Harmonization of Diffusion MRI

4 Alternative Approaches: with illustrative examples in ADNI, ENIGMA

Paul Thompson, Neda Jahanshad, Peter Kochunov, Sinead Kelly, Gary Donohoe, Sean Hatton, Talia Nir, Artemis Zavaliangos-Petropulu, Sophia Thomopoulos, Robert Reid, Bret Borowski, Matt Bernstein, Cliff Jack, Joaquim Radua, Dan Moyer, Greg ver Steeg, Chantal Tax, ADNI, ENIGMA, et al.

In multi-site studies, diffusion MRI can be collected with **multiple protocols and scanners** (GE, Siemens, Philips).

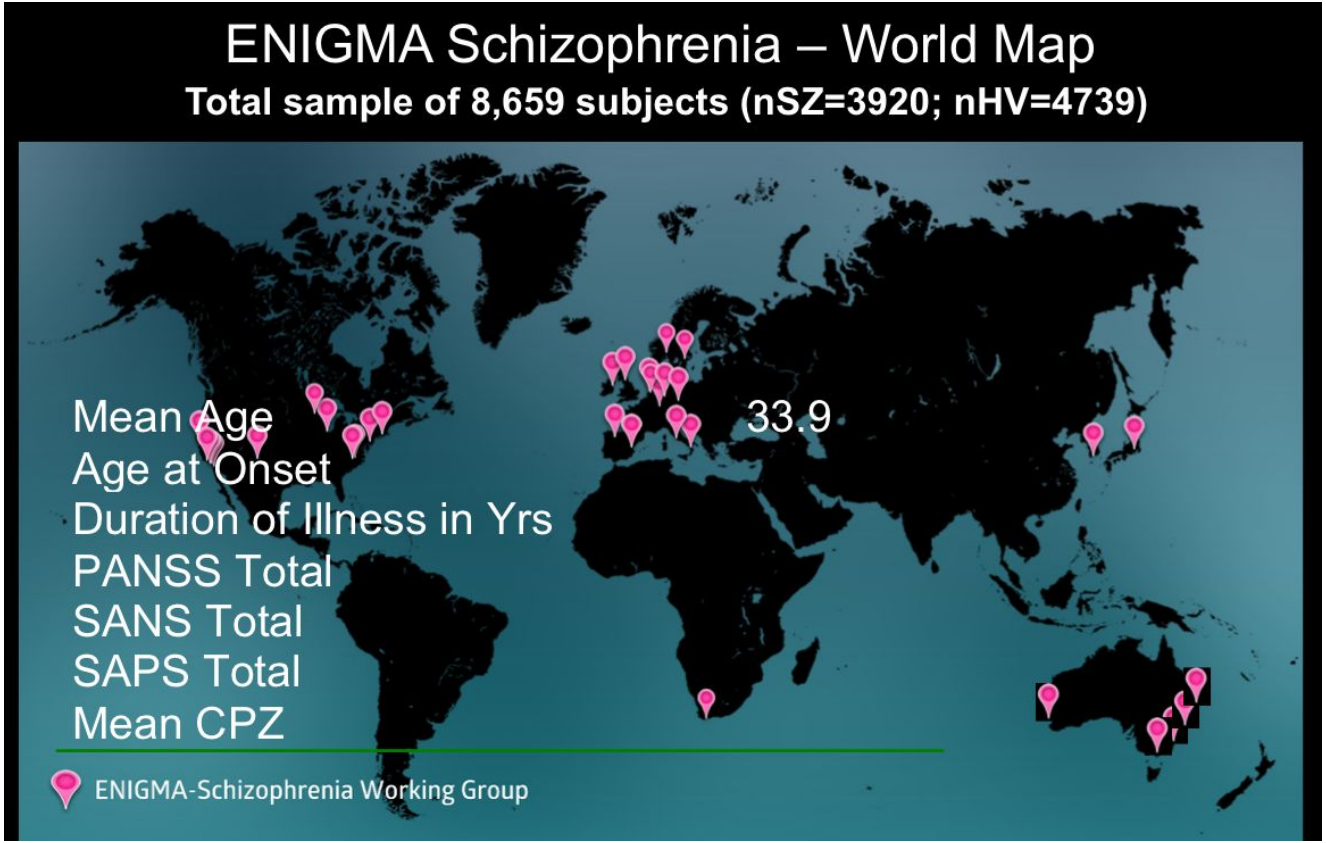
Harmonization refers to the mathematical adjustment of data from each scanner before it is combined.

We have studied 4 approaches, in order of complexity

1. **Meta-analysis of effects from each site (early ENIGMA)**
2. **Fit the site/scanner effect using random effects regression (needs centralized data)**
3. **Use ComBat to adjust data histograms before pooling across sites/scanners**
4. **Use Variational Autoencoder (site free data+site code) with Generative Adversarial Networks that make it hard to tell which site the data came from (Moyer et al., Magn Res Med 2020)**

Other methods include, e.g., Mirzaalian H et al., MICCAI 2015 - https://www.ncbi.nlm.nih.gov/pubmed/?term=rathi+y+harmonizing

1. **Meta-analysis of effects from each site (early ENIGMA; examples: ENIGMA Schizophrenia studies*, ENIGMA GWAS)**



*van Erp TGM et al., Biol Psych, 2018 https://www.ncbi.nlm.nih.gov/pubmed/29960671

1. Meta-analysis of effects from each site (e.g., ENIGMA DTI ; 5 ‘largest-ever’ disease studies now published: SCZ, BPD, MDD, PTSD, 22qDS)

Kelly S et al., Mol Psych 2018
https://www.ncbi.nlm.nih.gov/pubmed/29038599

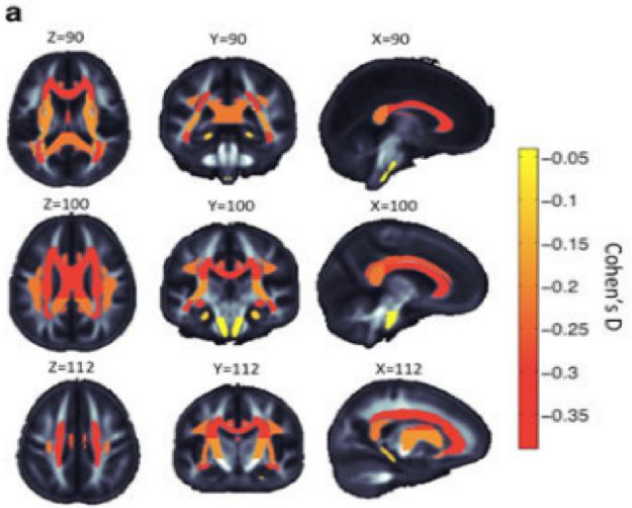
Van Velzen L Mol Psych 2019
https://www.ncbi.nlm.nih.gov/pubmed/31471575

BPD:
https://www.ncbi.nlm.nih.gov/pubmed/31434102

22qDS:
https://www.ncbi.nlm.nih.gov/pubmed/31358905
(meta-, mega-, ComBat)

Meta- slightly better than mega- (22qDS):
https://www.nature.com/articles/s41380-019-0450-0/figures/2

Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI



S Kelly, N Jahanshad, A Zalesky, P Kochunov, I Agartz, C Alloza, O A Andreassen, C Arango, N Banaj, S Bouix, C A Bousman, R M Brouwer, J Bruggemann, J Bustillo, W Cahn, V Calhoun, D Cannon, V Carr, S Catts, J Chen, J-x Chen, X Chen, C Chiapponi, Kl K Cho, V Ciullo, A S Corvin, B Crespo-Facorro, V Cropley, P De Rossi, C M Diaz-Caneja, E W Dickie, S Ehrlich, F-m Fan, J Faskowitz, H Fatouros-Bergman, L Flyckt, J M Ford, J-P Fouche, M Fukunaga, M Gill, D C Glahn, R Gollub, E D Goudzwaard, H Guo, R E Gur, R C Gur, T P Gurholt, R Hashimoto, S N Hatton, F A Henskens, D P Hibar, I B Hickie, L E Hong, J Horacek, F M Howells, H E Hulshoff Pol, C L Hyde, D Isaev, A Jablensky, P R Jansen, J Janssen, E G Jönsson, L A Jung, R S Kahn, Z Kikinis, K Liu, P Klauser, C Knöchel, M Kubicki, J Lagopoulos, C Langen, S Lawrie, R K Lenroot, K O Lim, C Lopez-Jaramillo, A Lyall, V Magnotta, R C W Mandl, D H Mathalon, R W McCarley, S McCarthy-Jones, C McDonald, S McEwen, A McIntosh, T Melicher, R I Mesholam-Gately, P T Michie, B Mowry, B A Mueller, D T Newell, P O'Donnell, V Oertel-Knöchel, L Oestreich, S A Paciga, C Pantelis, O Pasternak, G Pearlson, G R Pellicano, A Pereira, J Pineda Zapata, F Piras, S G Potkin, A Preda, P E Rasser, D R Roalf, R Roiz, A Roos, D Rotenberg, T D Satterthwaite, P Savadjiev, U Schall, R J Scott, M L Seal, L J Seidman, C Shannon Weickert, C D Whelan, M E Shenton, J S Kwon, G Spalletta, F Spaniel, E Sprooten, M Stäblein, D J Stein, S Sundram, Y Tan, S Tan, S Tang, H S Temmingh, L T Westlye, S Tønnesen, D Tordesillas-Gutierrez, N T Doan, J Vaidya, N E M van Haren, C D Vargas, D Vecchio, D Velakoulis, A Voineskos, J Q Voyvodic, Z Wang, P Wan, D Wei, T W Weickert, H Whalley, T White, T J Whitford, J D Wojcik, H Xiang, Z Xie, H Yamamori, F Yang, N Yao, G Zhang, J Zhao, T G M van Erp, J Turner, P M Thompson & G Donohoe - Show fewer authors

Molecular Psychiatry

1. Meta-analysis of effects from each site (ENIGMA)

This also works well for **morphometry** - **33 sites** measured the effect of schizophrenia on cortical thickness (van Erp et al., 2018*)

Weight the site effects by sample size of each cohort (or inverse-variance weighted), to get an overall estimate of effect

Largely consistent effects

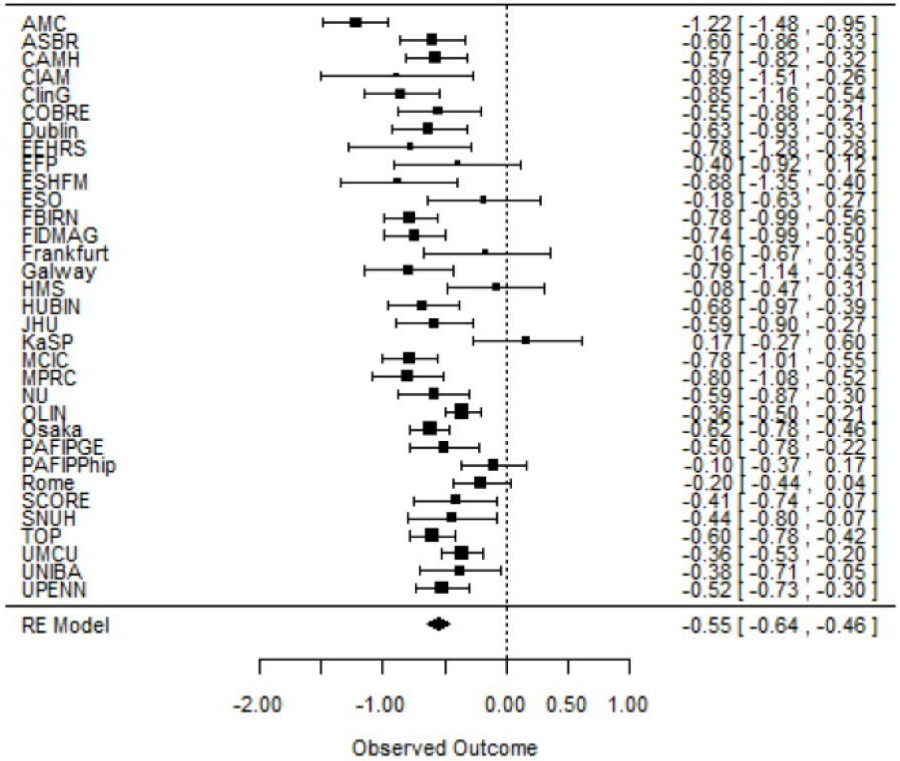
Used in GWAS (e.g., *Science* 2020)

*van Erp TGM et al., Biol Psych, 2018
https://www.ncbi.nlm.nih.gov/pubmed/29960671

Best ROI: Thinner fusiform gyrus

25 of 33 Cohorts

N=8,659



Cohen's d: -0.55

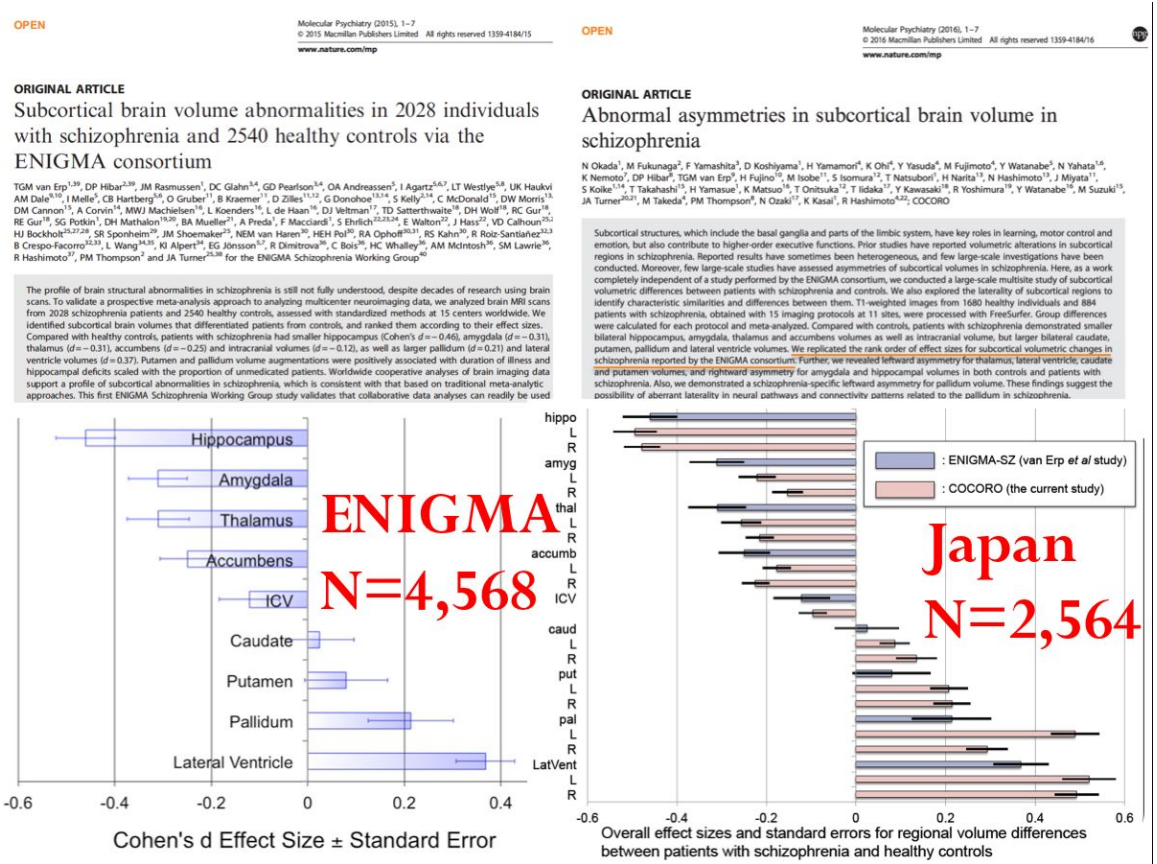
Mean fusiform

1. Meta-analysis of effects from each site (ENIGMA)

Meta-analyzed effects are also highly reproducible across continents - ENIGMA-COCORO Japan Collaboration

Same rank order for brain regions affected in schizophrenia

Similar effect sizes too



DTI:
Koshiyama et al., Mol Psych. 2020
https://www.ncbi.nlm.nih.gov/pubmed/32286531
Kochunov P et al., Hum Brain Mapp 2020 -
https://www.ncbi.nlm.nih.gov/pubmed/32301246

2. Fit the site/scanner effects using random effects* regression (needs centralized data)

https://www.frontiersin.org/articles/10.3389/fninf.2019.00002/full

*mean effect can vary across protocols/sites; fixed effects = same effect size, all protocols
https://www.meta-analysis.com/downloads/Meta-analysis%20Fixed-effect%20vs%20Random-effects%20models.pdf

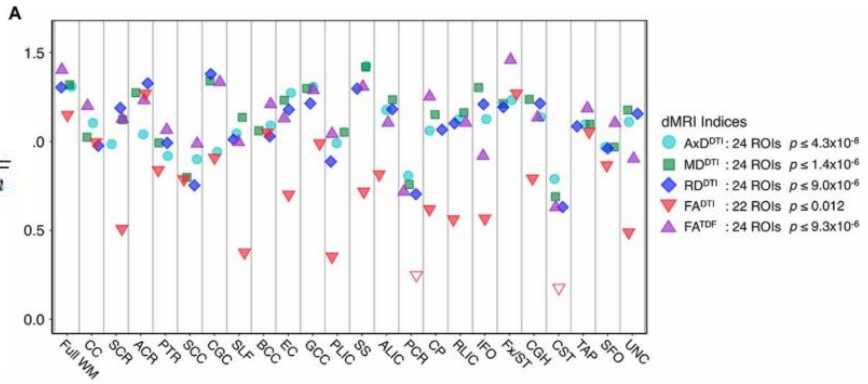
Diffusion MRI Indices and Their Relation to Cognitive Impairment in Brain Aging: The Updated Multi-protocol Approach in ADNI3

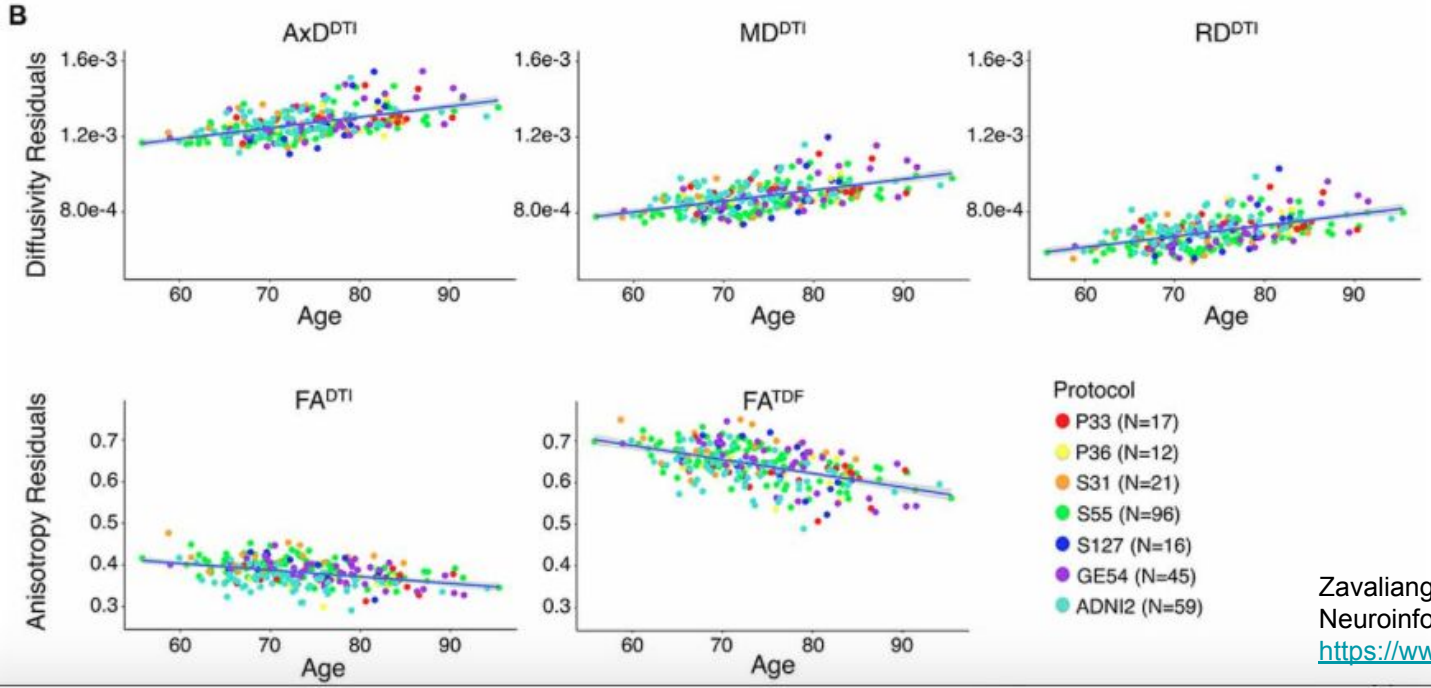
Artemis Zavaliangos-Petropulu[1†], Talia M. Nir[1†], Sophia I. Thomopoulos[1], Robert I. Reid[2], Matt A. Bernstein[3], Bret Borowski[3], Clifford R. Jack Jr.[3], Michael W. Weiner[4], Neda Jahanshad[1], Paul M. Thompson[1*] and the Alzheimer's Disease Neuroimaging Initiative (ADNI)[‡]

	Name	Scanner	Protocol	b_0 volumes	DWI volumes	Total volumes	Time (min)	Total *N*
ADNI3	GE36	GE	Basic Widebore 25x	4 b = 0 s/mm^2	32 b = 1,000 s/mm^2	36	9:52	–
	GE54	GE	Basic 25x	6 b = 0 s/mm^2	48 b = 1,000 s/mm^2	54	7:09	65
	P33	Philips	Basic Widebore	1 b = 0 s/mm^2	32 b = 1,000 s/mm^2	33	7:32	24
	P36	Philips	Basic Widebore R3	1 b = 0 s/mm^2 3 b = 2 s/mm^2	32 b = 1,000 s/mm^2	36	6:54	19
	P54	Philips	Basic R5	1 b = 0 s/mm^2 5 b = 2 s/mm^2	48 b = 1,000 s/mm^2	54	8:05	–
	S31	Siemens	Basic VB17	1 b = 0 s/mm^2	30 b = 1,000 s/mm^2	31	7:02	36
	S55	Siemens	Basic Skyra E11 and Prisma D13	7 b = 0 s/mm^2	48 b = 1,000 s/mm^2	55	9:18	153
	S127	Siemens	Advanced Prisma VE11C	13 b = 0 s/mm^2	48 b = 1,000 s/mm^2	61	7:25*	20
ADNI2	G46	GE	Discovery MR750 and MR750w, Signa HDx and HDxt	5 b = 0 s/mm^2	41 b = 1,000 s/mm^2	46	7:00–10:00	59

2. Fit the site/scanner effects using random effects regression (needs centralized data)

$$d = \frac{(2*Tvalue)}{\sqrt{Degrees\,of\,Freedom}}$$



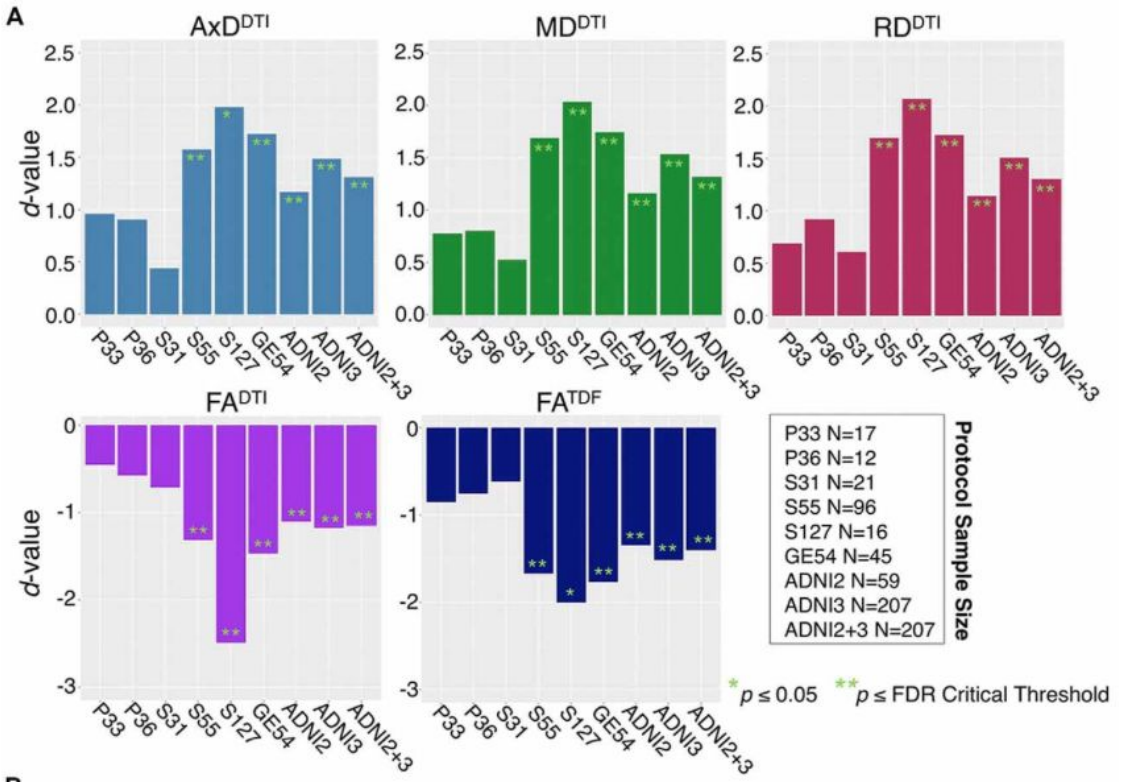


For each diffusion-weighted MRI (dMRI) index, the absolute values of effect sizes (*d*-value) are plotted for regional white matter (WM) microstructural **associations with age** when all ADNI3 dMRI data are pooled, adjusting for any site or protocol effects.

Zavaliangos-Petropulu A et al., Frontiers Neuroinform 2019
https://www.ncbi.nlm.nih.gov/pubmed/30837858

2. Fit the site/scanner effects using random effects regression
(needs centralized data)

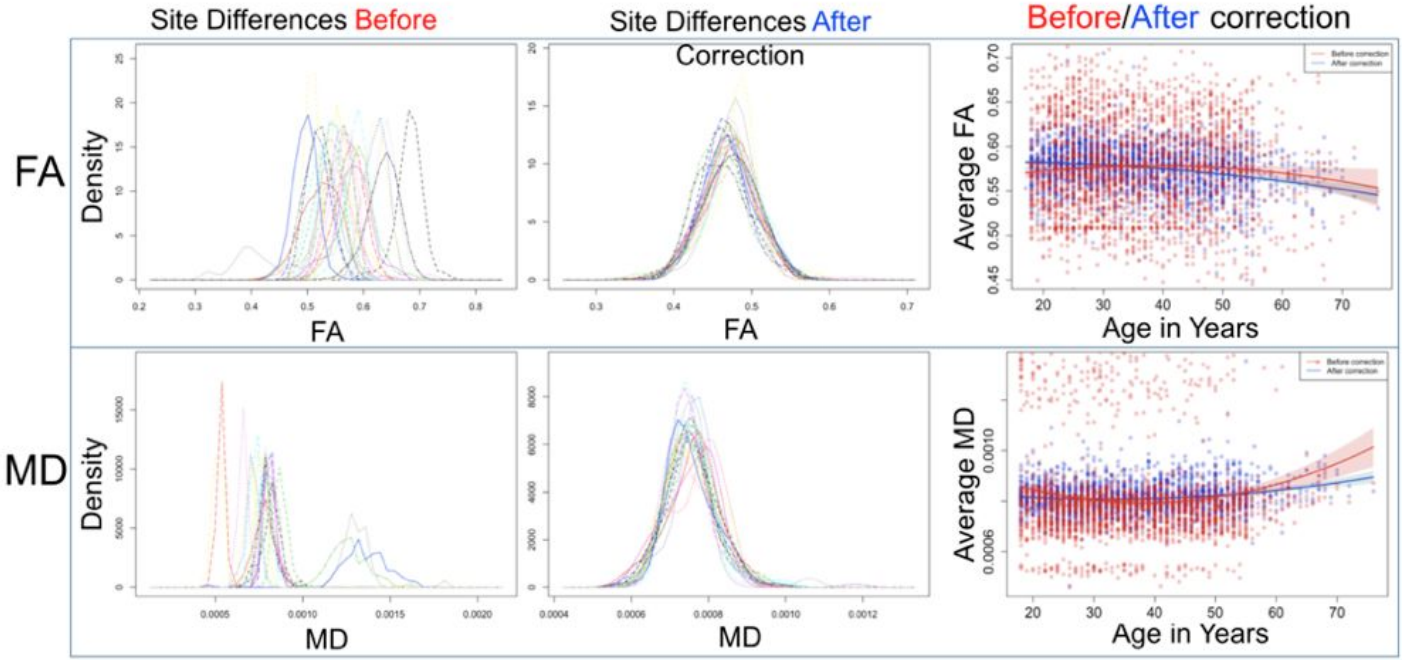
dMRI protocols with higher SNR (e.g., more diffusion gradients; S127) yield better group differentiation, as expected



Zavaliangos-Petropulu A et al., Frontiers Neuroinform 2019
https://www.ncbi.nlm.nih.gov/pubmed/30837858

3. Use ComBat (Fortin 2017) to adjust the data histograms before pooling across sites/scanners - Hatton 2020 (ENIGMA-Epilepsy study)

Harmonized DTI data from 24 sites to correct for scanner-specific variations in FA/MD:



Fortin JP et al., NeuroImage 2017 - https://www.ncbi.nlm.nih.gov/pubmed/28826946 Hatton SE et al., for the ENIGMA Epilepsy Group, submitted, 2020

4. Use Variational Autoencoder (site free data+site code) with Generative Adversarial Networks that make it hard to tell which site the data came from (Moyer et al., *Magn Res Med* 2020)

Scanner Invariant Representations for Diffusion MRI Harmonization

Daniel Moyer[1,2], Greg Ver Steeg[2], Chantal M. W. Tax[3], and Paul M. Thompson[1]

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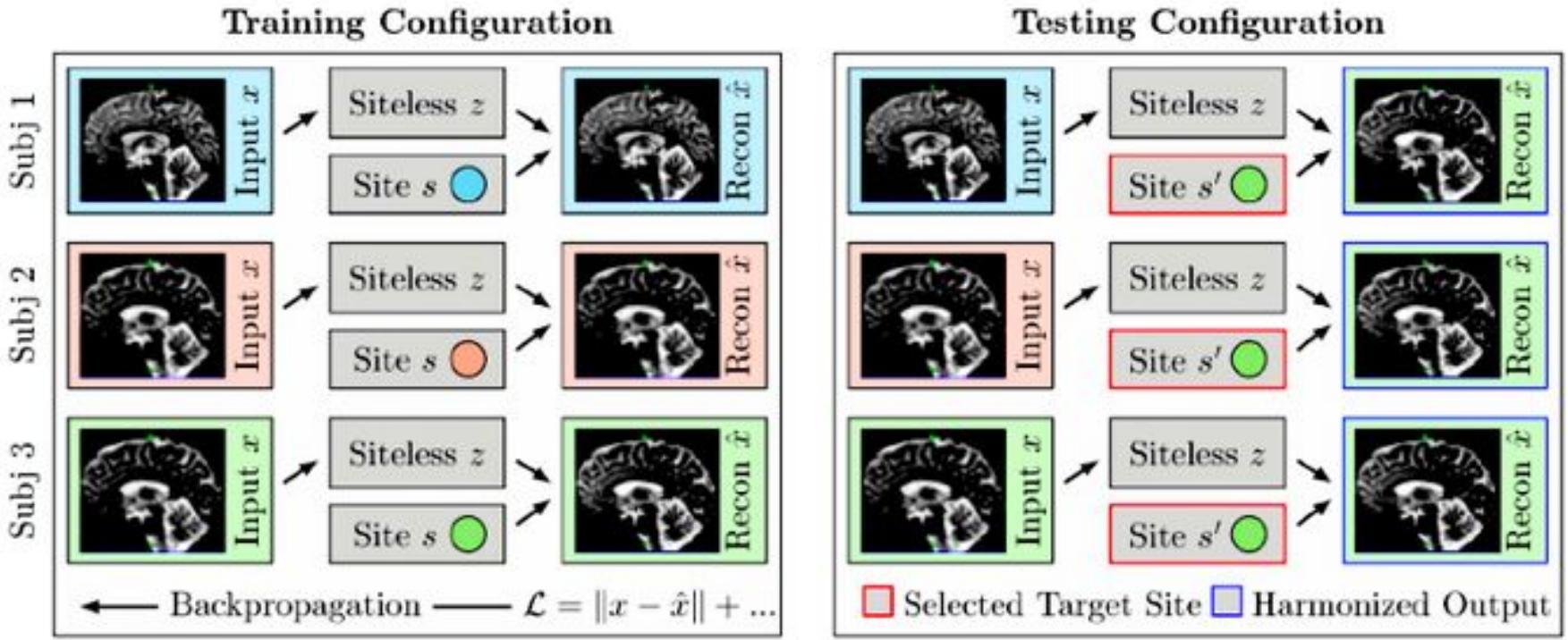
[2] Information Sciences Institute, Marina del Rey, CA, 90292 USA
[3] CUBRIC, School of Psychology, Cardiff University, Cardiff, United Kingdom
moyerd@usc.edu

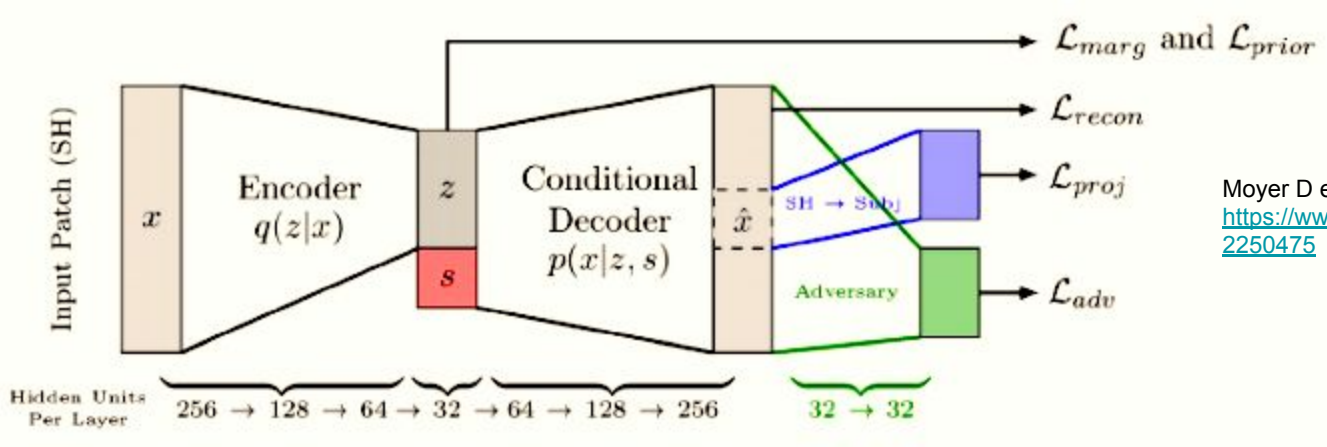
How would your brain look if you'd been scanned on a different scanner?

Moyer D et al., 2020, Magn Res Med https://www.ncbi.nlm.nih.gov/pubmed/32250475

Use **Deep Learning** and **Adversarial Networks** to **Inter-Convert Data Across Scanners**
Variational Autoencoder maps the data into a scanner invariant latent space, plus a site code
On **training**, the site identification loss and reconstruction error are jointly optimized
On **testing**, a site's data can be converted using a common site code z'



Moyer D et al., 2020, Magn Res Med https://www.ncbi.nlm.nih.gov/pubmed/32250475



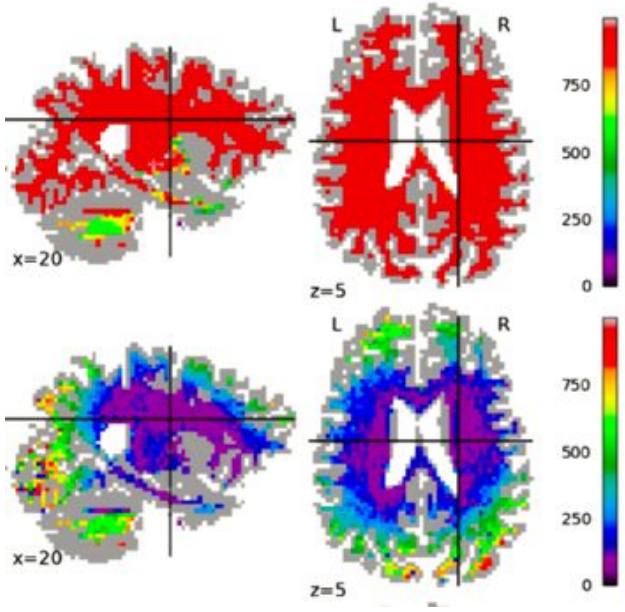
Moyer D et al., 2020, Magn Res Med
https://www.ncbi.nlm.nih.gov/pubmed/32250475

2.1 | Scanner invariant variational auto-encoders

We wish to learn a mapping q from data x (associated with scanner s) to some latent space z such that $z \perp s$, yet also where z is maximally relevant to x. We start by relaxing $z \perp s$ to $I(z, s)$, and then bounding $I(z, s)$ (detailed demonstration in Appendix A):

$$I(z,s) \leq \underbrace{-\mathbb{E}_{x,s,z\sim q}[\log p(x|z,s)]}_{\text{Conditional Reconstruction}} + \underbrace{\mathbb{E}_x[\, KL[\, q(z|x) \,\|\, q(z)\,]\,]}_{\text{Compression}} \underbrace{- H(x|s)}_{\text{Const}} \quad (1)$$

where $q(z)$ is the empirical marginal distribution of z under $q(z|x)$, the specified encoding which we control, and $p(x|z, s)$ is a variational approximation to the conditional likelihood of x given z and s again under $q(z|x)$. Here, KL denotes the Kullback-Leibler divergence and H denotes Shannon entropy.



Conclusions

In multi-site studies, diffusion MRI **can be pooled across multiple protocols and scanners** (GE, Siemens, Philips).

Harmonization refers to the mathematical adjustment of data from each scanner before it is combined. 4 approaches, in order of complexity

1. **Meta-analyze effects from each site (early ENIGMA; Kelly 2018)**
2. **Fit the site/scanner effect using random effects regression (needs centralized data; Zavaliangos-Petropulu 2019; Boedhoe 2019 compares #1-#2)**
3. **Use ComBat to adjust data histograms before pooling across sites/scanners (Fortin 2017; Hatton 2020 for DTI; Radua 2020 compares #1-#3 for morphometry)**
4. **Use Variational Autoencoder (site free data+site code) with Generative Adversarial Networks (Moyer et al., *Magn Res Med* 2020) - testing in progress**

Acknowledgments

ENIGMA DTI - Neda Jahanshad, Peter Kochunov, Sinead Kelly, Gary Donohoe, Sean Hatton et al.

ADNI DTI analysis - Talia Nir, Artemis Zavaliangos-Petropulu, Sophia Thomopoulos, Neda Jahanshad

ADNI DTI Core - Robert Reid, Bret Borowski, Matt Bernstein, Cliff Jack

ENIGMA ComBat study - Joaquim Radua et al.; algorithm by Fortin et al.

VAE/GAN method - Dan Moyer, Greg ver Steeg, Chantal Tax, Paul Thompson (MRM 2020)

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