Continuous Large-scale Neuroimaging Analyses

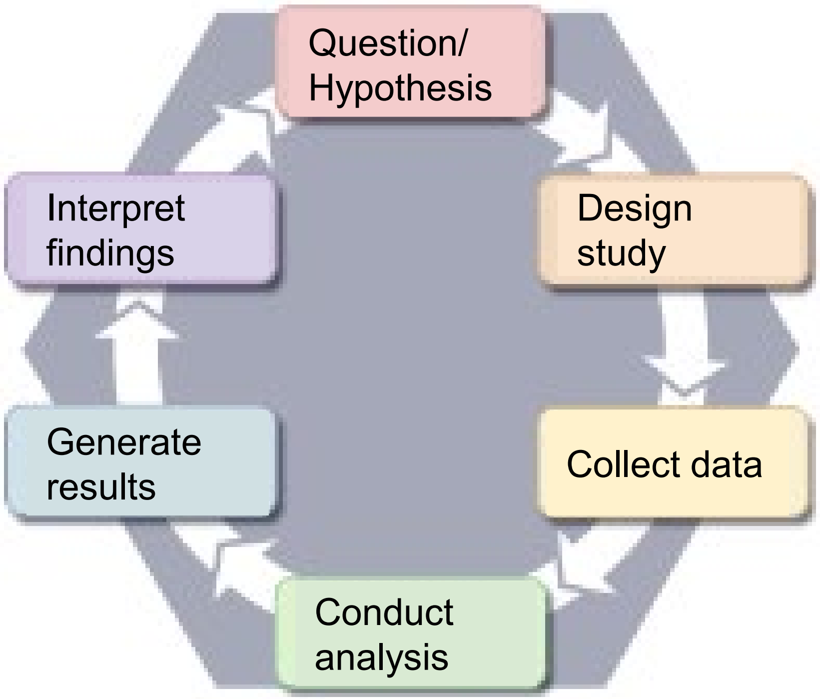
Neda Jahanshad, PhD
Assoc Prof Neurology & Biomedical Engineering
Director of USC **LoBeS**: Laboratory of Brain eScience
Assoc Director of the ENIGMA Consortium: http://enigma.usc.edu
Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine
Information Sciences Institute Affiliate
University of Southern California
neda.jahanshad@usc.edu

LoBeS

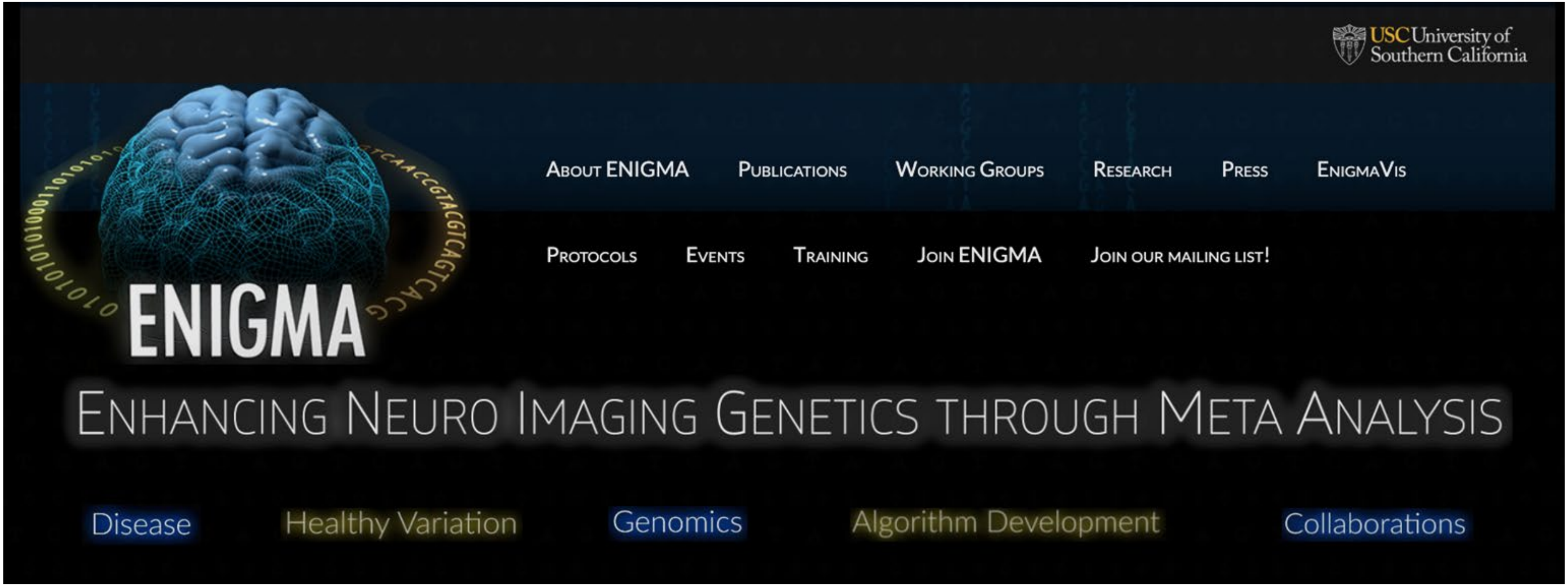
USC Mark and Mary Stevens
Neuroimaging and Informatics Institute

ENIGMA

Continuous Analysis in Research



Context: The ENIGMA Consortium



Background: **What** is ENIGMA? **Why** and **How** did it start?

A dynamic and collaborative investigator driven neuroimaging consortium that is organically expanding in scale and scope.

Motivation: Reproducibility, Reliability and Generalizability

Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Medicine | www.plosmedicine.org 0696 August 2005 | Volume 2 | Issue 8 | e124

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

NATURE REVIEWS | NEUROSCIENCE VOLUME 14 | MAY 2013 | 365

MOTHERBOARD
TECH BY VICE

Why Two Decades of Brain Research Could Be Seriously Flawed

A new paper casts doubt on 40,000 studies.

By Kate Lunau

Jul 5 2016, 10:10pm Share Tweet Snap

Nature: Brain Imaging Studies Are Most Likely False

Small MRI studies inflate effect sizes, leaving the brain imaging research literature cluttered with false positives.

By **Peter Simons** - March 21, 2022

4013 16

ENIGMA

Large-scale multi-site datasets

Biobanks and coordinated large scale studies are becoming more and more common. These are ***tremendous*** resources!

ADNI
Alzheimer's Disease Neuroimaging Initiative

Parkinson's Progression Markers Initiative
Play a Part in Parkinson's Research

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

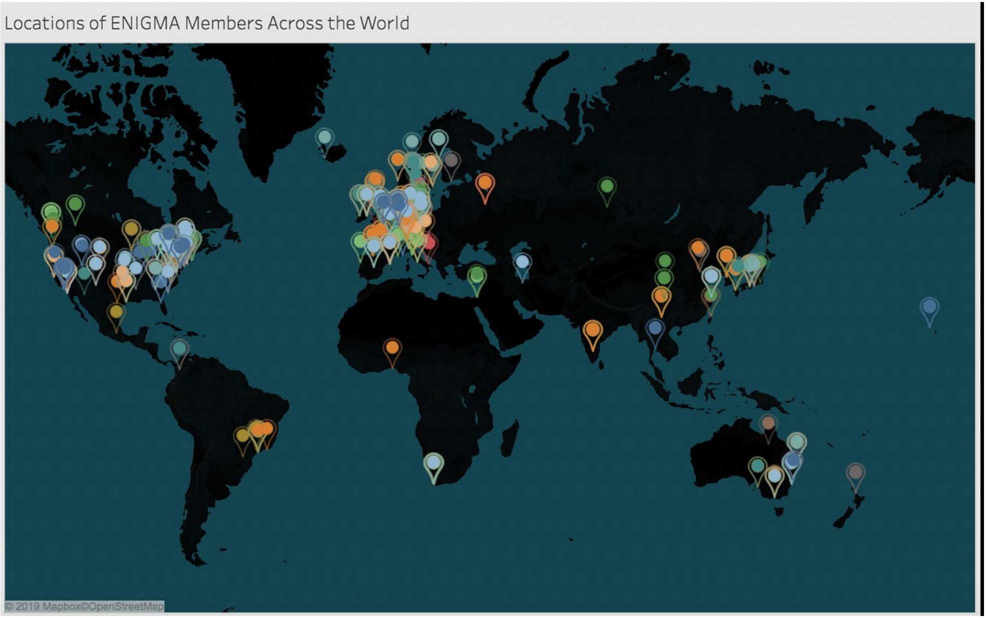
biobank uk

Human Connectome Project

And many others…

What about all the data from individual uncoordinated studies?

Many studies have been conducted that have collected neuroimaging data over the years, often having completed data collection years ago, and also completed the primary study. Many pilot studies that were on their own underpowered, data reuse!



Can still be used to help answer questions about the brain and its disorders

Study specific rare or uncommon conditions around the world

Help answer questions about reliability and generalizability

Can we work with data from private and public sources together?

Locations of ENIGMA Members Across the World

"Data" from individual sites can be combined with publicly available resources for larger scale initiatives, including numerous projects within (and across) ENIGMA.

Not all data can be openly shared, but collaboration is still possible

OpenNEURO

ADNI
Alzheimer's Disease Neuroimaging Initiative

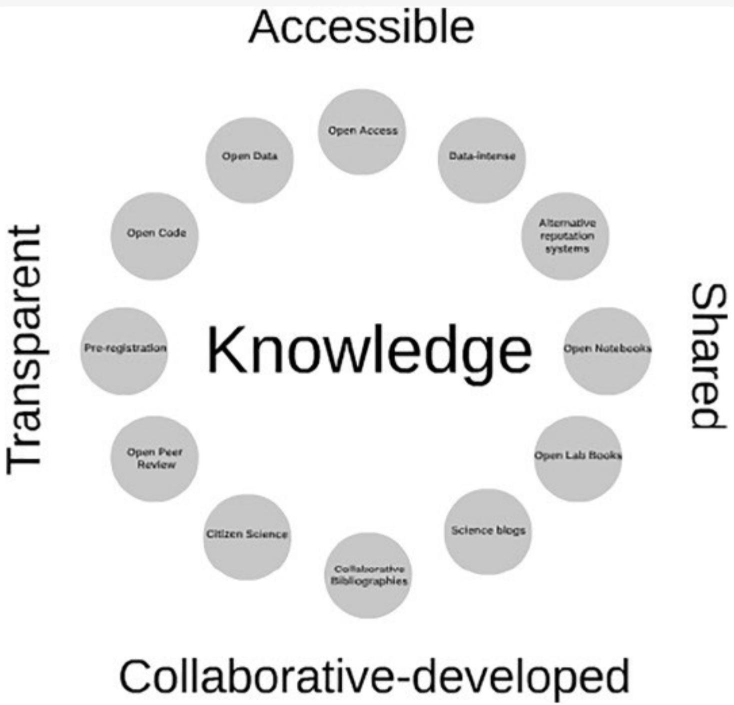
Parkinson's Progression Markers Initiative
Play a Part in Parkinson's Research

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

biobank uk

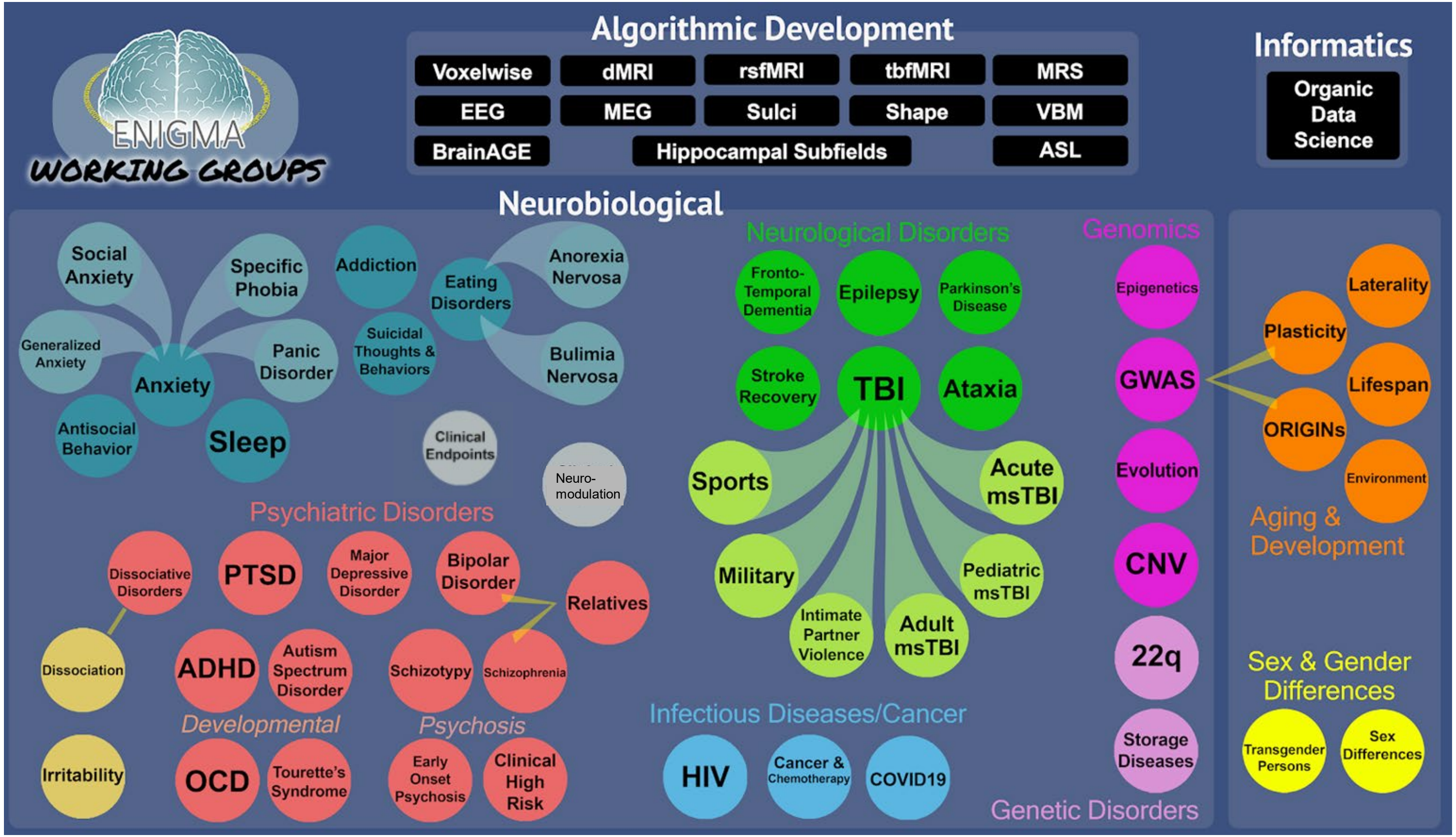
Not all data can be fully shared, but Open Science is still possible

Open Science is transparent and accessible knowledge that is shared and developed through collaborative networks



Vicente-Saez and Martinez-Fuentes,
Journal of Business Research 2018

ENIGMA Organization - Working Groups



ENIGMA contains numerous working groups (WG).

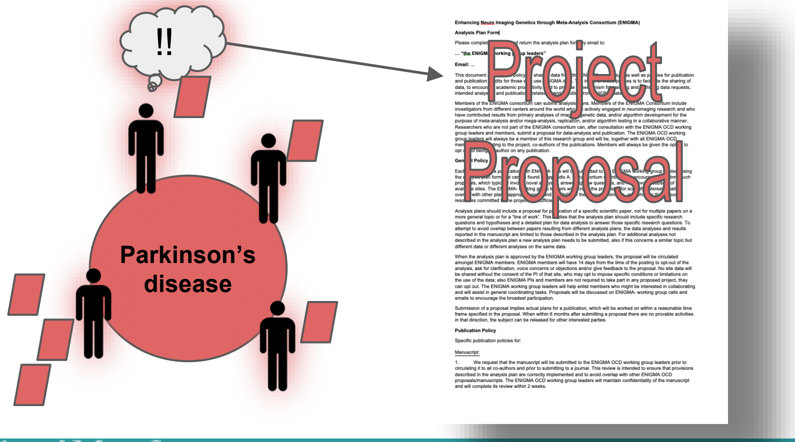
Computational: Imaging / data analytics / informatics

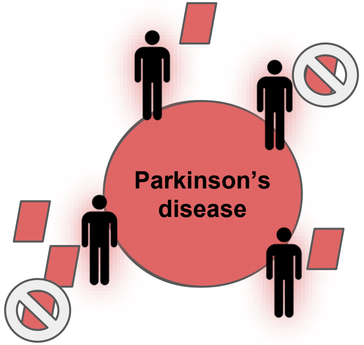
Neurobiological: Healthy variation / genetics / specific conditions or disorders / groups of disorders

ENIGMA Organization - Data (?)

ENIGMA is not a data repository. Data from participating sites / cohorts have a variety of different sharing and access rules.

However, any working group member can propose projects. Projects will need to be approved by WG chairs and presented to members, who can then opt in or out of the project. The project lead can then access data from groups that have opted-in through cohort-specific data access requirements. Projects are collaborative processes and updates and discussions occur on regular group-wide communications.





ENIGMA Organization - Working Groups Projects

Initial core WG projects aim to grow the network, establish collaborations, understand individual groups' strengths and limitations, and ask very straightforward and broad questions of the data from ALL participating sites/cohorts.

For example: assess the effect of the condition/trait/disease of interest on each of the available brain imaging traits (subcortical volumes, cortical thickness/area).

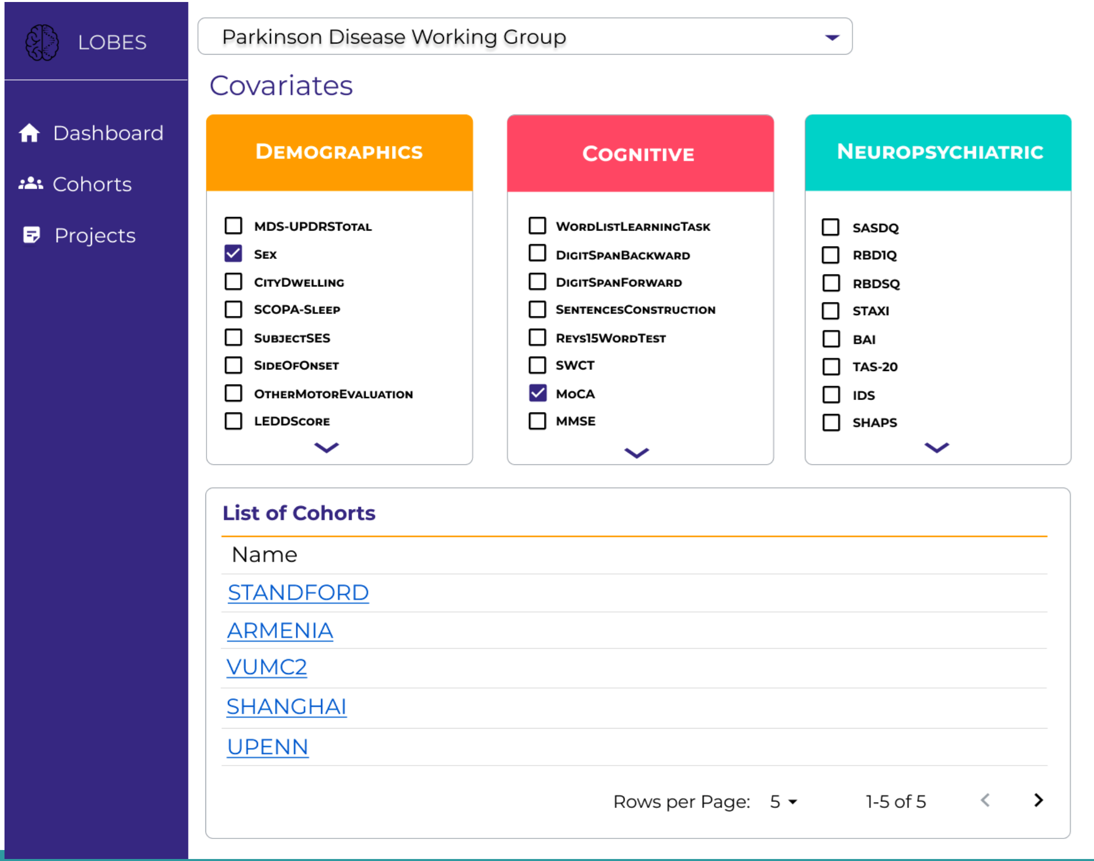
Any interested person (usually with relevant data/tool) can join at anytime.

There is no requirement to share individual participant level data to join ENIGMA.

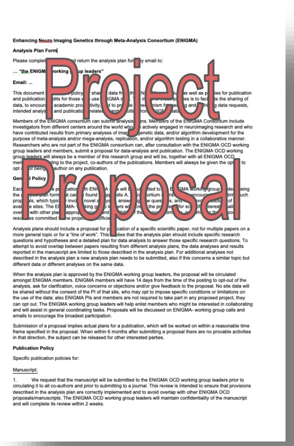
Analytic plans are discussed, agreed upon, documented and distributed. Developed and tested analysis protocols and workflows are distributed to individual cohorts representatives.

This initial project helps determine the scope and feasibility of future projects.

Data Structures can help formulate projects



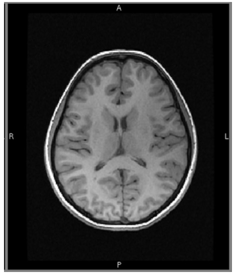
Project proposal can also act as a pre-registered analysis plan



How does it work?

Challenges of pooling diverse data

Imaging acquisitions are all different



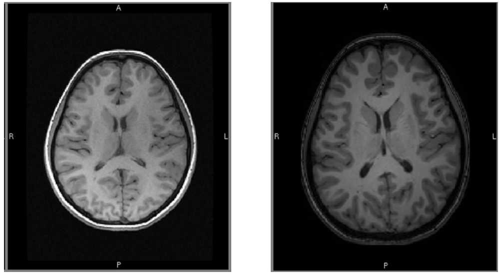
Study designs are often unique:

- Different populations
- Different inclusion/ exclusion criteria
- Different assessments/ batteries and instruments

ENIGMA

Challenges of pooling diverse data

Imaging acquisitions are different



that's ok!

Study designs are often unique:

- Different populations
- Different inclusion/ exclusion criteria
- Different assessments/ batteries and instruments

A biomarker has limited clinical utility if it is only evident when measured with instruments that are not widely available.

Motivation: Reproducibility, Reliability, and **Generalizability**

With large diverse, heterogeneous datasets, we can readily assess generalizability.

Will the findings hold in a different population? With a different method: acquisition / analytical ?

If not, why? Biological? Methodological?

Image Processing / Feature Extraction Workflows in ENIGMA

ENIGMA's general approach to **pooling diverse data** has largely revolved around analytical standardization.

Detailed and documented analytic plans are central to the workings of the consortium.

- Imaging metrics
- Clinical / biological metrics / covariates
- Quality assurance
- Statistical workflow
- Test / retest / evaluate

Feature Robustness, Detailed Documentation, Containerization

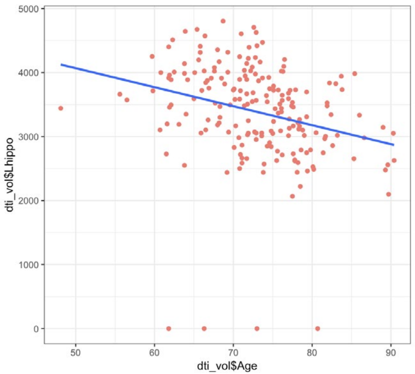
Imaging protocols

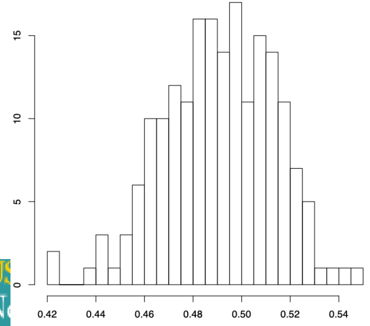
1) Does it work for multiple imaging acquisitions
2) Is it reliable across acquisitions? -- multiple test retest datasets
3) Is it straightforward to implement -- often build on existing commonly used tools
4) Are features biologically meaningful?

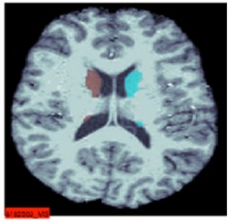
Analytical Harmonization: Quality Assurance

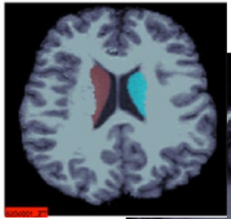
Specifying a single image processing workflow will help minimize methodological variability across multisite analyses. Even with containerization of workflows, some datasets may behave unexpectedly. Certain workflows may extract more accurate features for some datasets than others. Feasibility?

The documentation of quality assurance procedures is critical!

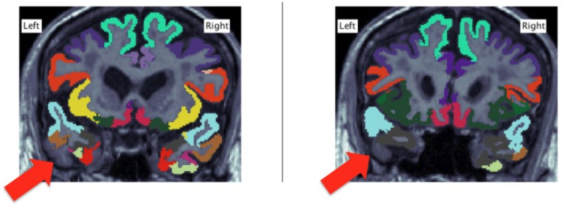








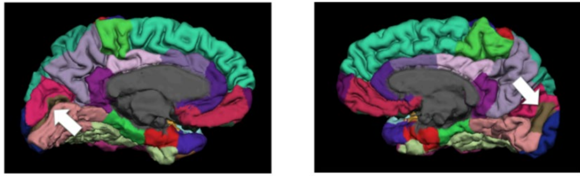
Internal QC: Moderate
Temporal Pole Underestimation



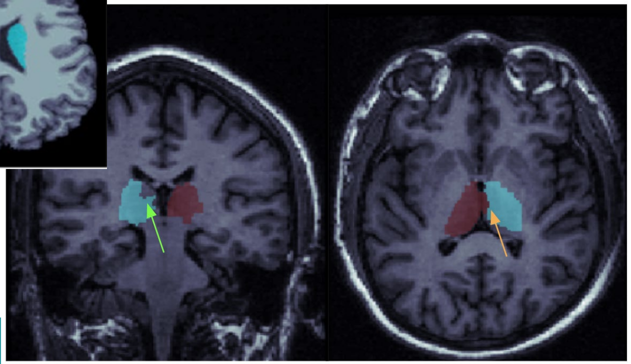
Pericalcarine Overestimations (<5% cases)

GOOD

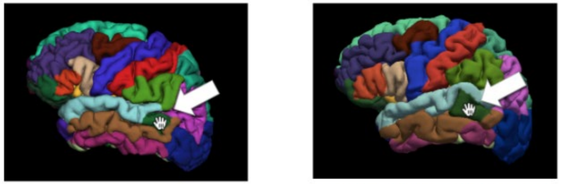
BAD



- Segmentation confined to calcarine sulcus
- Segmentation overestimates pericalcarine region



Bad examples BanksSTS
(List affected regions in QC sheet)



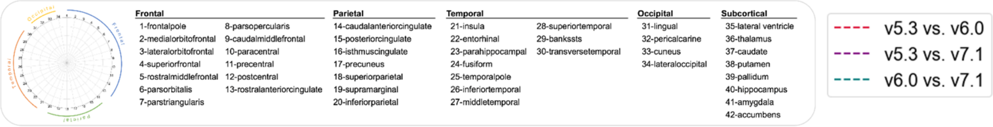
Fail BanksSTS + STG

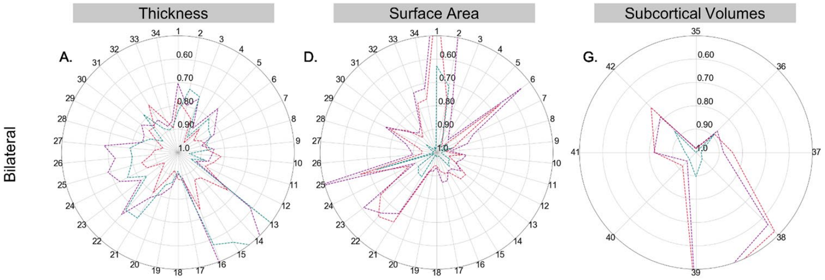
Fail BanksSTS + STG + MTG

New Updates? Test Reliability Reproducibility Compatibility

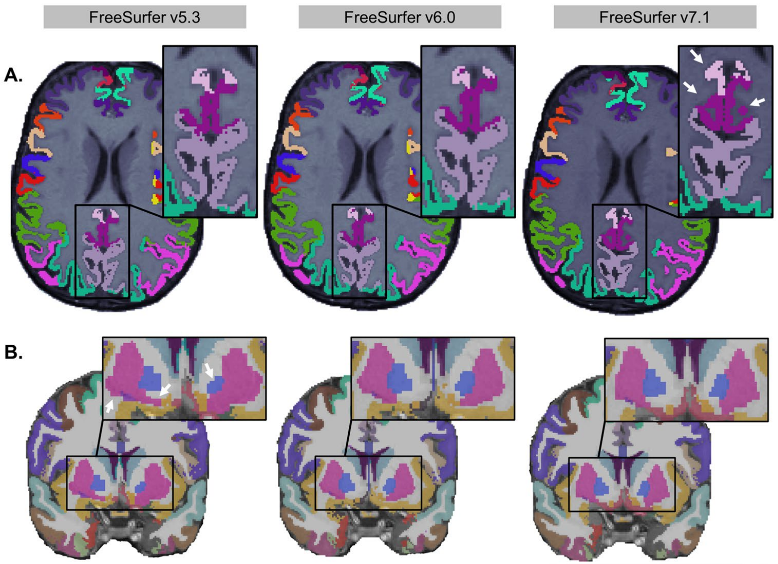
Numerous factors can contribute to differences in the derived imaging metrics (i.e., volume) even those from the same scan.

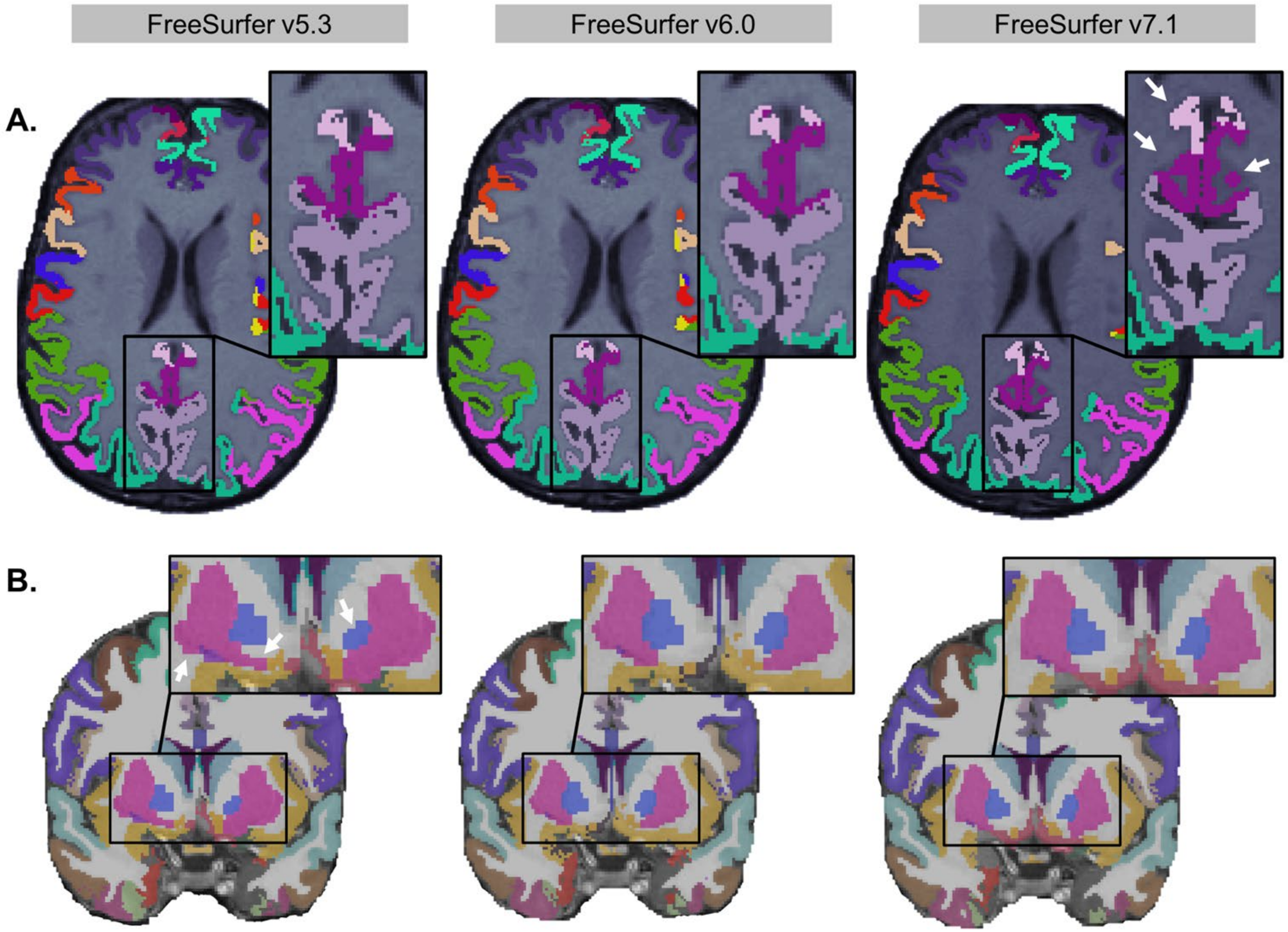
Can we quantify the degree to which these choices matter, and specifically for what features?





Elizabeth Haddad



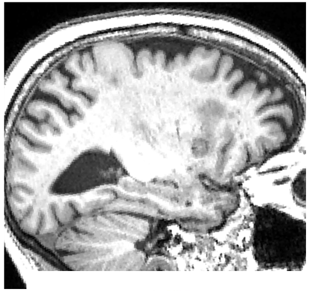


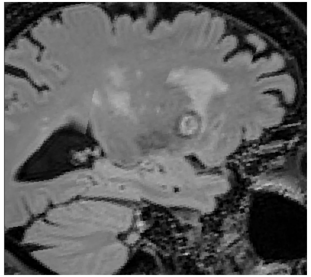
ENIGMA

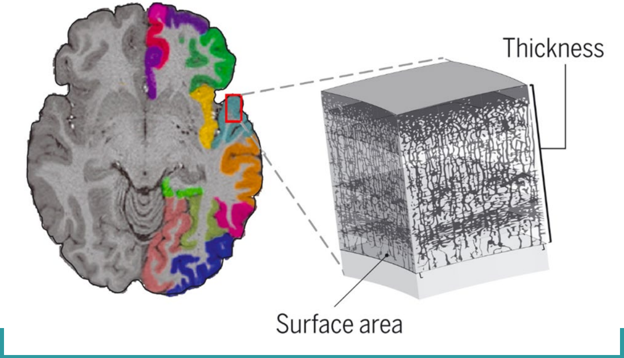
Different MRI modalities can reveal different structural and functional properties of biological tissue

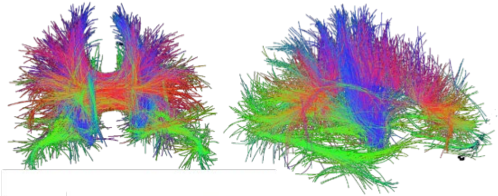
T2-FLAIR, susceptibility, diffusion, function - resting state, task

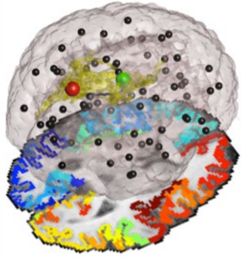
Continuous development of new protocols

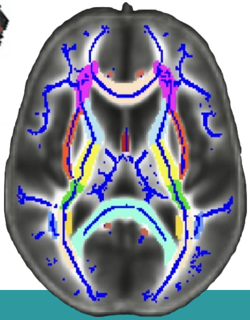


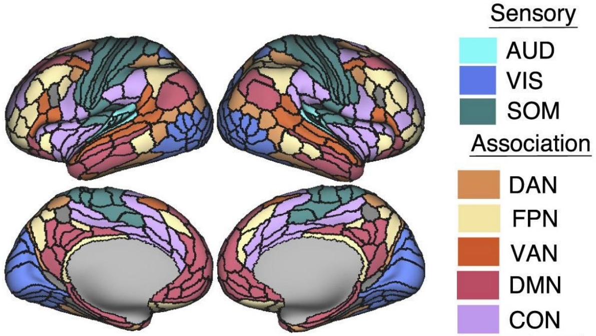


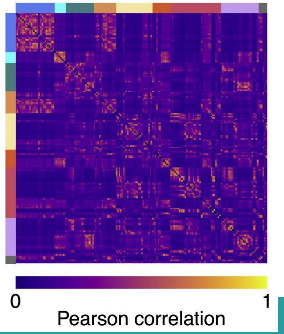












Continuously evolving through active multidisciplinary research

Standardization efforts are all accelerating the pace of multi-site, multi-study analyses

- Standardization of data formats (BIDS; Gorgolewski 2016) makes it more straightforward to develop new software that relies on particular framework / data
- Building on fMRIprep (Esteban 2019) → HALFPipe (Waller 2023)
- TBSS (Smith 2006) → ENIGMA-DTI (Jahanshad 2013)

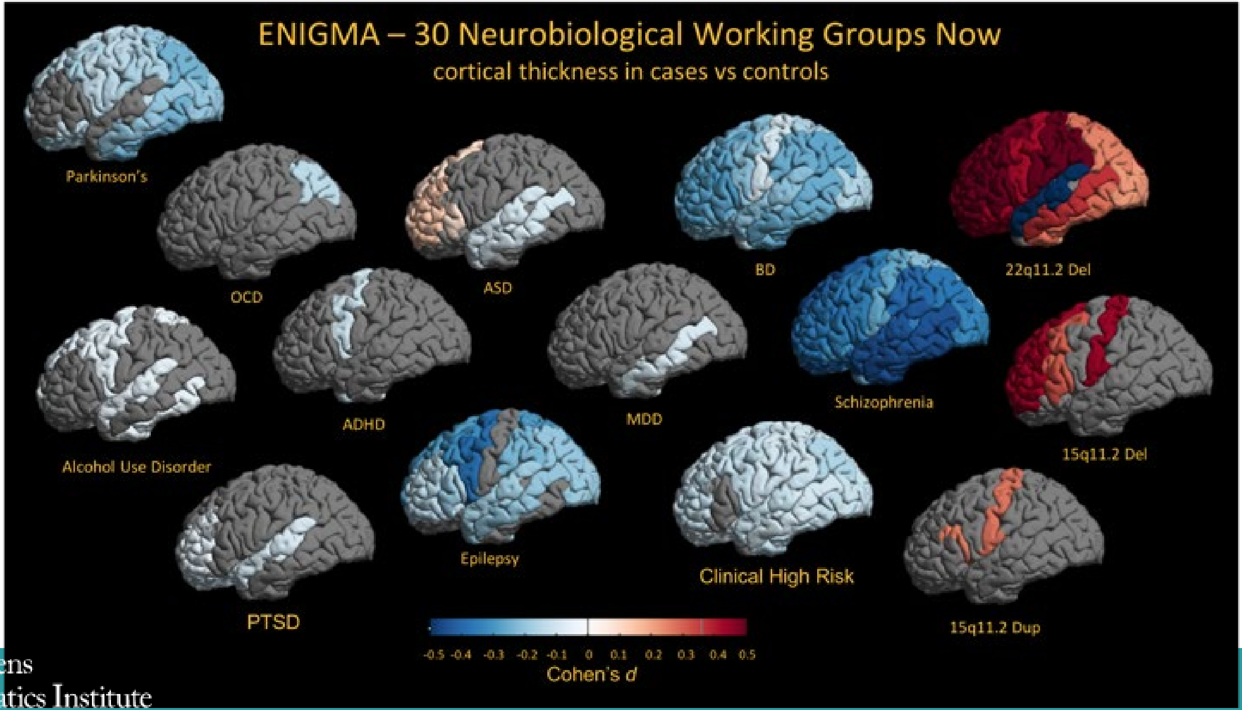
Projects and protocols routinely being re-evaluated and tested

- Automated volume extractions (old vs new versions) vs DL based extractions vs voxelwise analyses (VBM)

ENIGMA

Standardized Extractions, Detailed Documentation, Containerization

Documented protocols allow for projects across working groups to use the same image analysis approaches, and comparisons can be made across diagnostic groups

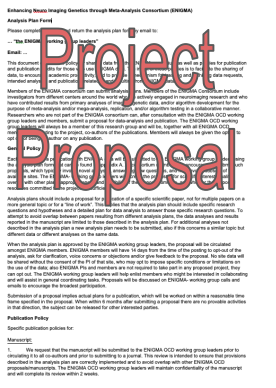


Meta and “Mega” analysis projects within ENIGMA

Meta-analysis projects require only summary statistics from each cohort. Overall effect sizes are a weighted average of individual cohorts (inverse variance).

Coordinated meta-analysis are different from literature based meta-analysis as they are not subject to publication bias and include results for all tested features for all cohorts

+ Easy to see heterogeneity/outliers in effects - site data/ analytics / processing effects
+ Distributed computation
- Analyses (generally*) limited to associations with common traits -- available across population (genetics), good distribution within each sample (most case/control)
- Can take lots of time / troubleshooting



Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium (ENIGMA)

Analysis Plan Form

Please complet[illegible] return the analysis plan for[illegible] email to:

… “the ENIGMA [illegible]orking [illegible]up leaders”

Email: …

This document [illegible] policy [illegible] shar[illegible] data fr[illegible] as well as p[illegible]ies for publication and publication [illegible]dits for those [illegible] use [illegible]IGMA d[illegible]. [illegible] is to faci[illegible]te the sharing of data, to encoura[illegible] academic pro[illegible]tivity, [illegible] to pr[illegible] data requests, intended analys[illegible] and publicatio[illegible] relate[illegible] data.

Members of the ENIGMA consortium can submit analysis [illegible]ns. Members of the ENIGMA Consortium include investigators from different centers around the world who [illegible] actively engaged in neuroimaging research and who have contributed results from primary analyses of imag[illegible] genetic data, and/or algorithm development for the purpose of meta-analysis and/or mega-analysis, replication, and/or algorithm testing in a collaborative manner. Researchers who are not part of the ENIGMA consortium can, after consultation with the ENIGMA OCD working group leaders and members, submit a proposal for data-analysis and publication. The ENIGMA OCD working group leaders will always be a member of this research group and will be, together with all ENIGMA OCD mem[illegible]ting to the project, co-authors of the publications. Members will always be given the op[illegible] to opt [illegible] of being [illegible] author on any publication.

Gen[illegible]l Policy

Eac[illegible] a p[illegible]cation [illegible]th ENI[illegible]A [illegible] will b[illegible] to [illegible] working group [illegible]der[illegible]sing the [illegible] form [illegible] found [illegible]pp[illegible]ndix A. [illegible] [illegible] [illegible]uch prop[illegible]ls, which typic[illegible] [illegible] novel [illegible] [illegible] ques[illegible] [illegible] avail[illegible] sites. The E[illegible]MA- [illegible] g[illegible] [illegible] the pr[illegible] for s[illegible] interest [illegible] over[illegible] with other pla[illegible] appro[illegible] [illegible] the [illegible] resou[illegible]s committed t[illegible] the project [illegible] sufficie[illegible]

Analysis plans should include a proposal for p[illegible]cation of a specific scientific paper, not for multiple papers on a more general topic or for a “line of work”. This [illegible]plies that the analysis plan should include specific research questions and hypotheses and a detailed plan for data analysis to answer those specific research questions. To attempt to avoid overlap between papers resulting from different analysis plans, the data analyses and results reported in the manuscript are limited to those described in the analysis plan. For additional analyses not described in the analysis plan a new analysis plan needs to be submitted, also if this concerns a similar topic but different data or different analyses on the same data.

When the analysis plan is approved by the ENIGMA working group leaders, the proposal will be circulated amongst ENIGMA members. ENIGMA members will have 14 days from the time of the posting to opt-out of the analysis, ask for clarification, voice concerns or objections and/or give feedback to the proposal. No site data will be shared without the consent of the PI of that site, who may opt to impose specific conditions or limitations on the use of the data; also ENIGMA PIs and members are not required to take part in any proposed project, they can opt out. The ENIGMA working group leaders will help enlist members who might be interested in collaborating and will assist in general coordinating tasks. Proposals will be discussed on ENIGMA- working group calls and emails to encourage the broadest participation.

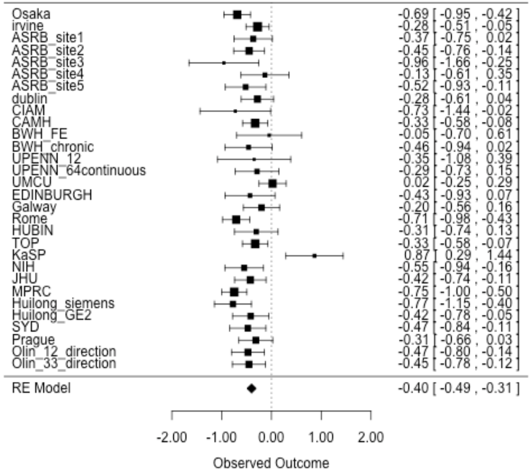
Submission of a proposal implies actual plans for a publication, which will be worked on within a reasonable time frame specified in the proposal. When within 6 months after submitting a proposal there are no provable activities in that direction, the subject can be released for other interested parties.

Publication Policy

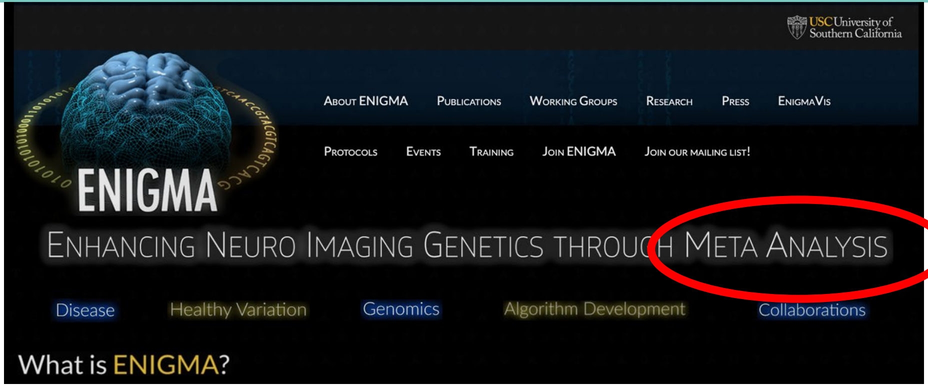
Specific publication policies for:

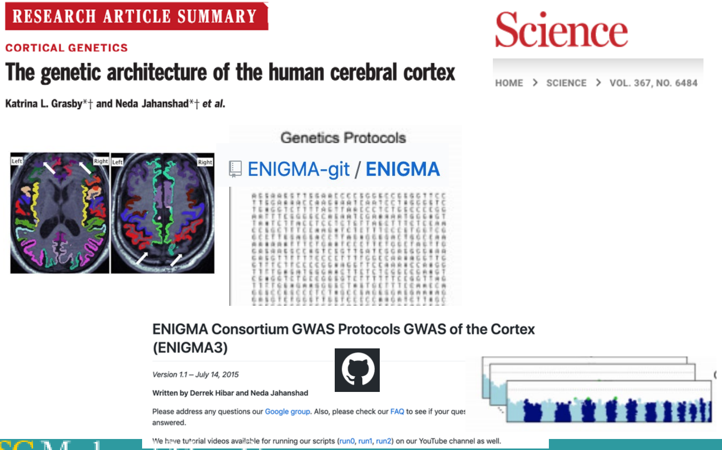
Manuscript:

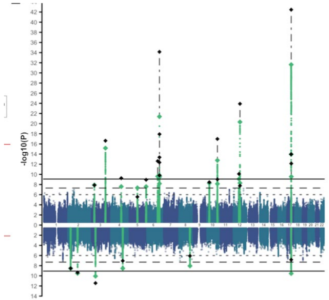
1. We request that the manuscript will be submitted to the ENIGMA OCD working group leaders prior to circulating it to all co-authors and prior to submitting to a journal. This review is intended to ensure that provisions described in the analysis plan are correctly implemented and to avoid overlap with other ENIGMA OCD proposals/manuscripts. The ENIGMA OCD working group leaders will maintain confidentiality of the manuscript and will complete its review within 2 weeks.

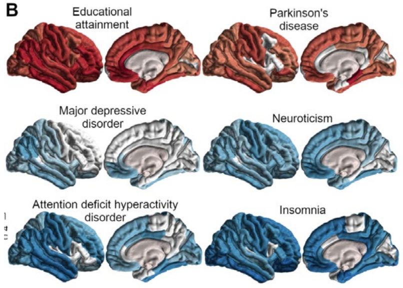


Genetic Projects within ENIGMA have all been Meta Analysis









Meta Analysis within Schizophrenia Working Group

Meta-Analysis > Biol Psychiatry. 2018 Nov 1;84(9):644-654.
doi: 10.1016/j.biopsych.2018.04.023. Epub 2018 May 14.

Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium

nature > molecular psychiatry > articles > article

Article | Open Access | Published: 09 December 2022

Brain ageing in schizophrenia: evidence from 26 international cohorts via the ENIGMA Schizophrenia consortium

> Mol Psychiatry. 2018 May;23(5):1261-1269. doi: 10.1038/mp.2017.170. Epub 2017 Oct 17.

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

nature > molecular psychiatry > original article > article

Open Access | Published: 02 June 2015

Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium

RESEARCH ARTICLE | MEDICAL SCIENCES |

Large-scale analysis of structural brain asymmetries in schizophrenia via the ENIGMA consortium

Dick Schijven, Merel C. Postema, Masaki Fukunaga, +145, and Clyde Francks Authors Info & Affiliations

Edited by Marcus Raichle, Washington University in St Louis School of Medicine, St. Louis, MO; received August 24, 2022; accepted February 3, 2023

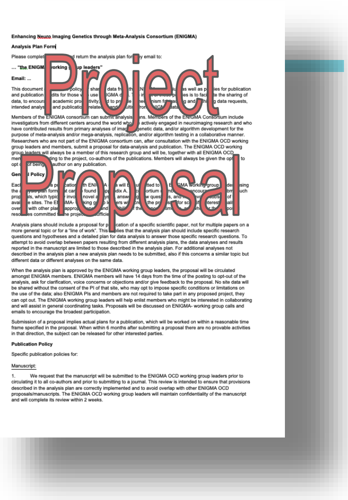
March 28, 2023 | 120 (14) e2213880120 | https://doi.org/10.1073/pnas.2213880120

Articles Full Access

The Relationship Between White Matter Microstructure and General Cognitive Ability in Patients With Schizophrenia and Healthy Participants in the ENIGMA Consortium

ENIGMA

Meta and "Mega" analysis projects within ENIGMA



"Mega" analysis in this case refers to the analysis of data centrally* with all subject level data, as opposed to meta-analysis of statistical results.

Often done using features already extracted from imaging protocols, rarely using raw images

+ Less back and forth with participating sites
+ Can assess rarer effects, data pooling for amassing sufficient sample sizes for a trait not well distributed at sites, can include sites that have cases/controls only, machine/deep learning
- Site effects need to be taken into consideration, data harmonization
- (Recommend always doing site-wise analysis for quality assurance / validation)

ENIGMA Parkinson’s disease working group

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

RESEARCH ARTICLE | Open Access

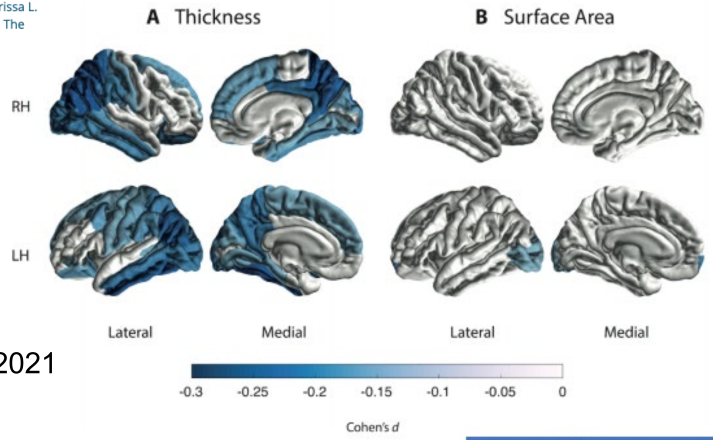
International Multicenter Analysis of Brain Structure Across Clinical Stages of Parkinson's Disease

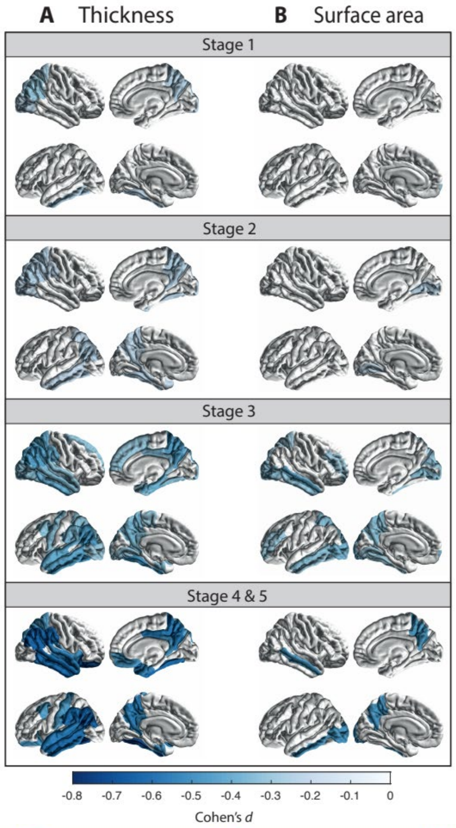
Max A. Laansma MSc, Joanna K. Bright BSc, Sarah Al-Bachari PhD, MBChB, Tim J. Anderson MD, PhD, Tyler Ard PhD, Francesca Assogna PhD, Katherine A. Baquero MSc, Henk W. Berendse MD, PhD, Jamie Blair PhD , Fernando Cendes MD, PhD, John C. Dalrymple-Alford PhD, Rob M.A. de Bie MD, PhD, Ines Debove MD, PhD, Michiel F. Dirkx MD, PhD, Jason Druzgal MD, PhD, Hedley C.A. Emsley PhD, FRCP, Gäetan Garraux PhD, Rachel P. Guimarães PhD, Boris A. Gutman PhD, Rick C. Helmich MD, PhD, Johannes C. Klein MD, PhD, Clare E. Mackay PhD, Corey T. McMillan PhD, Tracy R. Melzer PhD, Laura M. Parkes PhD, Fabrizio Piras PhD, Toni L. Pitcher PhD, Kathleen L. Poston MD, Mario Rango MD, PhD, Letícia F. Ribeiro MD, Cristiane S. Rocha PhD, Christian Rummel PhD, Lucas S.R. Santos MD, Reinhold Schmidt MD, PhD, Petra Schwingenschuh MD, PhD, Gianfranco Spalletta MD, PhD, Letizia Squarcina PhD, Odile A. van den Heuvel MD, PhD, Chris Vriend PhD, Jiun-Jie Wang PhD, Daniel Weintraub MD, PhD, Roland Wiest PhD, Clarissa L. Yasuda MD, PhD, Neda Jahanshad PhD, Paul M. Thompson PhD, Ysbrand D. van der Werf PhD, The ENIGMA-Parkinson's Study, ... See fewer authors

First published: 20 July 2021 | https://doi.org/10.1002/mds.28706

Laansma, Bright et al Movement Disorders 2021

Pooling data across sites allowed for well-powered analyses not only of PD cases vs controls, but also PD at various Hoehn & Yahr stages vs controls.





HY1	HY2	HY3	HY4&5
N_{PD} 437	N_{PD} 941	N_{PD} 263	N_{PD} 85
N_{HC} 847	N_{HC} 908	N_{HC} 502	N_{HC} 329

Many exciting developments in statistical data harmonization

README.md

ComBatHarmonization

Harmonization of multi-site imaging data with ComBat

Jean-Philippe Fortin, Drew Parker, Birkan Tunc, Takanori Watanabe, Ma
Elliott, Kosha Ruparel, David R Roalf, Theodore D Satterthwaite, Ruben C
Gur, Raquel E Gur, Robert T Schultz, Ragini Verma, Russell T Shinohara.
Harmonization Of Multi-Site Diffusion Tensor Imaging Data.
NeuroImage, 161, 149-170, 2017

Jean-Philippe Fortin, Nicholas Cullen, Yvette I. Sheline, Warren D. Taylo
Irem Aselcioglu, Philip A. Cook, Phil Adams, Crystal Cooper, Maurizio Fa
Patrick J. McGrath, Melvin McInnis, Mary L. Phillips, Madhukar H. Trived
Myrna M. Weissman, Russell T. Shinohara. **Harmonization of cortical thickness measurements across scanners and sites.** NeuroImage, 167
104-120, 2018

W. Evan Johnson and Cheng Li, **Adjusting batch effects in microarray expression data using empirical Bayes m**
127, 2007.

ELSEVIER
NeuroImage
Volume 220, 15 October 2020, 117129

Longitudinal ComBat: A method for harmonizing longitudinal multi-scanner imaging data ☆

Cook [c, d], Christos Davatzikos [e], Yvette I. Sheline [c, d, f], Russell
ner's Disease Neuroimaging Initiative

NEUROIMAGE ELSEVIER FREE Full-Text Article
Neuroimage. 2020 Oct 15; 220: 117127.
doi: 10.1016/j.neuroimage.2020.117127
PMCID: PMC7573655
PMID: 32634595

Neuroharmony: A new tool for harmonizing volumetric MRI data from unseen scanners

Rafael Garcia-Dias,[a,*] Cristina Scarpazza,[a,b] Lea Baecker,[a] Sandra Vieira,[a] Walter H.L. Pinaya,[a,c] Aiden Corvin,[d]
Alberto Redolfi,[e] Barnaby Nelson,[f,g] Benedicto Crespo-Facorro,[h,i,j,k] Colm McDonald,[l]
Diana Tordesillas-Gutiérrez,[h,m] Dara Cannon,[l] David Mothersill,[n] Dennis Hernaus,[o] Derek Morris,[p]
Esther Setien-Suero,[h,k] Gary Donohoe,[n] Giovanni Frisoni,[q,r] Giulia Tronchin,[l] João Sato,[c] Machteld Marcelis,[o]
Haren,[t] Oliver Gruber,[u,v] Patrick McGorry,[f,g] Paul Amminger,[f,g]
René S. Kahn,[z,aa] Rosa Ayesa-Arriola,[h,k] Therese van Amelsvoort,[o]
e Calhoun,[ab,s] Wiepke Cahn,[z] and Andrea Mechelli[a]

ELSEVIER
NeuroImage
Volume 208, March 2020, 116450

Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan

Raymond Pomponio [a], Guray Erus [a], Mohamad Habes [a, b], Jimit Doshi [a], Dhivya Srinivasan [a], Elizabeth Mamourian [a], Vishnu Bashyam [a], Ilya M. Nasrallah [a, g], Theodore D. Satterthwaite [l], Yong Fan [a], Lenore J. Launer [c], Colin L. Masters [d], Paul Maruff [d], Chuanjun Zhuo [e, f], Henry Völzke [h], Sterling C. Johnson [i], Jurgen Fripp [j], Nikolaos Koutsouleris [k], Daniel H. Wolf [l], Raquel Gur [g, l], Ruben Gur [g, l], John Morris [m], Marilyn S. Albert [n], Hans J. Grabe [o], Susan M. Resnick [p], R. Nick Bryan [q], David A. Wolk [b], Russell T. Shinohara [a, r, s], Haochang Shou [a, r, s], Christos Davatzikos [a, 1, 2]

Accommodating site variation in neuroimaging data using normative and hierarchical Bayesian models

Johanna M. M. Bayer, Richard Dinga, Seyed Mostafa Kia, Akhil R. Kottaram, Thomas Wolfers, Jinglei Lv, Andrew Zalesky, Lianne Schmaal, Andre Marquand

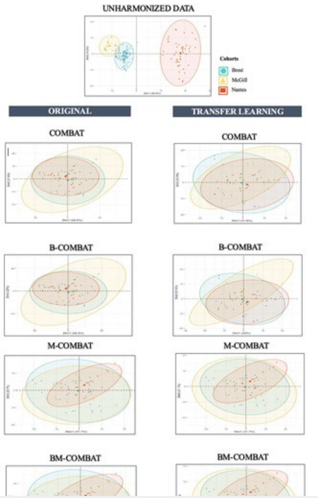
doi: https://doi.org/10.1101/2021.02.09.430363

This article is a preprint and has not been certified by peer review [what does this mean?].

PLOS ONE
OPEN ACCESS PEER-REVIEWED
RESEARCH ARTICLE

A transfer learning approach to facilitate ComBat-base harmonization of multicentre radiomic features in new datasets

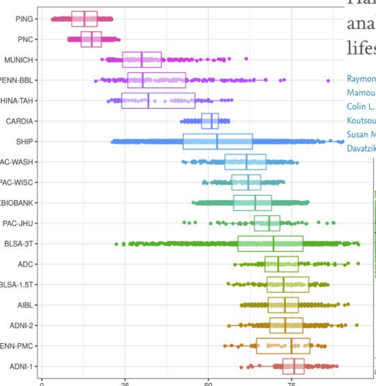
Ronrick Da-ano, François Lucia, Ingrid Masson, Ronan Abgral, Joanne Alfieri, Caroline Rousseau, Augustin Mer
Caroline Reinhold, Olivier Pradier, Ulrike Schick, Dimitris Visvikis, Mathieu Hatt

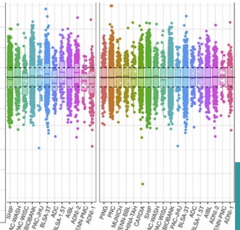


ELSEVIER
NeuroImage
Volume 245, 15 December 2021, 118703

A multi-scanner neuroimaging data harmonization using RAVEL and ComBat

Mahbaneh Eshaghzadeh Torbati [a], Davneet S. Minhas [b], Ghasan Ahmad [c], Erin E. O'Connor [c], John Muschelli [d], Charles M. Laymon [b], Zixi Yang [b], Ann D. Cohen [e], Howard J. Aizenstein [e], William E. Klunk [e], Bradley T. Christian [f], Seong Jae Hwang [a, g], Ciprian M. Crainiceanu [d], Dana L. Tudorascu [e, h]





ENIGMA

Harmonization Approaches - Very active field of research

Many site adjustment / harmonization approaches are statistical harmonization techniques.

Neuroimage. 2020 Sep;218:116956. doi: 10.1016/j.neuroimage.2020.116956. Epub 2020 May 26.

Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA

Joa

Front. Neuroinform., 08 January 2019
Volume 12 - 2018 |
https://doi.org/10.3389/fninf.2018.00102

This article is part of the Research Topic
Collaborative Efforts for Understanding the Human Brain
View all 15 Articles

An Empirical Comparison of Meta- and Mega-Analysis With Data From the ENIGMA Obsessive-Compulsive Disorder Working Group

ELSEVIER
NeuroImage
Volume 261, 1 November 2022, 119509
NeuroIma

A comparison of methods to harmonize cortical thickness measurements across scanners and sites

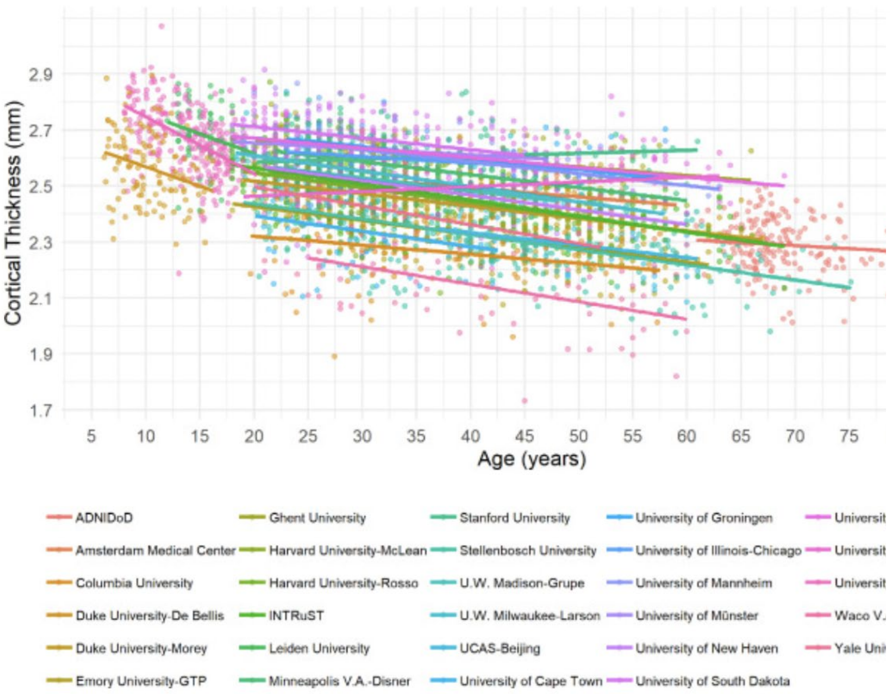
Delin Sun [1 2 66], Gopalkumar Rakesh [1 2], Courtney C. Haswell [1 2], Mark Logue [3 4 5 6], C. Lexi Baird [1 2], Erin N. O'Leary [7], Andrew S. Cotton [7], Hong Xie [7], Marijo Tamburrino [7], Tian Chen [7 8], Emily L. Dennis [8 9 10 11], Neda Jahanshad [9], Lauren E. Salminen [9], Sophia I. Thomopoulos [9], Faisal Rashid [9], Christopher R.K. Ching [9], Saskia B.J. Koch [12 13], Jessie L. Frijling [12], Laura Nawijn [12 14], Mirjam van Zuiden [12]...Rajendra A. Morey [1 2]

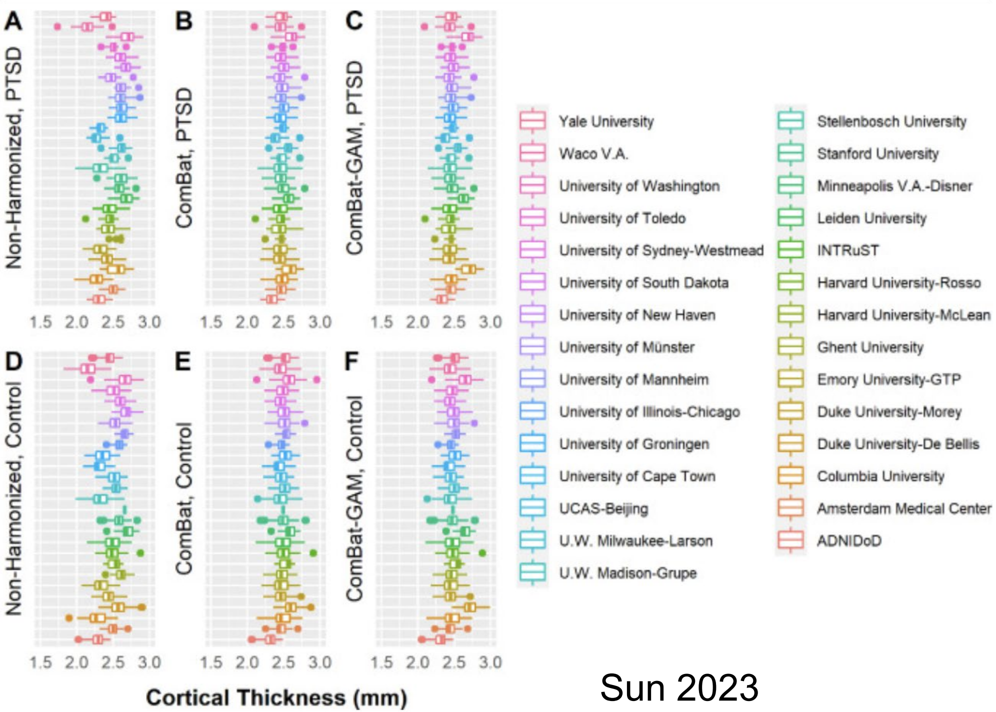
ENIGMA

Harmonization Approaches - Very active field of research

Many harmonization approaches are statistical harmonization techniques.

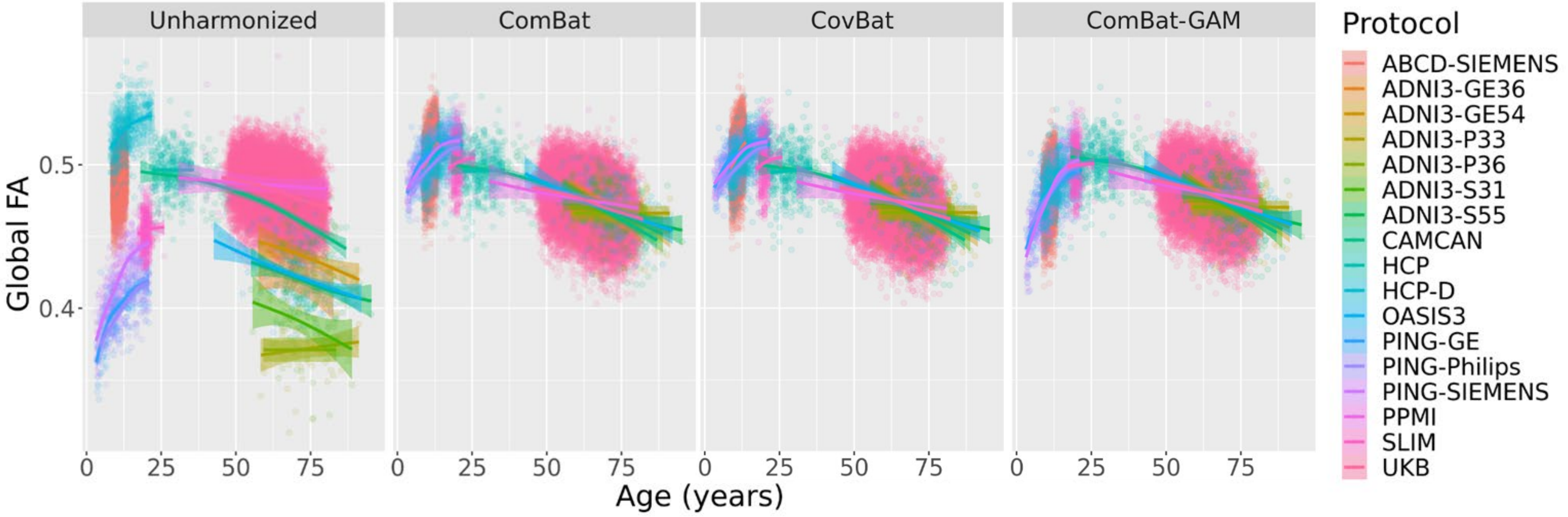
COMBAT - very often used family of statistical harmonization methods





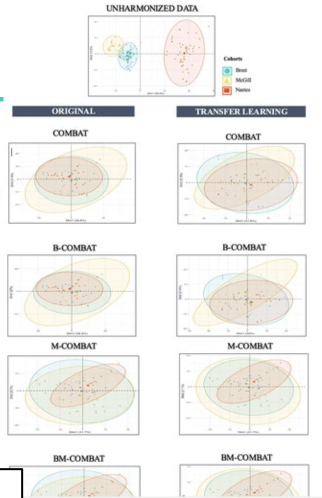
Sun 2023

ComBat-GAM preserves expected non-linear lifespan trajectories



Zhu et al - eHarmonize - in preparation

Many exciting developments in statistical data harmonization



README.md

ComBatHarmonization

Harmonization of multi-site imaging data with ComBat

Jean-Philippe Fortin, Drew Parker, Birkan Tunc, Takanori Watanabe, Ma Elliott, Kosha Ruparel, David R Roalf, Theodore D Satterthwaite, Ruben Gur, Raquel E Gur, Robert T Schultz, Ragini Verma, Russell T Shinohara. **Harmonization Of Multi-Site Diffusion Tensor Imaging Data.** NeuroImage, 161, 149-170, 2017

Jean-Philippe Fortin, Nicholas Cullen, Yvette I. Sheline, Warren D. Taylo Irem Aselcioglu, Philip A. Cook, Phil Adams, Crystal Cooper, Maurizio Fa Patrick J. McGrath, Melvin McInnis Myrna M. Weissman, Russell T. Shi **thickness measurements across** 104-120, 2018

W. Evan Johnson and Cheng Li, Ad **expression data using empirical B** 127, 2007.

ELSEVIER

NeuroImage
Volume 220, 15 October 2020, 117129

Longitudinal ComBat: A method for harmonizing longitudinal multi-scanner imaging data ☆

Cook, Christos Davatzikos, Yvette I. Sheline, Russell
ner's Disease Neuroimaging Initiative

NEUROIMAGE ELSEVIER FREE Full-Text Article

Neuroimage. 2020 Oct 15; 220: 117127. PMCID: PMC7573655
doi: 10.1016/j.neuroimage.2020.117127 PMID: 32634595

Neuroharmony: A new tool for harmonizing volumetric MRI data from

What if site differences are too vast or confounded?

ONE

rning approach to facilitate ComBat-base
n of multicentre radiomic features in ne

Lucia, Ingrid Masson, Ronan Abgral, Joanne Alfieri, Caroline Rousseau, Augustin Mer
adier, Ulrike Schick, Dimitris Visvikis, Mathieu Hatt

Raymond Pomponio, Guray Erus, Mohamad Habes, Jimit Doshi, Dhivya Srinivasan, Elizabeth Mamourian, Vishnu Bashyam, Ilya M. Nasrallah, Theodore D. Satterthwaite, Yong Fan, Lenore J. Launer, Colin L. Masters, Paul Maruff, Chuanjun Zhuo, Henry Völzke, Sterling C. Johnson, Jurgen Fripp, Nikolaos Koutsouleris, Daniel H. Wolf, Raquel Gur, Ruben Gur, John Morris, Marilyn S. Albert, Hans J. Grabe, Susan M. Resnick, R. Nick Bryan, David A. Wolk, Russell T. Shinohara, Haochang Shou, Christos Davatzikos

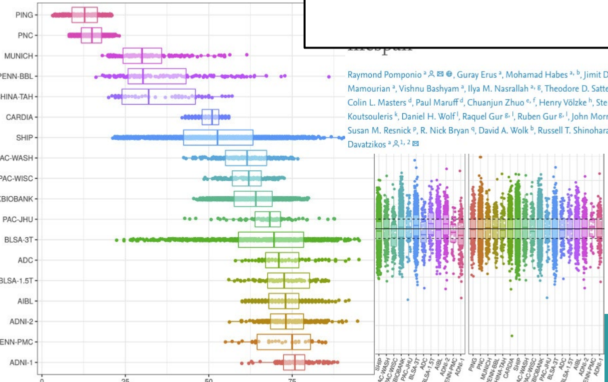
Jinglei Lv, Andrew Zalesky, Lianne Schmaal, Andre Marquand
doi: https://doi.org/10.1101/2021.02.09.430363
This article is a preprint and has not been certified by peer review [what does this mean?].

ELSEVIER

NeuroImage
Volume 245, 15 December 2021, 118703

A multi-scanner neuroimaging data harmonization using RAVEL and ComBat

Mahbaneh Eshaghzadeh Torbati, Davneet S. Minhas, Ghasan Ahmad, Erin E. O'Connor, John Muschelli, Charles M. Laymon, Zixi Yang, Ann D. Cohen, Howard J. Aizenstein, William E. Klunk, Bradley T. Christian, Seong Jae Hwang, Ciprian M. Crainiceanu, Dana L. Tudorascu



ENIGMA

Harmonization Needs Care - Confounded Cases

Talia Nir, PhD

Dan Stein MD, PhD

JAMA Network | Open

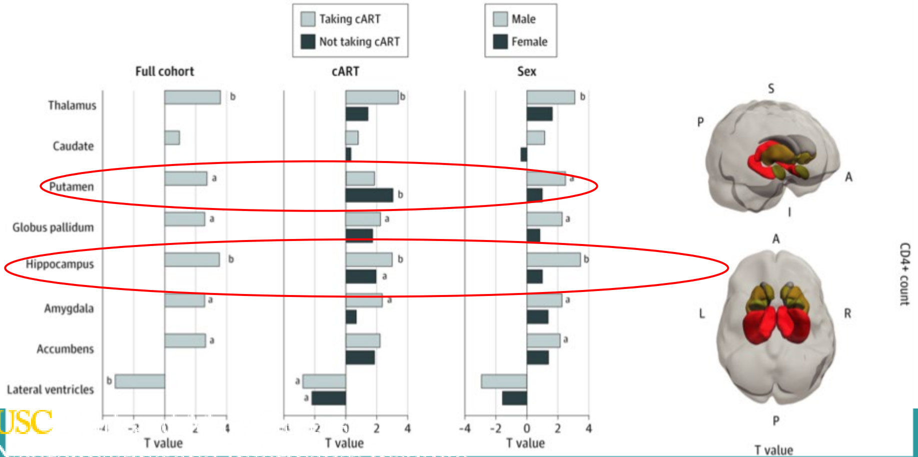
Original Investigation | Infectious Diseases

Association of Immunosuppression and Viral Load With Subcortical Brain Volume in an International Sample of People Living With HIV

Talia M. Nir, PhD; Jean-Paul Fouche, PhD; Jintanat Ananworanich, MD, PhD; Beau M. Ances, MD, PhD; Jasmina Boban, MD, PhD; Bruce J. Brew, MD; Joga R. Chaganti, MD; Linda Chang, MD, MS; Christopher R. K. Ching, PhD; Lucette A. Cysique, PhD; Thomas Ernst, PhD; Joshua Faskowitz, BA; Vikash Gupta, PhD; Jaroslaw Harezlak, PhD; Jodi M. Heaps-Woodruff, PhD; Charles H. Hinkin, PhD; Jacqueline Hoare, PhD; John A. Joska, PhD; Kalpana J. Kallianpur, PhD; Taylor Kuhn, PhD; Hei Y. Lam, BA; Meng Law, MD; Christine Lebrun-Frénay, MD, PhD; Andrew J. Levine, PhD; Lydiane Mondot, MD; Beau K. Nakamoto, MD; Bradford A. Navia, MD, PhD; Xavier Pennec, PhD; Eric C. Porges, PhD; Lauren E. Salminen, PhD; Cecilia M. Shikuma, MD; Wesley Surento, MS; April D. Thames, PhD; Victor Valcour, MD, PhD; Matteo Vassallo, MD; Adam J. Woods, PhD; Paul M. Thompson, PhD; Ronald A. Cohen, PhD; Robert Paul, PhD; Dan J. Stein, PhD; Neda Jahanshad, PhD

CD4 continuous

A Subcortical volumes and CD4+ cell counts



Site/Cohort confounded by demographic variables

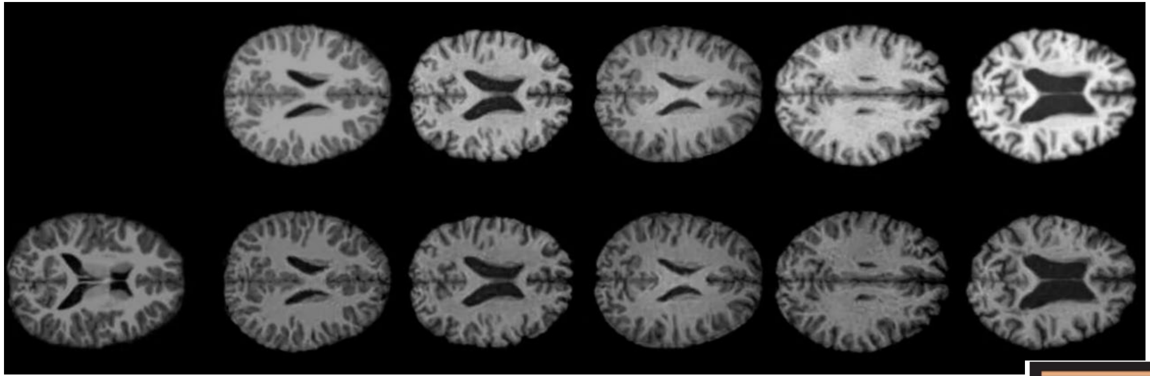
Table 1. Demographic and Clinical Information by Study and Scanning Site

Site	Total, No.	Male, No. (%)	Age, mean (SD) [range], y	No. (%) of participants: Taking cART	No. (%) of participants: Detectable viral load	CD4+ cell count, mean (SD), /μL	No. (%) of participants: CD4+ cell count <200/μL	No. (%) of participants: Viral load >400 copies/mL
HIVNC (7 sites), US	218	187 (86)	48.5 (8.3) [24-71]	218 (100)	61 (28) [n = 217]	378.0 (231.9)	48 (22)	39 (18) [n = 217]
Site 1: University of California, San Diego	21	21 (100)	47.6 (5.0) [37-56]	21 (100)	13 (65) [n = 20]	313.7 (328.4)	11 (52)	7 (35) [n = 20]
Site 2: Harbor UCLA Medical Center, Los Angeles, California	52	42 (81)	46.6 (9.1) [24-70]	52 (100)	8 (15)	350.2 (173.0)	14 (27)	5 (10)
Site 3: Stanford University, Stanford, California	10	9 (90)	46.4 (10.4) [31-62]	10 (100)	0	313.5 (157.5)	2 (20)	0
Site 4: Colorado	35	34 (97)	49.2 (7.9) [31-66]	35 (100)	14 (40)	446.6 (246.0)	4 (11)	6 (17)
Site 5: Pittsburgh, Pennsylvania	19	18 (95)	49.9 (9.7) [34-71]	19 (100)	4 (21)	438.9 (298.2)	3 (16)	3 (16)
Site 6: Rochester University, Rochester, New York	41	26 (63)	48.4 (7.7) [26-62]	41 (100)	11 (27)	382.0 (207.8)	6 (15)	7 (17)
Site 7: University of California, Los Angeles	40	37 (93)	50.7 (8.4) [28-69]	40 (100)	11 (28)	370.7 (224.7)	8 (20)	11 (28)
University of Hawaii, Honolulu, US[17]	175	159 (91)	47.6 (10.5) [20-74]	157 (90)	54 (33) [n = 164]	475.2 (281.4)	31 (18)	38 (23) [n = 164]
University of Hawaii, Honolulu, US[18]	53	45 (85)	50.9 (8.0) [40-71]	53 (100)	6 (11)	491.1 (208.5)	4 (8)	2 (4)
University of California, San Francisco, US	50	49 (98)	63.6 (2.5) [60-69]	49 (98)	14 (29) [n = 49]	529.3 (218.5)	0	4 (8) [n = 49]
Brown University, Providence, Rhode Island, US	79	48 (61)	45.2 (9.5) [23-65]	66 (84)	22 (28)	476.2 (228.8)	7 (9)	21 (27)
University of California, Los Angeles, US[19]	12	12 (100)	46.2 (8.5) [26-57]	9 (75)	6 (50)	604.1 (289.1)	1 (8)	4 (33)
University of California, Los Angeles, US[20]	51	46 (90)	50.9 (13.2) [24-76]	51 (100)	21 (41)	603.2 (287.7)	2 (4)	9 (18)
University of New South Wales, New South Wales, Australia[21]	39	38 (97)	52.8 (8.2) [39-75]	39 (100)	10 (26)	612.5 (269.0)	0	6 (15)
University of New South Wales, New South Wales, Australia[22]	68	68 (100)	55.3 (6.7) [44-69]	68 (100)	1 (1)	549.5 (273.6)	5 (7)	1 (1)
SEARCH-011 Consortium, Bangkok, Thailand	61	26 (43)	34.2 (7.0) [22-56]	0	61 (100)	236.0 (139.0)	25 (41)	61 (100)
University of Cape Town, South Africa	181	25 (14)	32.4 (5.0) [22-46]	0	148 (97) [n = 152]	225.5 (149.2)	95 (53)	129 (88) [n = 147]
Nice University, Nice, France	155	122 (79)	45.4 (10.0) [22-81]	126 (76)	56 (36)	580.9 (277.6)	11 (7)	39 (25)
University of Novi Sad, Novi Sad, Serbia	61	55 (90)	44.3 (10.9) [25-66]	61 (100)	10 (16)	616.3 (346.2)	1 (2)	10 (16)

Abbreviations: cART, combination antiretroviral therapy; HIVNC, HIV Neuroimaging Consortium; SEARCH, South East Asian Research Collaboration in HIV.

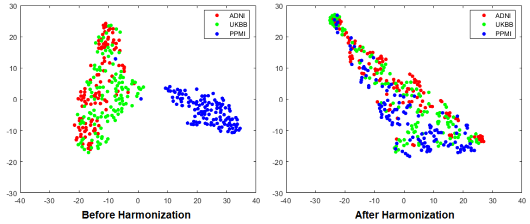
More Active Research in Harmonization Methods

Image Harmonization with Style-Encoding GAN



Liu et al, MICCAI 2021

Mengting Liu, PhD



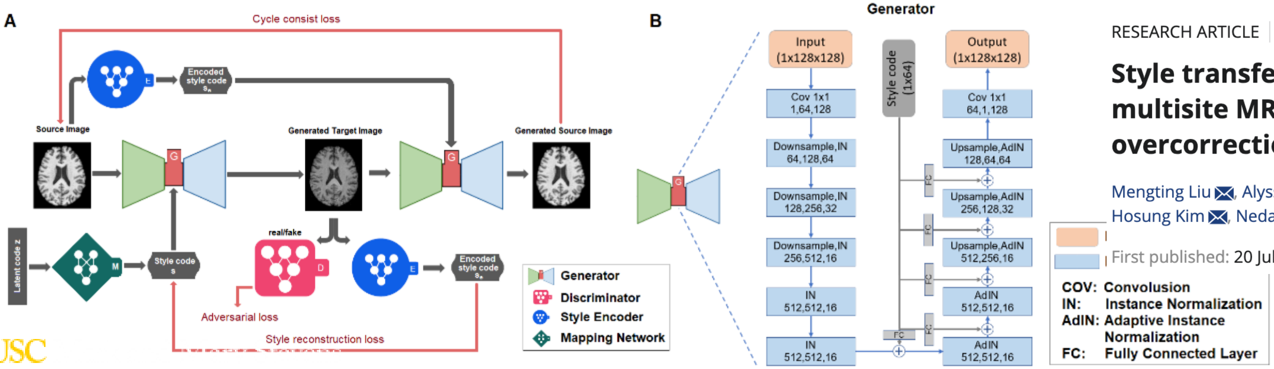
HUMAN BRAIN MAPPING

RESEARCH ARTICLE | Open Access

Style transfer generative adversarial networks to harmonize multisite MRI to a single reference image to avoid overcorrection

Mengting Liu, Alyssa H. Zhu, Piyush Maiti, Sophia I. Thomopoulos, Shruti Gadewar, Yaqiong Chai, Hosung Kim, Neda Jahanshad, for the Alzheimer's Disease Neuroimaging Initiative

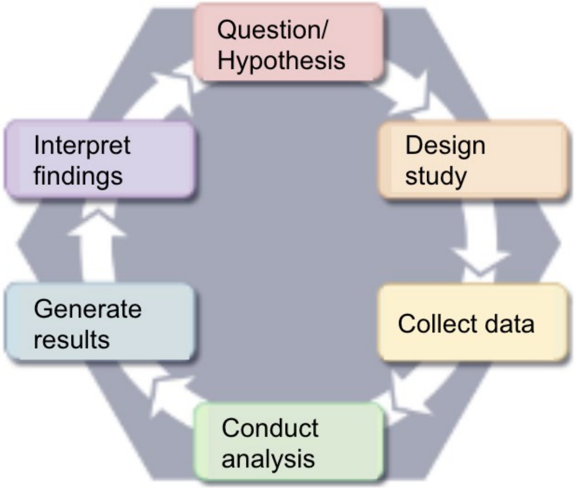
First published: 20 July 2023 | https://doi.org/10.1002/hbm.26422



USC

ENIGMA

We can continuously integrate more data



More studies can be aggregated

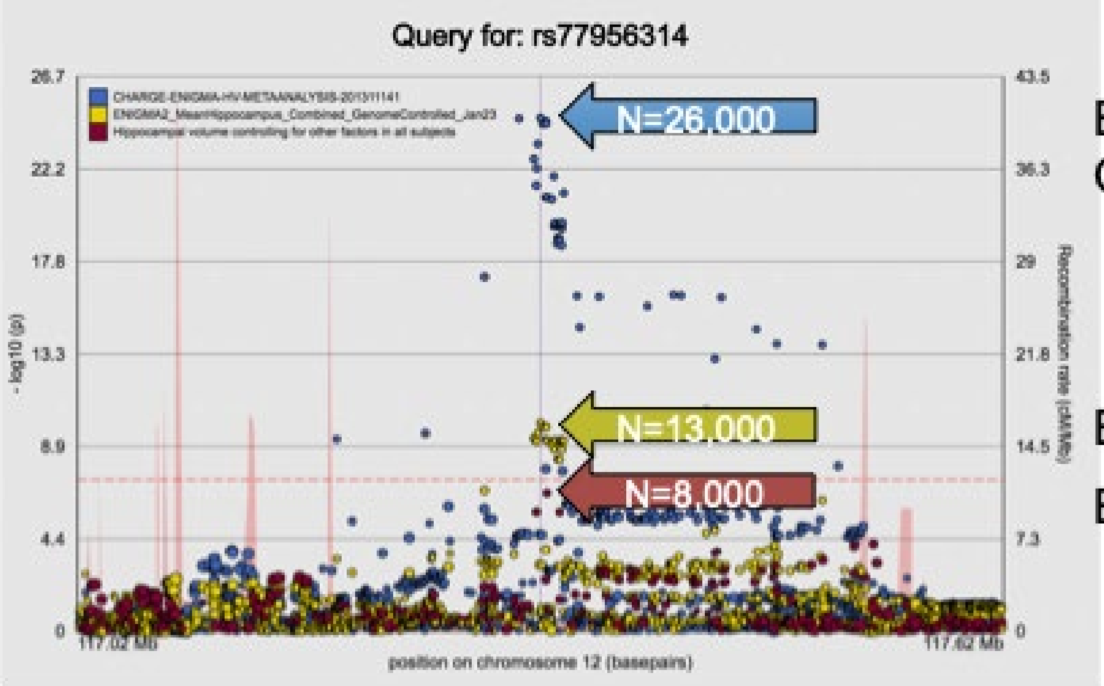
New populations

New technologies

Or nothing new! Can also be used to validate findings, refine conclusions and confidence

Can always expand on published work

Hippocampal volume GWAS across initiatives



ENIGMA2 + CHARGE

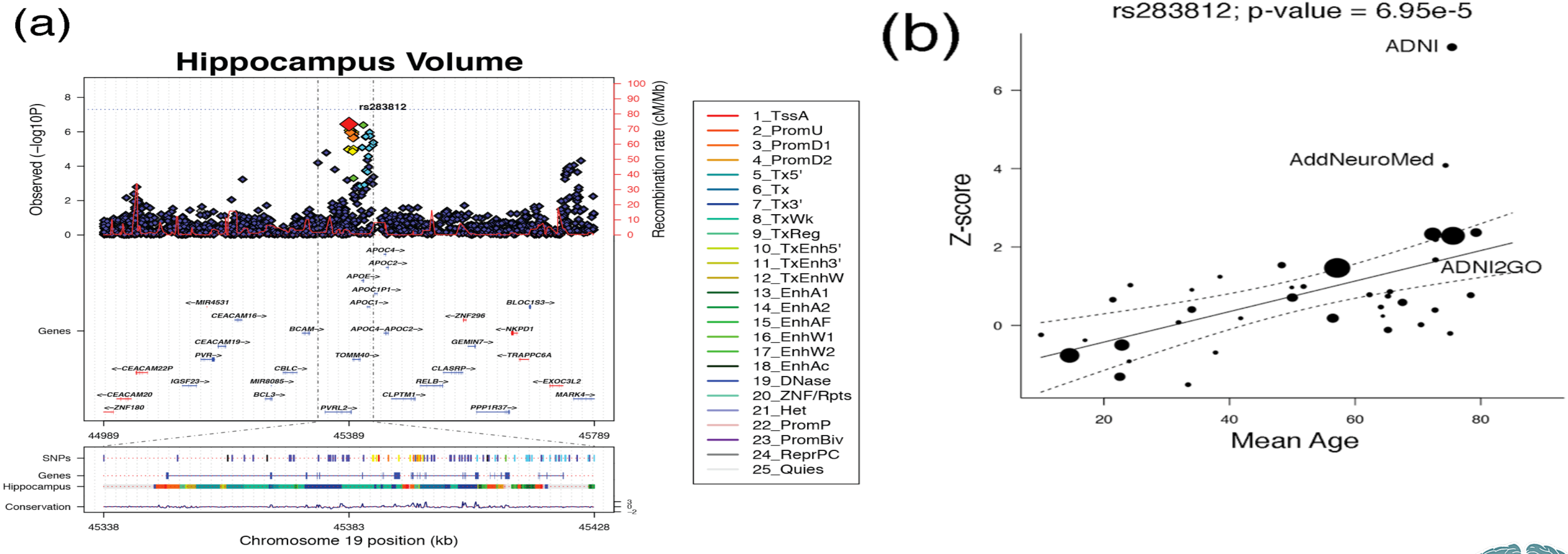
ENIGMA2

ENIGMA1

GWAS results available: http://enigma.usc.edu/enigma-vis/

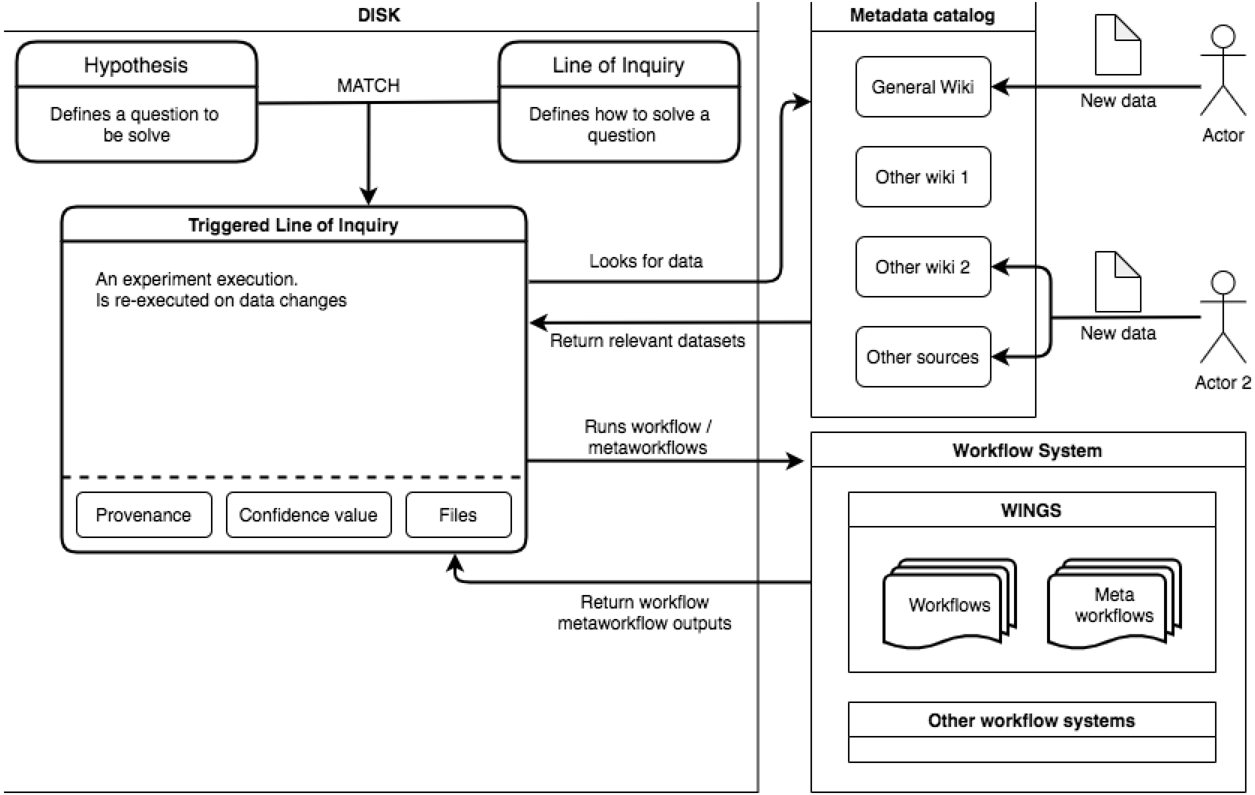
Explore Generalizability / Lack of

APOE – Near GWAS Significance - Why?

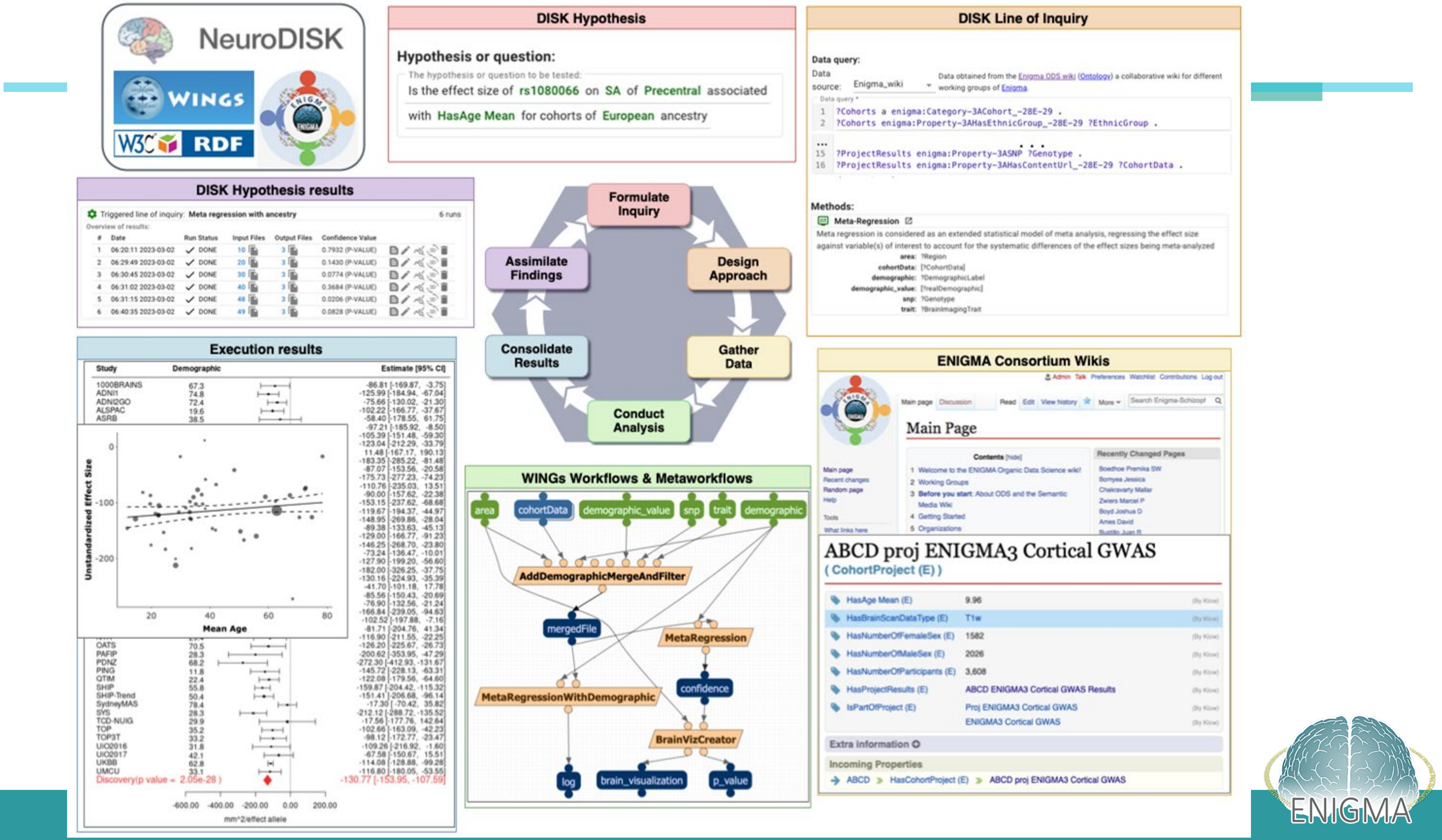


NeuroDISK

https://neuro.disk.isi.edu/



Data Standards
Documentation /
Containerization
Analytic
Provenance

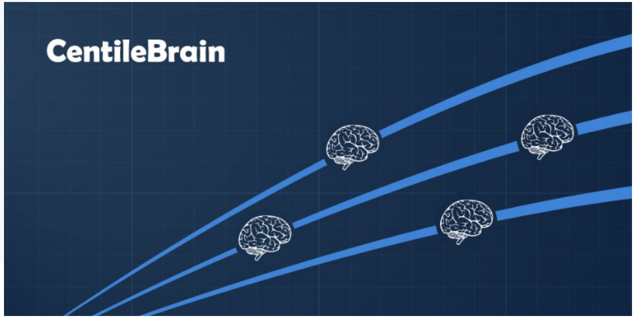

NeuroDISK
WINGS
W3C RDF
ENIGMA
DISK Hypothesis
Hypothesis or question:
The hypothesis or question to be tested:
Is the effect size of rs1080066 on SA of Precentral associated with HasAge Mean for cohorts of European ancestry
DISK Line of Inquiry
Data query:
Data source: Enigma_wiki
Data obtained from the Enigma ODS wiki (Ontology) a collaborative wiki for different working groups of Enigma.
Data query *
1 ?Cohorts a enigma:Category-3ACohort_-28E-29 .
2 ?Cohorts enigma:Property-3AHasEthnicGroup_-28E-29 ?EthnicGroup .
...
15 ?ProjectResults enigma:Property-3ASNP ?Genotype .
16 ?ProjectResults enigma:Property-3AHasContentUrl_-28E-29 ?CohortData .
Methods:
Meta-Regression
Meta regression is considered as an extended statistical model of meta analysis, regressing the effect size against variable(s) of interest to account for the systematic differences of the effect sizes being meta-analyzed
area: ?Region
cohortData: [?CohortData]
demographic: ?DemographicLabel
demographic_value: [?realDemographic]
snp: ?Genotype
trait: ?BrainImagingTrait
DISK Hypothesis results
Triggered line of inquiry: Meta regression with ancestry
6 runs
Overview of results:
Date Run Status Input Files Output Files Confidence Value
1 06:20:11 2023-03-02 DONE 10 3 0.7932 (P-VALUE)
2 06:29:49 2023-03-02 DONE 20 3 0.1430 (P-VALUE)
3 06:30:45 2023-03-02 DONE 30 3 0.0774 (P-VALUE)
4 06:31:02 2023-03-02 DONE 40 3 0.3684 (P-VALUE)
5 06:31:15 2023-03-02 DONE 48 3 0.0206 (P-VALUE)
6 06:40:35 2023-03-02 DONE 49 3 0.0828 (P-VALUE)
Formulate Inquiry
Design Approach
Gather Data
Conduct Analysis
Consolidate Results
Assimilate Findings
Execution results
Study
Demographic
Estimate [95% CI]
Unstandardized Effect Size
Mean Age
Discovery(p value = 2.05e-28)
-130.77 [-153.95, -107.59]
mm^2/effect allele
WINGs Workflows & Metaworkflows
area
cohortData
demographic_value
snp
trait
demographic
AddDemographicMergeAndFilter
mergedFile
MetaRegression
confidence
MetaRegressionWithDemographic
BrainVizCreator
log
brain_visualization
p_value
ENIGMA Consortium Wikis
Main Page
ABCD proj ENIGMA3 Cortical GWAS
(CohortProject (E))
HasAge Mean (E) 9.96
HasBrainScanDataType (E) T1w
HasNumberOfFemaleSex (E) 1582
HasNumberOfMaleSex (E) 2026
HasNumberOfParticipants (E) 3,608
HasProjectResults (E) ABCD ENIGMA3 Cortical GWAS Results
IsPartOfProject (E) Proj ENIGMA3 Cortical GWAS
ENIGMA3 Cortical GWAS
Extra information
Incoming Properties
ABCD HasCohortProject (E) ABCD proj ENIGMA3 Cortical GWAS
ENIGMA

ENIGMA Resources - continuously being updated

ENIGMA-git

Protocols

- ENIGMA sMRI Imaging
- ENIGMA DTI Imaging
- ENIGMA Genetics Protocols
- ENIGMA Functional Imaging
- ENIGMA Statistical Protocols
- ENIGMA Visualization tools



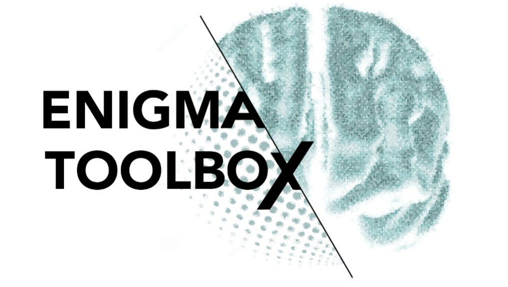
ENIGMA-U: Free Online Neuroscience and Neuroimaging Course

https://biabl.org/enigma-u/

ENIGMA-VIS

ABOUT DATASETS GALLERY PUBLICATIONS

Welcome to the ENIGMA TOOLBOX 👋



ENIGMA

Thank you to the thousands of ENIGMA participants-- group leads, investigators and research volunteers!

QUESTIONS?

Contact:
Neda.Jahanshad@ini.usc.edu

Join ENIGMA:
http://enigma.ini.usc.edu

LoBeS

ENIGMA and Global Neuroscience: A Decade of Large-Scale Studies of the Brain in Health and Disease across more than 40 Countries

AUTHORS

Paul Thompson, Neda Jahanshad, Christopher R. K. Ching, Lauren E. Salminen, Sophia Thomopoulos, Joanna Bright, Bernhard T. Baune, Sara Bertolín, Janita Bralten, Willem B. Bruin, Robin Bülow, Jian Chen, Yann Chye, Udo Dannlowski, Carolien de Kovel, Gary Donohoe, Lisa Eyler, Stephen V. Faraone, Pauline Favre, Courtney Filippi, Thomas Frodl, Daniel Garijo, Yolanda Gil, Hans J. Grabe, Katrina L. Grasby, Tomas Hajek, Laura Han, Sean Hatton, Kevin Hilbert, Tiffany C. Ho, Laurena Holleran, Georg Homuth, Norbert Hosten, Josselin Houenou, Iliyan Ivanov, Tianye Jia, Sinead Kelly, Marieke Klein, Jun Soo Kwon, Max A. Laansma, Jeanne Leerssen, Ulrike Lueken, Abraham Nunes, Joseph O'Neill, Nils Opel, Fabrizio Piras, Federica Piras, Merel Postema, Elena Pozzi, Natalia Shatokhina, Carles Soriano-Mas, Gianfranco Spalletta, Daqiang Sun, Alexander Teumer, Amanda K. Tilot, Leonardo Tozzi, Celia van der Merwe, Eus J. W. Van Someren, Guido van Wingen, Henry Völzke, Esther Walton, Lei Wang, Anderson M. Winkler, Katharina Wittfeld, Margaret J. Wright, Je-Yeon Yun, Guohao Zhang, Yanli Zhang-James, Bhim M. Adhikari, Ingrid Agartz, Moji Aghajani, André Aleman, Robert R. Althoff, Andre Altmann, Ole A. Andreassen, David A. Baron, Brenda L. Bartnik-Olson, Janna Marie Bas-Hoogendam, Arielle R. Baskin-Sommers, Carrie E. Bearden, Laura A. Berner, Premika S. W. Boedhoe, Rachel M. Brouwer, Jan K. Buitelaar, Karen Caeyenberghs, Charlotte A. M. Cecil, Ronald A. Cohen, James Cole, Patricia J. Conrod, Stephane De Brito, Sonja M. C. de Zwarte, Emily Dennis, Sylvane Desrivieres, Danai Dima, Stefan Ehrlich, Carrie Esopenko, Graeme Fairchild, Simon E. Fisher, Jean-Paul Fouche, Clyde Francks, Sophia Frangou, Barbara Franke, Hugh P. Garavan, David C. Glahn, Nynke A. Groenewold, Tiril Gurholt, Boris A. Gutman, Tim Hahn, Ian Harding, Dennis Hernaus, Derrek P. Hibar, Frank Hillary, Martine Hoogman, Hilleke E. Hulshoff Pol, Maria Jalbrzikowski, George A. Karkashadze, Eduard Klapwijk, Rebecca C. Knickmeyer, Peter Kochunov, Inga K. Koerte, Xiang-Zhen Kong, Sook-Lei Liew, Alexander P. Lin, Mark W. Logue, Eileen Luders, Fabio Macciardi, Scott Mackey, Andrew R. Mayer, Carrie R. McDonald, Agnes B. McMahon, Sarah E. Medland, Gemma Modinos, Rajendra A. Morey, Sven Mueller, Pratik Mukherjee, Leyla Namazova-Baranova, Talia M. Nir, Alexander Olsen, Peristera Paschou, Daniel Pine, Fabrizio Pizzagalli, Miguel E. Rentería, Jonathan D. Rohrer, Philipp G. Sämann, Lianne Schmaal, Gunter Schumann, Mark S. Shiroishi, Sanjay M. Sisodiya, Dirk J. A. Smit, Ida E. Sønderby, Dan J. Stein, Jason L. Stein, Masoud Tahmasian, David Tate, Jessica Turner, Odile van den Heuvel, Nic van der Wee, Ysbrand D. van der Werf, Theo G. M. van Erp, Neeltje van Haren, Daan van Rooij, Laura S. van Velzen, Ilya Veer, Dick J. Veltman, Julio E. Villalon-Reina, Henrik Walter, Christopher D. Whelan, Elisabeth A. Wilde, Mojtaba Zarei, Vladimir Zelman

Individual cohort studies would not be possible without international and national support:

NHMRC, DCRC, BMBF, Swedish Research Council, German Ministry of Cultural Affairs, Social Ministry of the Federal State of Mecklenburg-West Pomerania, NGFN, Siemens, ISCIII, SENY Fundació, NOW, BBMRI-NL, CBF, Hersenstichting Nederland, Alzheimer's Australia Dementia Research MJFF Foundation, Autism Speaks, NIDA, NIMH, NIBIB, NICHD, NINDS, NIA
Kavli Foundation

ENIGMA

Questions?

neda.jahanshad@usc.edu

ENIGMA

Data-quality dependent protocols

Sometimes, may need to restrict participating sites and datasets based on image acquisition protocols

Much of the clinically focused datasets are optimized to collect information from multiple domains and may limit time in the scanner, so acquisition protocols are not always optimal for all analyses

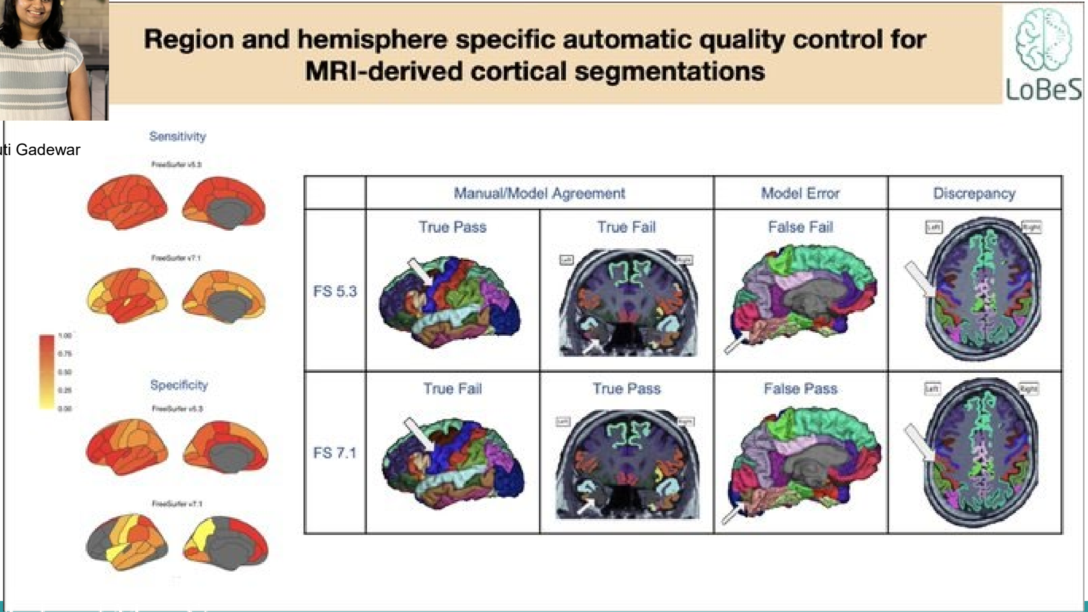
% of ENIGMA	**DTI** b<=2000	**HARDI** b<=2000	**Multishell** b<=2000	**DTI** b>=3000	**HARDI** b>=3000	**Multishell** b>=3000
> 2.5mm	~10%	~2%				
2-2.5mm	**~70%**	~10%	~5%	~2%		
< 2mm						Max tracts

Analytical Harmonization: Quality Assurance

Tens of thousands of scans have been visually assessed for quality according to ENIGMA guidelines → Let's use this information!

We are working to develop tools that help <u>automate</u> much of the process.

Shruti Gadewar



2021 IEEE 18th International Symposium on Biomedical Imaging (ISBI)
April 13-16, 2021, Nice, France

REGION SPECIFIC AUTOMATIC QUALITY ASSURANCE FOR MRI-DERIVED CORTICAL SEGMENTATIONS

Shruti Gadewar, Alyssa H. Zhu, Sophia I. Thomopoulos, Zhuocheng Li, Iyad Ba Gari, Piyush Maiti, Paul M. Thompson, Neda Jahanshad

Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

ENIGMA Suicidal Thoughts and Behaviors

Site	Age HC (years)	Age CC (years)	Age Attempt	% female HC	% female CC	% female Attempt	Total *N* HC	Total *N* CC	Total *N* Attempt
A. Mood disorders only sample									
DEP-ARREST-CLIN - MOODS (France)	-	22.0 (18–25)	19.0 (18–23)	-	70.0	55.6	0	10	9
Houston BD (USA)	14.0 (8–25)	15.0 (8–25)	17.0 (11–24)	48.5	34.7	69.2	97	75	13
Sydney Bipolar Kids and Siblings	21.0 (13–25)	22.5 (16–25)	22.0 (18–25)	50.0	62.5	66.7	64	16	9
Sydney Brain and Mind Centre (Australia)	-	19.5 (15–25)	20.5 (15–24)	-	66.7	100.0	0	48	8
University of Minnesota (USA)	16.0 (14–20)	16.0 (12–19)	17.5 (12–19)	66.7	78.0	62.5	12	41	8
University of Texas- Austin - Bipolar Seed Program (USA)	21.0 (18–25)	21.0 (18–25)	21.0 (19–25)	69.2	77.8	66.7	26	18	9
UWashington/Harvard (USA)	11.5 (8–16)	15.0 (12–16)	14.5 (9–17)	53.7	55.6	75.0	54	9	8
Total	16.0 (8–25)	17.0 (8–25)	19.0 (9–25)	53.0	58.1	70.3	253	217	64
B. Transdiagnostic sample									
DEP-ARREST-CLIN - MOODS (France)		22.0 (18–25)	19.0 (18–23)		70.0	55.6	0	10	9
Fondazione Santa Lucia - Schizophrenia sample (Italy)		23.0 (16–25)	24.0 (20–25)		5.3	57.1	0	19	7
Houston BD (USA)	14.0 (8–25)	15.0 (8–25)	17.0 (11–24)	48.5	34.7	69.2	97	75	13
PAFIP1 (Spain)		22.0 (17–25)	22.0 (19–24)		25.5	14.3	0	51	7
PAFIP2 (Spain)		21.0 (17–25)	22.5 (17–25)		24.1	50.0	0	58	10
Sydney Bipolar Kids and Siblings (Australia)	21.0 (13–25)	22.0 (16–25)	22.0 (18–25)	50.0	60.9	66.7	64	23	9
Sydney Brain and Mind Centre (Australia)		19.0 (13–25)	19.0 (15–24)		68.3	100	0	101	10
University of Minnesota (USA)	16.0 (14–20)	16.0 (12–19)	17.5 (12–19)	66.7	78.0	62.5	12	41	8
University of Texas- Austin - Bipolar Seed Program (USA)	21.0 (18–25)	21.0 (18–25)	21.0 (19–25)	69.2	77.8	66.7	26	18	9
UWashington/Harvard (USA)	11.5 (8–16)	12.5 (8–16)	13.0 (9–17)	53.7	52.8	77.8	54	36	9
Total	16.0 (8–25)	19.5 (8–25)	20.0 (9–25)	53.0	48.4	63.7	253	432	91