Neuroimaging Harmonization: Approaches, Considerations, and Gaps

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Goals for today

- Understand the importance of harmonization for neuroimaging data
- Explain types of harmonization and considerations for these
- Review gaps in the field

Focus on neuroimaging in TBI but most approaches and considerations apply to many types of biomarkers across psychiatric and neurological disorders

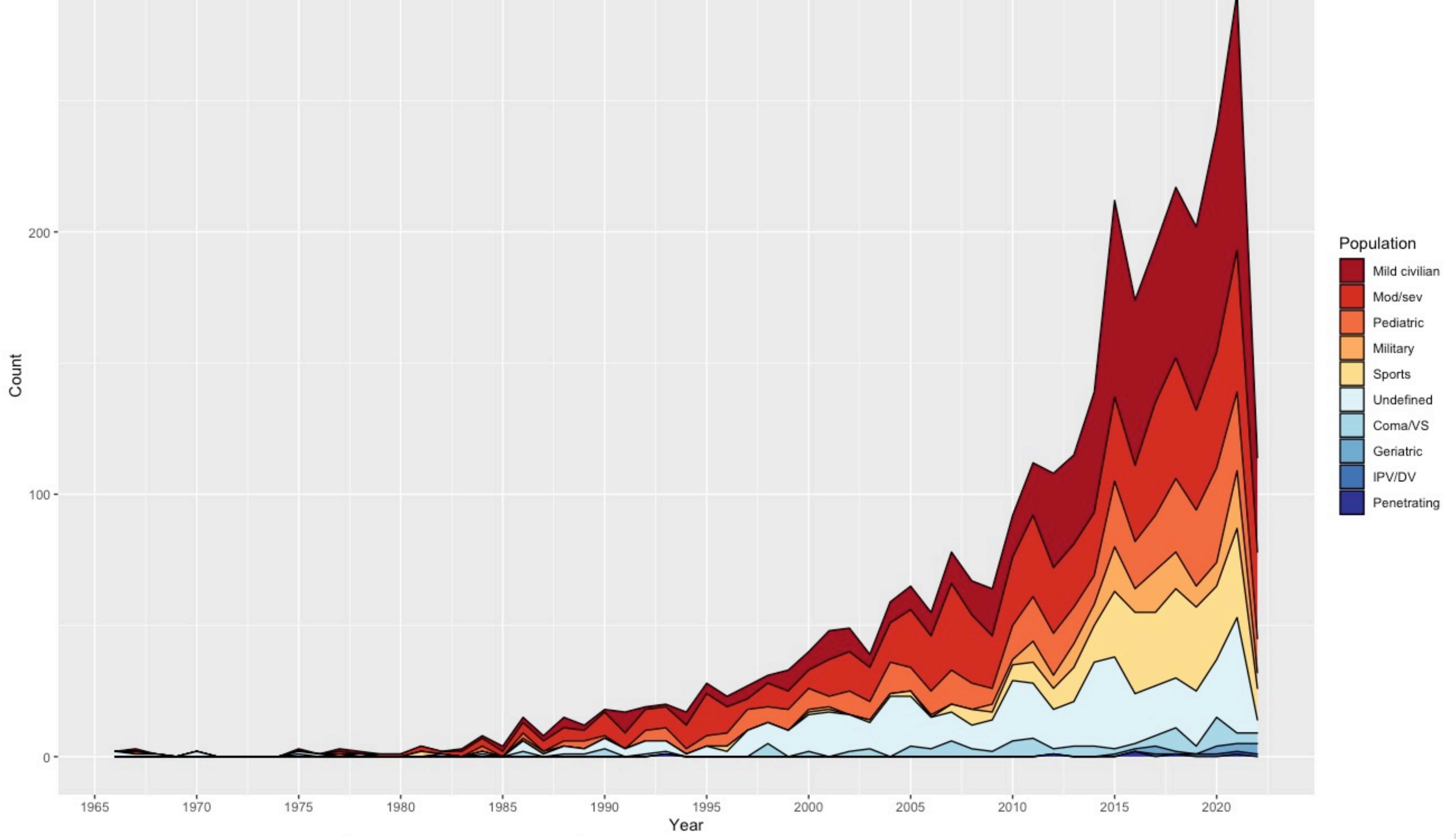
Why is harmonization important?

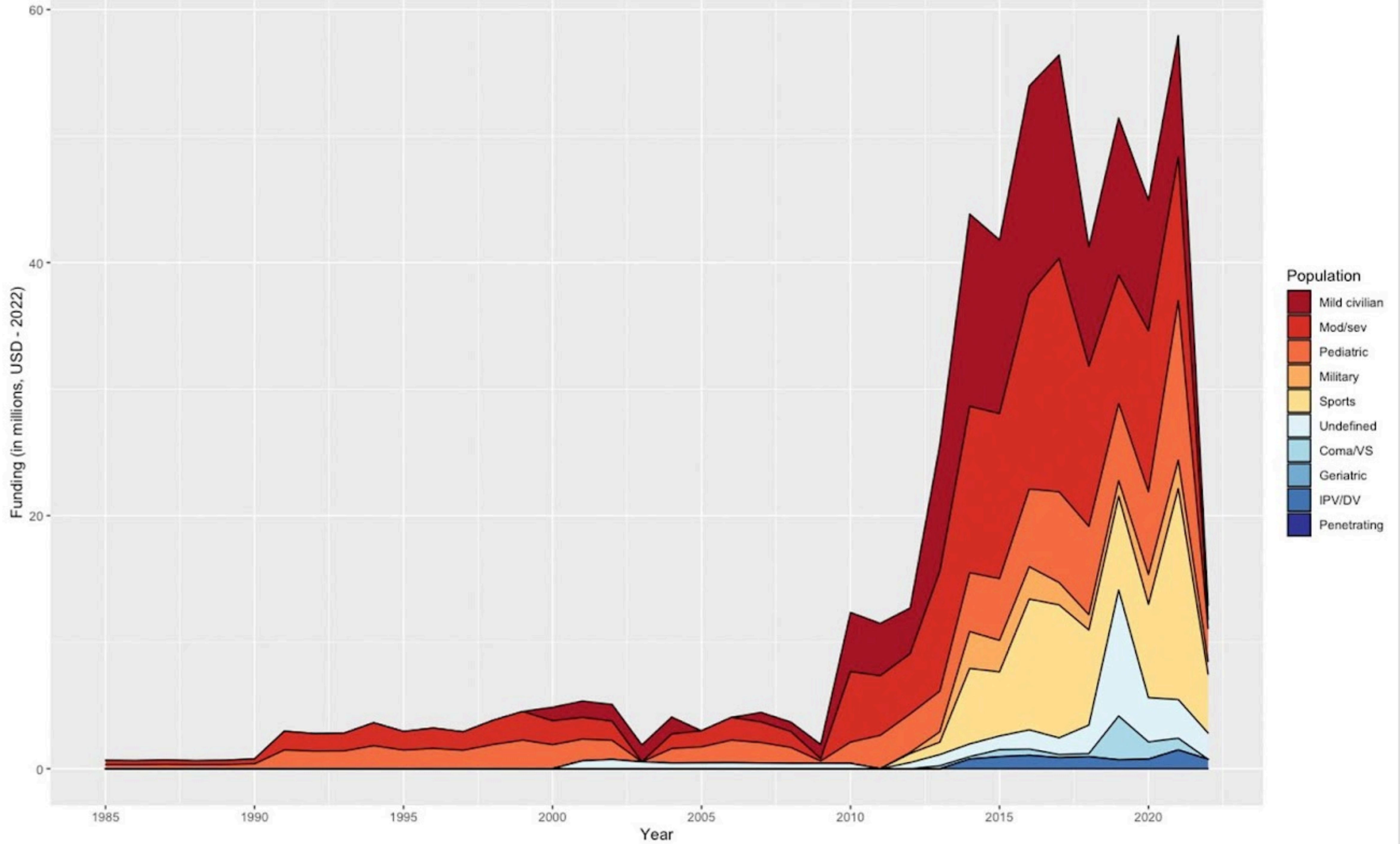
- Rate of publication and funding in TBI neuroimaging is accelerating but successful translation can be hampered by small sample sizes limiting generalizability

- Increasing understanding of the need for multi-site/multi-cohort analyses

- Data must be comparable however to avoid garbage-in/garbage-out

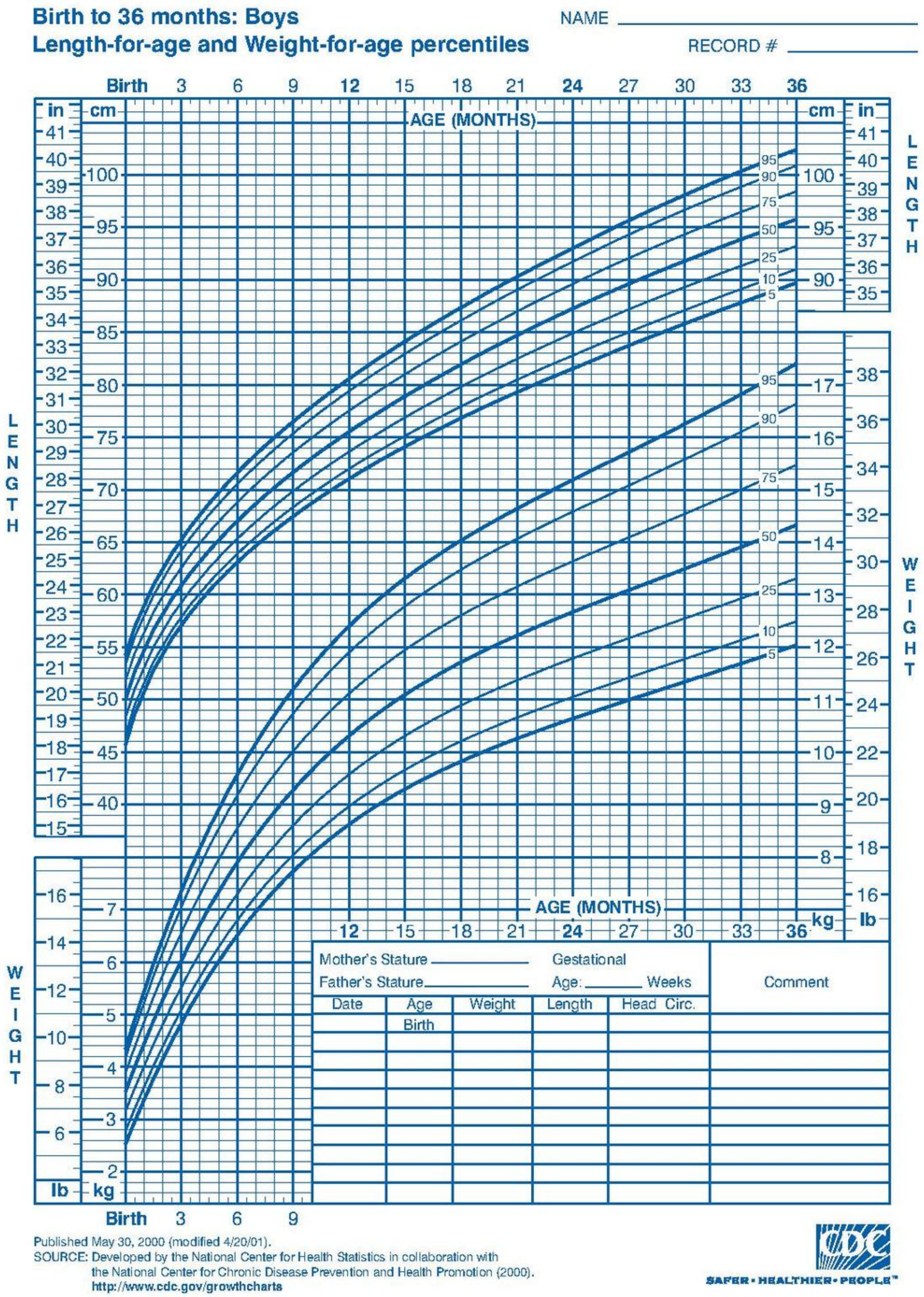
Dennis et al., BIP 2023





Why is harmonization important for biomarker development?

- Standardization is necessary to make biomarkers usable clinically
  - Imagine every doctors office using different units of measurement - inches, cm, hands, bananas, etc.
- Historically there hasn't been much consideration of this with MRI
  - Disincentive for having data that could be combined



Many sources of site effects

- Methodological sources
  - Scanner platform - SNR/CNR, coil inhomogeneity
  - Scan sequence - sensitivity to tissue differences, sensitivity to motion
  - Acquisition procedure - task details, instructions, time of day, motion
  - Postprocessing

- Biological
  - Age
  - Sex/Gender
  - Severity/chronicity of condition - treatment, medication
  - Background demographics - SES, race/ethnicity, genetics, environmental exposures
  - Control samples
  - Inclusion/exclusion criteria

Bayer et al., Front Neurol. 2022

Prospective harmonization

- Synchronizing scan parameters prior to data collection
  - Sequences coordinated across vendors - not identical
  - Some sequences vary within individual within scanner
    - DWI/DTI, fMRI, ASL
    - Hydration, caffeine
  - Often use "human phantoms"
- Examples
  - ADNI
  - ABCD
  - TRACK-TBI
  - LIMBIC-CENC
  - CARE Consortium and CARE4Kids

Neuroimaging Parameters

Siemens	Matrix	Slices	FOV	% FOV phase	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip Angle (deg)	Parallel Imaging	MultiBand Acceleration	Phase partial Fourier	Diffusion Directions	b-values	Acquisition Time
T1	256 x 256	176	256 x 256	100%	1.0 x 1.0 x 1.0	2500	2.88	1060	8	2x	Off	Off	N/A	N/A	7:12
T2	256 x 256	176	256 x 256	100%	1.0 x 1.0 x 1.0	3200	565	N/A	Variable	2x	Off	Off	N/A	N/A	6:35
Diffusion	140 x 140	81	240 x 240	100%	1.7 x 1.7 x 1.7	4100	88	N/A	90	Off	3	6/8	96	500 (6-dirs) 1000 (15-dirs) 2000 (15-dirs) 3000 (60-dirs)	7:31
fMRI	90 x 90	60	216 x 216	100%	2.4 x 2.4 x 2.4	800	30	N/A	52	Off	6	Off	N/A	N/A	

Philips	Matrix	Slices	FOV	% FOV phase	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip Angle (deg)	Parallel Imaging	MultiBand Acceleration	Half Scan Factor	Diffusion Directions	b-values	Acquisition Time
T1	256 x 256	225	256 x 240	93.75%	1.0 x 1.0 x 1.0	6.31	2.9	1060	8	1.5 x 2.2	Off	N/A	N/A	N/A	5:38
T2	256 x 256	256	256 x 256	100%	1.0 x 1.0 x 1.0	2500	251.6	N/A	90	1.5 x 2.0	Off	N/A	N/A	N/A	2:53
Diffusion	140 x 140	81	240 x 240	100%	1.7 x 1.7 x 1.7	5300	89	N/A	78	Off	3	0.6	96	500 (6-dirs) 1000 (15-dirs) 2000 (15-dirs) 3000 (60-dirs)	9:14
fMRI	90 x 90	60	216 x 216	100%	2.4 x 2.4 x 2.4	800	30	N/A	52	Off	6	0.9	N/A	N/A	

GE	Matrix	Slices	FOV	% FOV phase	Resolution (mm)	TR (ms)	TE (ms)	TI (ms)	Flip Angle (deg)	Parallel Imaging	MultiBand Acceleration	Phase partial Fourier	Diffusion Directions	b-values	Acquisition Time
T1	256 x 256	208	256 x 256	100%	1.0 x 1.0 x 1.0	2500	2	1060	8	2x	Off	Off	N/A	N/A	6:09
T2	256 x 256	208	256 x 256	100%	1.0 x 1.0 x 1.0	3200	60	N/A	Variable	2x	Off	Off	N/A	N/A	5:50
Diffusion	140 x 140	81	240 x 240	100%	1.7 x 1.7 x 1.7	4100	81.9	N/A	77	Off	3	5.5/8	96	500 (6-dirs) 1000 (15-dirs) 2000 (15-dirs) 3000 (60-dirs)	7:30
fMRI	90 x 90	60	216 x 216	100%	2.4 x 2.4 x 2.4	800	30	N/A	52	Off	6	Off	N/A	N/A	

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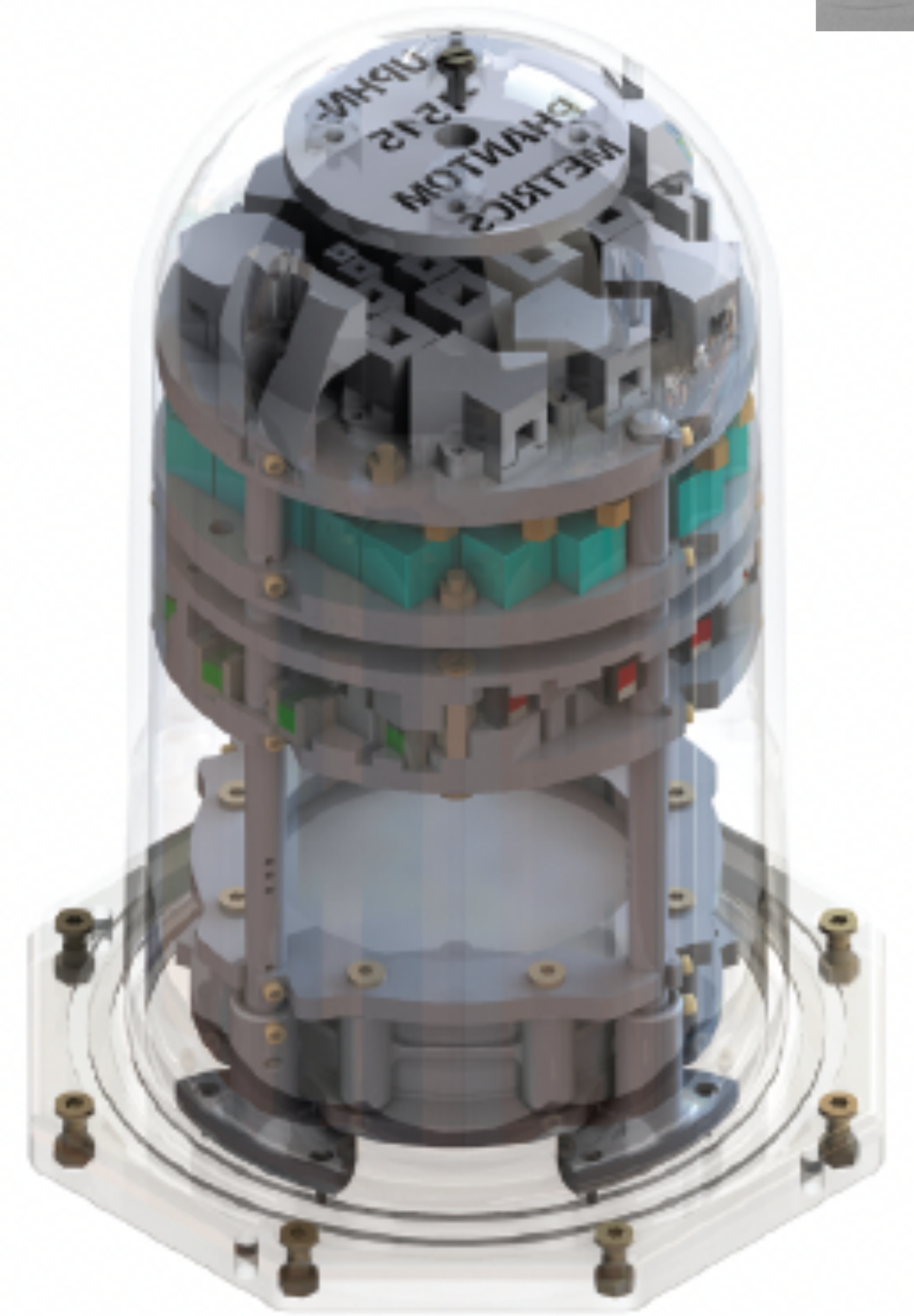
Phantom harmonization

CHIPS Project

- Use of novel phantom objects where models of tissue with known properties can be used to assess scanner accuracy
- CHIPS project currently working to use phantoms across VAs to improve scanner accuracy and data comparability
  - Example: anisotropic diffusion can be measured with hollow 6-10 μm fibers arranged to mimic white matter tracts
  - Measurements can be compared to known diffusion properties and correction algorithm can be applied

Phantom Laboratory



Psychology Software Tools

Ground truth

- Phantom harmonization - closest to ground truth, but it’s not biological tissue
- Prospective sequence harmonization with traveling human phantoms - next best thing
- But what about retrospective harmonization? How to identify ground truth?
- No single answer yet - common approach is to model a known biological effect before and after harmonization to ensure it is preserved
- Room for improvement here!

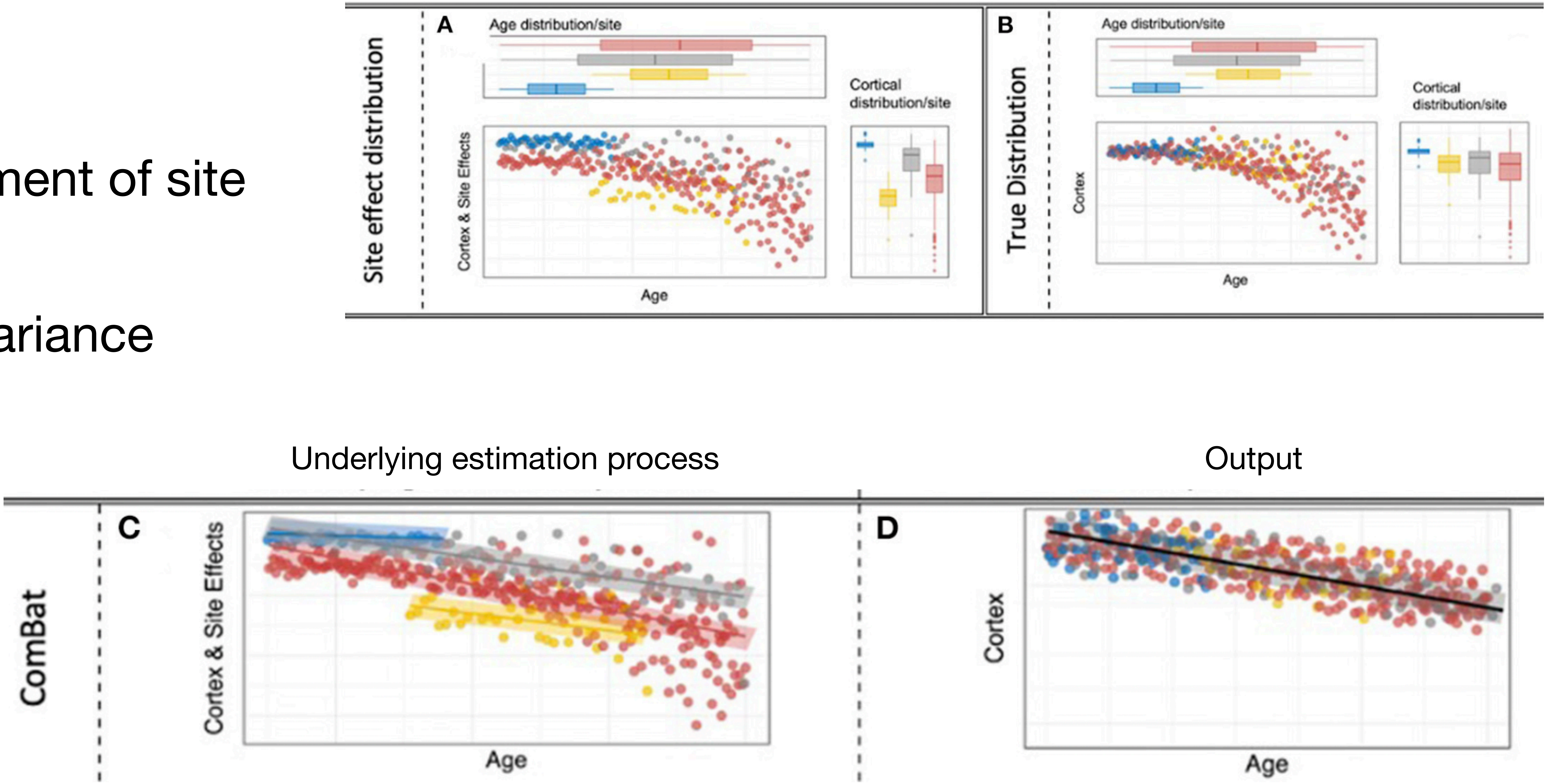
Retrospective harmonization techniques

- Next slides review several approaches for statistical harmonization
- Key take-away is how do the outputs vary

Retrospective harmonization

ComBat

- Linear adjustment of site means
- Scaling site variance differences
- Can preserve specific covariate effects

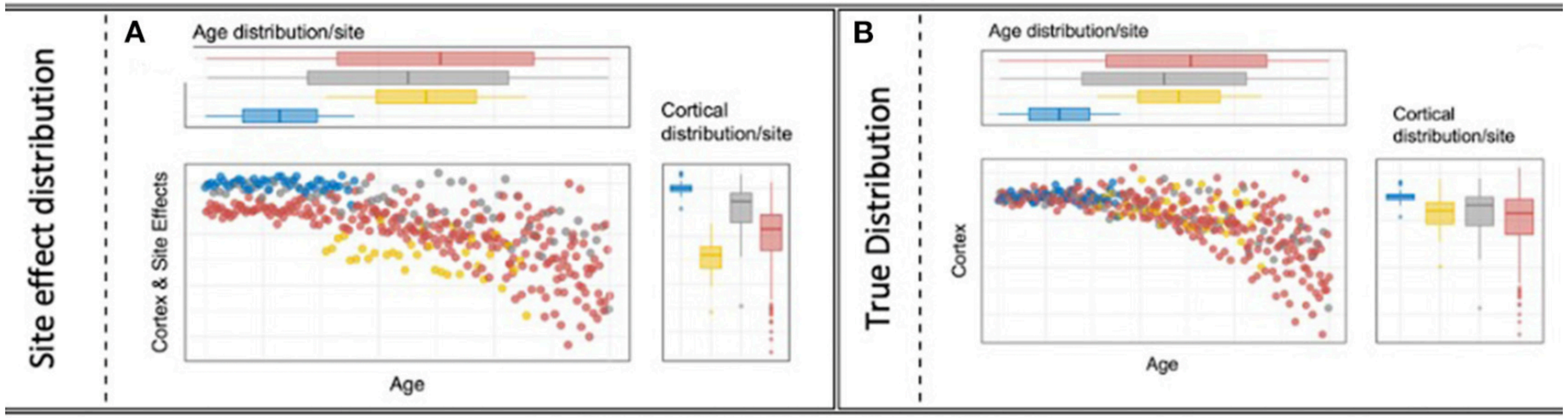


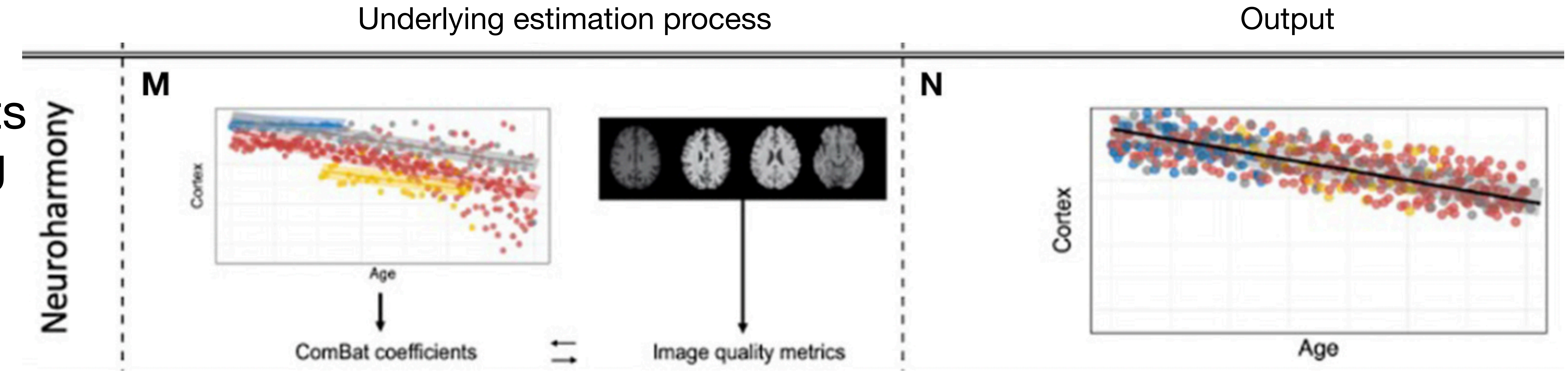
Bayer et al., Front Neurol. 2022

Retrospective harmonization

Neuroharmony

- Calculate image quality metrics
- Use these as predictors in ComBat
- Apply coefficients to imaging features





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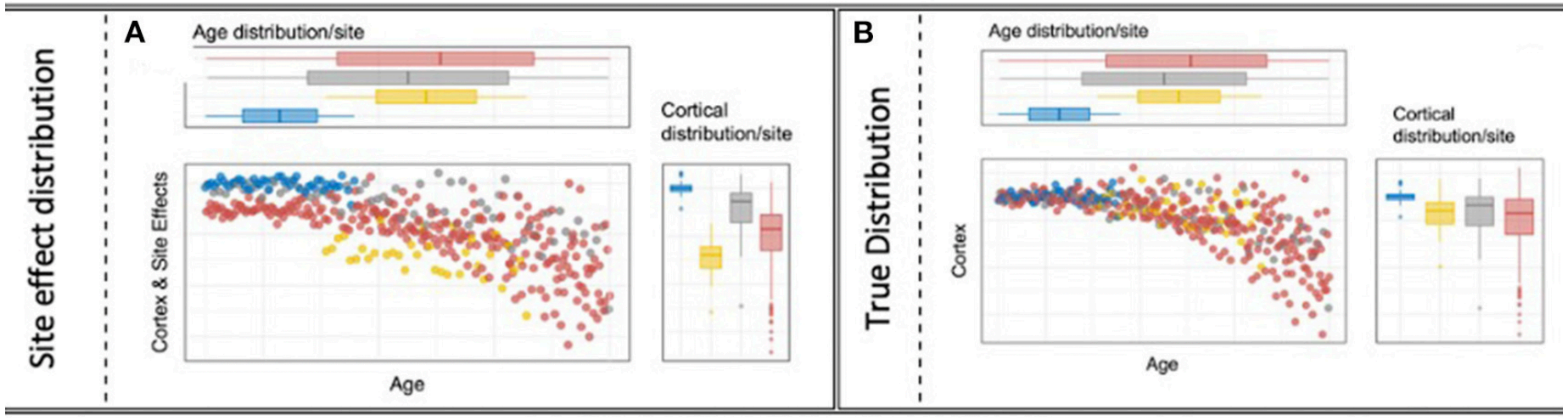
Retrospective harmonization

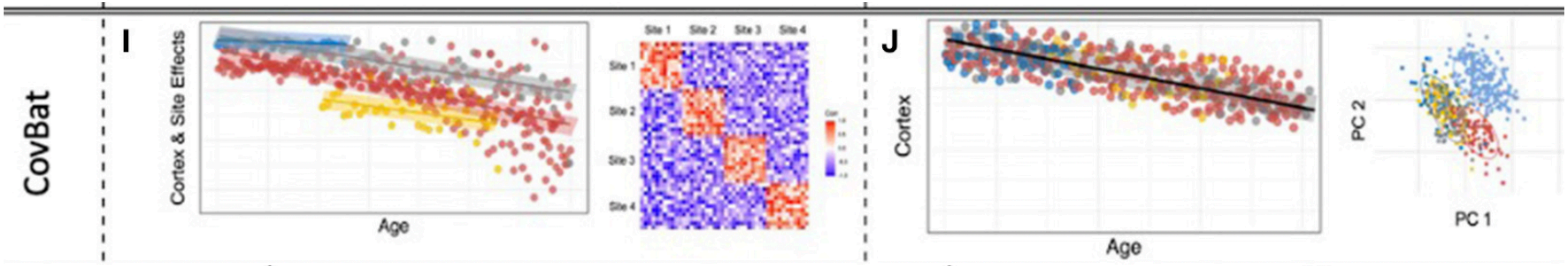
CovBat



- 2 runs of ComBat
  - First as usual
  - Second on a PCA of the residuals from the first to harmonize the covariance

Underlying estimation process

Output

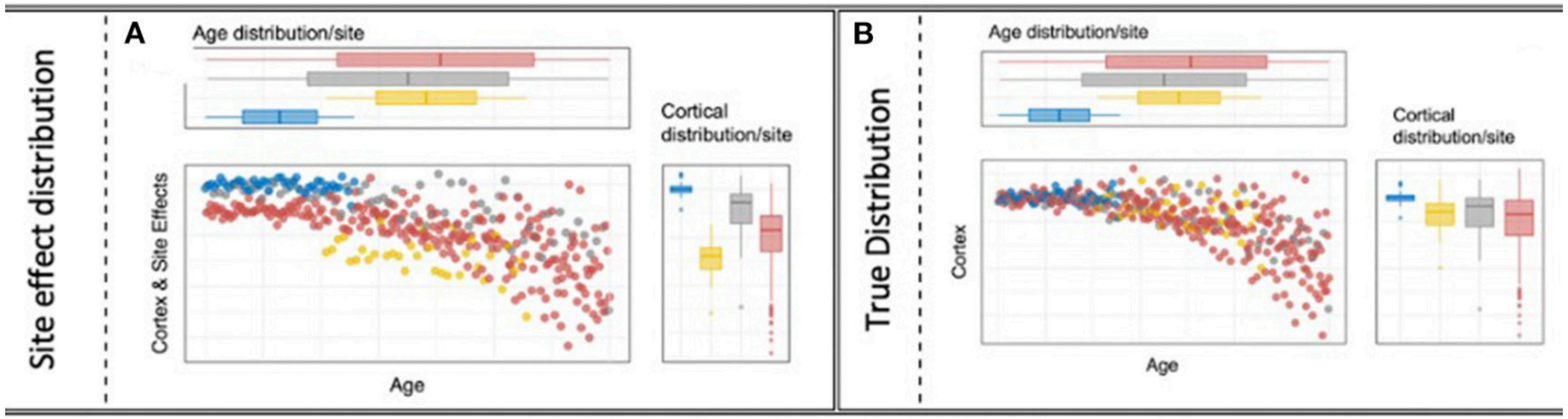


Bayer et al., Front Neurol. 2022

Retrospective harmonization

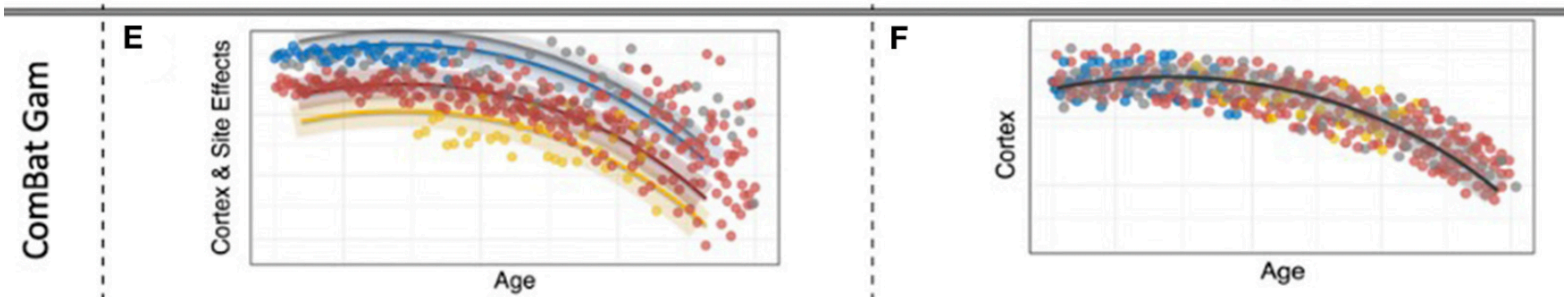
ComBat-GAM

- Similar to ComBat
- Non-linear adjustment



Underlying estimation process

Output



There are many more variations on ComBat, including some that use federated learning so that raw data sharing isn't required

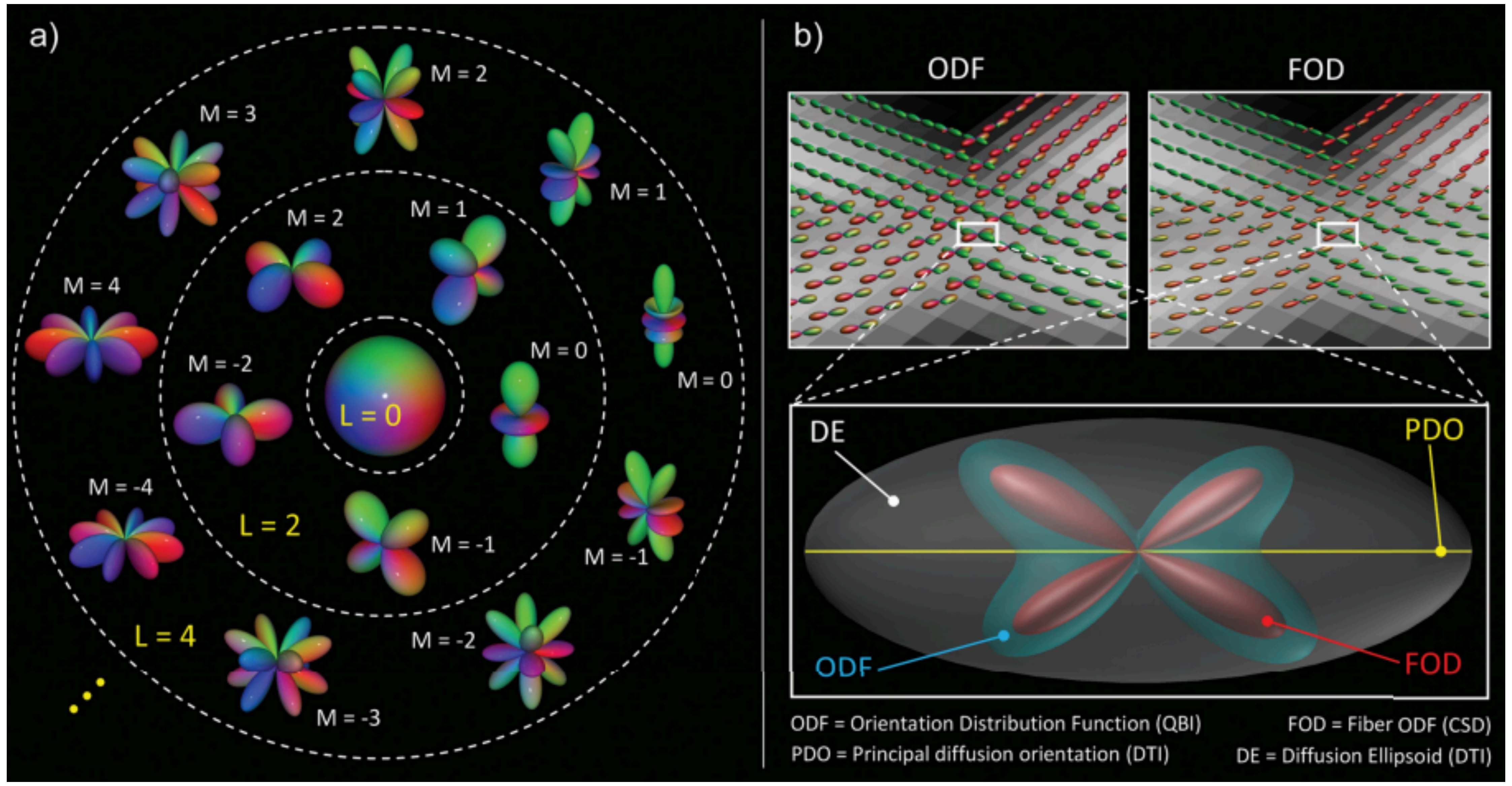
Bayer et al., Front Neurol. 2022

When to harmonize

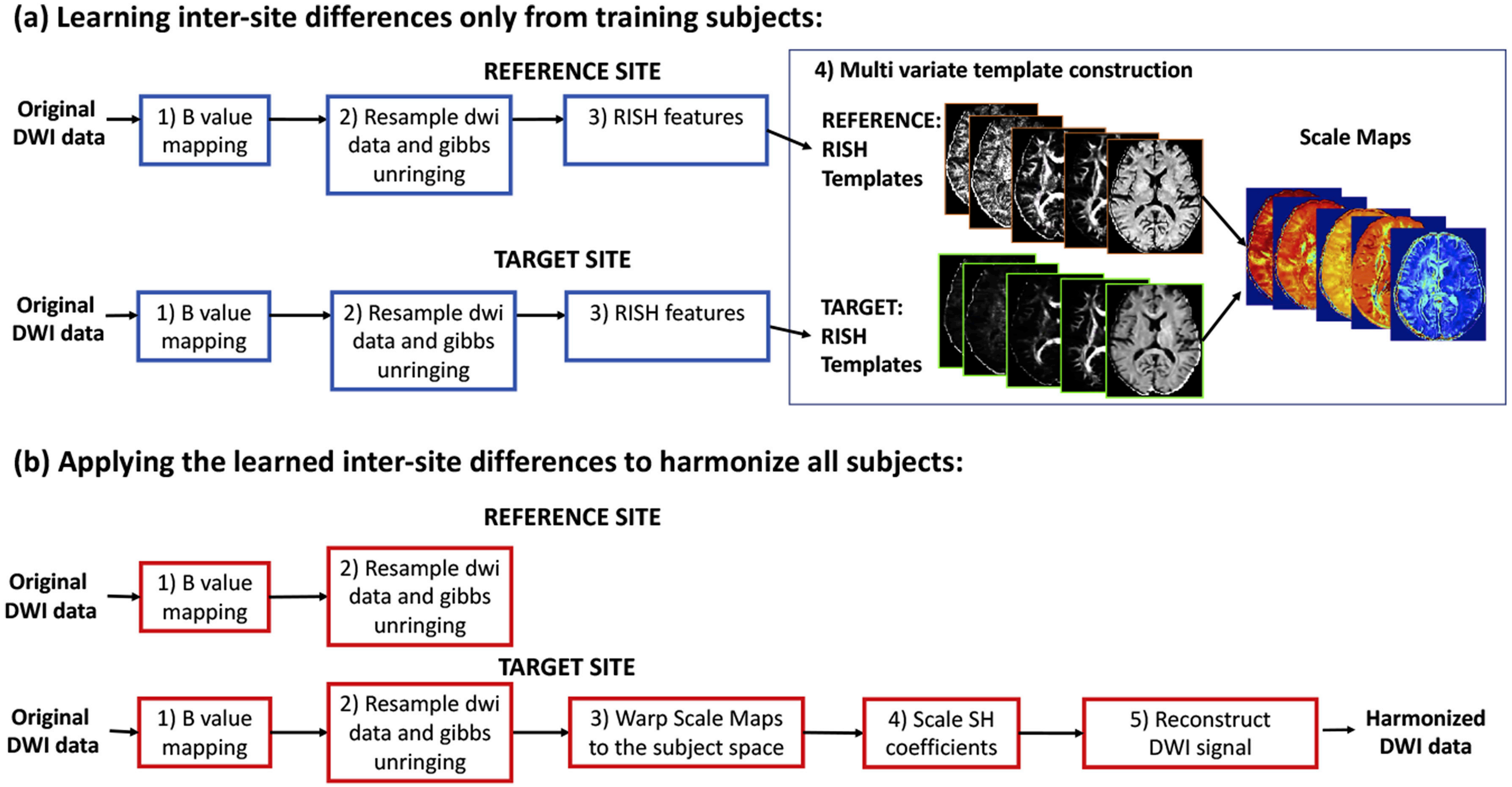
- Raw imaging data
- Derived imaging metrics
- Summary imaging metrics

Harmonization of raw diffusion MRI

- Matched controls
- Scale *b*-values
- Upsample data to standardize voxel resolution
- Signal at each voxel is represented by spherical harmonics (equations to describe a sphere)
- Harmonics can be scaled and applied to dataset



Leemans, Diffusion MRI 2010



Cetin-Karayumak et al., NIMG 2019

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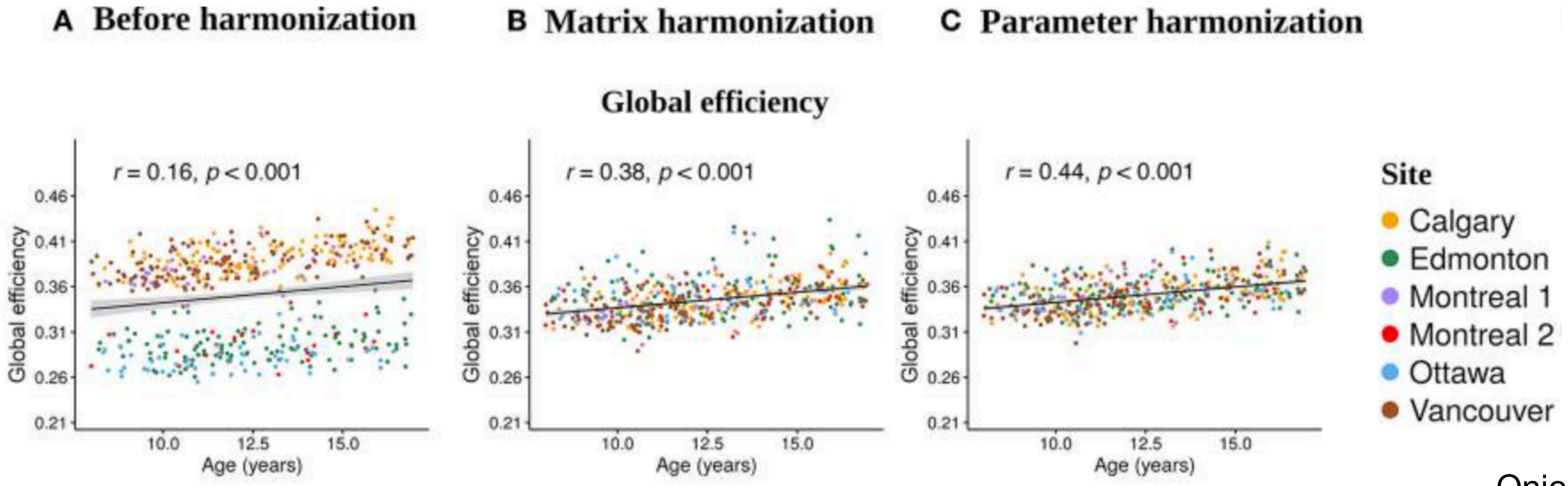
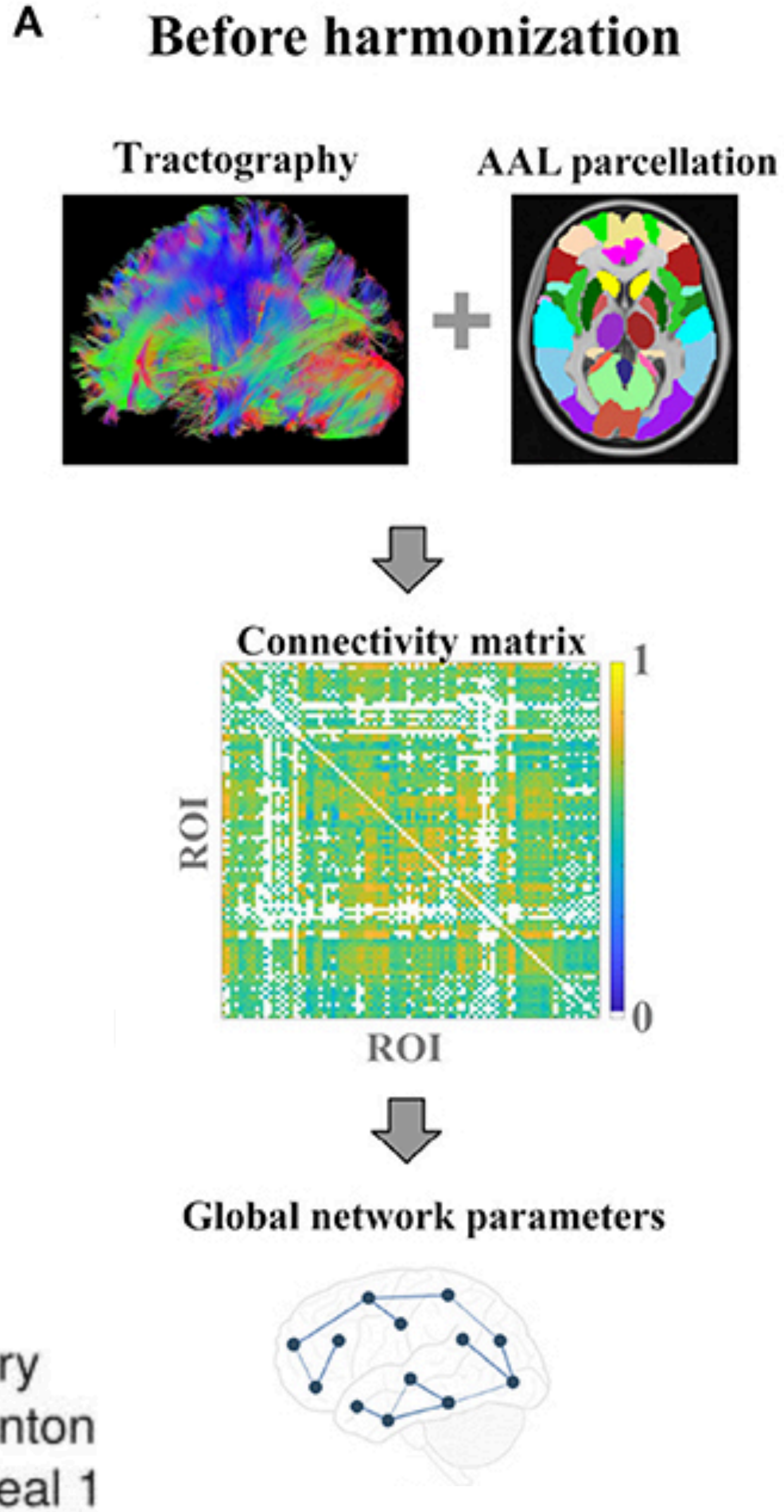
- Summary imaging metrics





Onicas et al., Front. Neurol. 2022

Summary

- Why is this important for biomarker development?
  - We should be able to leverage the vast amount of data that has been collected already to develop normative databases for a whole range of imaging metrics
- There have been tremendous advances in this area in the last decade
  - Technical - better computer hardware makes computationally intensive algorithms and programs feasible
  - Sociological - increasingly willingness and enthusiasm for collaboration and data sharing
    - Federal archives like FITBIR and NDA support these efforts

Each advancement brings us closer to the goal of being able to place an individual scan in context, furthering precision medicine efforts

References

- Bayer, Johanna MM, et al. “Site effects how-to and when: An overview of retrospective techniques to accommodate site effects in multi-site neuroimaging analyses.” *Frontiers in Neurology* 13 (2022).

- Cetin-Karayumak, Suheyla, et al. “Retrospective harmonization of multi-site diffusion MRI data acquired with different acquisition parameters.” *Neuroimage* 184 (2019): 180-200.

- Onicas, Adrian I, et al. “Multisite harmonization of structural DTI networks in children: An A-CAP study.” *Frontiers in Neurology* 13 (2022).