

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.

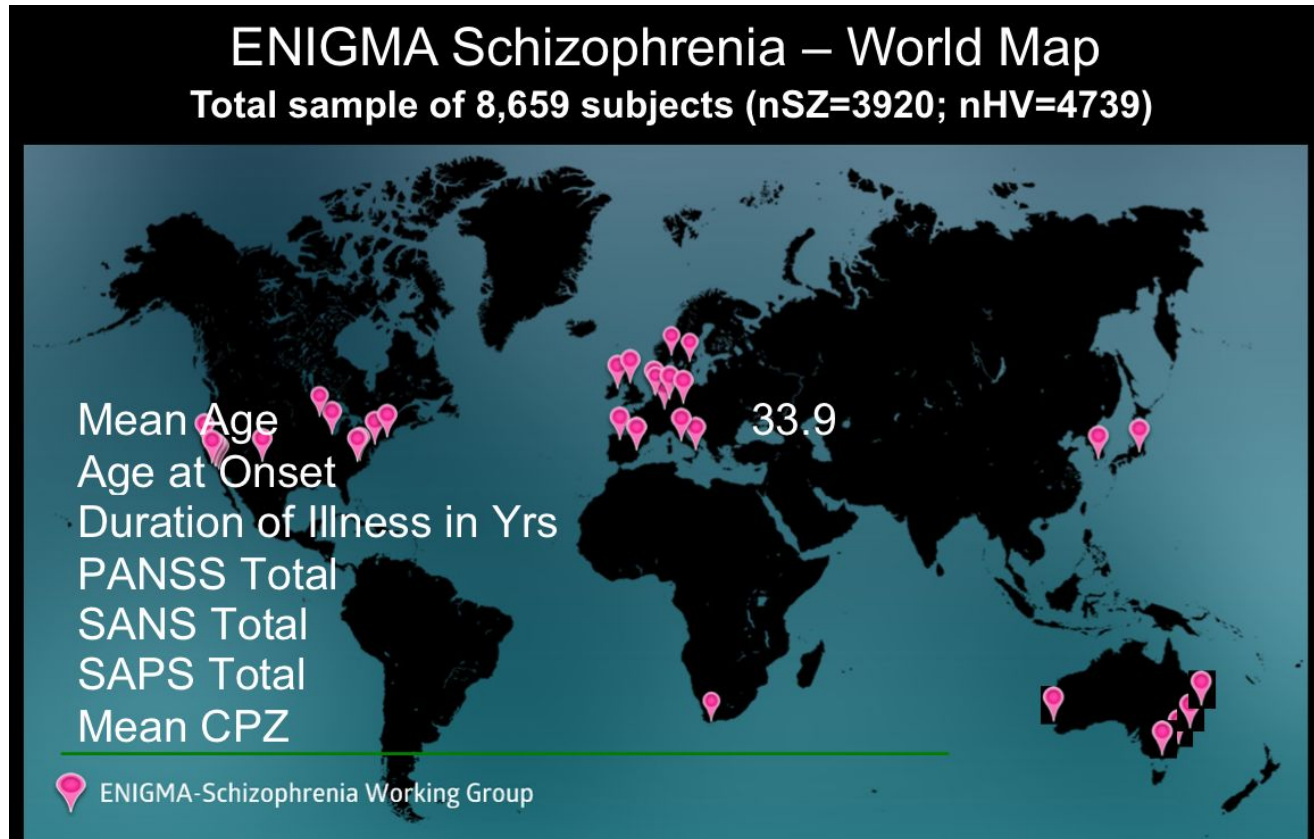
In multi-site studies, diffusion MRI can be collected with **multiple protocols and scanners** (GE, Siemens, Philips).

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)

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



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:

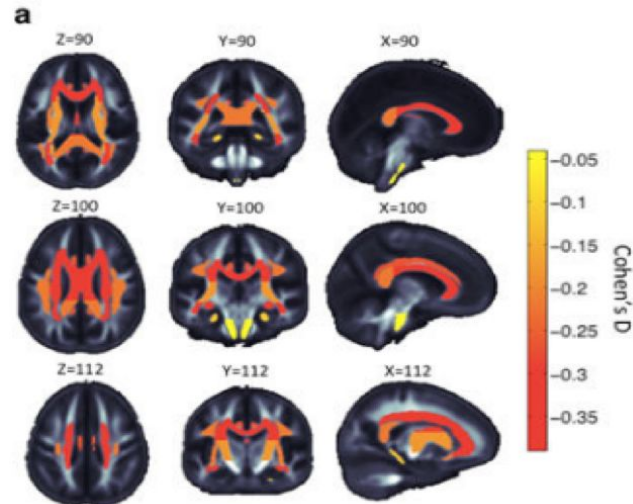
<https://www.ncbi.nlm.nih.gov/pubmed/31358905>

(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 Croyley, 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

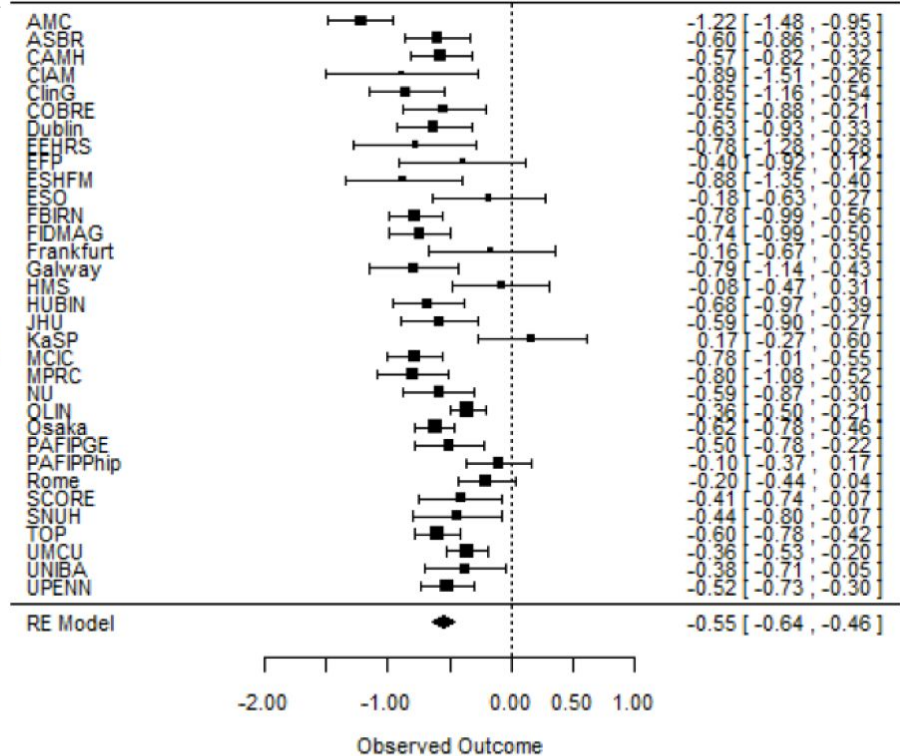
Largely consistent effects

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

**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

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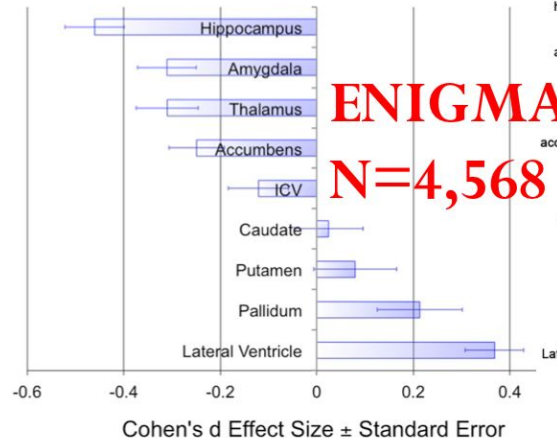
Molecular Psychiatry (2015), 1–7
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www.nature.com/mp

ORIGINAL ARTICLE

Subcortical brain volume abnormalities in 2828 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium

TGM van Erp^{1,2,3}, DP Hibar^{2,3,9}, JM Rasmussen^{1,4}, DC Glahn^{1,4}, GD Pearson^{1,4}, OA Andreassen⁵, I Agartz^{2,6,7}, LT Westlye^{6,8}, UK Haukvik¹⁰, AM Dale¹¹, I Melle¹², CB Hartberg¹³, D Gruber¹⁴, B Kraemer¹⁵, D Zilles^{16,17}, G Donohoe^{18,19}, S Kelly¹⁹, C McDonald²⁰, DW Morris²¹, DM Cannon²², A Corvin²³, MWJ Macchiaren²⁴, L Koenders²⁵, L de Haan²⁶, DJ Veltrous²⁷, TD Satterthwaite²⁸, DJ Walhovd²⁹, RE Gur¹⁹, SG Potkin³⁰, DH Mathalon^{31,32}, BA Mueller³³, A Preda³⁴, F Maciardi³⁵, S Ehrlich^{32,33,34}, E Walton³², J Haas³², VD Calhoun^{32,35}, HJ Bockholt^{32,36}, SR Sponheim³⁷, JM Shoemaker³⁸, NEM van Haren³⁹, HEH Pol⁴⁰, RA Ophof^{41,42}, RS Kahn⁴³, R Roiz-Santiañez⁴⁴, B Crespo-Facorro^{45,46}, L Wang^{46,47}, YD Alpert⁴⁸, EC Jensen⁴⁹, R Diminich⁵⁰, C Bui⁵¹, HC Whalley⁵², AM McIntosh⁵³, SM Lawrie⁵⁴, R Hashimoto⁵⁵, PM Thompson⁵⁶ and JA Turner⁵⁷ for the ENIGMA Schizophrenia Working Group

The profile of brain structural abnormalities in schizophrenia is still not fully understood, despite decades of research using brain scans. To validate a prospective meta-analysis approach to analyzing multicenter neuroimaging data, we analyzed brain MRI scans from 2028 schizophrenia patients and 2540 healthy controls, assessed with standardized methods at 15 centers worldwide. We identified subcortical brain volumes that differentiated patients from controls, and ranked them according to their effect sizes. Compared with healthy controls, patients with schizophrenia had smaller hippocampus (Cohen's $d = -0.46$), amygdala ($d = -0.31$), thalamus ($d = -0.31$), accumbens ($d = -0.25$) and intracranial volumes ($d = -0.12$), as well as larger pallidum ($d = 0.21$) and lateral ventricle volumes ($d = 0.37$). Putamen and pallidum volume augmentations were positively associated with duration of illness and hippocampal deficits scaled with the proportion of unmedicated patients. Worldwide cooperative analyses of brain imaging data support a profile of subcortical abnormalities in schizophrenia, which is consistent with that based on traditional meta-analytic approaches. This first ENIGMA Schizophrenia Working Group study validates that collaborative data analyses can readily be used



OPEN

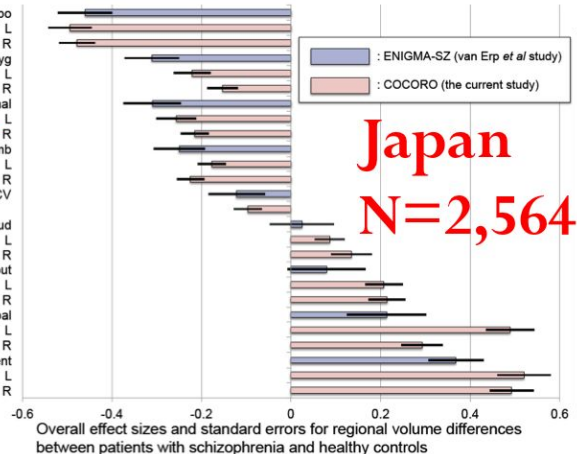
Molecular Psychiatry (2016), 1–7
© 2016 Macmillan Publishers Limited All rights reserved 1359-4184/16
www.nature.com/mp

ORIGINAL ARTICLE

Abnormal asymmetries in subcortical brain volume in schizophrenia

N Okada¹, M Fukunaga², F Yamashita³, D Koshiyama¹, H Yamamoto⁴, K Ono⁵, Y Yasuda⁶, M Fujimoto⁵, Y Watanabe⁵, N Yahata^{1,6}, K Nemoto⁷, DP Hibar⁸, TGM van Erp⁹, H Fujino¹⁰, M Isobe¹¹, S Isonuma¹², T Natsubori¹³, H Narita¹⁴, N Hashimoto¹⁵, J Miyata¹⁶, S Koike^{11,14}, T Takahashi¹³, H Yamase¹⁷, K Matsuo¹⁸, T Onitsuka¹², T Iidaka¹⁷, Y Kawasaki¹⁸, R Yoshimura¹⁹, Y Watanabe¹⁹, M Suzuki¹⁹, JA Turner^{20,21}, M Takeda²², PM Thompson²³, N Ozaki²⁴, K Kasai²⁵, R Hashimoto^{24,25}, COCORO

Subcortical structures, which include the basal ganglia and parts of the limbic system, have key roles in learning, motor control and emotion, but also contribute to higher-order executive functions. Prior studies have reported volumetric alterations in subcortical regions in schizophrenia. Reported results have sometimes been heterogeneous, and few large-scale investigations have been conducted. Moreover, few large-scale studies have assessed asymmetries of subcortical volumes in schizophrenia. Here, as a work completely independent of a study performed by the ENIGMA consortium, we conducted a large-scale multisite study of subcortical volumetric differences between patients with schizophrenia and controls. We also explored the laterality of subcortical regions to identify characteristic similarities and differences between them. T1-weighted images from 1680 healthy individuals and 884 patients with schizophrenia, obtained with 15 imaging protocols at 11 sites, were processed with FreeSurfer. Group differences were calculated for each protocol and meta-analyzed. Compared with controls, patients with schizophrenia demonstrated smaller bilateral hippocampus, amygdala, thalamus and accumbens volumes, as well as intracranial volume, but larger bilateral caudate, putamen, pallidum and lateral ventricle volumes. We replicated the rank order of effect sizes for subcortical volumetric changes in schizophrenia reported by the ENIGMA consortium. Further, we revealed leftward asymmetry for thalamus, lateral ventricle, caudate and putamen volumes; and rightward asymmetry for amygdala and hippocampal volumes in both controls and patients with schizophrenia. Also, we demonstrated a schizophrenia-specific leftward asymmetry for pallidum volume. These findings suggest the possibility of aberrant laterality in neural pathways and connectivity patterns related to the pallidum in schizophrenia.



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>

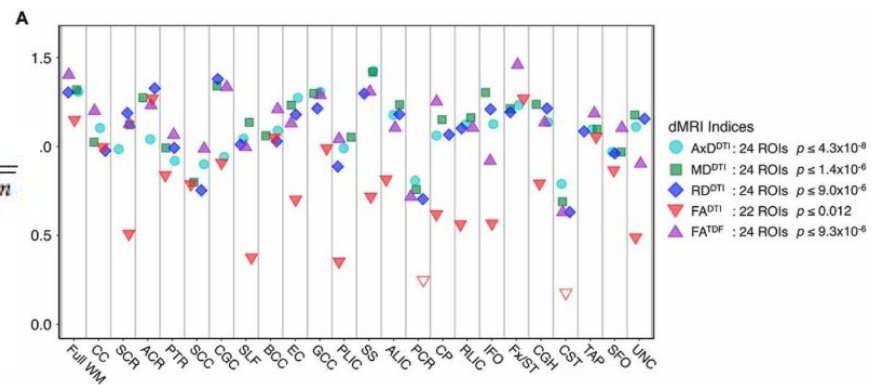
Diffusion MRI Indices and Their Relation to Cognitive Impairment in Brain Aging: The Updated Multi-protocol Approach in ADNI3

 Artemis Zavaliangos-Petropulu^{1†},  Talia M. Nir^{1†},  Sophia I. Thomopoulos¹,  Robert I. Reid²,  Matt A. Bernstein³,  Bret Borowski³,  Clifford R. Jack Jr.³,  Michael W. Weiner⁴,  Neda Jahanshad¹,  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 | 32 $b = 1,000$ s/mm ² | 36 | 6:54 | 19 |
| | P54 | Philips | Basic R5 | 3 $b = 2$ s/mm ² | 48 $b = 1,000$ s/mm ² | 54 | 8:05 | – |
| | | | | 1 $b = 0$ s/mm ² | | | | |
| | | | | 5 $b = 2$ s/mm ² | | | | |
| | 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 |

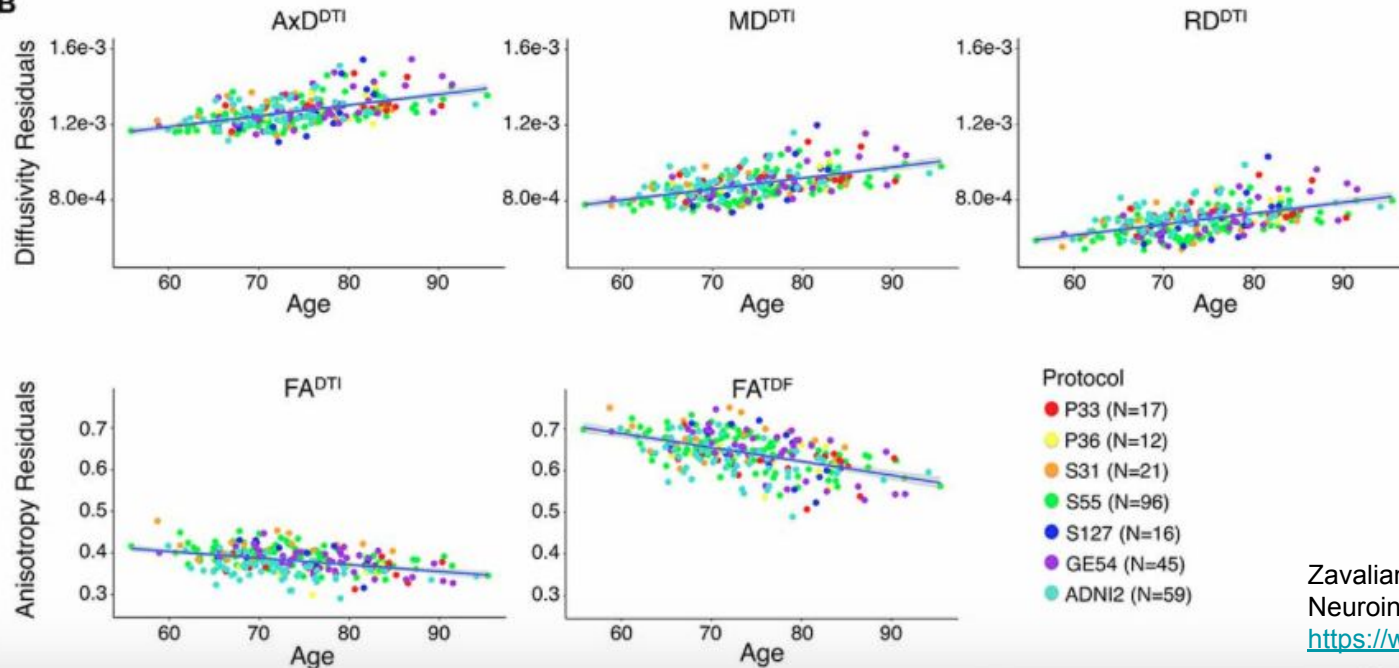
2. Fit the site/scanner effects using random effects regression (needs centralized data)

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



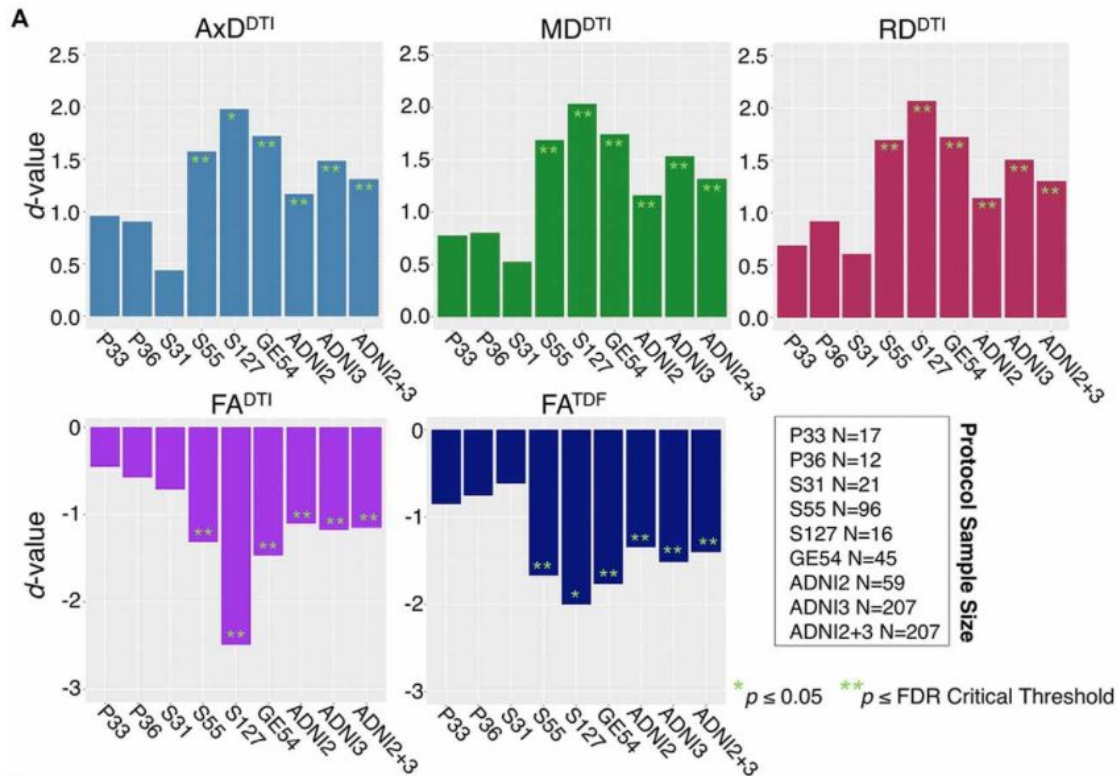
For each diffusion-weighted MRI (dMRI) index, the absolute values of effect sizes (d -value) are plotted for regional white matter (WM) microstructural associations with age when all ADNI3 dMRI data are pooled, adjusting for any site or protocol effects.

B



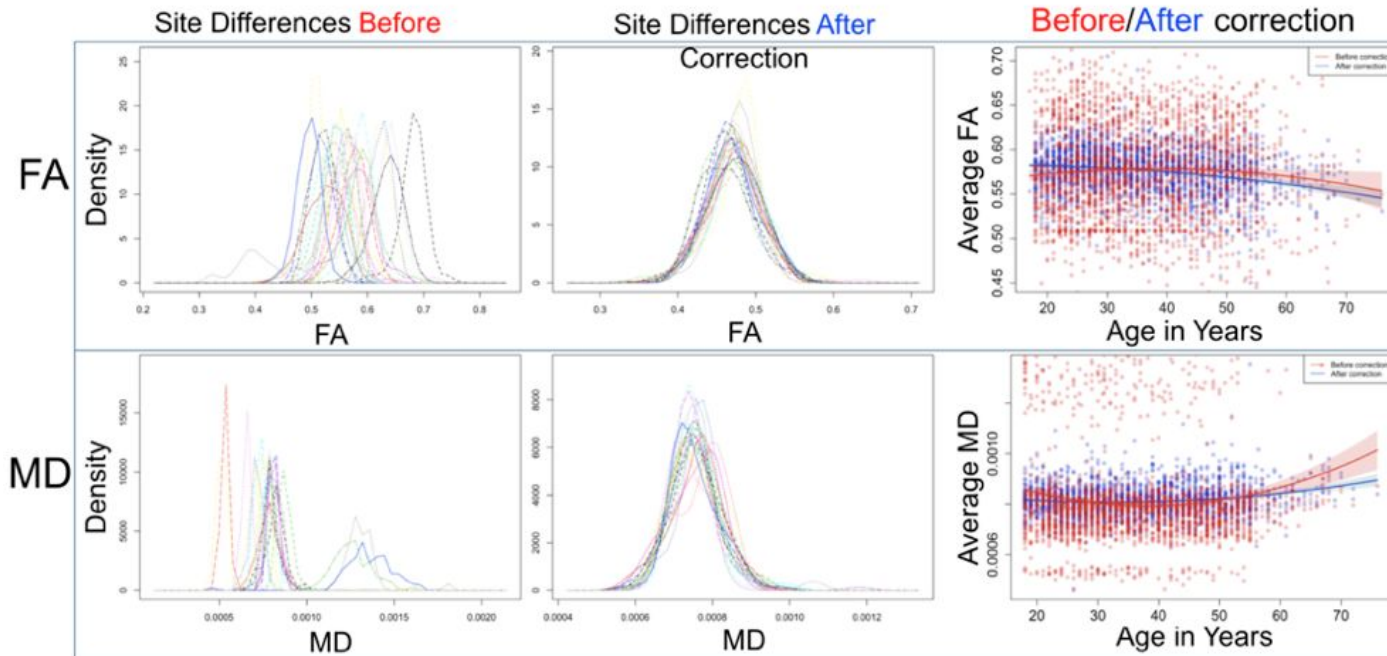
2. Fit the site/scanner effects using **random effects regression** (needs centralized data)

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



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:



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 Steeg², Chantal M. W. Tax³, and Paul M. Thompson¹

¹ University of Southern California, Los Angeles, CA, 90007 USA

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?

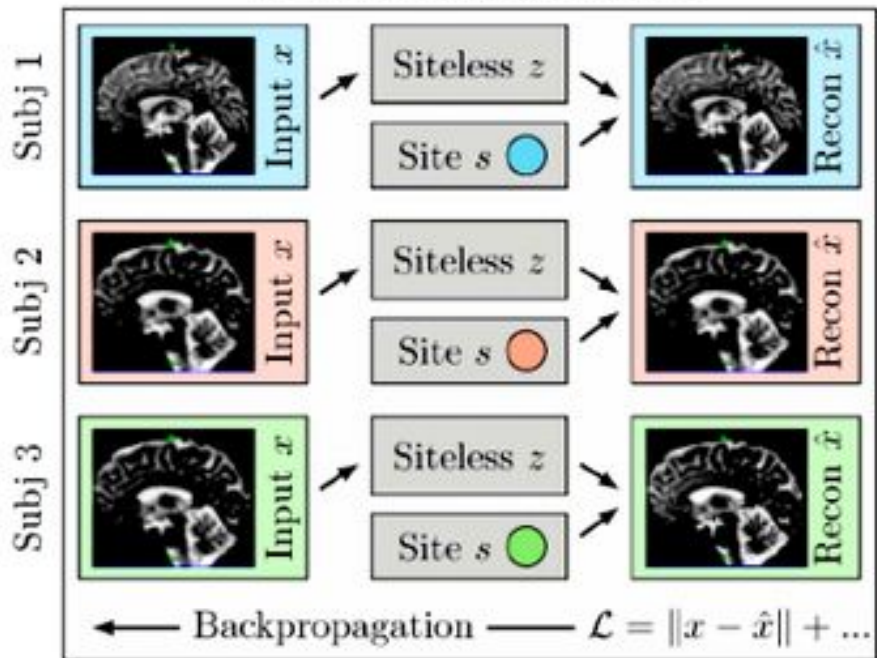
Use Deep Learning and Adversarial Networks to Inter-Convert Data Across Scanners

Variational Autoencoder maps the data into a scanner invariant latent space, plus a site code

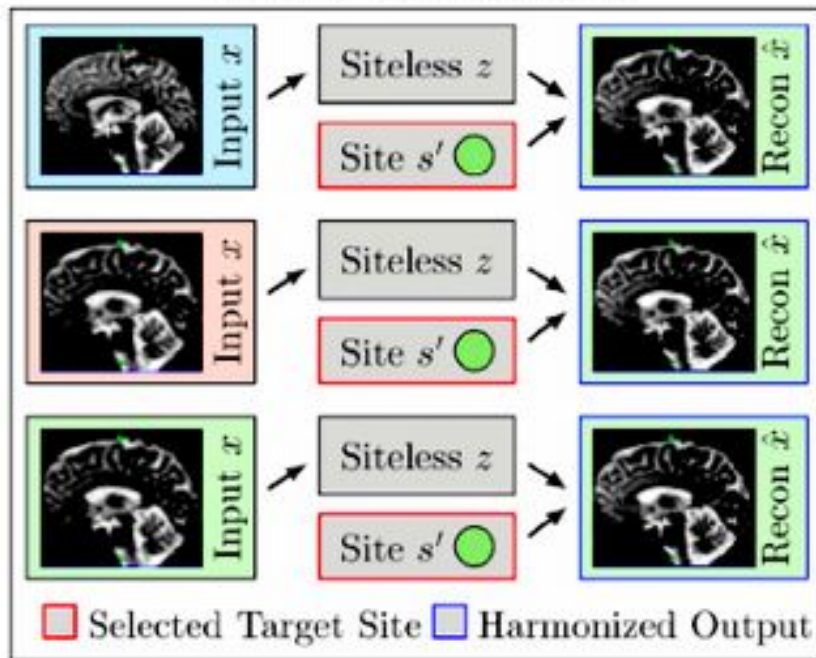
On **training**, the site identification loss and reconstruction error are jointly optimized

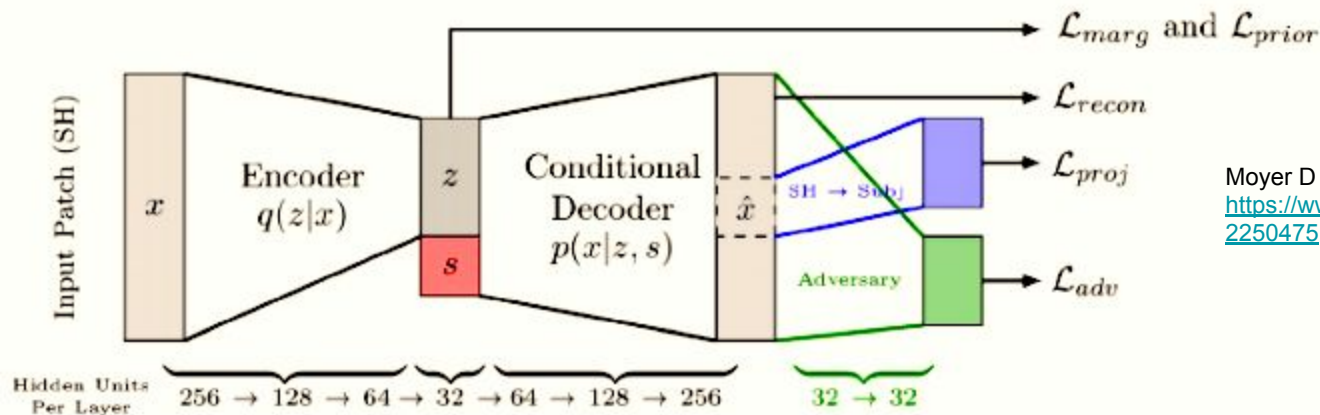
On **testing**, a site's data can be converted using a common site code z'

Training Configuration



Testing Configuration





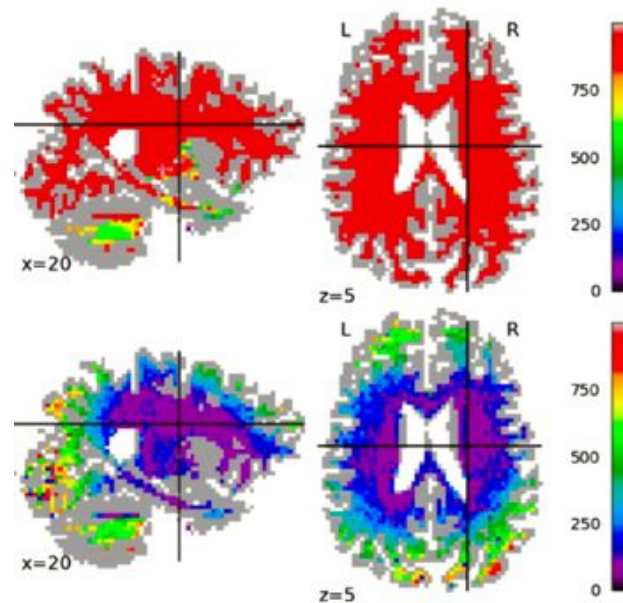
Moyer D et al., 2020, Magn Res Med
<https://www.ncbi.nlm.nih.gov/pubmed/32250475>

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):

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

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)

NIH funding (mainly P41 NIBIB and ADNI)