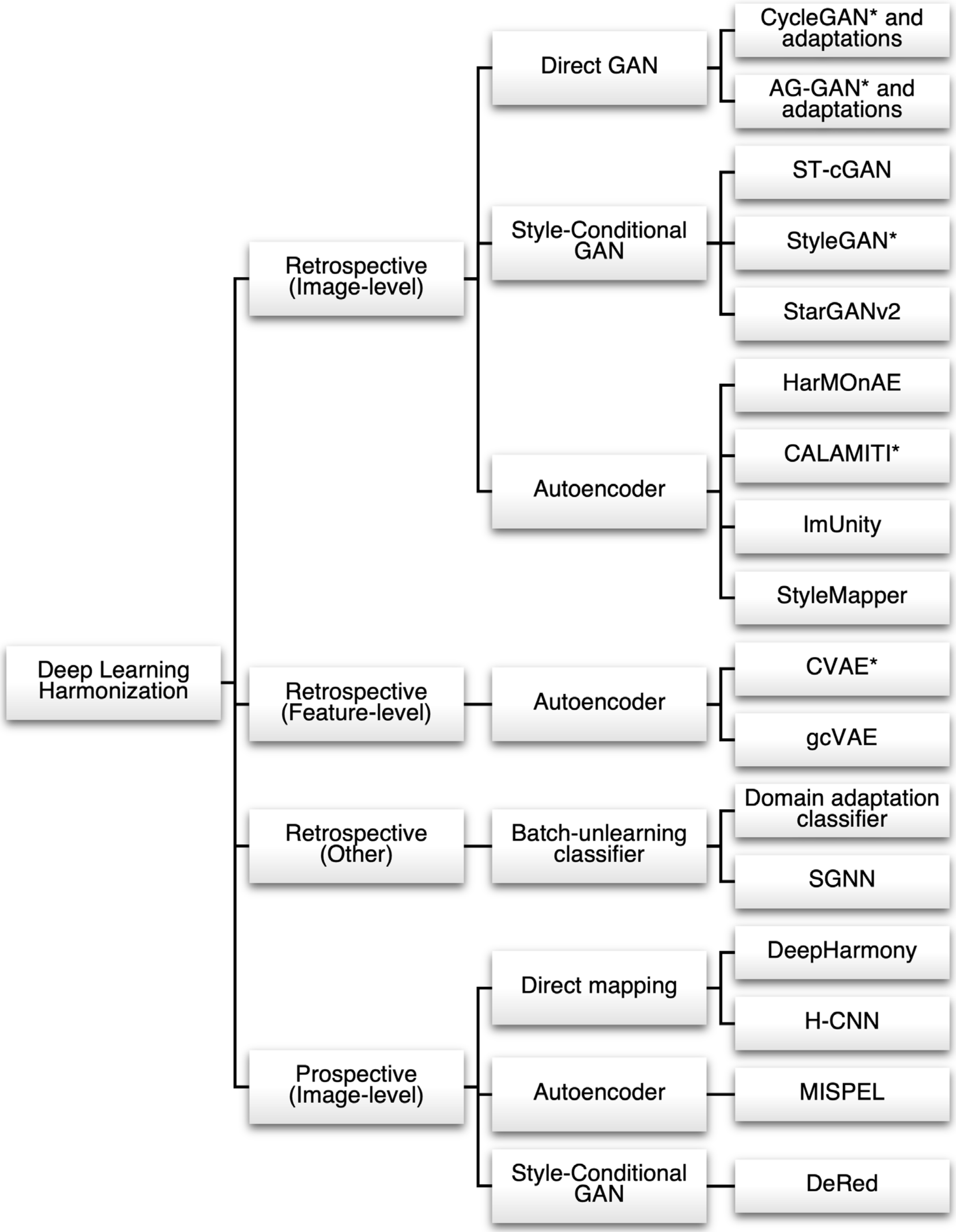
PubMed



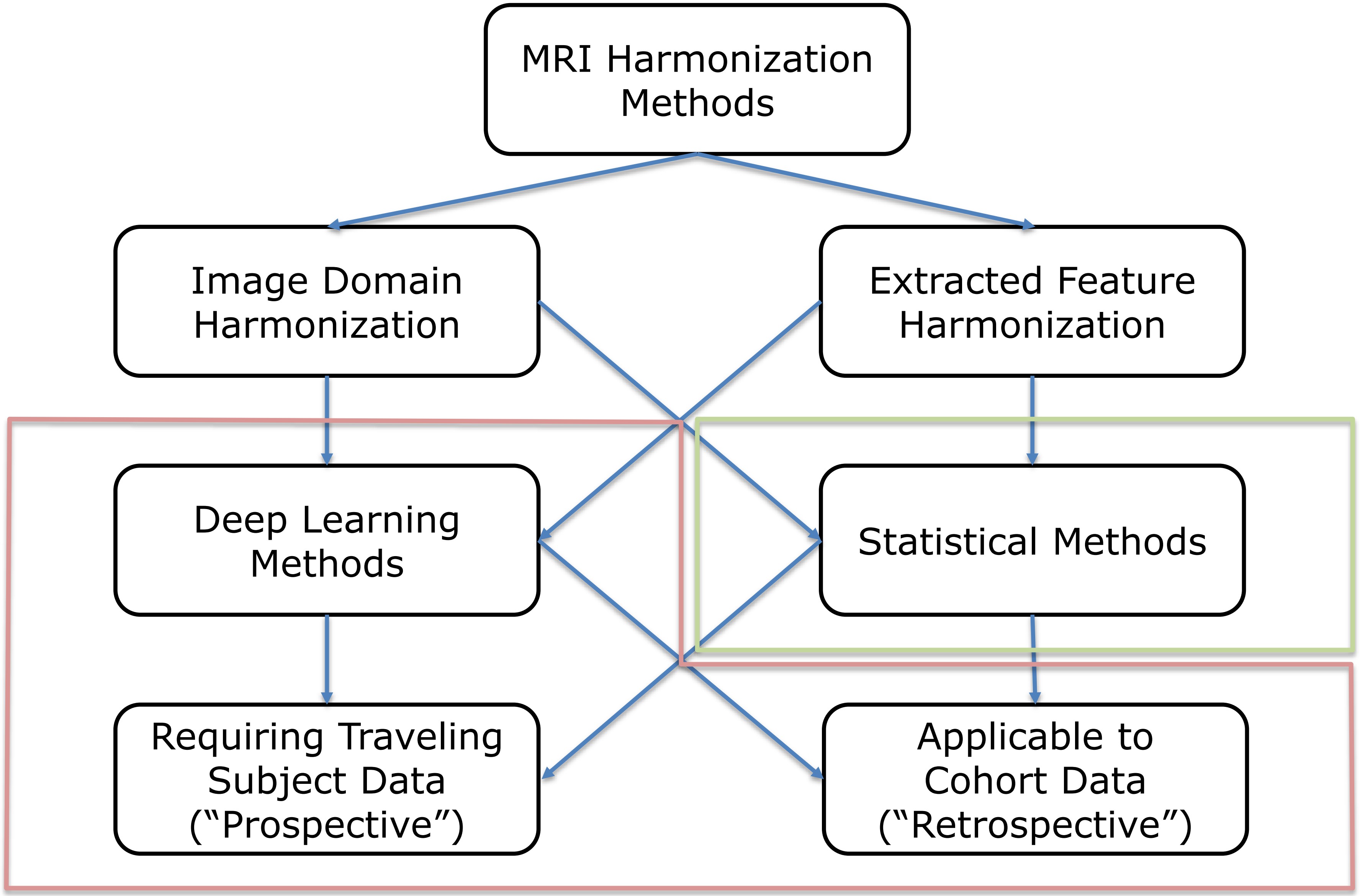

MRI Harmonization Methods
Image Domain Harmonization
Extracted Feature Harmonization
Deep Learning Methods
Statistical Methods
Requiring Traveling Subject Data ("Prospective")
Applicable to Cohort Data ("Retrospective")

Deep Learning Harmonization Methodology

(Not exhaustive)

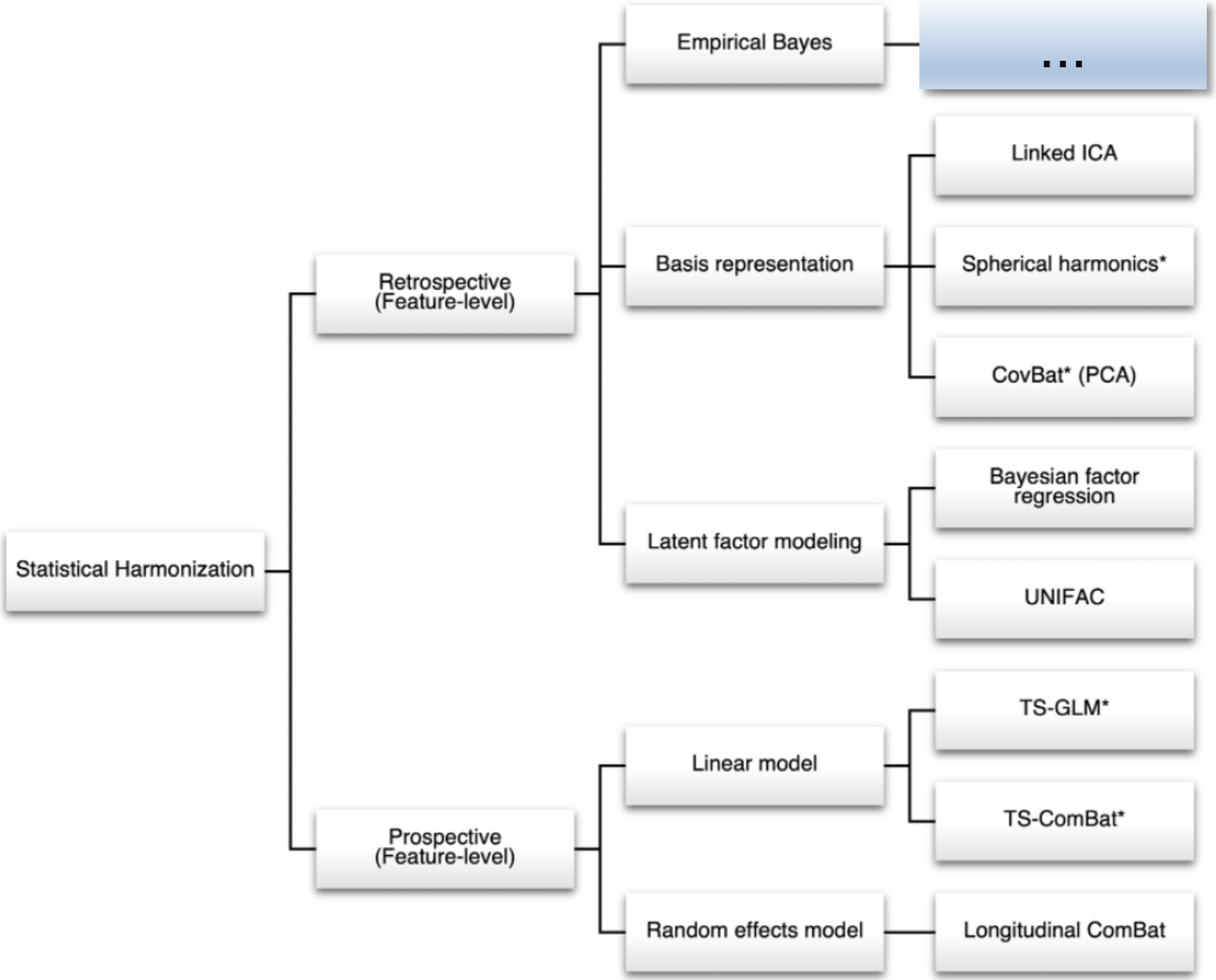


Hu et al. (*NeuroImage, 2023*)


MRI Harmonization Methods
Image Domain Harmonization
Extracted Feature Harmonization
Deep Learning Methods
Statistical Methods
Requiring Traveling Subject Data ("Prospective")
Applicable to Cohort Data ("Retrospective")

Statistical Harmonization Methodology

(Not exhaustive)



Hu et al. (*NeuroImage, 2023*)

A Brief Introduction to ComBat

Harmonization of Multi-Site DTI data

Site 1 — n=105

- Siemens TIM Trio
- Field: 3T
- 64 gradient directions

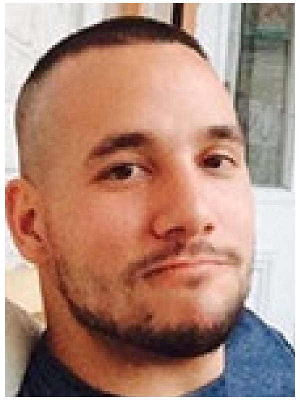
Matched for age and sex

Site 2 — n=105

- Siemens Verio
- Field: 3T
- 30 gradient directions

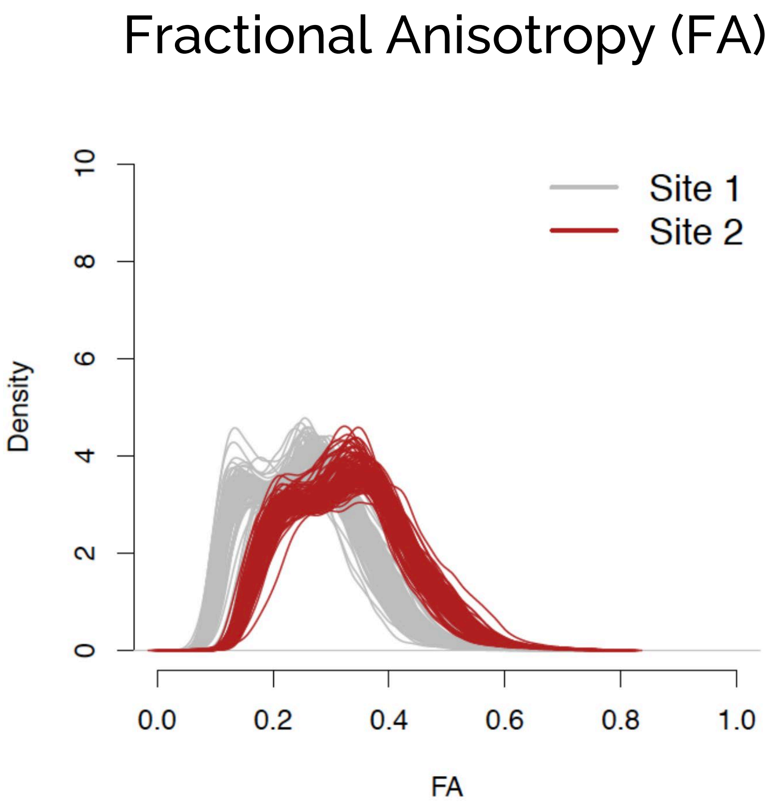
Subjects

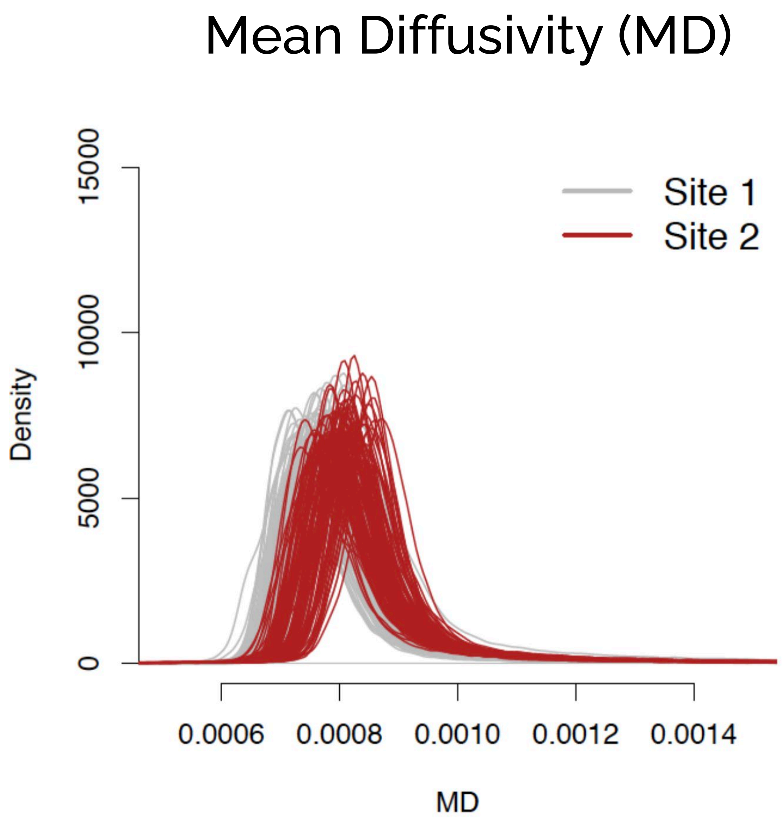
- Healthy
- Adolescents (8 to 18 years)
- 22 females vs 83 males



Fortin, Parker, Tunc et al. (2017)

Site Effects in the White Matter





Statistical Approaches to Batch Effect Correction

Biostatistics (2012), **13**, 3, *pp.* 539–552
doi:10.1093/biostatistics/kxr034
Advance Access publication on November 17, 2011

Using control genes to correct for unwanted variation in microarray data

JOHANN A. GAGNON-BARTSCH*
Department of Statistics, University of California at Berkeley, Berkeley, CA 94720-3860, USA
johann@stat.berkeley.edu

TERENCE P. SPEED
Department of Statistics, University of California at Berkeley, Berkeley, CA 94720-3860, USA and Bioinformatics Division, Walter and Eliza Hall Institute, Victoria 3050, Australia

Biostatistics (2007), **8**, 1, *pp.* 118–127
doi:10.1093/biostatistics/kxj037
Advance Access publication on April 21, 2006

Adjusting batch effects in microarray expression data using empirical Bayes methods

W. EVAN JOHNSON, CHENG LI*
Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA and Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA
cli@hsph.harvard.edu

ARIEL RABINOVIC
Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA, USA

OPEN ACCESS Freely available online PLoS GENETICS

Capturing Heterogeneity in Gene Expression Studies by Surrogate Variable Analysis

Jeffrey T. Leek[1], John D. Storey[1,2*]

1 Department of Biostatistics, University of Washington, Seattle, Washington, United States of America, **2** Department of Genome Sciences, University of Washington, Seattle, Washington, United States of America

Fortin *et al. Genome Biology* 2014, **15**:503
http://genomebiology.com/2014/15/11/503

Genome **Biology**

METHOD **Open Access**

Functional normalization of 450k methylation array data improves replication in large cancer studies

Jean-Philippe Fortin[1], Aurélie Labbe[2,3,4], Mathieu Lemire[5], Brent W Zanke[6], Thomas J Hudson[5,7], Elana J Fertig[8], Celia MT Greenwood[2,9,10] and Kasper D Hansen[1,11*]

ELSEVIER
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

Removing inter-subject technical variability in magnetic resonance imaging studies

CrossMark

Jean-Philippe Fortin [a], Elizabeth M. Sweeney [a], John Muschelli [a], Ciprian M. Crainiceanu [a], Russell T. Shinohara [b,*], The Alzheimer's Disease Neuroimaging Initiative [1]

[a] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[b] Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

ComBat: Location/scale model + empirical Bayes

$$Y_{ijv} = a_v + X_{ij}\beta_v + \gamma_{iv} + \delta_{iv}\epsilon_{ijv}$$

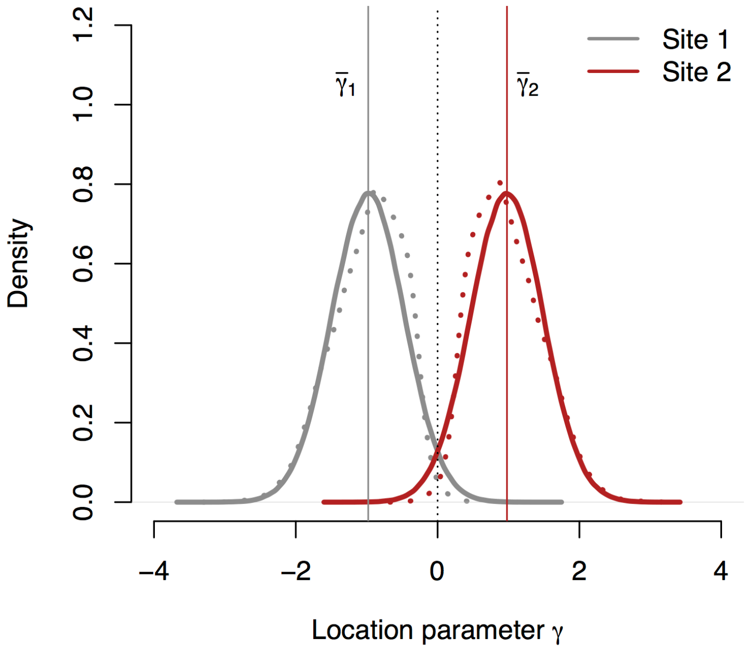
- Y_{ijv}: intensity for site i, sample j, and voxel v
- a_v: average intensity for voxel v
- X_{ij}: covariates of interest
- β_v: voxel−specific coefficients
- γ_{iv}: voxel−specific location parameter for site i
- δ_{iv}: voxel−specific scale parameter for site i
- ϵ_{ijv}: normally distributed error with mean 0 and variance σ_v^2

Johnson, Li, Rabinovic (2007)

Empirical Bayesian Framework

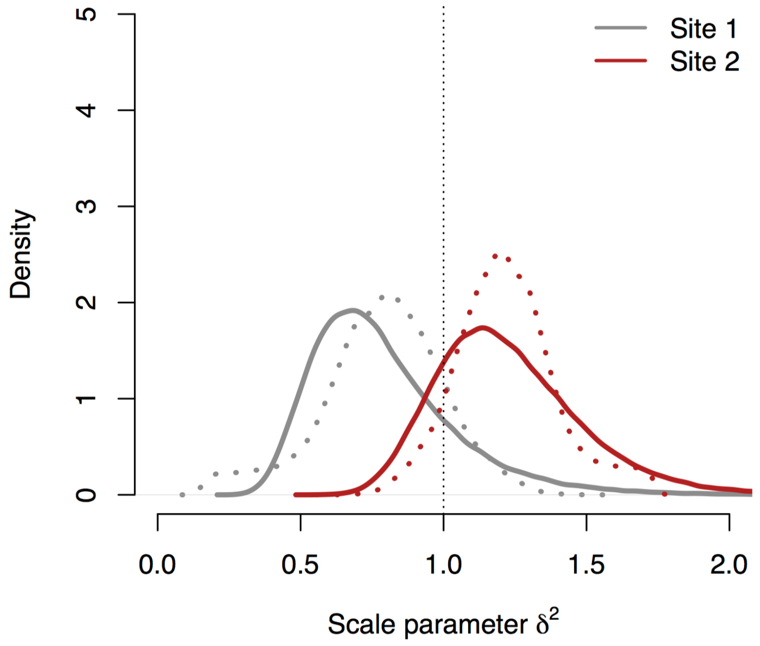
Data model: $Y_{ijv}|\gamma_{iv}, \delta^2_{iv} \sim N(\gamma_{iv}, \delta^2_{iv})$

Prior distribution for additive effects



$\gamma_{iv} \sim N(\gamma_i, \tau^2_i)$

Prior distribution for scaling effects



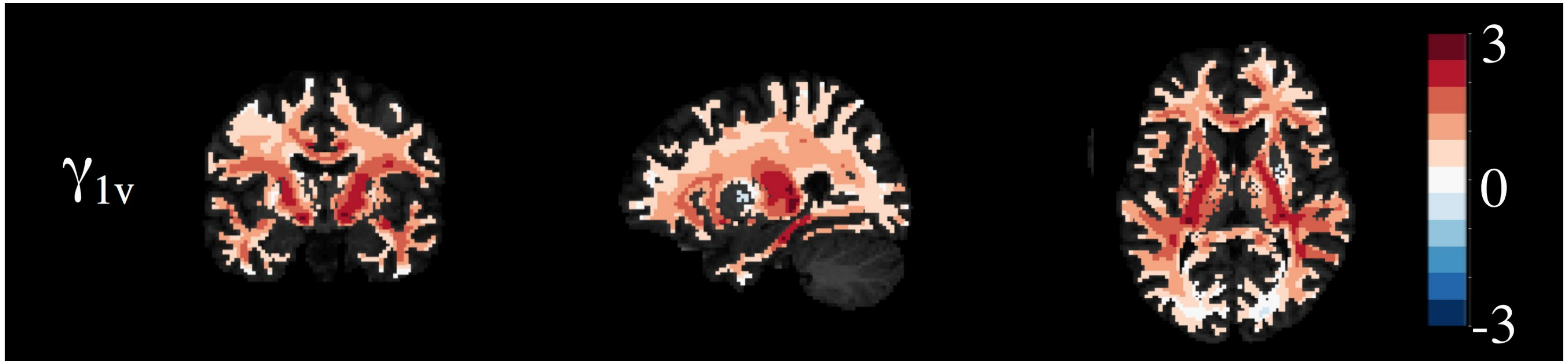
$\delta^2_{iv} \sim \text{Inverse Gamma}(\lambda_i, \theta_i)$

Posterior Means

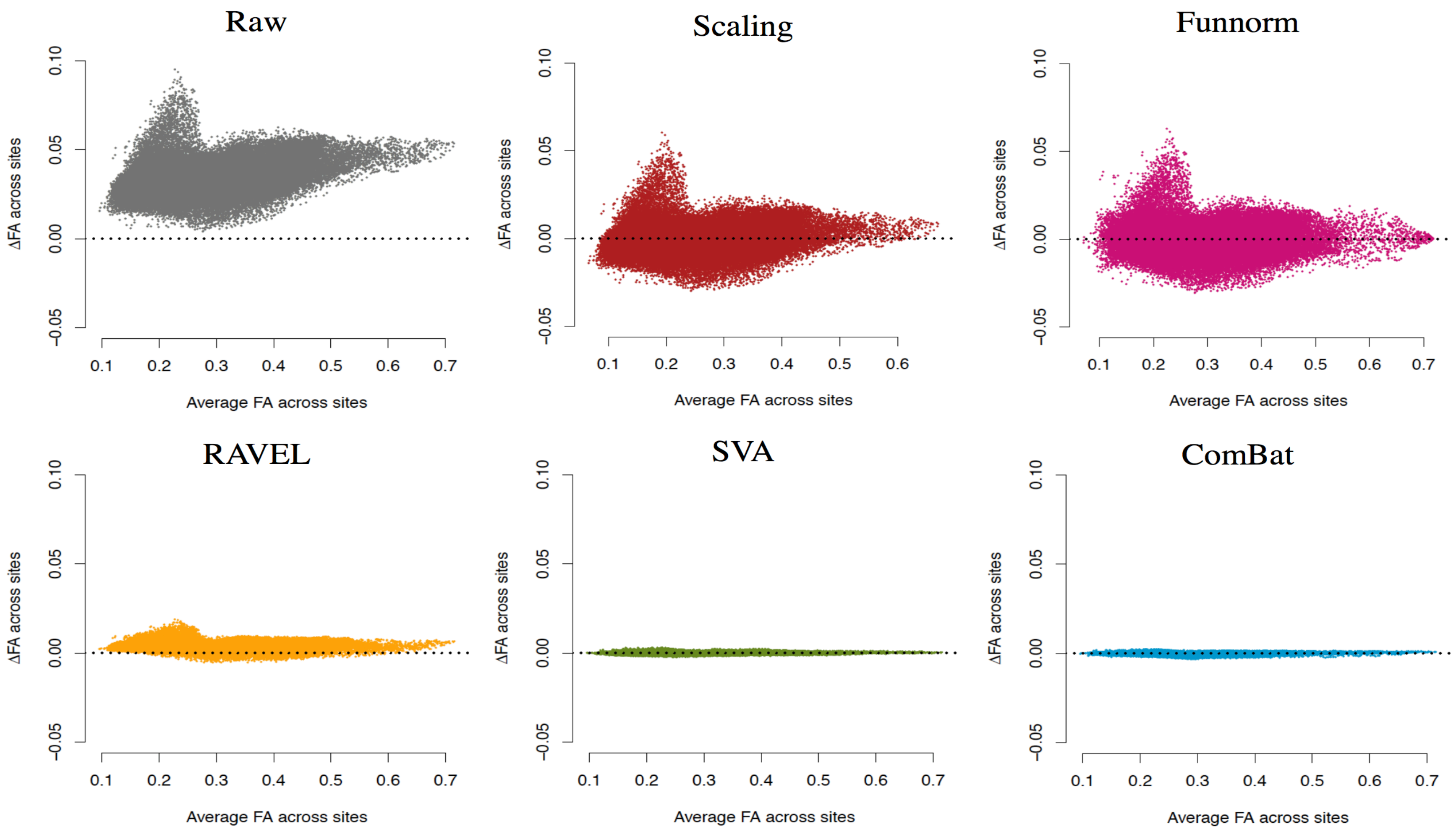
$$\gamma_{iv}^{*} = \frac{n_i \tau_i^2 \hat{\gamma}_{iv} + \delta_{iv}^{2*} \overline{\gamma_i}}{n_i \tau_i^2 + \delta_{iv}^{2*}}$$

$$\delta_{iv}^{2*} = \frac{\theta_i + \frac{1}{n} \sum (Y_{ijv} - \gamma_{iv}^{*})^2}{n/2 + \lambda_i - 1}$$

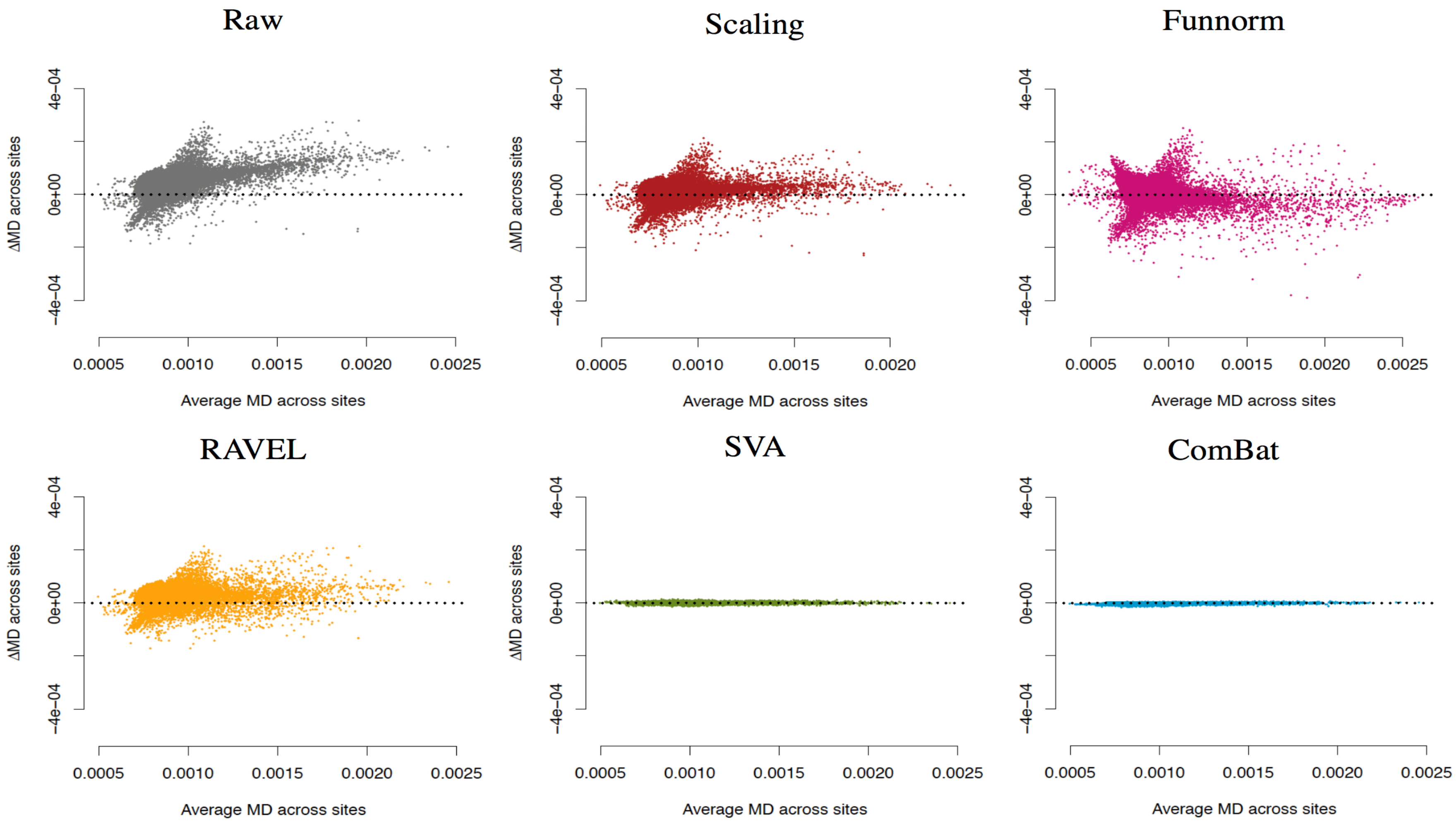
Solved iteratively



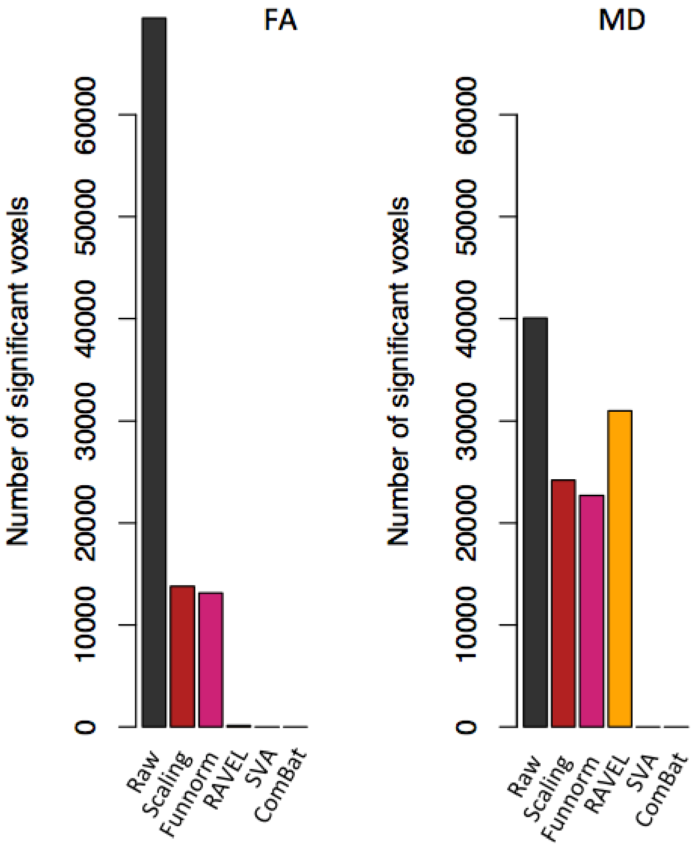
MA plots (Bland-Altman plots) in the WM for FA



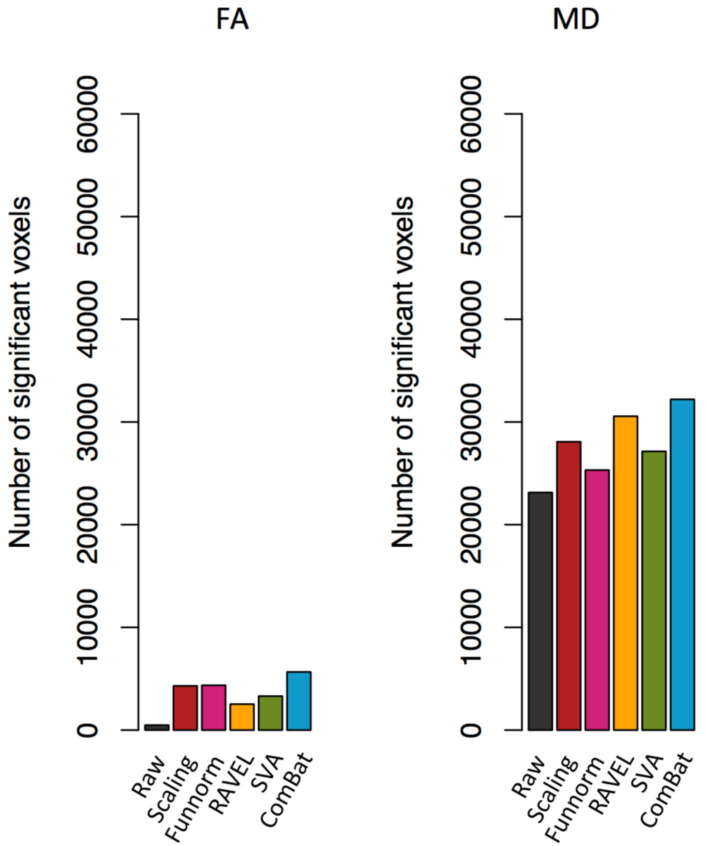
MA plots (Bland-Altman plots) in the WM for MD



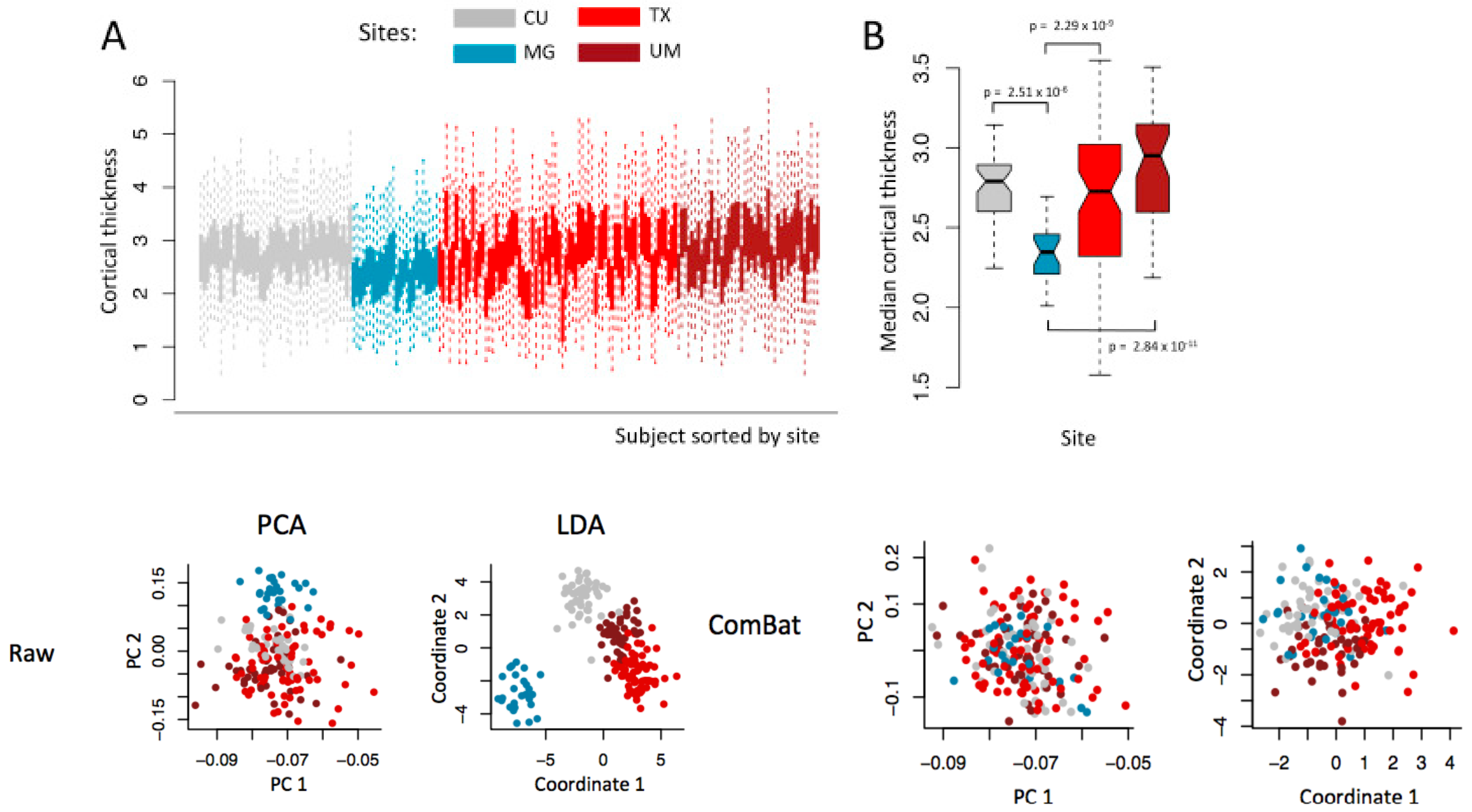
Number of voxels associated with site



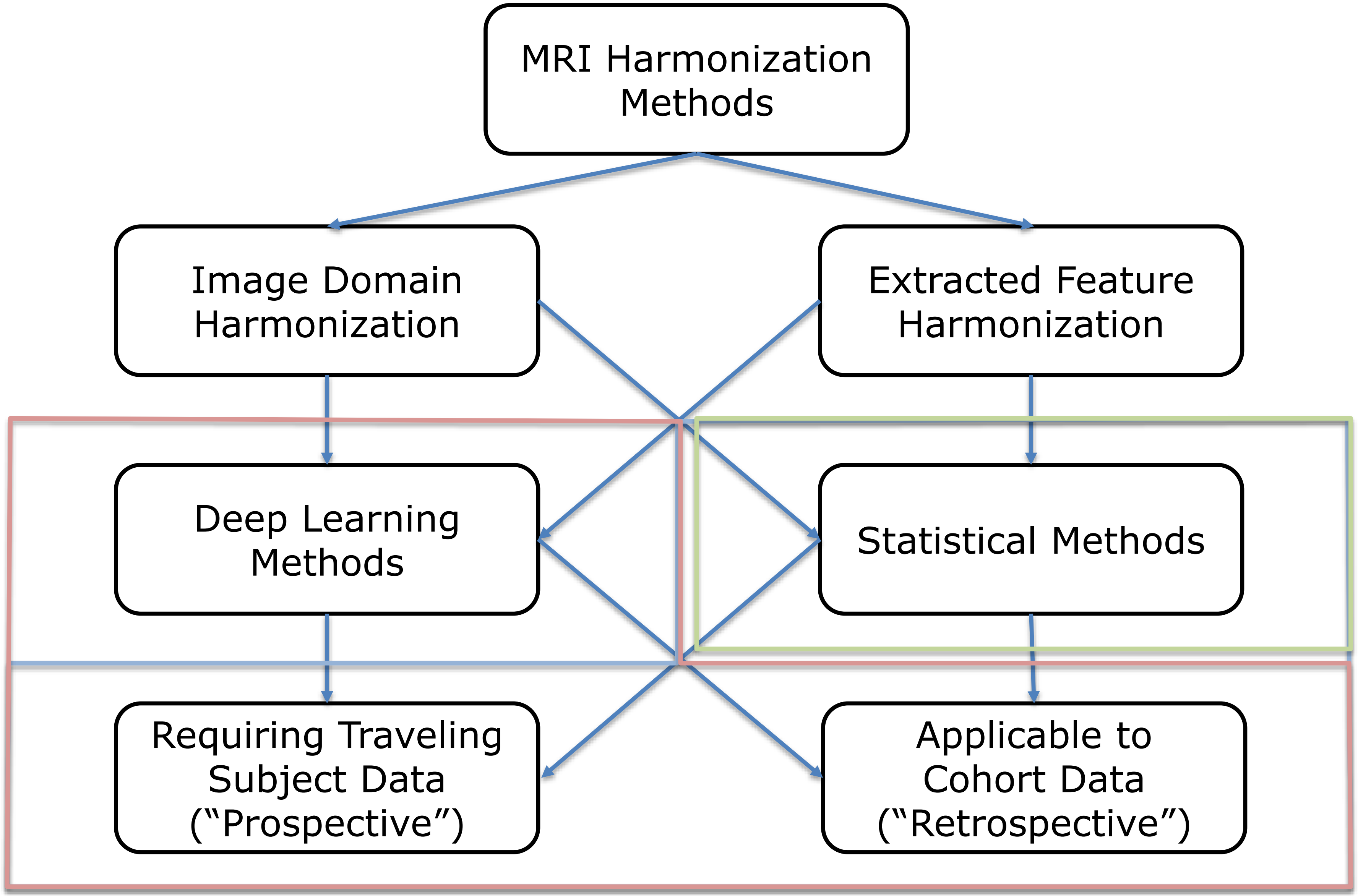
Number of voxels associated with age



ComBat for Cortical Thickness

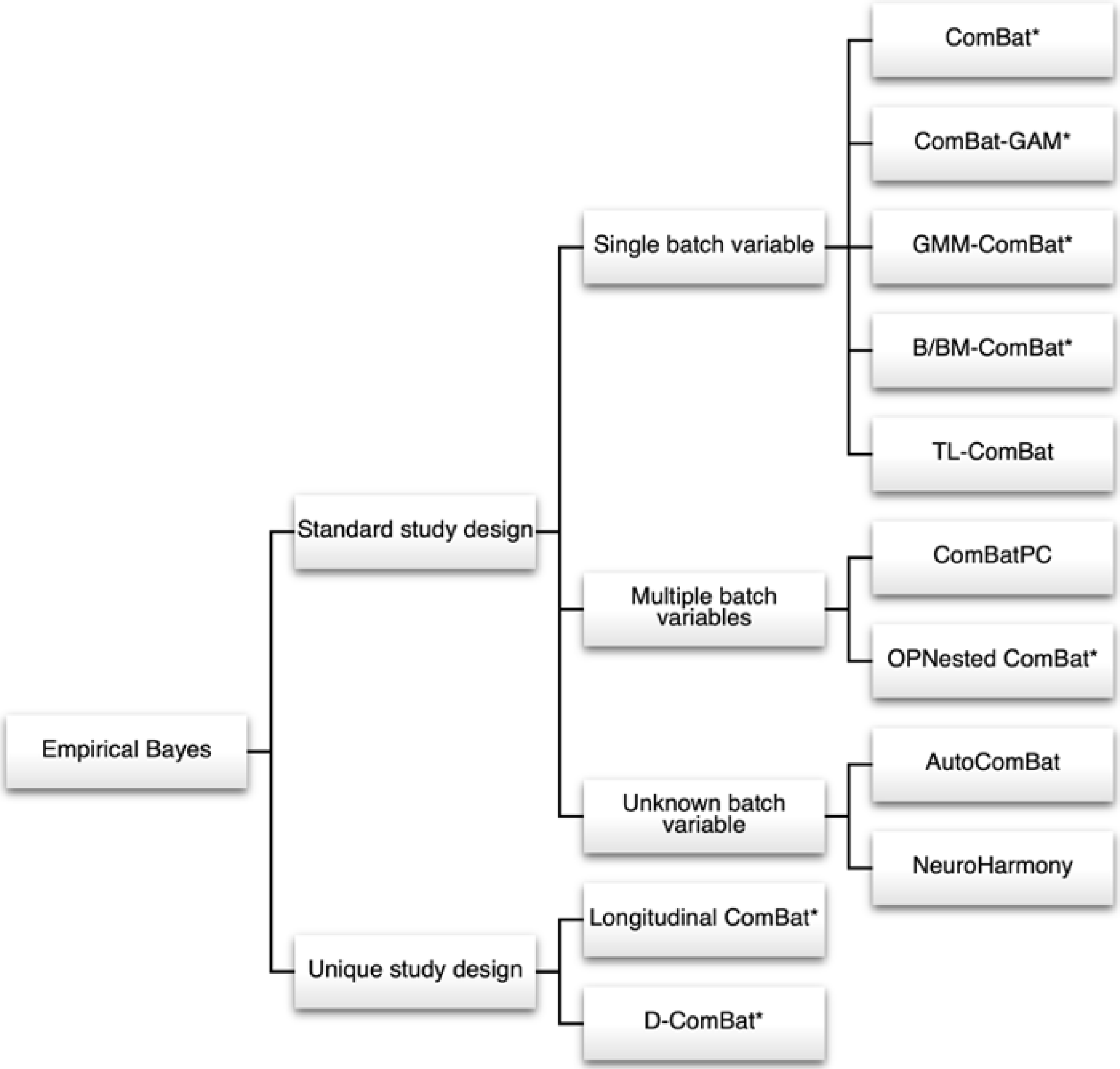


Fortin, Cullen, Sheline et al. (2018)


MRI Harmonization Methods
Image Domain Harmonization
Extracted Feature Harmonization
Deep Learning Methods
Statistical Methods
Requiring Traveling Subject Data ("Prospective")
Applicable to Cohort Data ("Retrospective")

ComBat-Based Harmonization Methodology

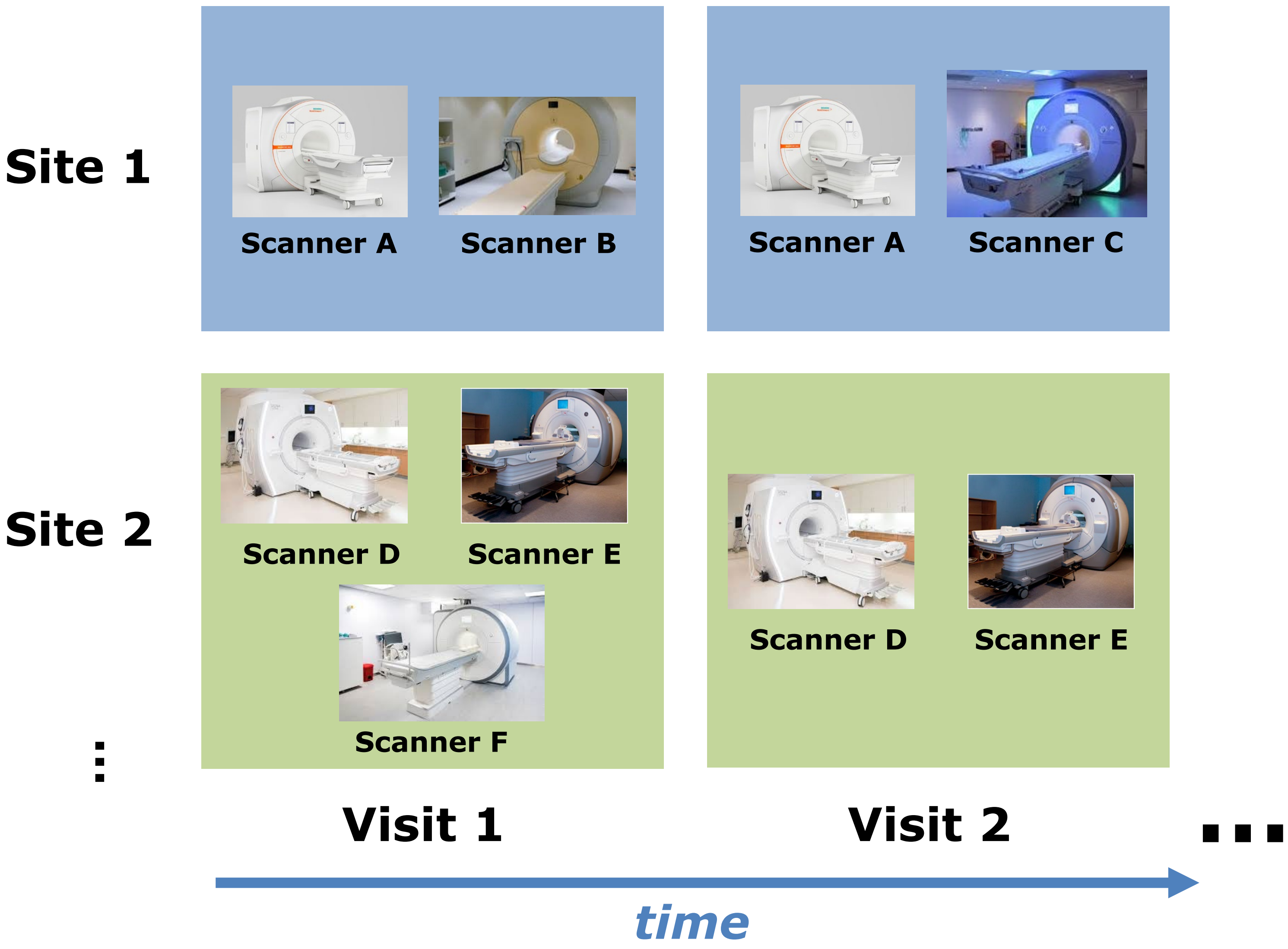
(Not exhaustive)



Hu et al. (*NeuroImage, 2023*)

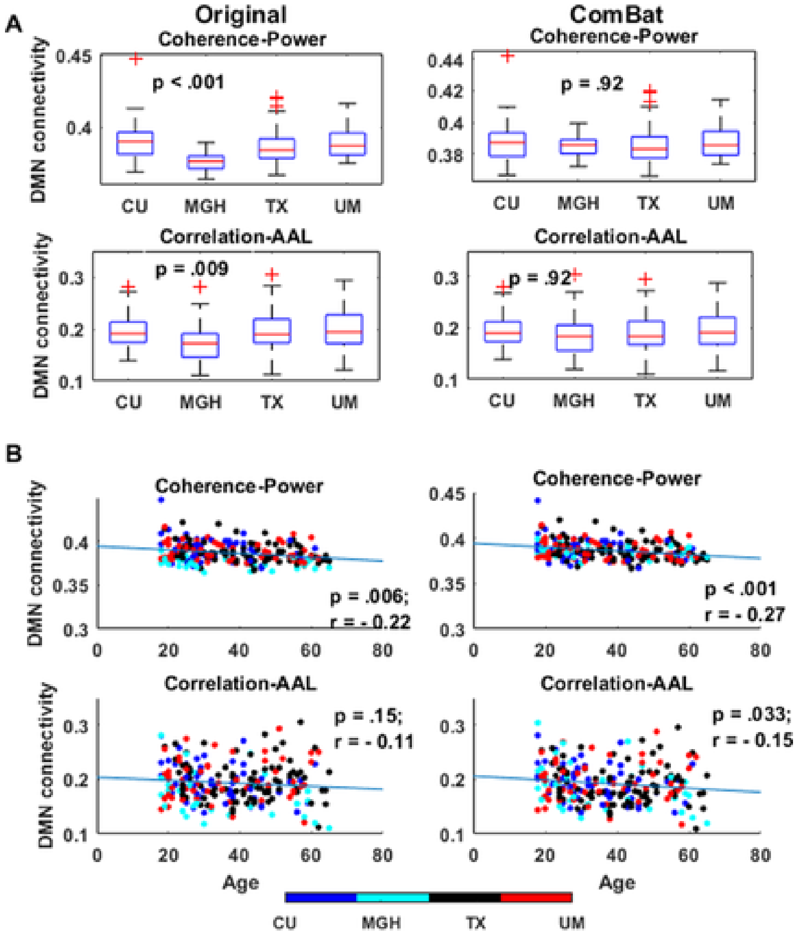
A Few Examples of Extensions

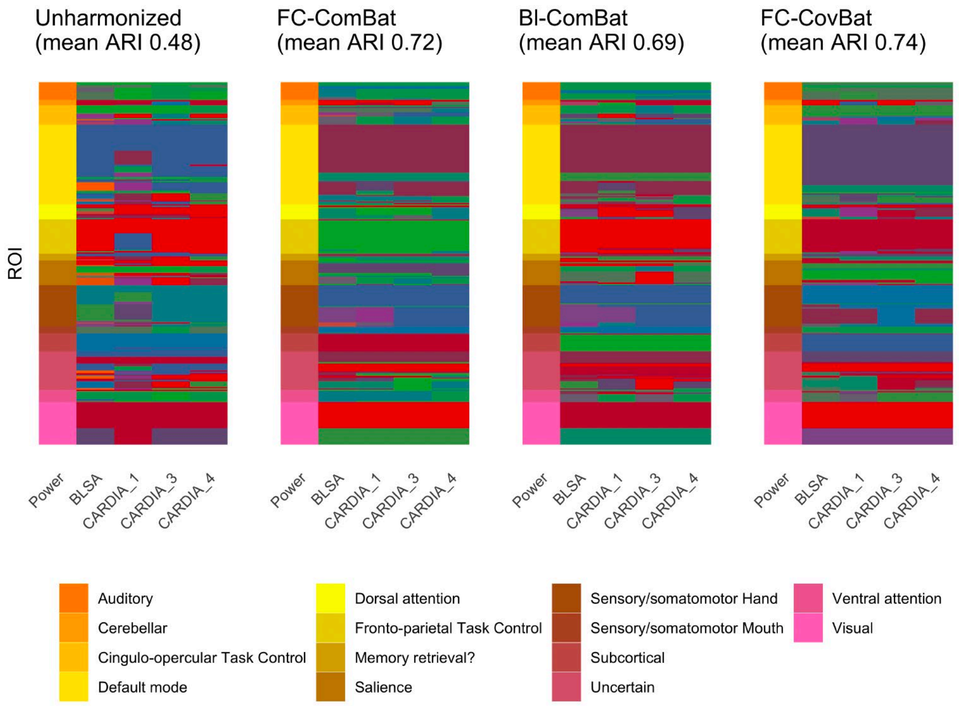
Longitudinal Study Designs



Beer, Tustison, Cook et al. (*NeuroImage*, 2020)

ComBat for Resting-State fMRI

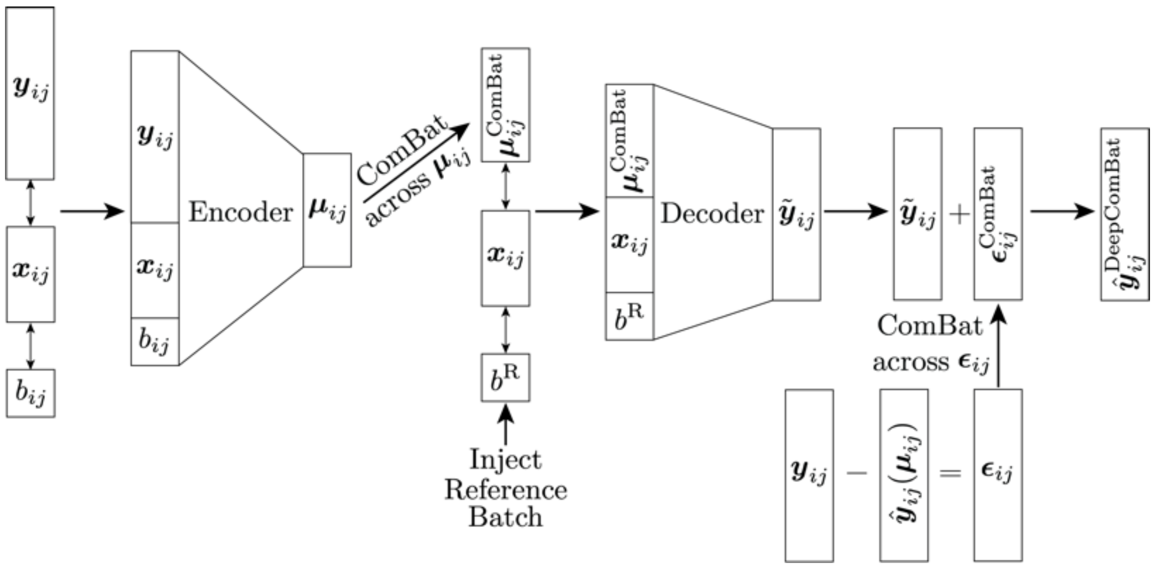


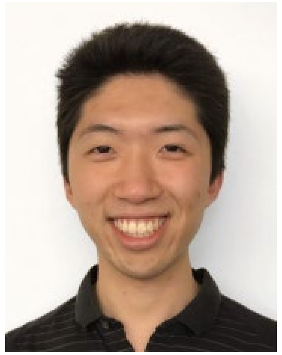


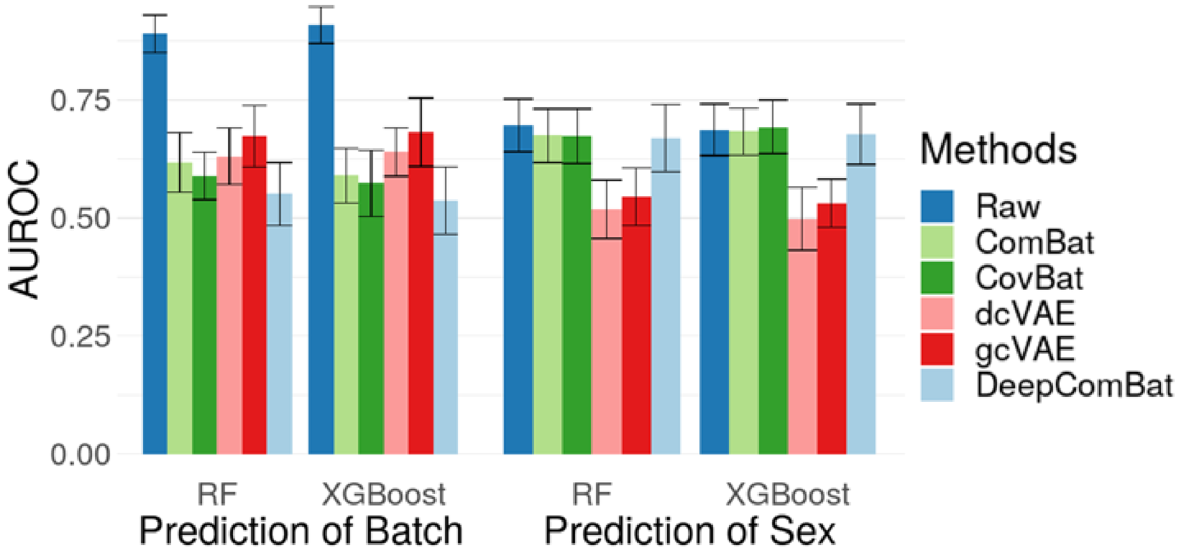
Yu, Linn, Cook et al. (2021)

Chen, Beer, Tustison et al. (2022)

Nonlinear Feature Harmonization methods







Hu et al., *Under Review* (2023+)

Future Directions

Key Areas for Continued Development

- More *flexible* models, as statistical and deep learning models continue to evolve.
- Approaches for harmonization in the context of *new analysis settings.*
- Further leveraging *traveling subject* study designs.
- Next generation *image-domain* harmonization methods

PENNSIVE
Penn Statistics in Imaging and Visualization Endeavor

Thank You!

Funding acknowledgements: This research was supported by awards R01MH123550 and R01MH112847 from the NIMH, R01NS085211, R01NS112274, and R01NS060910 from the NINDS, U24CA189523 from NCI, as well as RG-1707-28586 from the NMSS. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.