



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

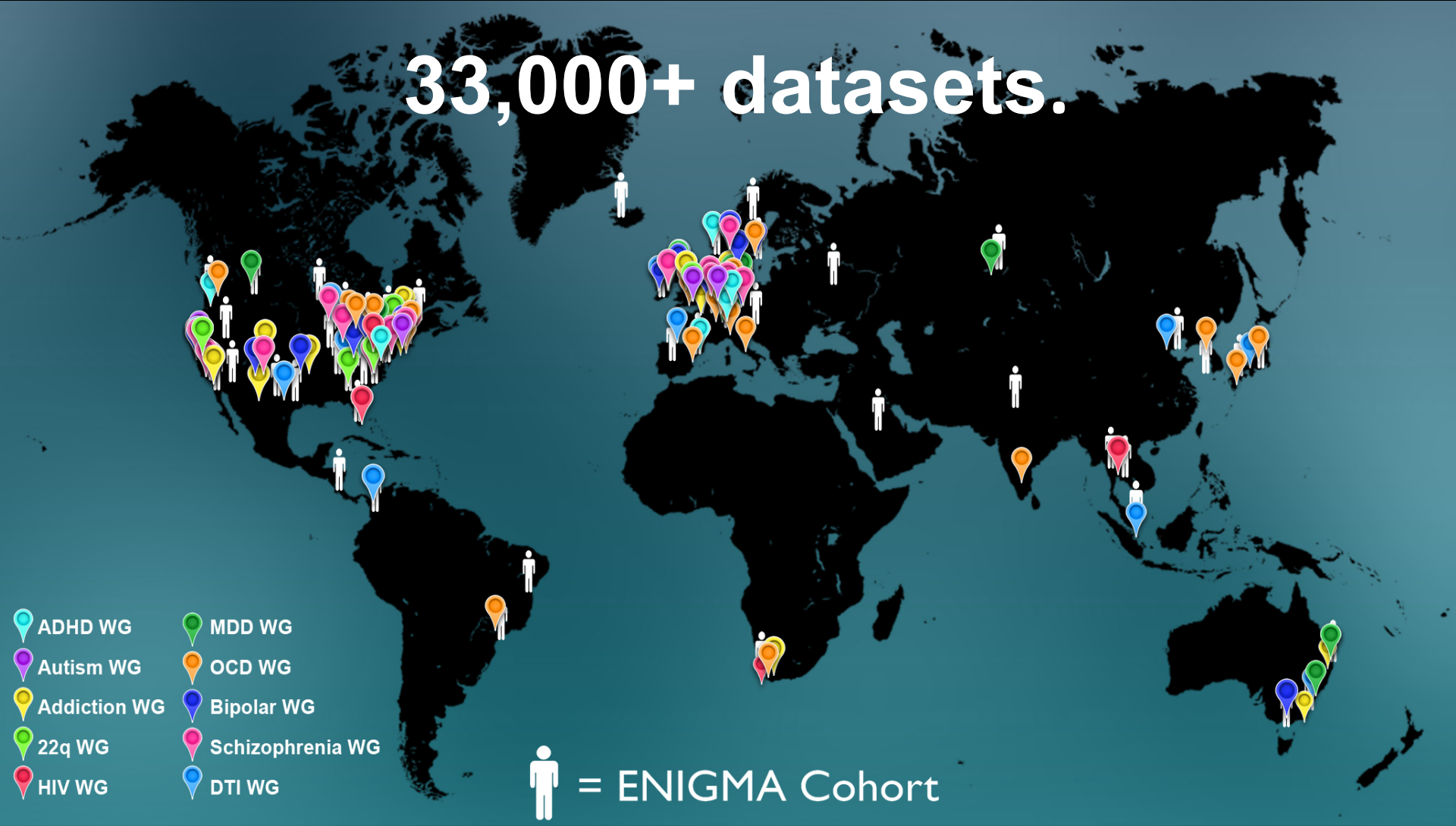
Derrek Paul Hibar  
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for the ENIGMA Consortium

[enigma.ini.usc.edu](http://enigma.ini.usc.edu)

# Map of ENIGMA Members

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

33,000+ datasets.



- ADHD WG
- Autism WG
- Addiction WG
- 22q WG
- HIV WG
- MDD WG
- OCD WG
- Bipolar WG
- Schizophrenia WG
- DTI WG

 = ENIGMA Cohort

# What is ENIGMA?

## 3 general directions of activity

### ENIGMA GWAS

#### ENIGMA '1'

Hippocampus + ICV  
GWAS

#### ENIGMA '2'

Subcortical GWAS

ENIGMA-  
Cortex

ENIGMA-DTI

### ENIGMA disease working groups

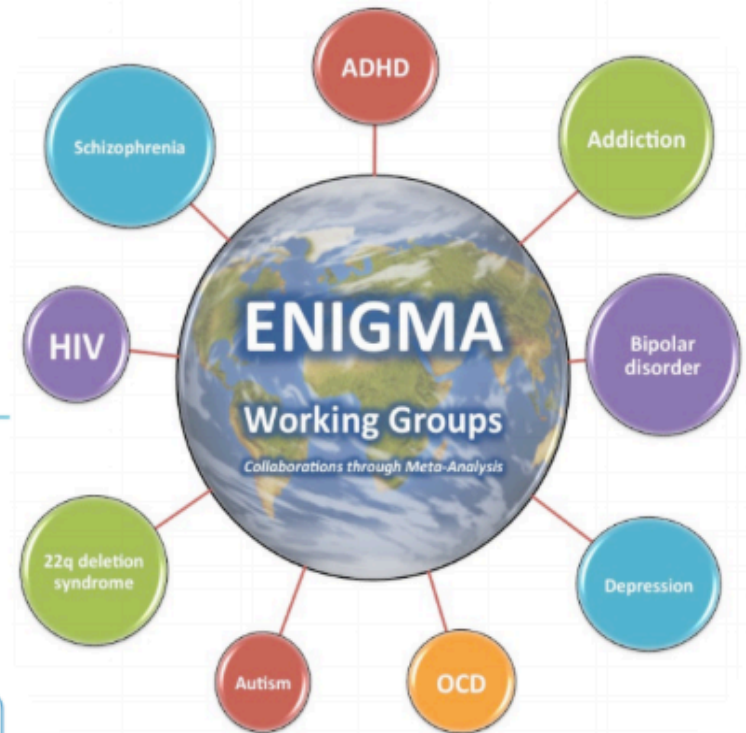
### Methods development groups

ENIGMA-  
Plasticity

ENIGMA-  
Shape

ENIGMA-DTI

ENIGMA-  
Connectome



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

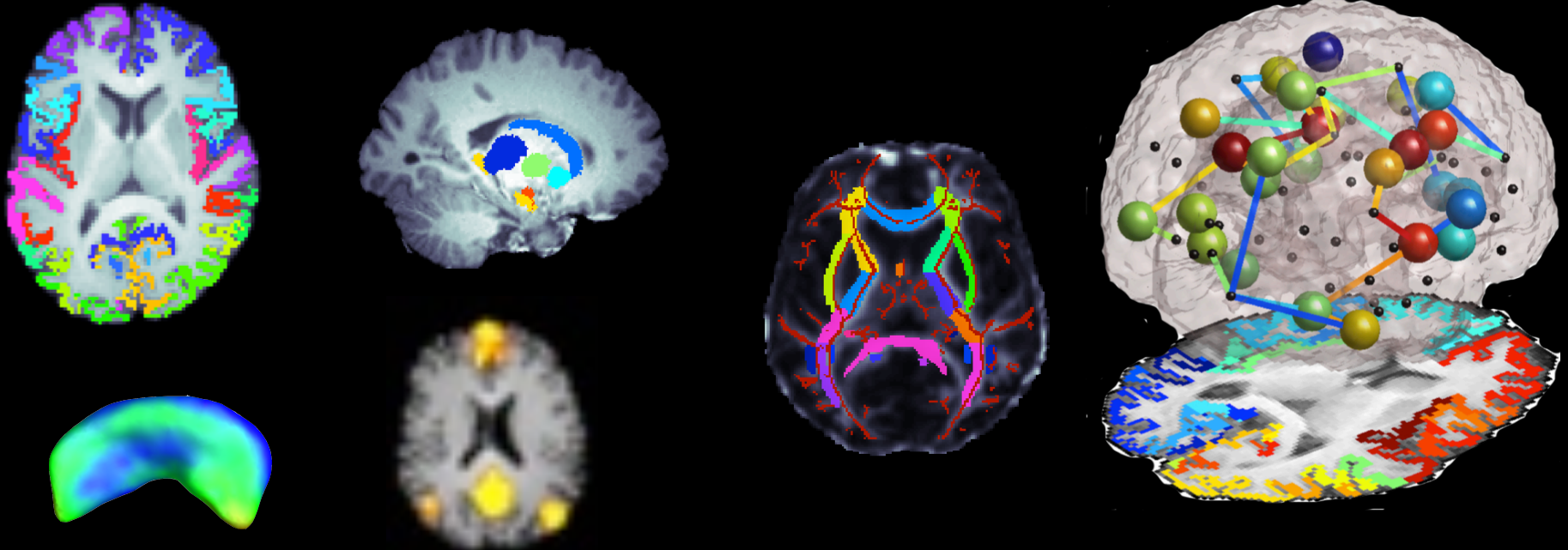
- ENIGMA-Disease working groups
  - Schizophrenia
  - Bipolar Disorder
  - Major Depression
  - Autism
  - Attention Deficit Hyperactivity Disorder
  - Obsessive Compulsive Disorder
  - Addiction
  - 22q11 deletion syndrome
  - HIV
  - Parkinson's disease
  - Epilepsy

[enigma.ini.usc.edu/ongoing/](http://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

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

### ORIGINAL ARTICLE

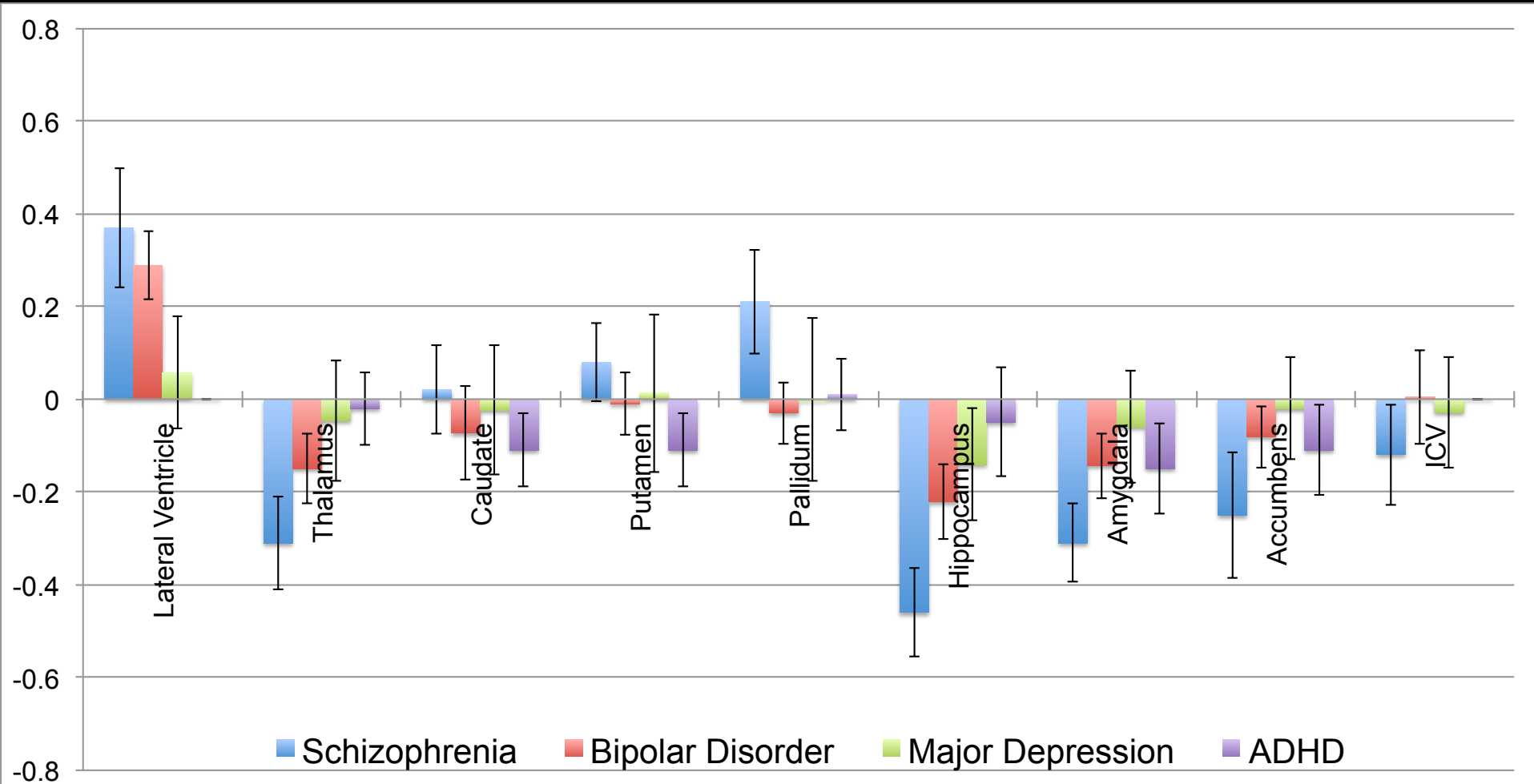
## Subcortical brain alterations in major depressive disorder: findings from the enigma major depressive disorder working group

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

The profile of brain structural abnormalities from 2028 schizophrenia patients and 2540 healthy controls via the ENIGMA consortium.

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)

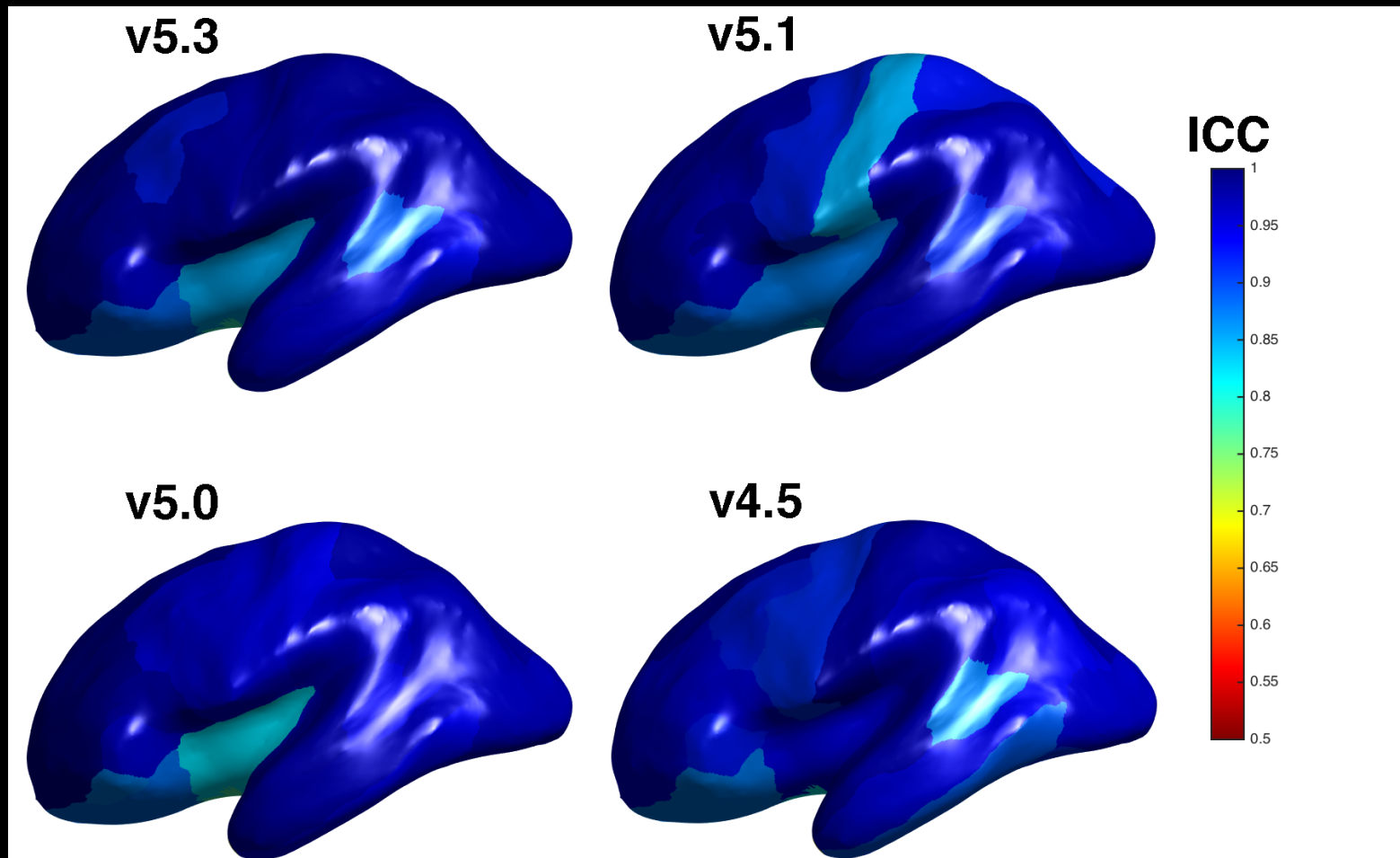
	v5.3	v5.1	v5.0	v4.5	v4.4	v4.2
Thalamus	0.936	0.918	0.936	0.951	0.952	0.947
Caudate	0.972	0.970	0.975	0.971	0.971	0.968
Putamen	0.942	0.938	0.961	0.960	0.960	0.951
Pallidum	0.865	0.902	0.907	0.872	0.872	0.802
Hippocampus	0.962	0.953	0.941	0.968	0.968	0.970
Amygdala	0.893	0.881	0.899	0.891	0.891	0.897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



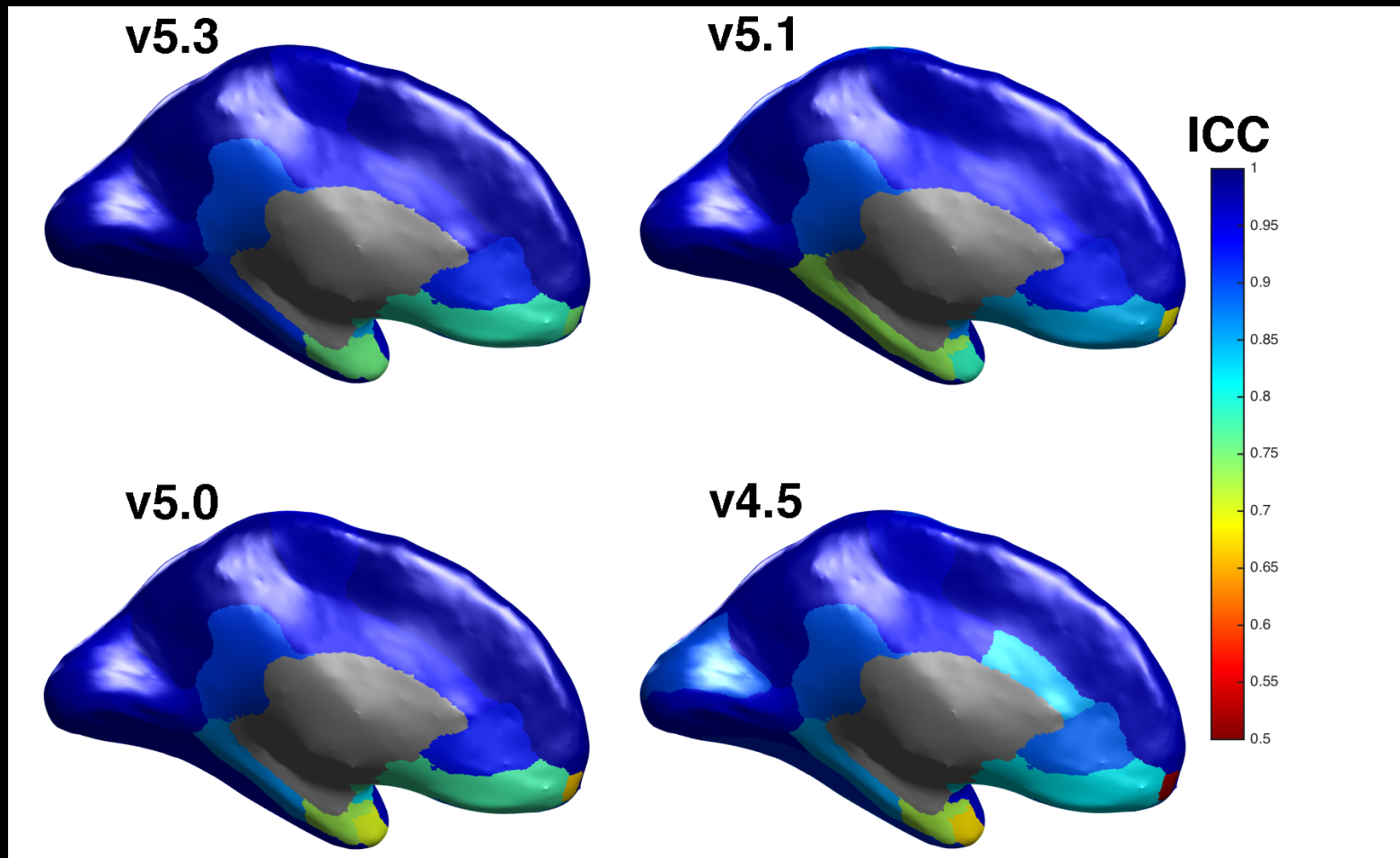
# Test-Retest Reliability in the Cortex

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

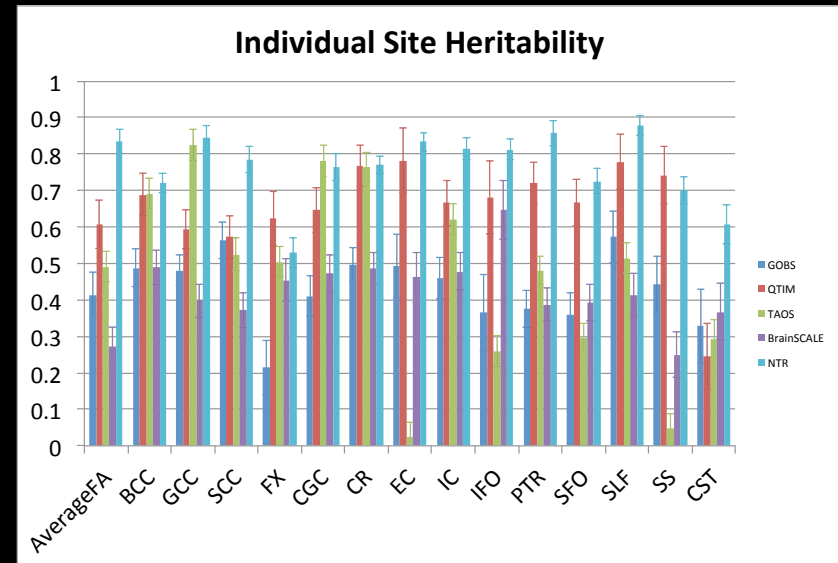
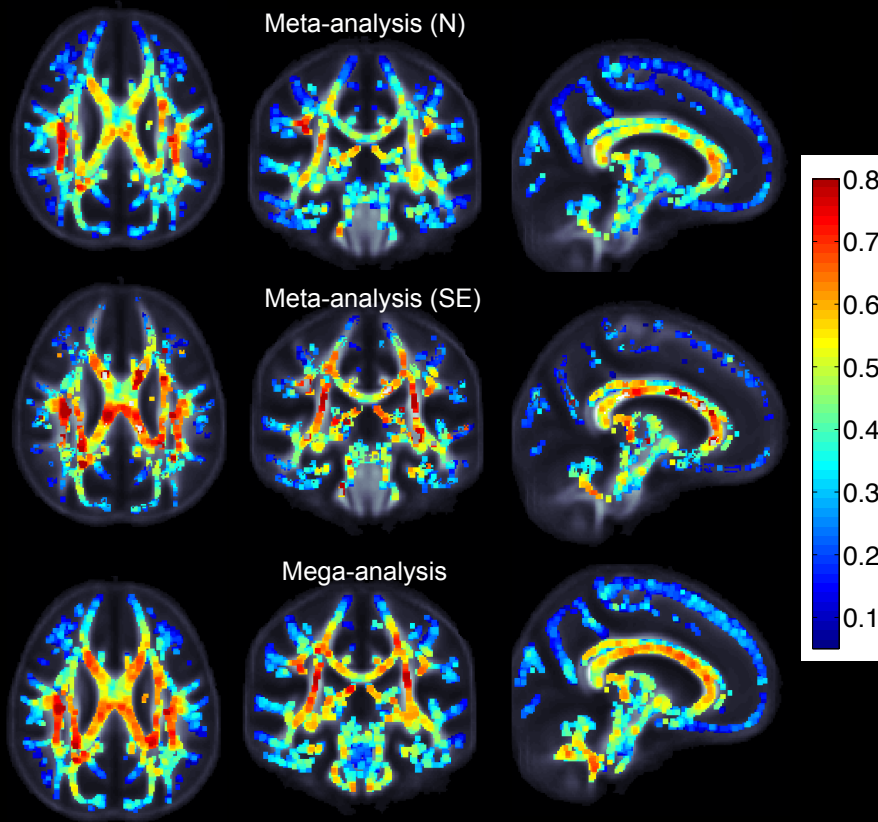


# Test-Retest Reliability in the Cortex

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



# ENIGMA - DTI



**Neda Jahanshad ([neda.jahanshad@ini.usc.edu](mailto:neda.jahanshad@ini.usc.edu))**

[enigma.ini.usc.edu/ongoing/dti-working-group](http://enigma.ini.usc.edu/ongoing/dti-working-group)

# Novel Shape Modeling Software – Multisite comparisons in Schizophrenia

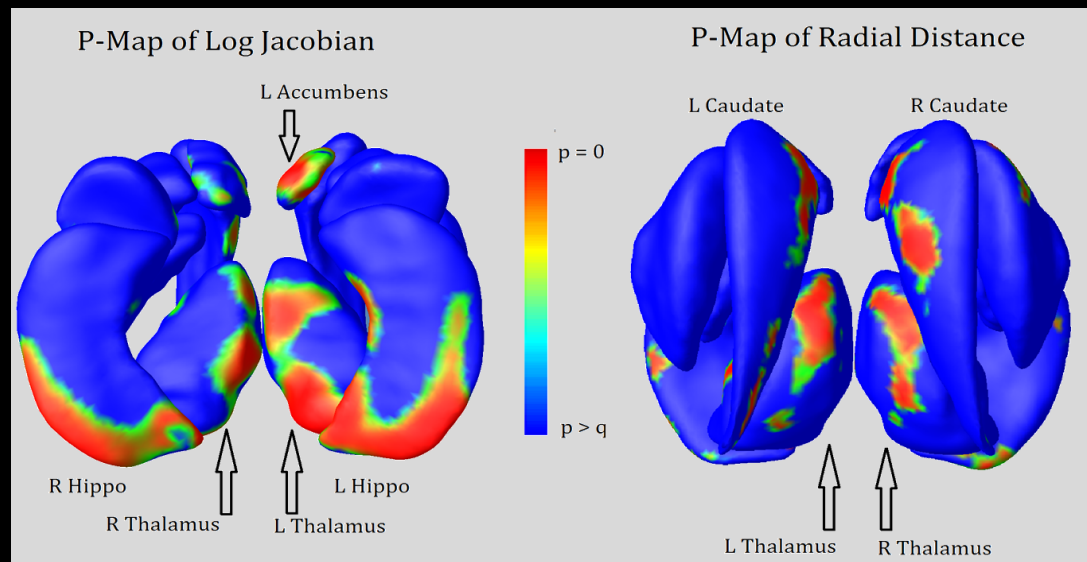
Novel shape modeling software (Surface TBM and Radial Distance Measures)

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)

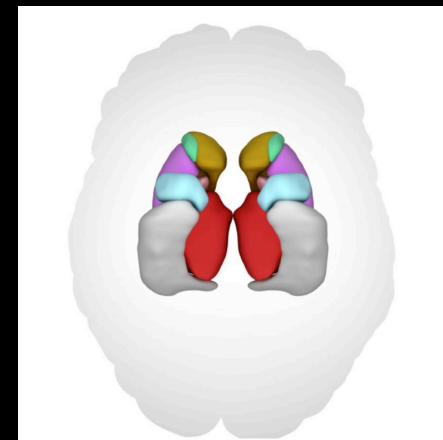
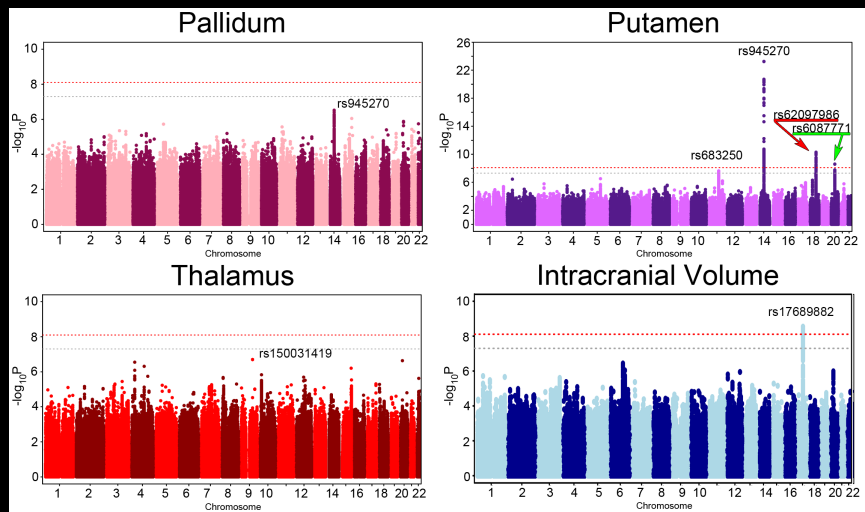
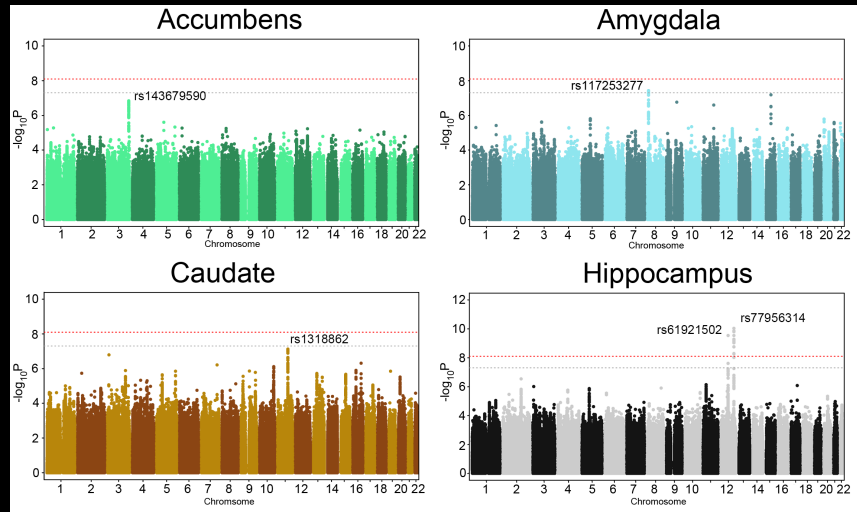
Gutman, et al., ISBI 2015;  
Gutman, et al., ISBI 2012



# 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](mailto: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

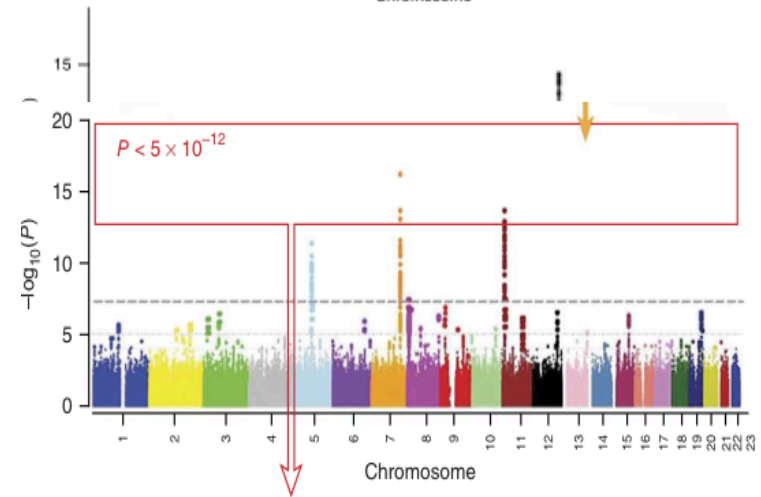
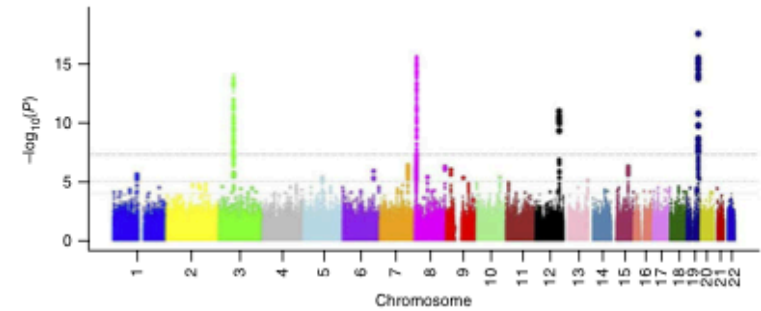
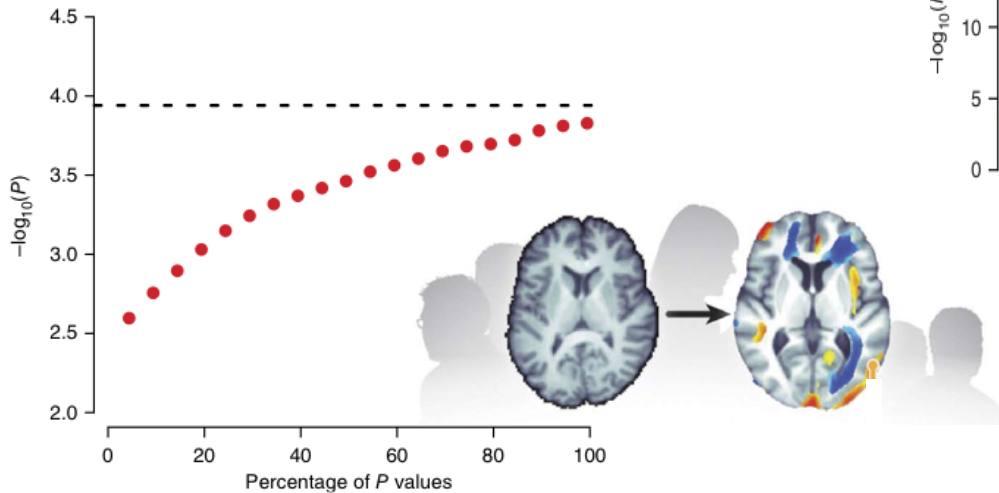
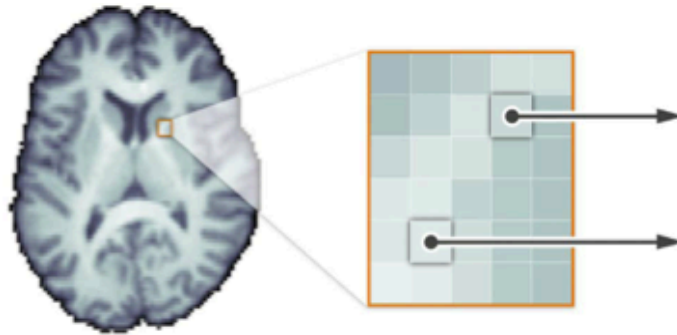
# ENIGMA2: Genetics of Brain Structure (Hibar +287 authors, *Nature*, Jan. 2015); enrichment testing in AD, PD, OCD, MS, SCZ



Total Sample Size: 30,717 individuals at 50 sites

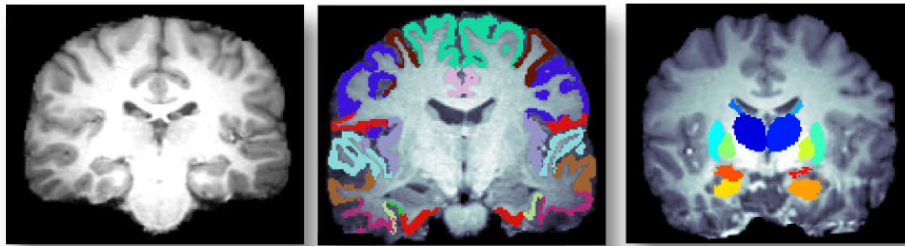
# Look for genes that affect the brain by searching the **entire brain** and the **entire genome**:

## vGWAS



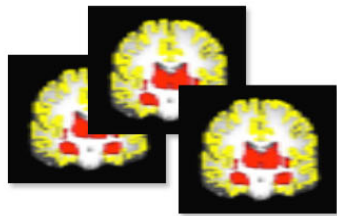
Disease association study



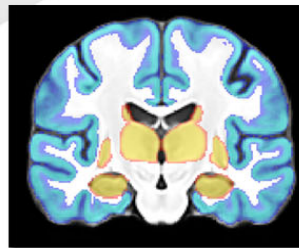
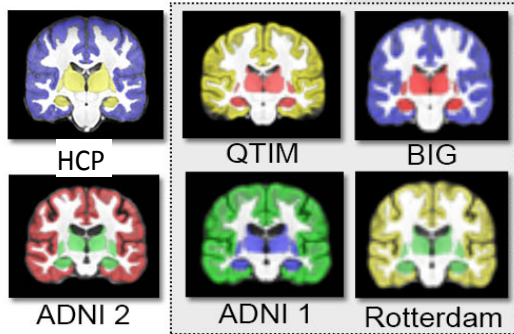


MNI alignment of 3 channels:

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

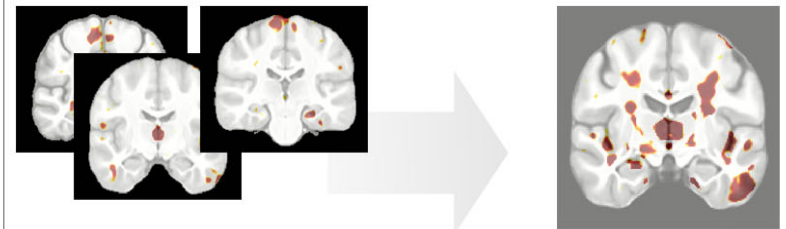


ANTs multichannel minimal deformation template ( $3MDT_j$ ) created from a representative subset for each cohort



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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Paul Thompson, IGC  
 Sarah Medland, QIMR  
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 Neda Jahanshad, IGC  
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 Margie Wright, QIMR  
 Nick Martin QIMR

## NIH Big Data to Knowledge Program

(BD2K)

300+ ENIGMA co-authors and PIs

185 institutions around the world

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



Imaging Genetics Center

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, ISCI, SENY Fundació, NOW, BBMRI-NL, CBF, Hersenstichting Nederland, Alzheimer’s Australia Dementia Research Foundation, Autism Speaks, NIMH, NIBIB, NICHD, NINDS, NIA

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