Coordinated Analysis of Brain Imaging, Genomic, and Clinical Data in the ENIGMA Consortium

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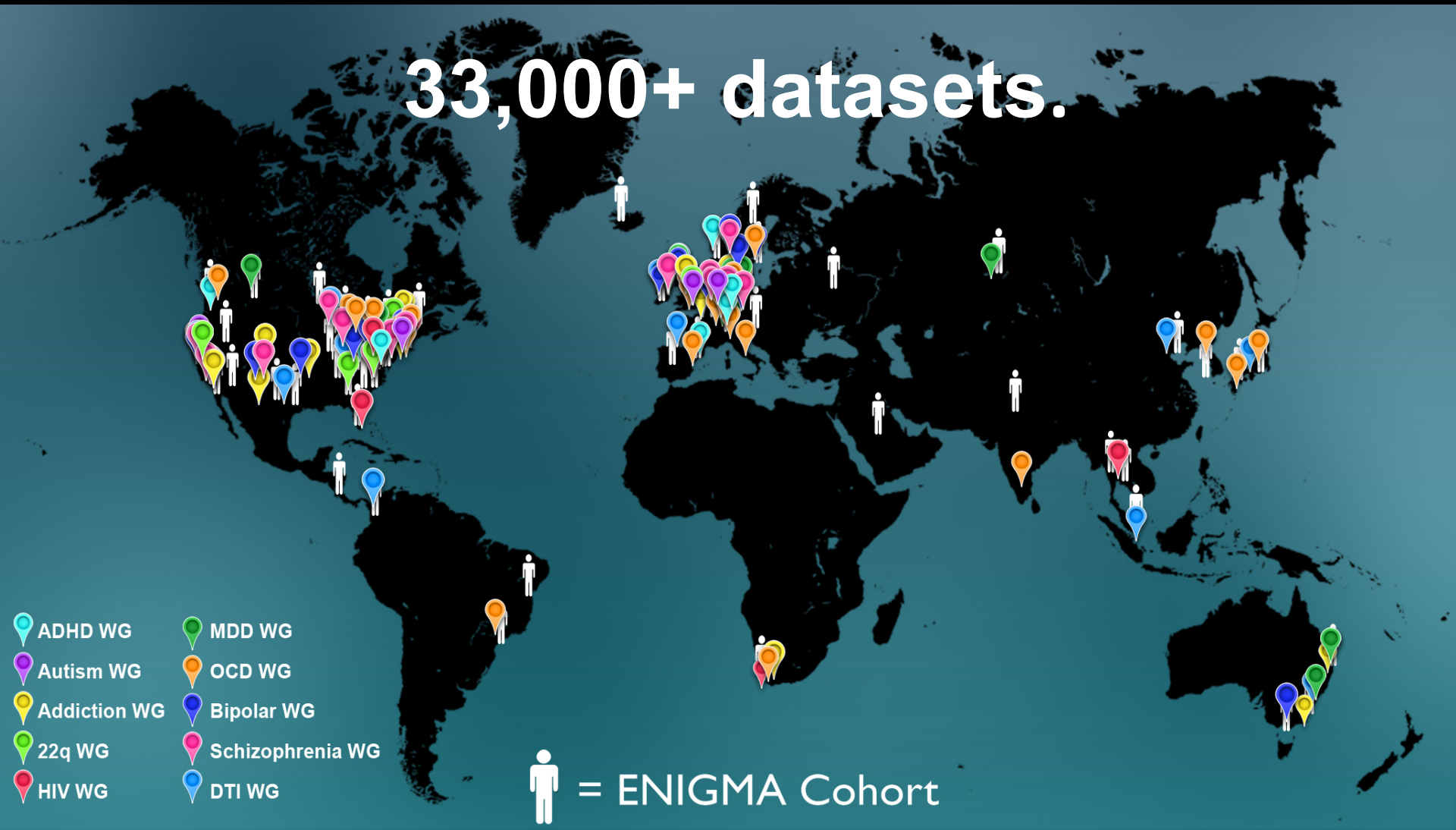
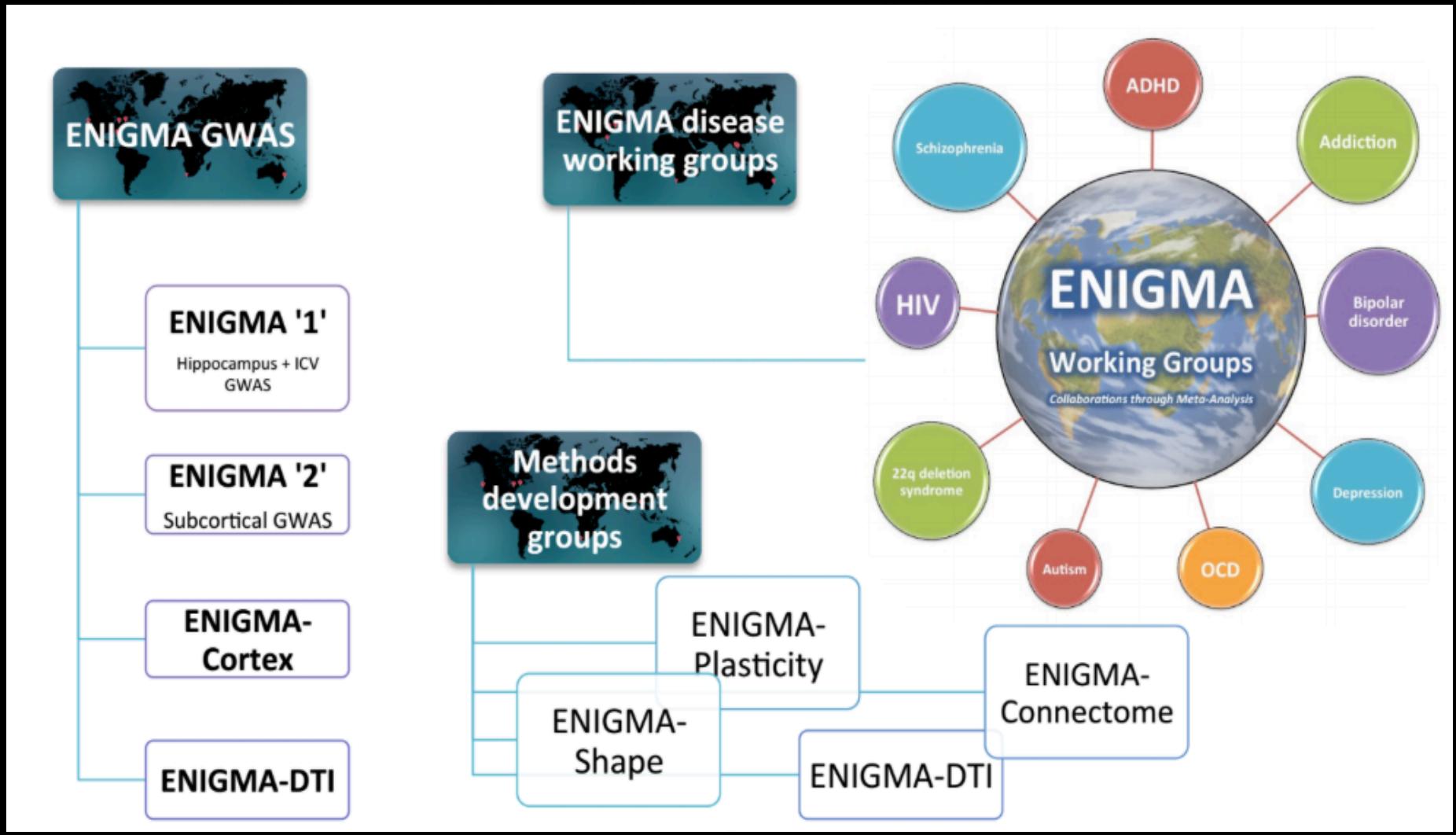
Map of ENIGMA Members – Largest-Ever Worldwide Analysis of Brain Scans and Genetic Data (33,000 people)



What is ENIGMA?
3 general directions of activity



Collaboration and meta-analysis is beneficial to all aspects of neuroimaging

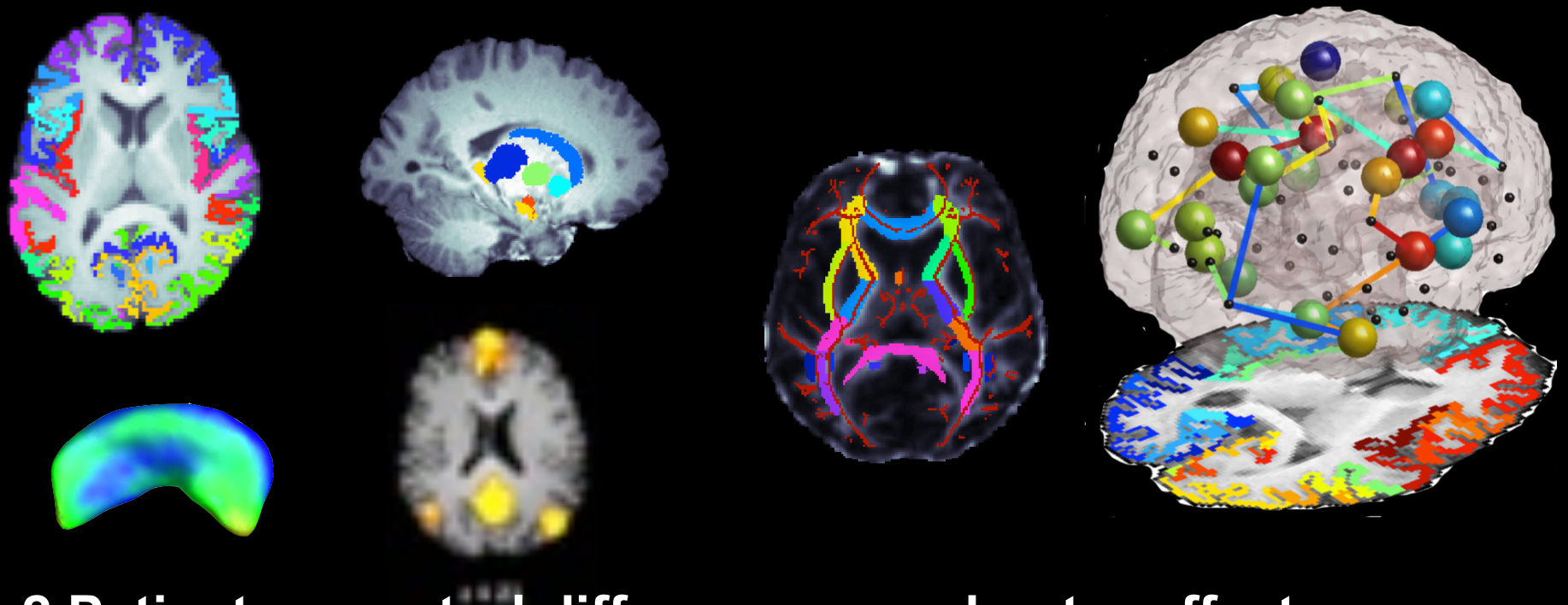
- ENIGMA-Disease working groups
  - Schizophrenia
  - Bipolar Disorder
  - Major Depression
  - Autism
  - Attention Deficit Hyperactivity Disorder
  - Obsessive Compulsive Disorder
  - Addiction
  - 22q11 deletion syndrome
  - HIV
  - Parkinson's disease
  - Epilepsy

enigma.ini.usc.edu/ongoing/

ENIGMA Studies of Disease

1 Compute brain measures from scans

(harmonized protocol for image analysis + QC)



2 Patient vs control differences, moderator effects

(harmonized protocol for covariates, QC, + analysis)

3 Meta-analysis: combine effects across sites –

make sure effects are reproducible, boosts power to pick up effects no site could pick on its own

ENIGMA Disease Working Groups

Subcortical Papers finished for SCZ, MDD, BPD, ADHD

In press at Mol. Psych.

ORIGINAL ARTICLE

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

TGM van Erp[1], DP Hibar[2], JM Rasmussen[1], DC Glahn[3,4], GD Pearlson[3,4], OA Andreassen[5], I Agartz[5,6,7], LT Westlye[5,8], UK Haukvik[5], AM Dale[9,10], I Melle[5], CB Hartberg[5,6], O Gruber[11], B Kraemer[11], D Zilles[11,12], G Donohoe[13,14], S Kelly[2,14], C McDonald[15], DW Morris[13,14], DM Cannon[15], A Corvin[14], MWJ Machielsen[16], L Koenders[16], L de Haan[16], DJ Veltman[17], TD Satterthwaite[18], DH Wolf[18], RC Gur[18], RE Gur[18], SG Potkin[1], DH Mathalon[19,20], BA Mueller[21], A Preda[1], F Macciardi[1], S Ehrlich[22,23,24], E Walton[22], J Hass[22], VD Calhoun[25,26], HJ Bockholt[25,27,28], SR Sponheim[29], JM Shoemaker[25], NEM van Haren[30], HEH Pol[30], RA Ophoff[30,31], RS Kahn[30], R Roiz-Santiañez[32,33], B Crespo-Facorro[32,33], L Wang[34,35], KI Alpert[34], EG Jönsson[5,7], R Dimitrova[36], C Bois[36], HC Whalley[36], AM McIntosh[36], SM Lawrie[36], R Hashimoto[37], PM Thompson[2] and JA Turner[25,38] for the ENIGMA Schizophrenia Working Group[39]

The profile of brain structural abno
scans. To validate a prospective me
from 2028 schizophrenia patients a

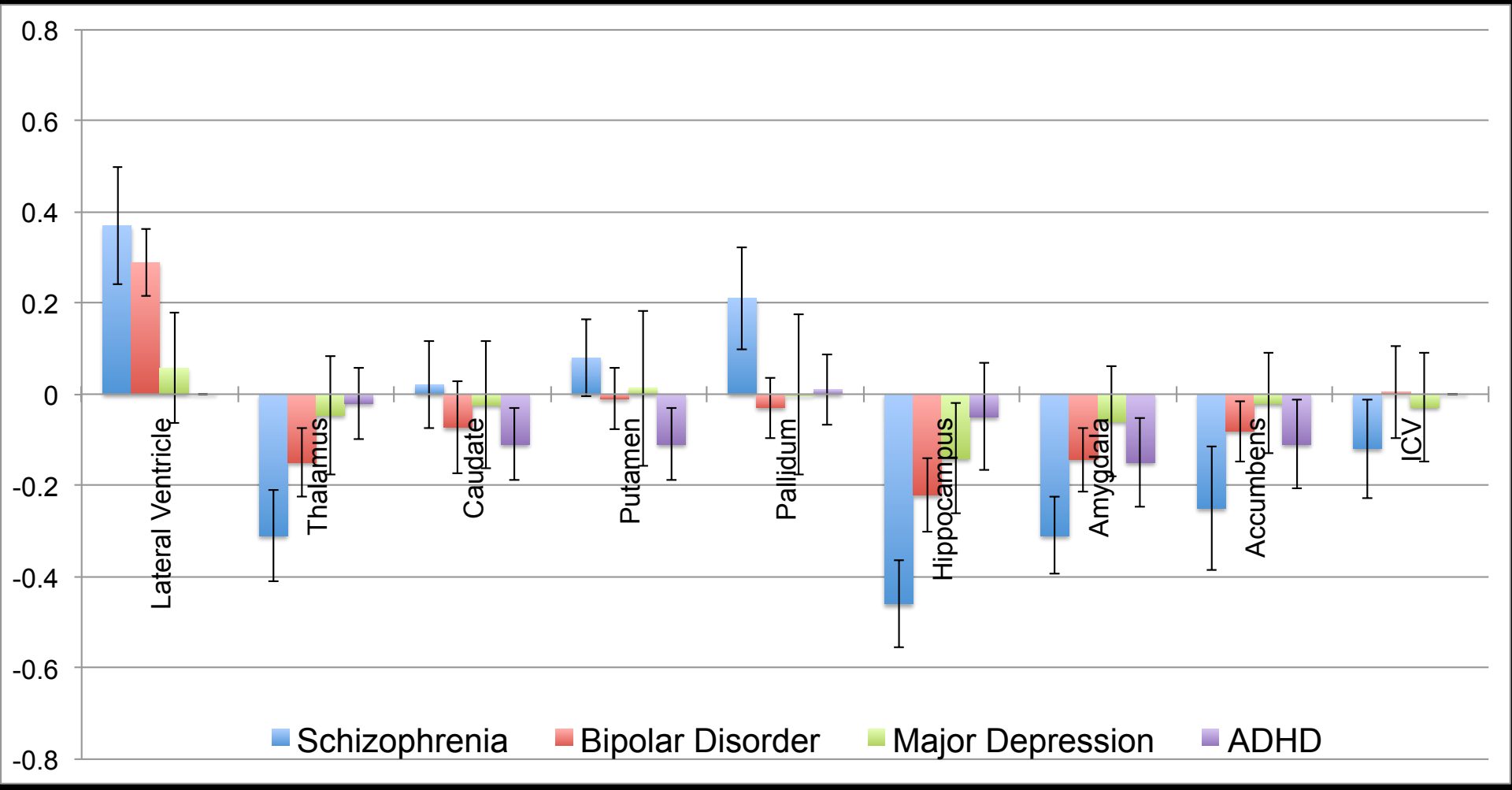
ORIGINAL ARTICLE

Subcortical brain alterations in major depressive disorder: findings from the enigma major depressive disorder working group

L Schmaal[1], DJ Veltman[1], TGM van Erp[2], PG Sämann[3], T Frodl[4,5], N Jahanshad[6], E Loehrer[7], H Tiemeier[7,8], A Hofman[7], WJ Niessen[9,10], MW Vernooij[7,9], MA Ikram[7,9,11], K Wittfeld[12], HJ Grabe[12,13,14], A Block[13], K Hegenscheid[15], H Völzke[16], D Hoehn[3], M Czisch[3], J Lagopoulos[17], SN Hatton[17], IB Hickie[17], R Goya-Maldonado[18], B Krämer[18], O Gruber[18], B Couvy-Duchesne[19,20,21], ME Rentería[19], LT Strike[19], NT Mills[19,22], GI de Zubicaray[20], KL McMahon[21], SE Medland[19], NG Martin[19], NA Gillespie[23], MJ Wright[19], GB Hall[24,25], GM MacQueen[26], EM Frey[4], A Carballedo[27], LS van Velzen[1], MJ van Tol[28], NJ van der Wee[29,30], IM Veer[31], H Walter[31], K Schnell[32], E Schramm[33,34], C Normann[33], D Schoepf[35], C Konrad[36], B Zurowski[37], T Nickson[38], AM McIntosh[38,39], M Papmeyer[38], HC Whalley[38], JE Sussmann[38], BR Godlewska[40], PJ Cowen[40], FH Fischer[41,42], M Rose[41,43], BWJH Penninx[1], PM Thompson[6] and DP Hibar[6] for the ENIGMA-Major Depressive Disorder Working Group[44]

The pattern of structural brain alterations associated with major depressive disorder (MDD) remains unresolved. This is in part due to small sample sizes of neuroimaging studies resulting in limited statistical power, disease heterogeneity and the complex interactions

Cross Disorder Effects



Test-Retest Reliability

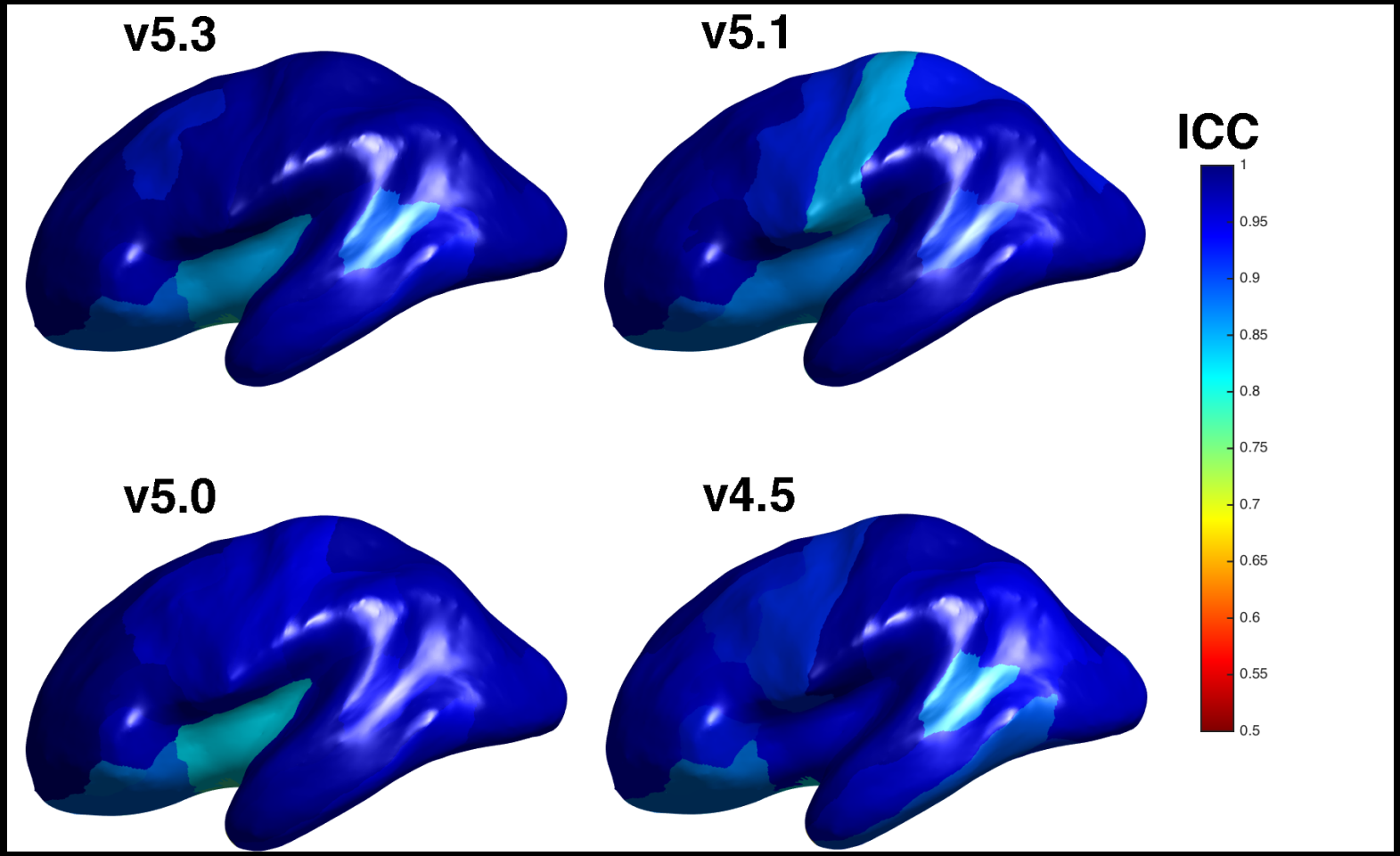
- Intraclass Correlation Coefficient (ICC) for mean bilateral volume for different versions of FreeSurfer
- Calculated in 161 healthy elderly controls from the ADNI2 (repeat scans 3 months apart)

	v5.3	v5.1	v5.0	v4.5	v4.4	v4.2
Thalamus	0.936	0.918	0.936	0.951	0.952	0.947
Caudate	0.972	0.970	0.975	0.971	0.971	0.968
Putamen	0.942	0.938	0.961	0.960	0.960	0.951
Pallidum	0.865	0.902	0.907	0.872	0.872	0.802
Hippocampus	0.962	0.953	0.941	0.968	0.968	0.970
Amygdala	0.893	0.881	0.899	0.891	0.891	0.897
Accumbens	0.853	0.825	0.817	0.764	0.763	0.812
ICV	0.853	0.996	0.998	0.996	0.996	0.953

Subcortical structures are reliably segmented in FreeSurfer regardless of version; smaller structures tend to have a lower test-retest reliability.

Test-Retest Reliability in the Cortex

ICC of Cortical Thickness in FreeSurfer ROIs (161 healthy elderly controls)



Test-Retest Reliability in the Cortex

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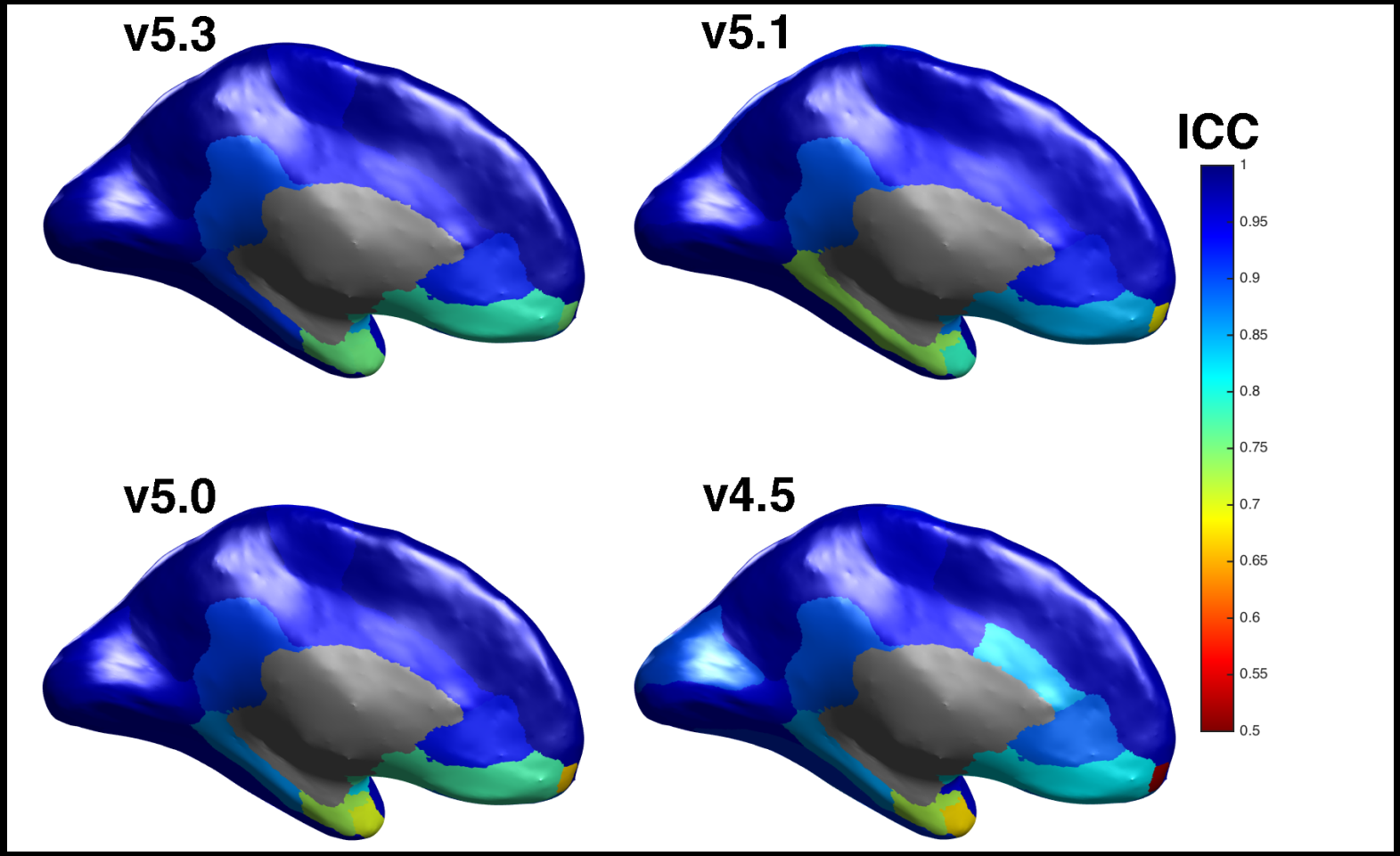
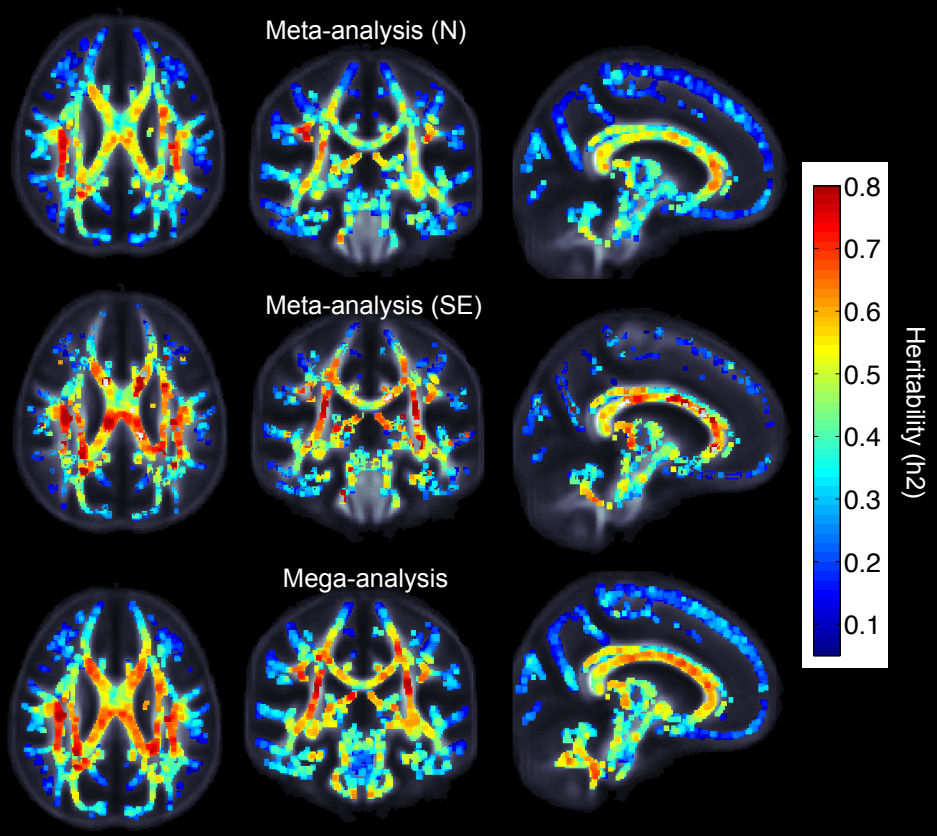
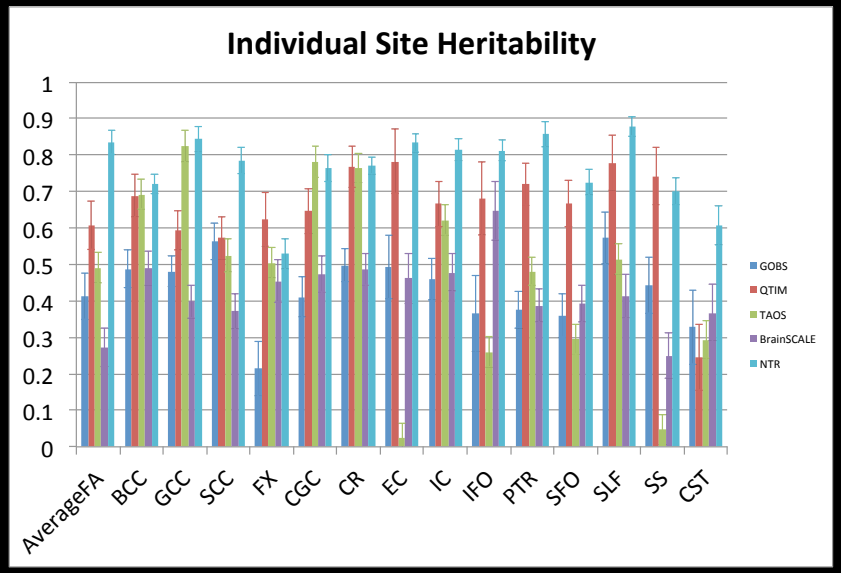


ENIGMA - DTI





Neda Jahanshad (neda.jahanshad@ini.usc.edu)

enigma.ini.usc.edu/ongoing/dti-working-group

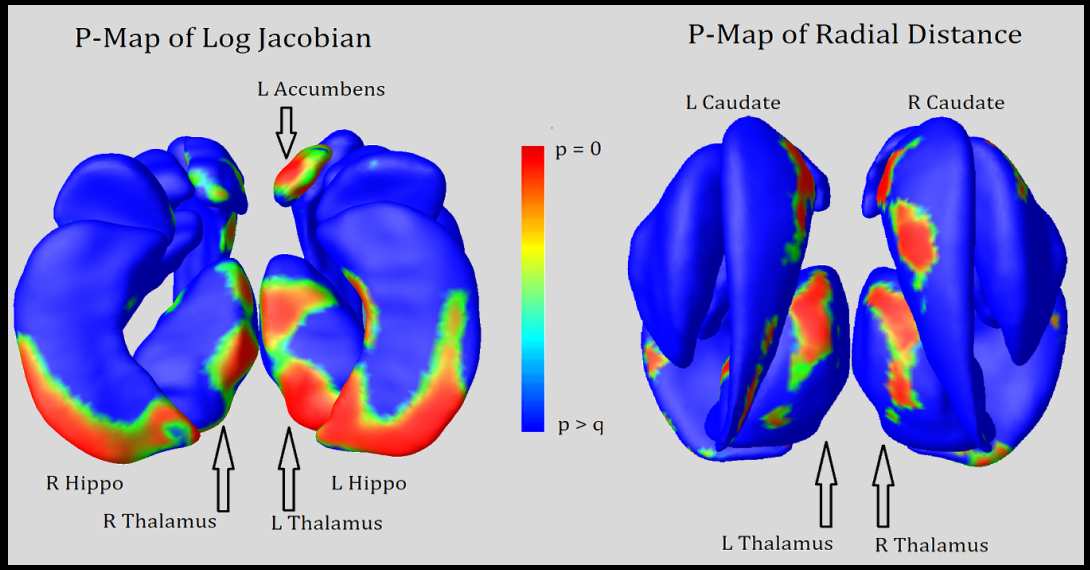
Novel Shape Modeling Software – Multisite comparisons in Schizophrenia

Novel shape modeling software (Surface TBM and Radial Distance Measures)

Software package developed to be plug-and-play for any interested site

Standardized template allows for cross-site comparison

Example:
Shape meta-analysis in Schizophrenia (2 cohorts)

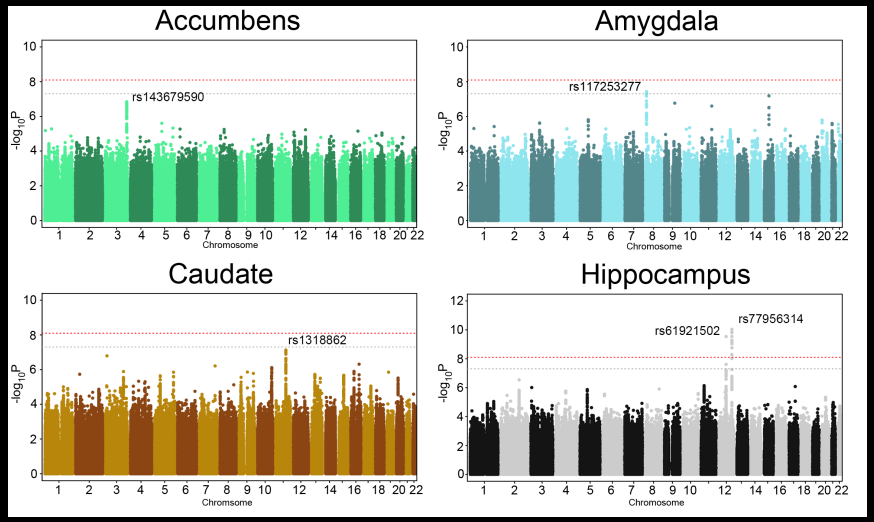


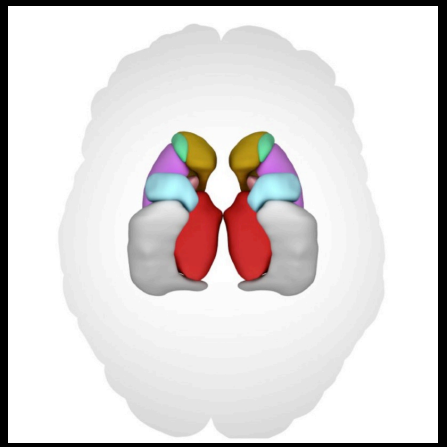
Gutman, et al., ISBI 2015;
Gutman, et al., ISBI 2012

Lines of work in ENIGMA: Genetics

- GWAS or Genome-Wide Association Studies
- MRI – ENIGMA1 (HV, ICV, TBV)
  - ENIGMA2 (subcortical)
  - ENIGMA3 (cortical)
  - vGWAS meta-analysis (image-wide)
- DTI – GWAS (N>13,500)
  - Neda Jahanshad (neda.jahanshad@ini.usc.edu)
- Enrichment testing of results – AD* (ENIGMA2-CHARGE/ADSP), PGC-SCZ; PD*, OCD*; ILAE, IMSGC*; "secondary proposals", e.g., kinome, biological pathways; Methylation and CNVs

ENIGMA2: Genetics of Brain Structure (Hibar +287 authors, *Nature*, Jan. 2015); enrichment testing in AD, PD, OCD, MS, SCZ

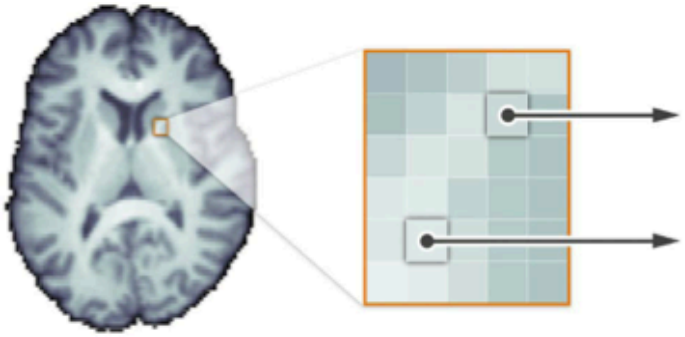


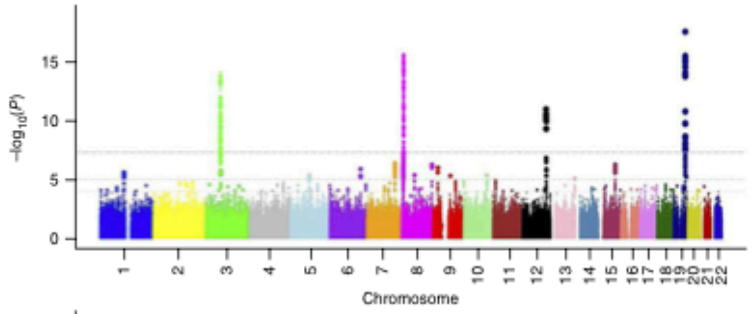


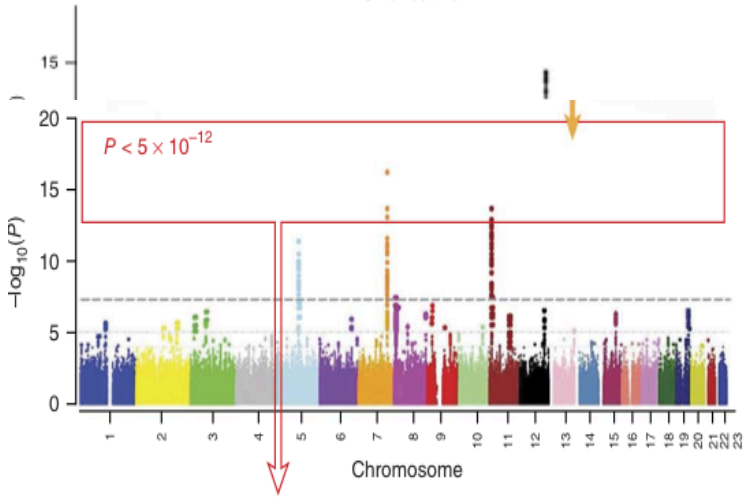
Total Sample Size: 30,717 individuals at 50 sites

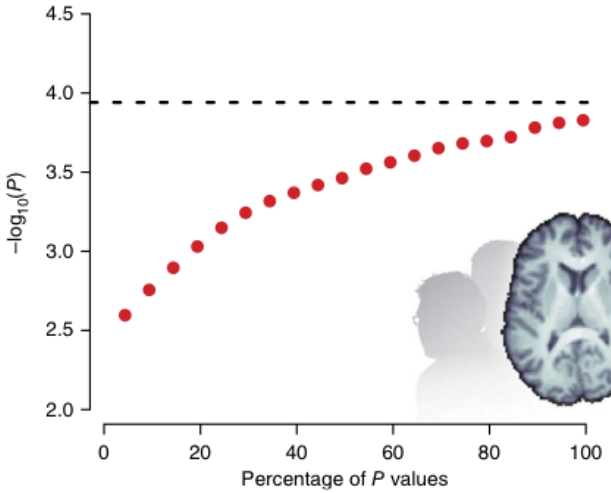
Look for genes that affect the brain by searching the **entire brain** and the **entire genome**:

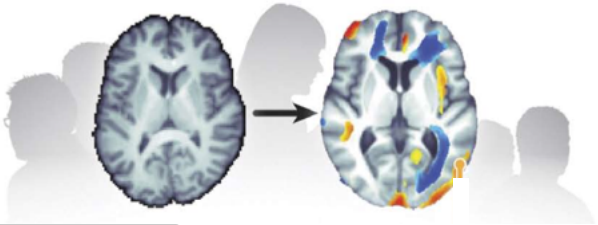
vGWAS





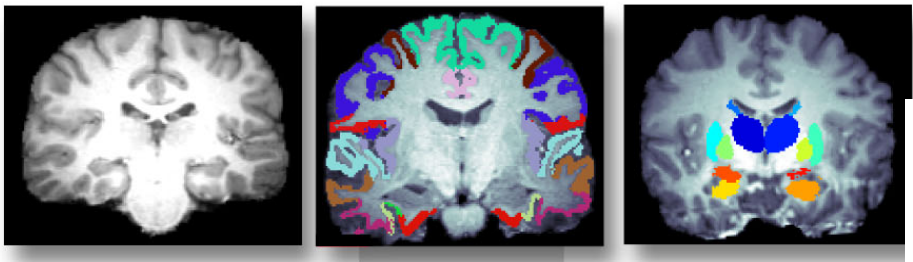






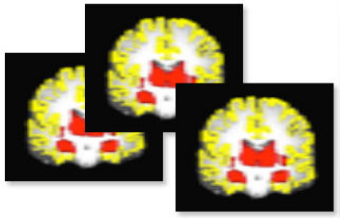
Disease association study

Medland*, Jahanshad*, Neale, Thompson Nature Neuroscience 2014

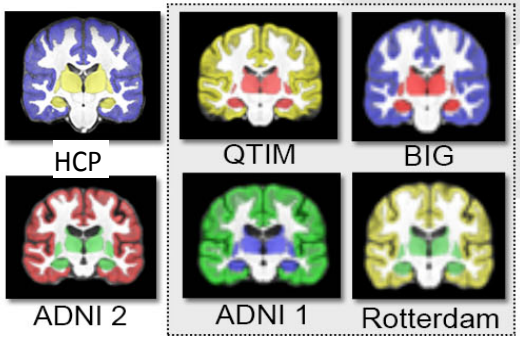


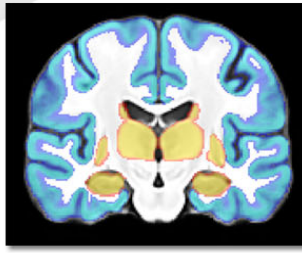
MNI alignment of 3 channels:

1) T1-weighted image
2) Binarized cortical ribbon
3) Binarized subcortical set



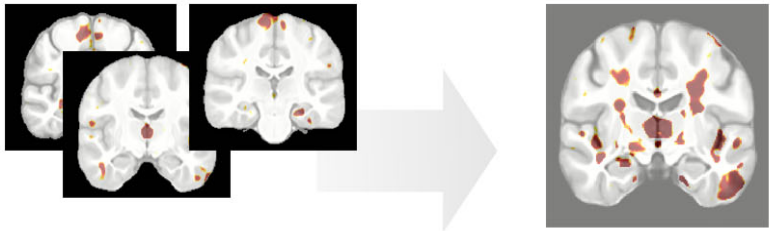
ANTs multichannel minimal deformation template ($3MDT_j$) created from a representative subset for each cohort





Multichannel MDT created from 4 MDTs ($3MDT_{3MDT}$)

For each subject *i* in cohort *j* one 3D Jacobian map (Jac), mapping the subject's 3 channels to the cohort's 3-channel MDT ($3MDT_j$), was analyzed as that subject's feature set.



For each cohort *j*, voxel-wise maps of Beta and SE were warped to the $3MDT_{3MDT}$ by applying the corresponding warp.

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Nick Martin QIMR

ENIGMA Working Groups:
ENIGMA1, ENIGMA2
ENIGMA-DTI, ENIGMA-EEG
ENIGMA-SZ, BPD, MDD, ADHD,
22q, HIV, Addiction, OCD, Autism,
CHARGE, PGC2

NIH Big Data to Knowledge Program (BD2K)

300+ ENIGMA co-authors and PIs

185 institutions around the world

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