PGC Worldwide Lab Call Details

- Friday, October 11, 2013
- PRESENTERS:
  - Dr. Dr. Paul Thompson; Associate Dean for Research, University of Southern California; Professor of Neurology and Psychiatry, Imaging Genetics Center/LONI, UCLA School of Medicine; founder ENIGMA Consortium
  - Barbara Franke, PhD; Professor of Molecular Psychiatry, Radboud University Medical Centre in Nijmegen, the Netherlands; Member of ENIGMA Consortium Support Team
- TITLE: *"The ENIGMA Consortium – Exploring the Genetic Architecture of Human Brain Structure."*
- *Start and Duration: We will begin promptly on the hour and end within 60 minutes.*
  - 10:00 EDT - US East Coast
  - 07:00 PDT - US West Coast
  - 03:00 BST – UK
  - 04:00 CEST - Central Europe
  - 01:00 AEST – Australia
- PASSCODE: **275 694 38** and TELEPHONE:
  - US Toll free: 1 866 515 2912
  - International Direct: +1 617 399 5126
  - Global Access Numbers: There may be a toll-free number from your country. See http://www.btconferencing.com/globalaccess/?bid=75_public
- Operators will be on standby to assist with technical issues. "*0" will get you assistance.
- The conference line can handle up to 300 participants.

Lines are muted NOW

- Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.
- **Operators announce callers one at a time during question and answer sessions.**
- **Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.**
- **Dial *0 if you need operator assistance at any time during the duration of the call.**

UPCOMING PGC Worldwide Lab

- Date: Friday, November 8, 2013
- Presenters:
  - To be announced

The ENIGMA Consortium: Exploring the Genetic Architecture of Human Brain Structure

Barbara Franke[1] and Paul M. Thompson[2]
For the ENIGMA Consortium (307 authors)[3]

[1] Radboud University Medical Centre in Nijmegen, NL
[2] University of Southern California, Los Angeles, CA, USA
[3] http://enigma.ini.usc.edu

Introduction: What is ENIGMA?

"**E**nhancing **N**euro **I**maging **G**enetics through **M**eta-**A**nalysis"

- Largest brain imaging studies in the world (*Nature Genetics*, Apr 15 2012; 21,151 subjects with CHARGE) in partnership with IMAGEN and other European consortia, Australian consortia, …
- Worldwide consortium – 32 cohorts, 125 author affiliations, 307 co-authors (massive global collaboration; "Crowd-sourcing", Wikipedia)
- Use GWAS and meta-analysis to discover genetic variants associated with brain measures from MRI, DTI, … (global & regional brain volumes, integrity/connectivity of fiber tracts)
- ENIGMA Working Groups focus on particular diseases – schizophrenia (N=4,600), bipolar, major depression, ADHD; just starting on 22qDS, Addiction (N=8,000; 10 sites), HIV, OCD, …
- Find brain measures that best differentiate patients from controls

What is "Imaging Genetics"?

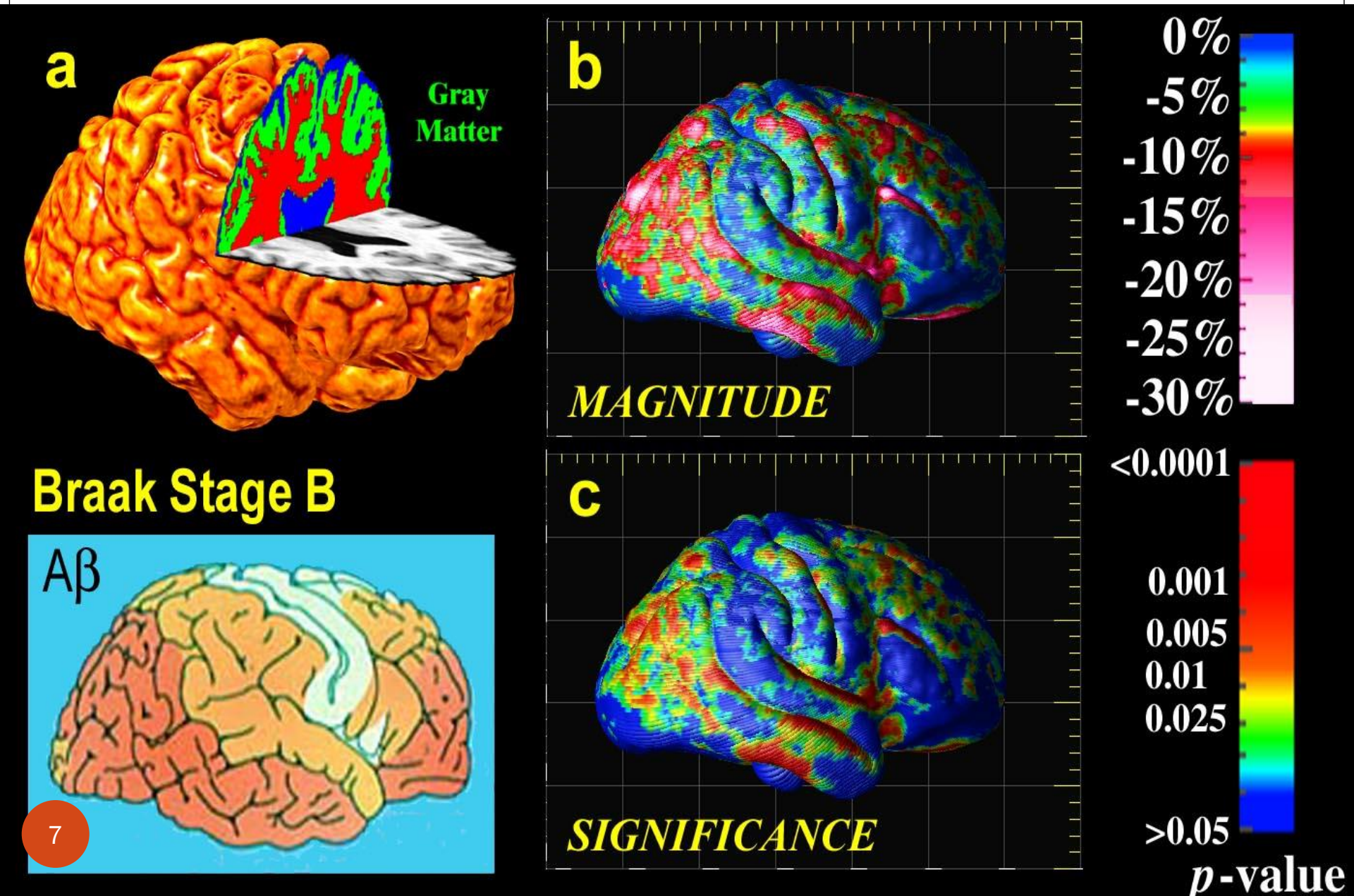
2 ways to use images:

- First find common DNA variants associated with disease (Alzheimer's, schizophrenia, autism, …); e.g., PGC, ADGC
- How do these genetic variants affect *the brain*? Could screen images to find differences associated with risk genes

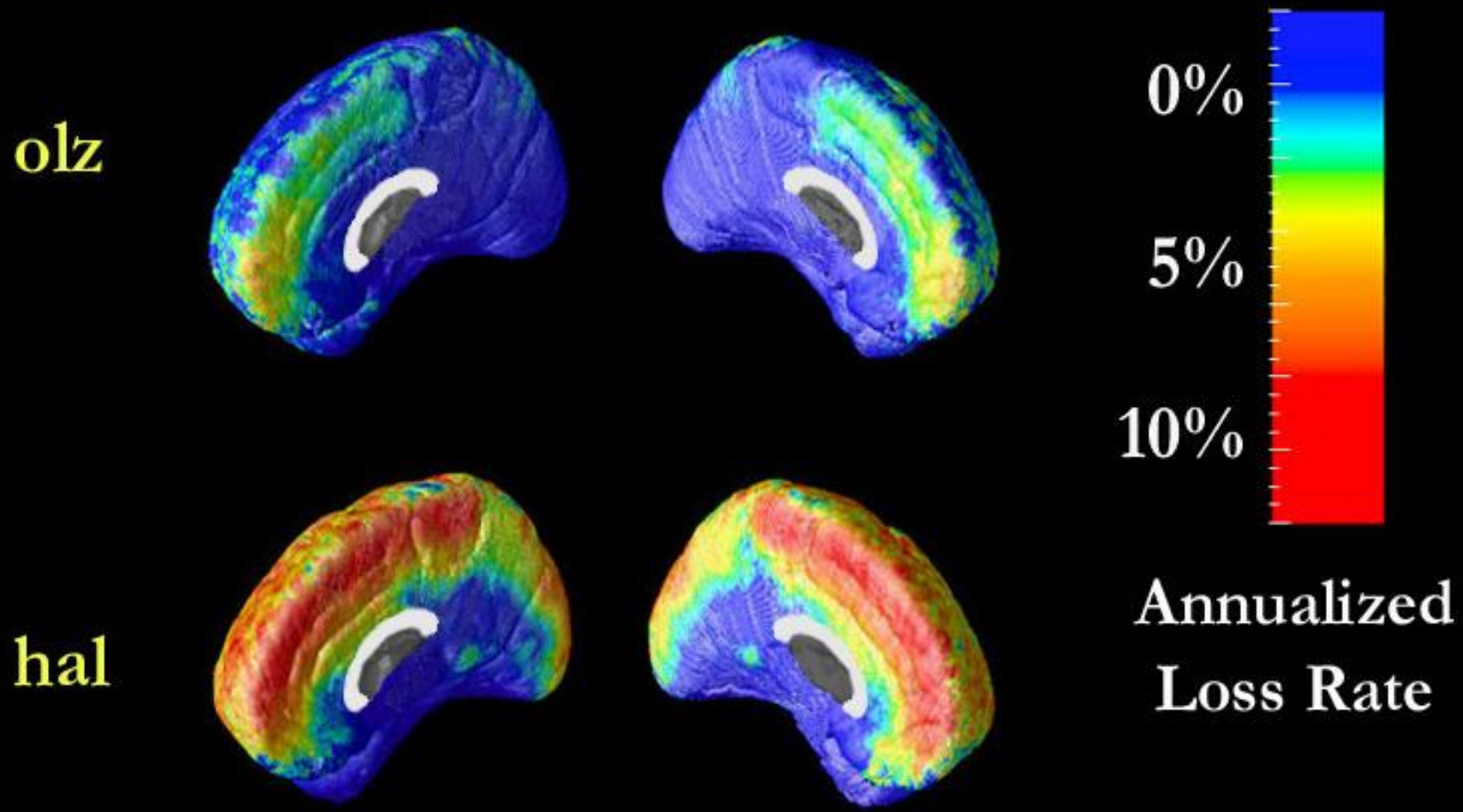
OR

- Directly screen brain images to identify SNPs associated with brain measures on MRI – morphometry; DTI – integrity/connectivity. Work with PGC to see how they relate to disease risk
- ENIGMA project – pool data from around the world; reproducibility / credibility of brain imaging (most brain imaging studies are N=20-1,000 subjects)

MRI of Alzheimer's Disease – Measures Disease Burden, used in Drug Trials; Endophenotype



Imaging Endophenotypes in Psychiatry – Olanzapine as a schizophrenia treatment; we discovered that it slows brain tissue loss

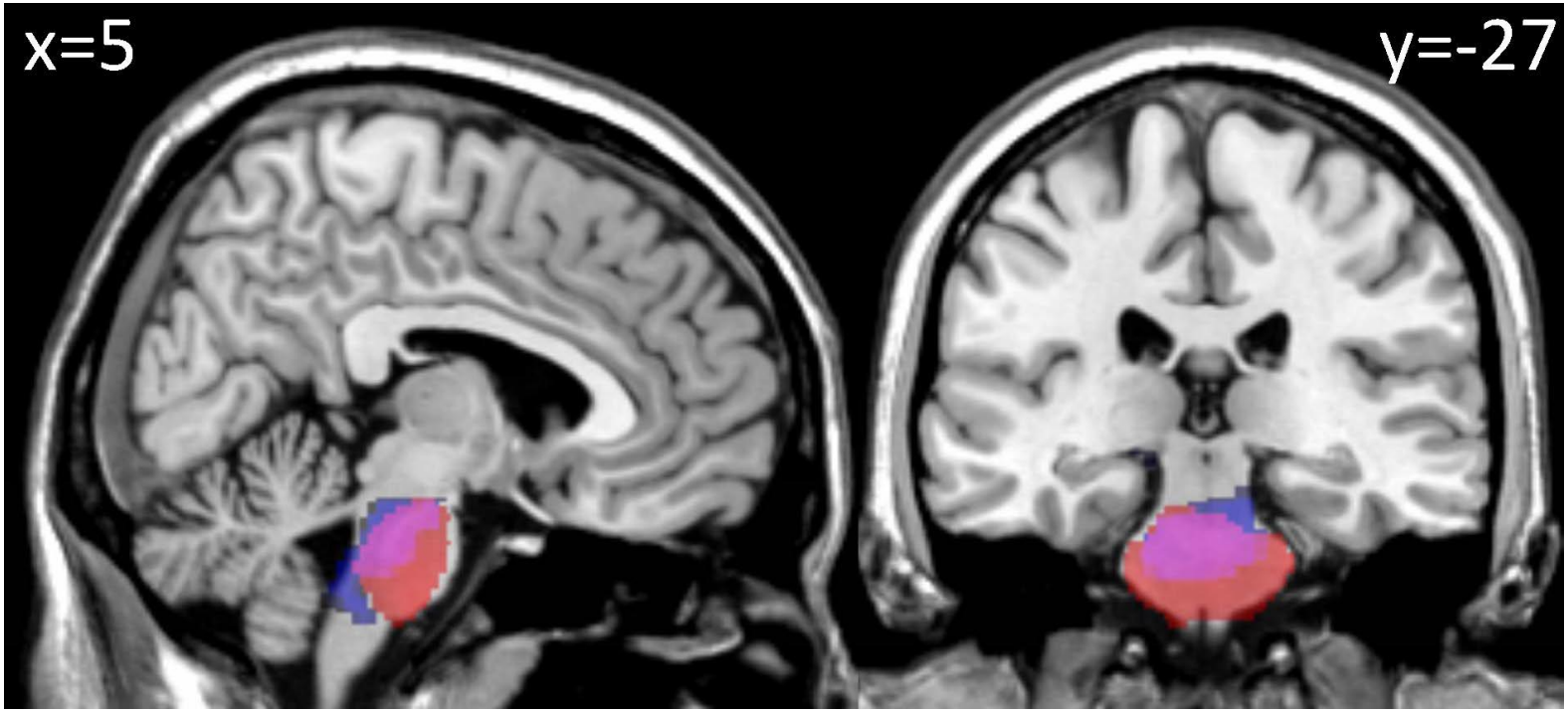


Thompson/Lieberman/Eli Lilly Inc. – HGDH Drug Trial 2008; *PNAS* 2001

Candidate genes & imaging:

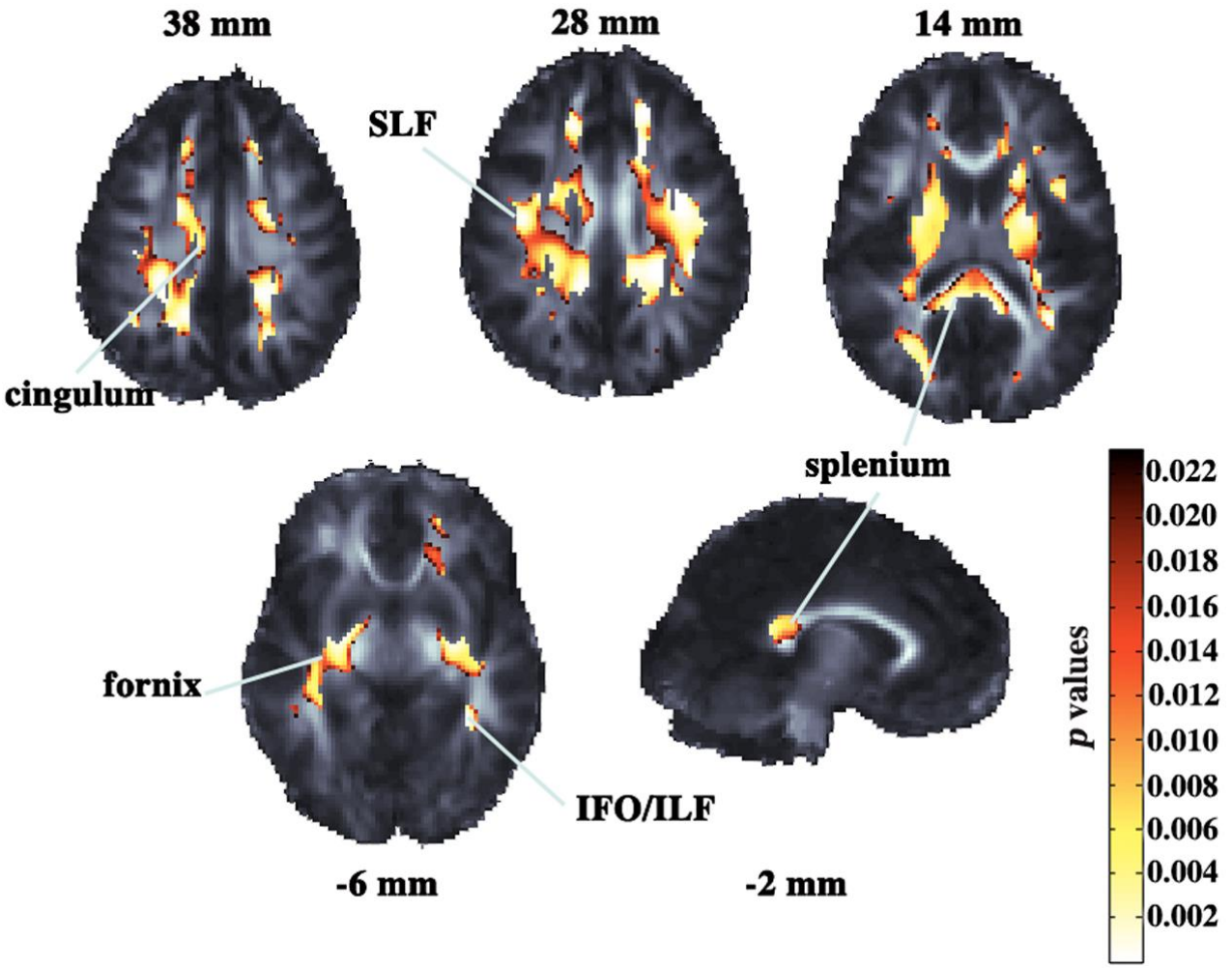
SNPs in the cross-disorder psychiatry risk gene CACNA1C reproducibly alter brainstem volume

(Franke et al., Biol Psychiatry 2010)



1.5 Tesla (in red): n=282
3 Tesla (in blue): n= 304
Overlap in pink

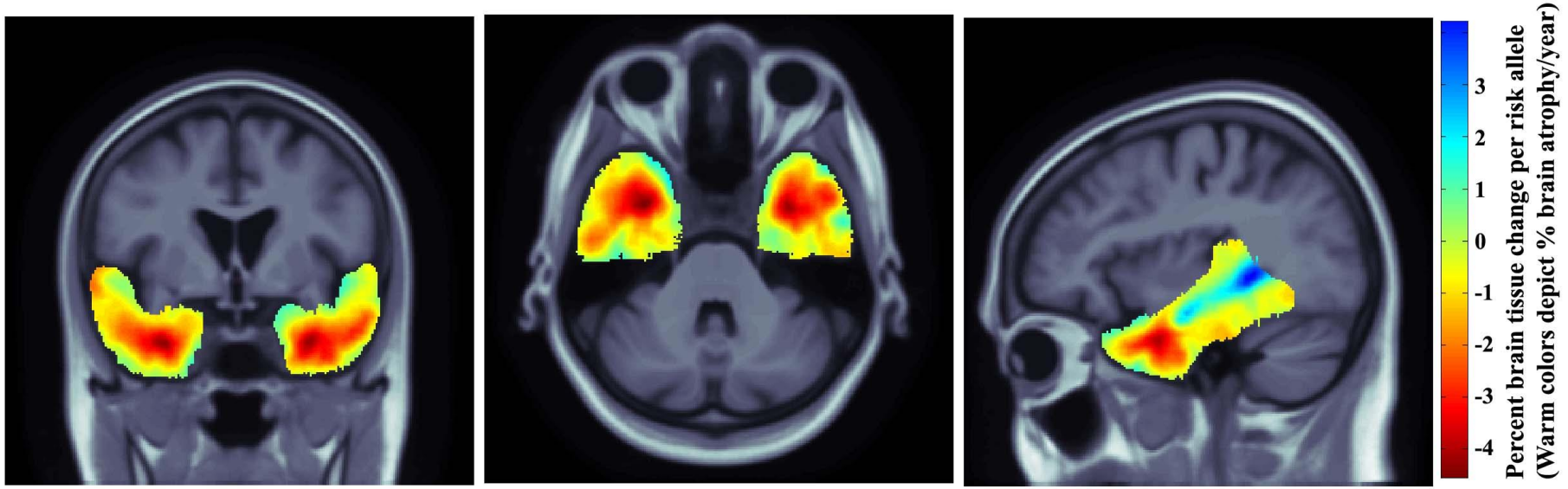
Alzheimer's risk gene carriers (*CLU*-C) have lower fiber integrity even when young (N=398), 50 years before disease typically hits [News covered in 20 countries]



Voxels where *CLU* allele C (at rs11136000) is associated with lower FA after adjusting for age, sex, and kinship in 398 young adults (68 T/T; 220 C/T; 110 C/C). FDR critical $p = 0.023$. Left hem. on Right

Braskie et al., Journal of Neuroscience, May 4 2011

Carriers of some genetic variants lose brain tissue faster



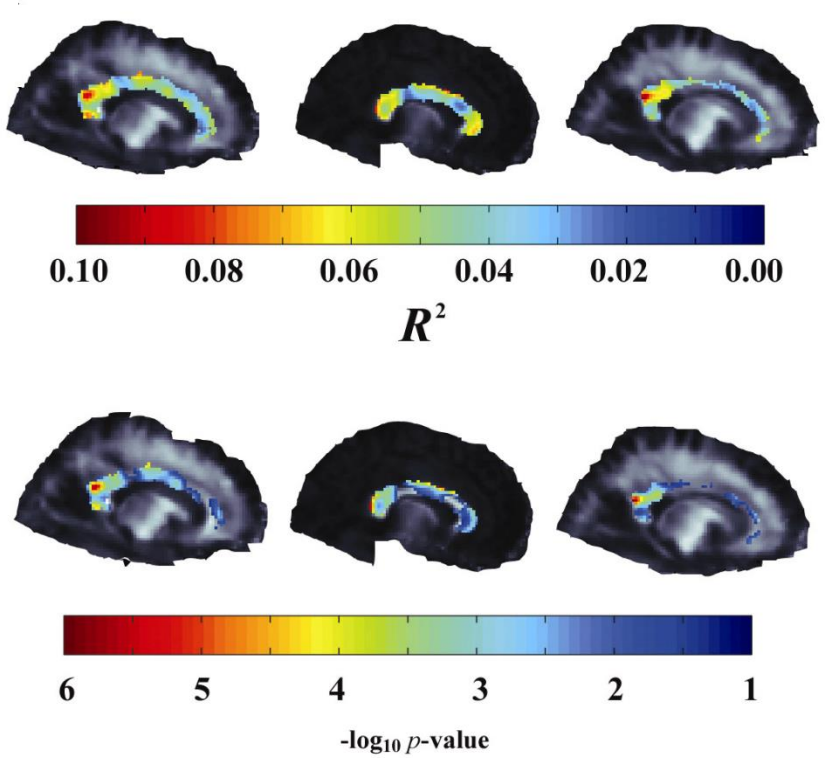
Useful for drug trial "enrichment" – enroll people likely to decline faster

Rajagopalan, Hibar, Thompson (2013). **NEJM**, Oct. 2013.

Polygenic tests to **predict your brain integrity**

(7 SNPs) or rate of brain loss (empower drug trials)

Neuro-chemical genes	*COMT*
	NTRK1
Neuro-developmental genes	*ErbB4*
	BDNF
Neuro-degenerative risk genes	*HFE*
	CLU



A significant fraction of variability in white matter structure of the corpus callosum (measured with DTI) is predictable from SNPs.

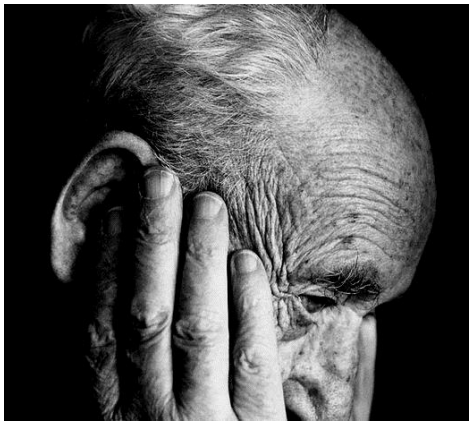
Kohannim O, *et al*. Predicting white matter integrity from multiple common genetic variants. *Neuropsychopharmacology* 2012.

How do we find ***more genetic variants*** that help or harm the brain?

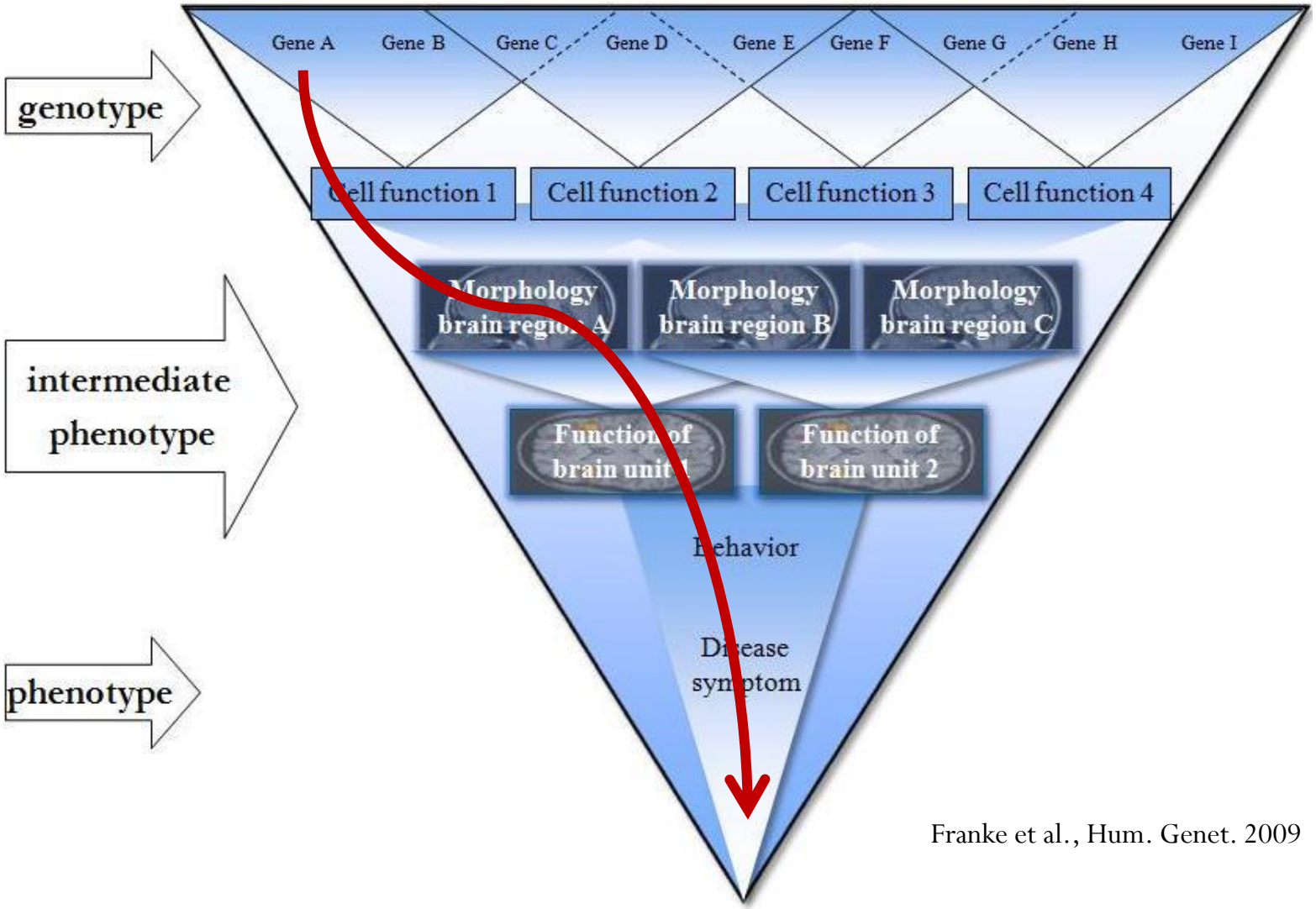
Brain measures may be a good target for genetic analysis – may be easier to find genetic variants that ***affect the brain***

difficult

May require 10,000-100,000 people
e.g., the Psychiatric Genomics Consortium (PGC) studies



Pathways from gene to disease



Franke et al., Hum. Genet. 2009

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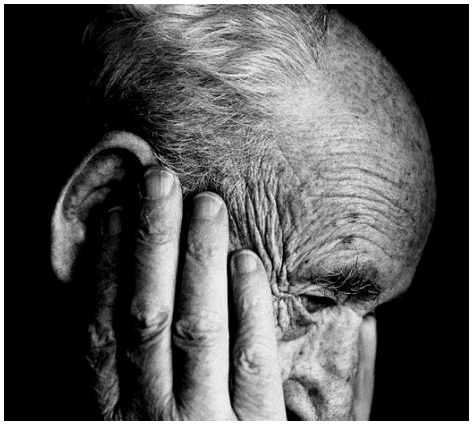
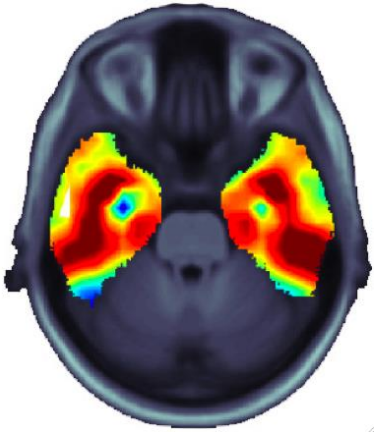


Some have argued smaller samples sizes may suffice for GWAS
(testable hypothesis)



Gene variants may affect brain measures directly, close to site of gene action

Some brain measures (biomarkers) relate to disease status

Precisely and reproducibly measured (1%)

"Endophenotype" or "biomarker" hypothesis

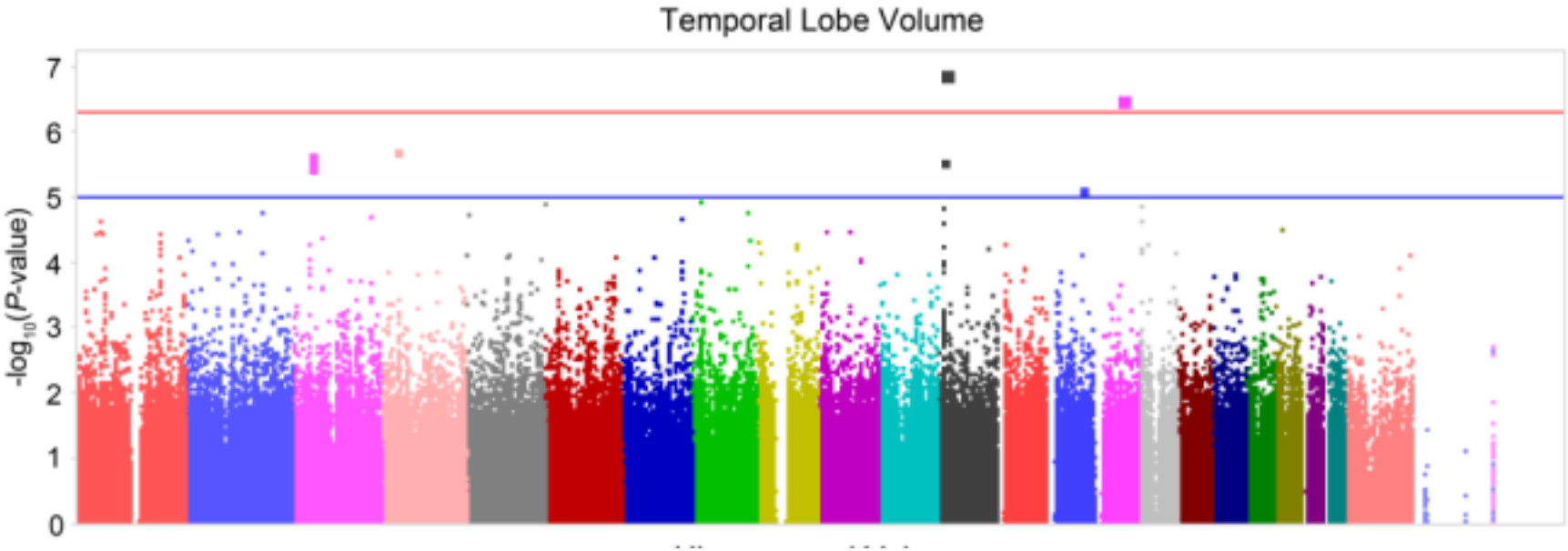
We created the ENIGMA Consortium, 2009 ….

>125 centers worldwide collect brain scans and DNA from 1000s of people, 32 cohorts – needed each other for replication in partnerships with CHARGE, total is 26,000+; ENIGMA 16,000+ and growing

Additional contributing sites are in **ENIGMA Working Groups** (joint analyses with the PGC, DTI, 8 disease working groups)
Several neuroimaging consortia participate, e.g. US ADNI, IMAGEN, Cognomics.

First Genome-Wide Screens of Brain Images in ADNI (2009-2010) were not genome-wide significant but some hits replicated across cohorts (Stein 2010; Stein 2012, caudate volume study in Mol. Psych.)

GRIN2B genetic variant is associated with 2.8% temporal lobe volume deficit. The NMDA-type glutamate receptor is a target of memantine therapy; detected with GWAS in **N=742 subjects;** later replicated in younger cohort

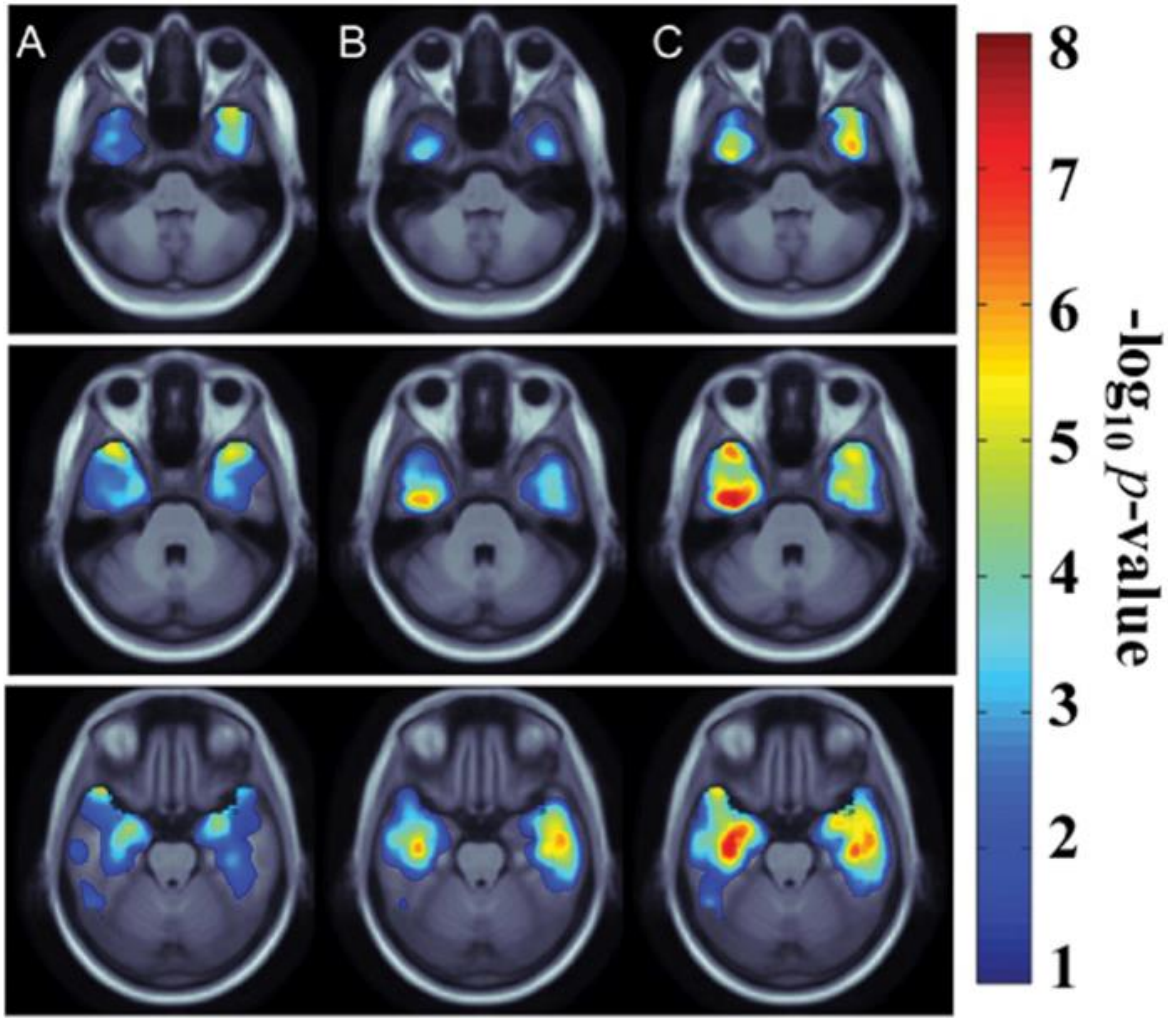


Later ADNI studies:

-*FRMD6* AD risk variants were found in 4 independent imaging studies then later found in large case-control GWAS of AD

Jason L. Stein[1], Xue Hua PhD[1], Jonathan H. Morra PhD[1], Suh Lee[1], April J. Ho[1], Alex D. Leow MD PhD[1,2], Arthur W. Toga PhD[1], Jae Hoon Sul[3], Hyun Min Kang[4], Eleazar Eskin PhD[3,5], Andrew J. Saykin PsyD[6], Li Shen PhD[6], Tatiana Foroud PhD[7], Nathan Pankratz[7], Matthew J. Huentelman PhD[8], David W. Craig PhD[8], Jill D. Gerber[8], April Allen[8], Jason J. Corneveaux[8], Dietrich A. Stephan[8], Jennifer Webster[8], Bryan M. DeChairo PhD[9], Steven G. Potkin MD[10], Clifford R. Jack Jr MD[11], Michael W. Weiner MD[12,13], Paul M. Thompson PhD[1,*], and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease, NeuroImage 2010.**

GRIN2b (glutamate receptor) association with brain volume; TT carriers have 2.8% more temporal lobe atrophy



Effect was later replicated in a younger cohort (Kohannim 2011)

Jason L. Stein[1], Xue Hua PhD[1], Jonathan H. Morra PhD[1], Suh Lee[1], April J. Ho[1], Alex D. Leow MD PhD[1,2], Arthur W. Toga PhD[1], Jae Hoon Sul[3], Hyun Min Kang[4], Eleazar Eskin PhD[3,5], Andrew J. Saykin PsyD[6], Li Shen PhD[6], Tatiana Foroud PhD[7], Nathan Pankratz[7], Matthew J. Huentelman PhD[8], David W. Craig PhD[8], Jill D. Gerber[8], April Allen[8], Jason J. Corneveaux[8], Dietrich A. Stephan[8], Jennifer Webster[8], Bryan M. DeChairo PhD[9], Steven G. Potkin MD[10], Clifford R. Jack Jr MD[11], Michael W. Weiner MD[12,13], Paul M. Thompson PhD[1,*], and the ADNI (2010). **Genome-Wide Analysis Reveals Novel Genes Influencing Temporal Lobe Structure with Relevance to Neurodegeneration in Alzheimer's Disease, NeuroImage, 2010.**

Transition Page

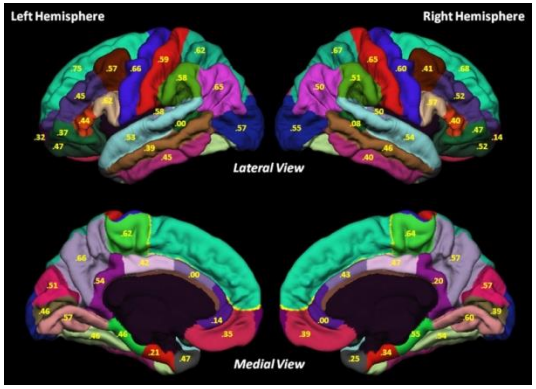
The ENIGMA Consortium: Exploring the Genetic Architecture of Human Brain Structure

What do ENIGMA members do with their scans?

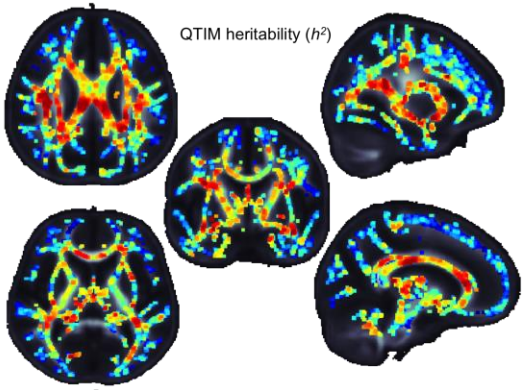
1. Compute brain measures from scans

(harmonized protocol for image analysis + QC; 125 institutions)

Anatomical MRI: Cortical+ subcortical volumes; FreeSurfer / FSL



DTI: FA, MD for Tracts and ROIs Defined on ENIGMA-DTI template



2. GWAS: Test associations between brain measures and 1,000,000+ SNPs

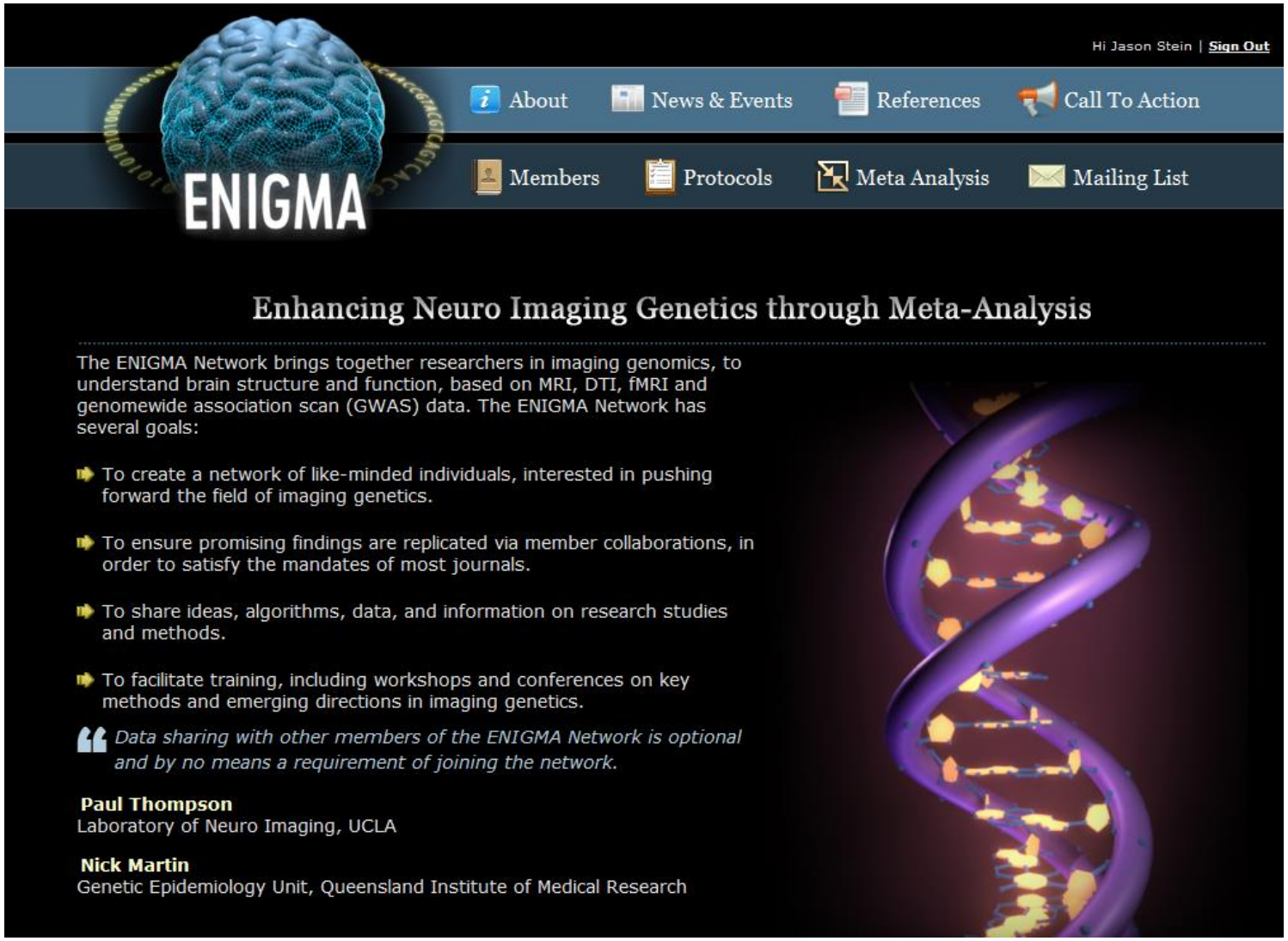
(harmonized protocol for genetic imputation, QC, + analysis)

3. Meta-analysis: combine effects across sites: each site's "vote" depends on the sample size

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

ENIGMA protocols freely available

http://ENIGMA.ini.usc.edu



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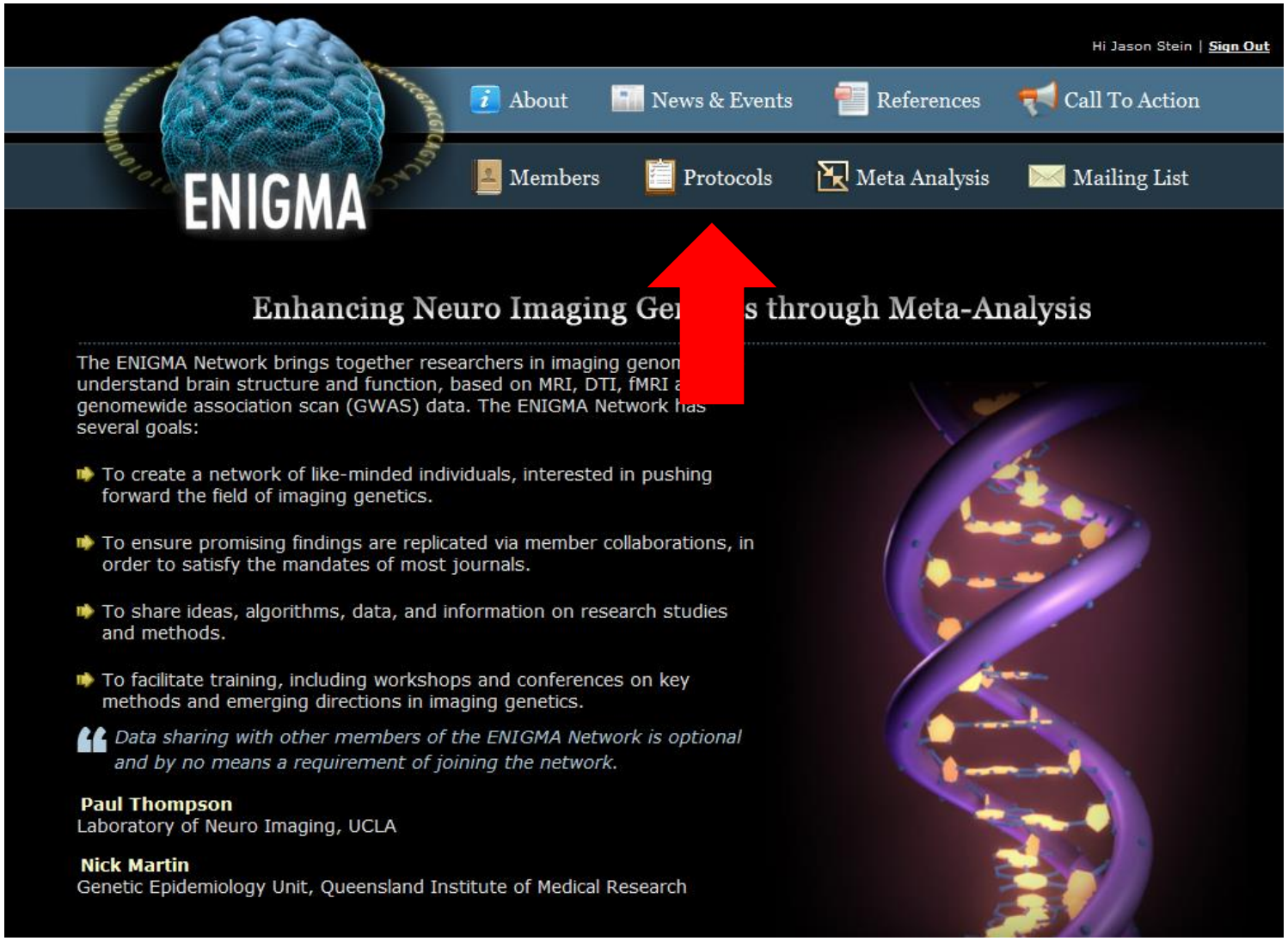
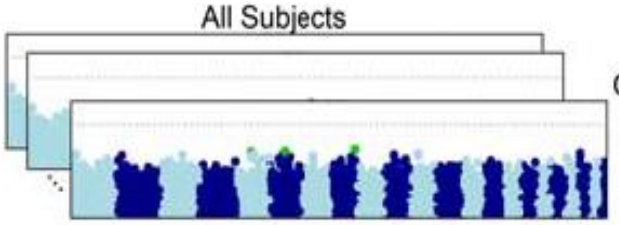


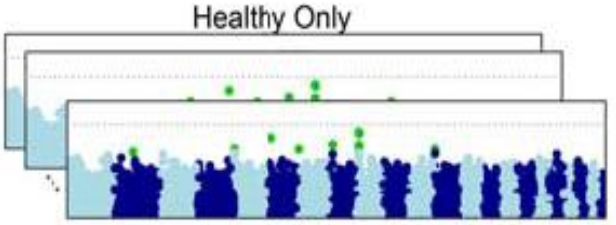
First ENIGMA project

Which genes contribute to hippocampus volume (HV) and measures of total brain volume (ICV)?

ENIGMA project: the approach



Genome-wide association to imaging phenotypes using dosage data (accounting for kinship in related samples)



Phenotypes
Hippocampal Volume
Brain Volume
ICV

Covariates
Brain Volume
ICV
Age
Sex
Age^2
Sex*Age
Sex*Age^2
4 MDS components
Dummy covariates for acquisitions

17 sites uploaded (N=7795)

17 sites uploaded (N=5776)

Quality Checking and Filtering (MAF < 0.01, R^2 < 0.3)

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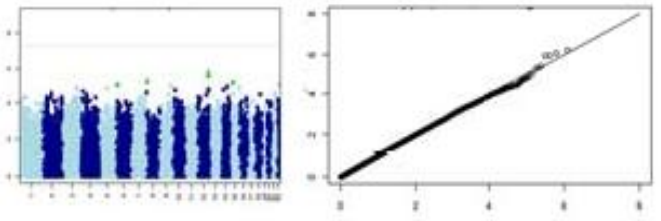
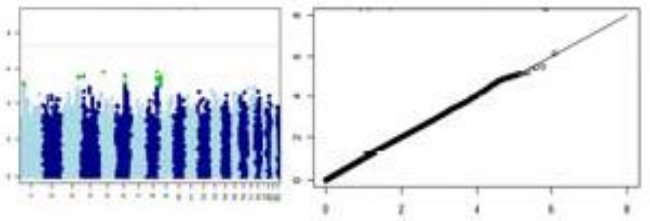
Fixed effects meta-analysis
Random effects meta-analysis

Fixed effects meta-analysis
Random effects meta-analysis

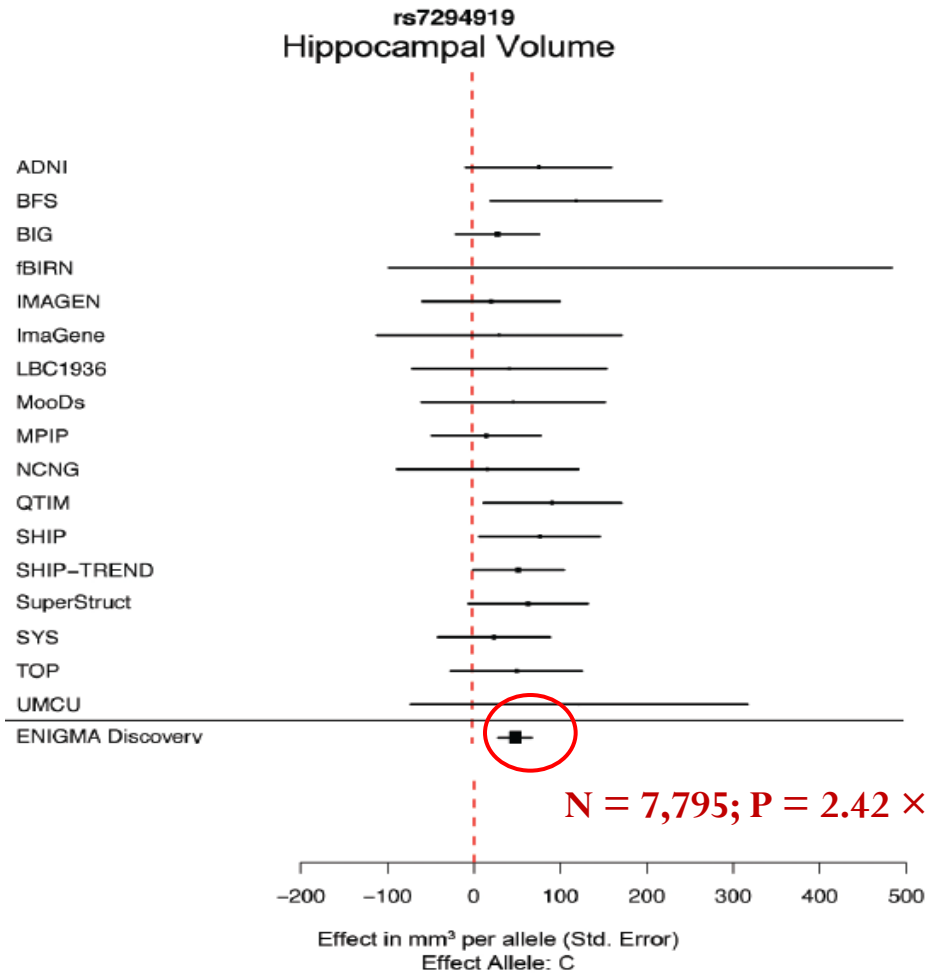
MA: sample-size weighted

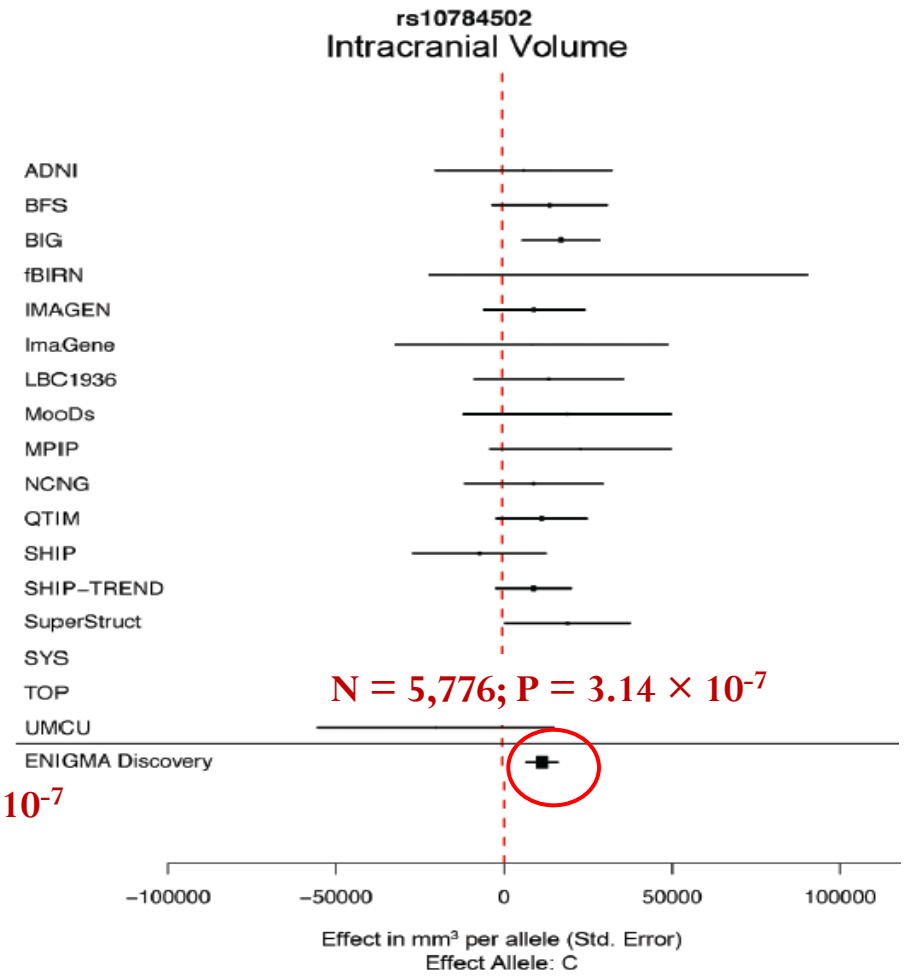




oaded to ENIGMA server for analysis at central site

First ENIGMA project: the findings





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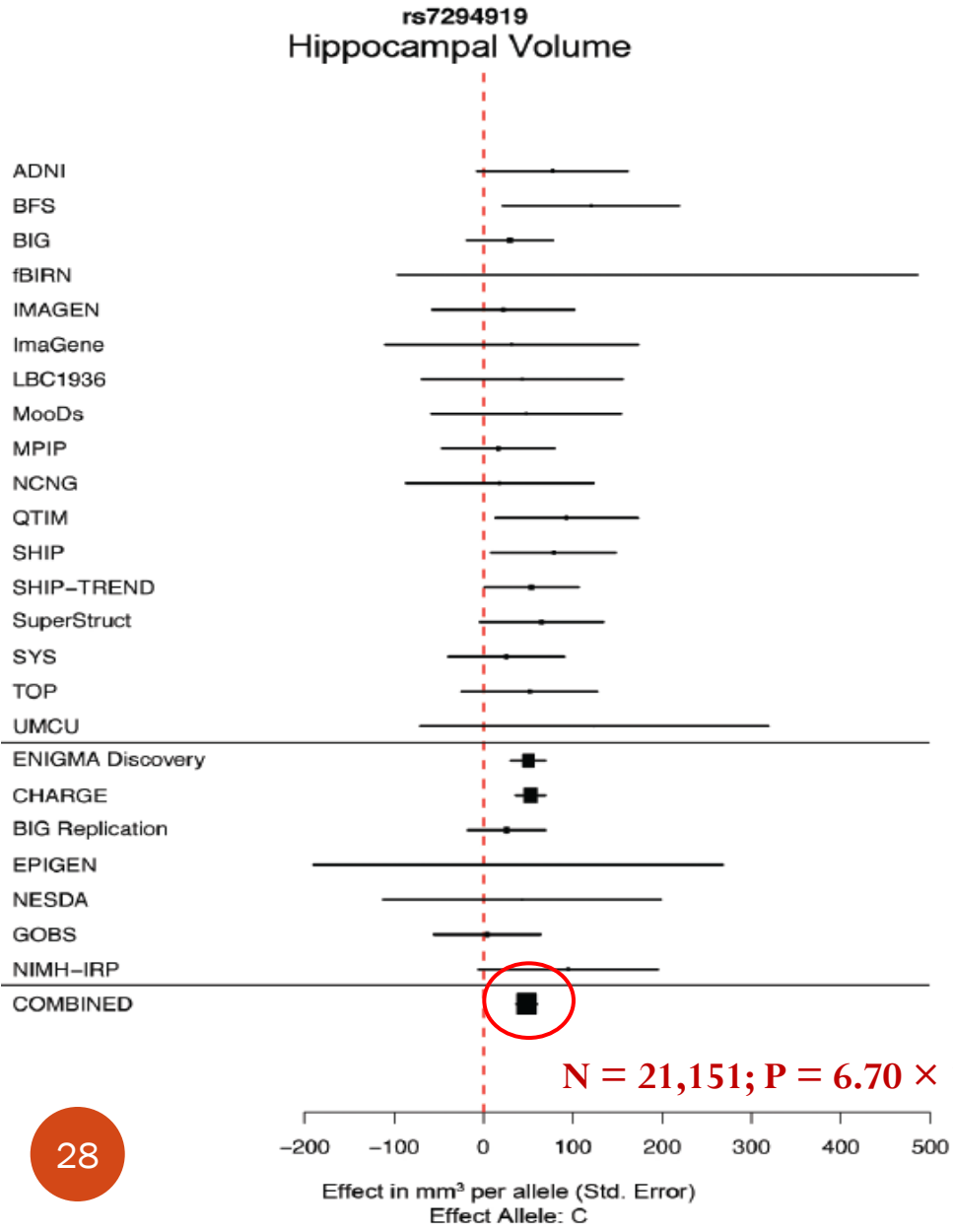
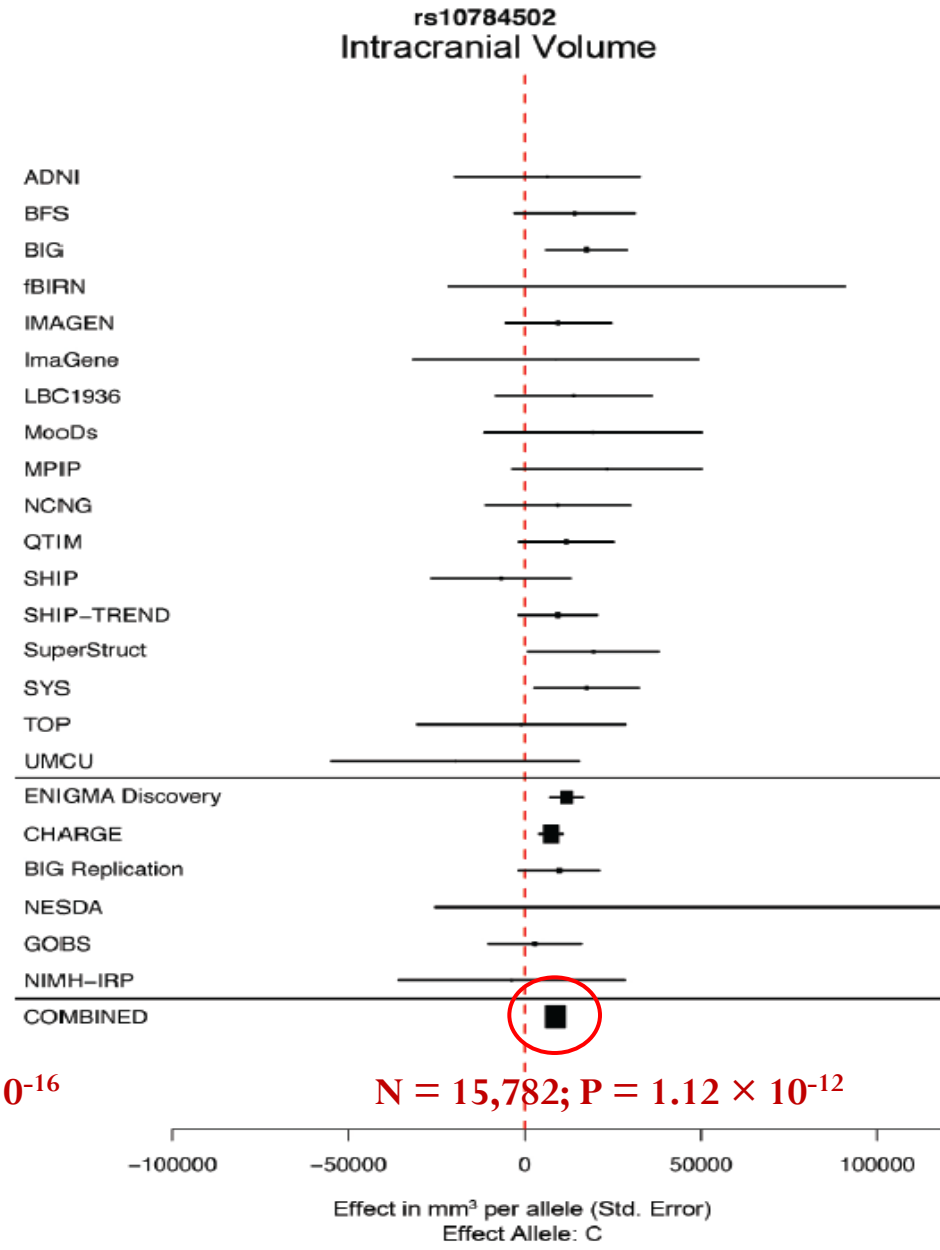
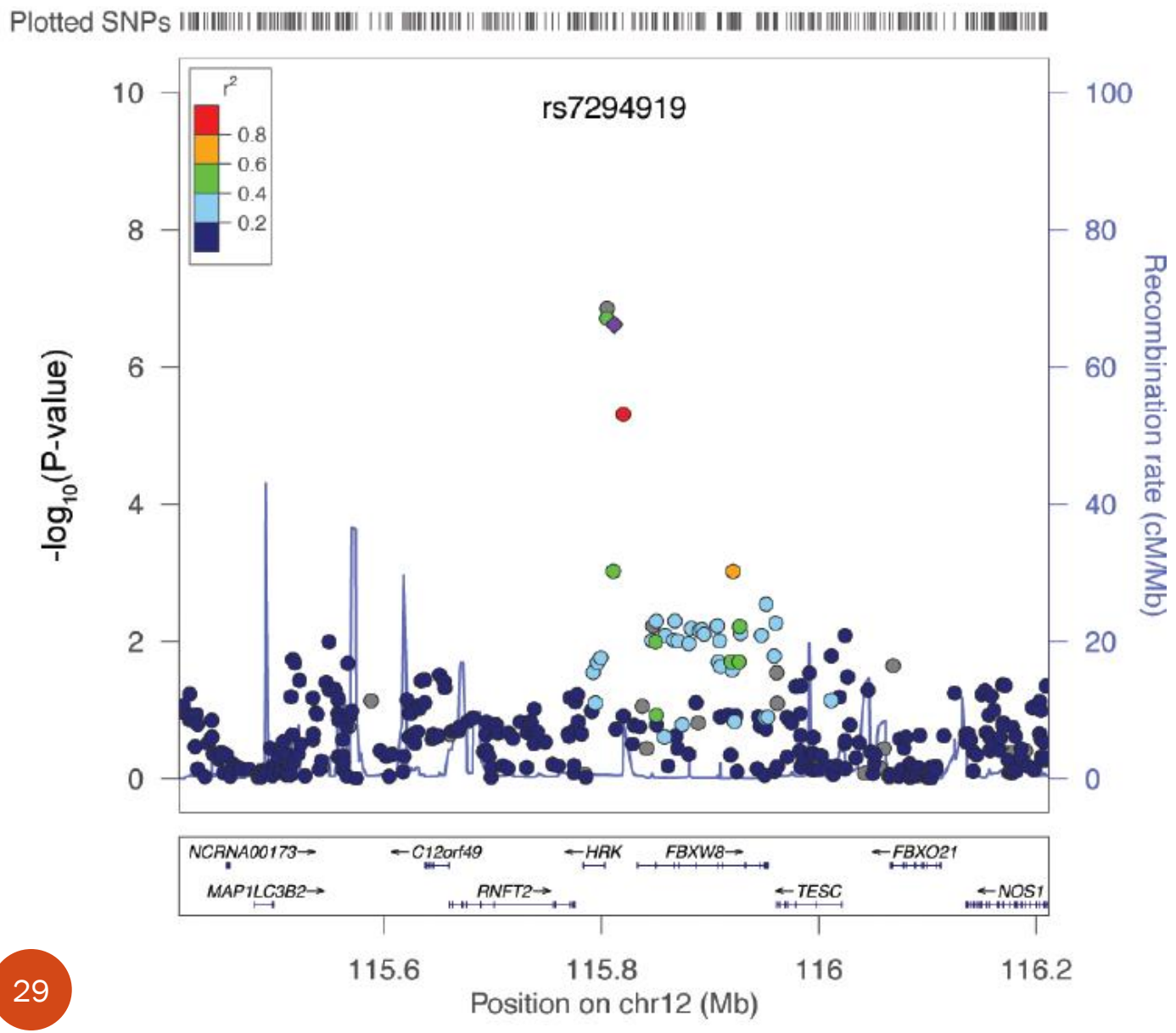




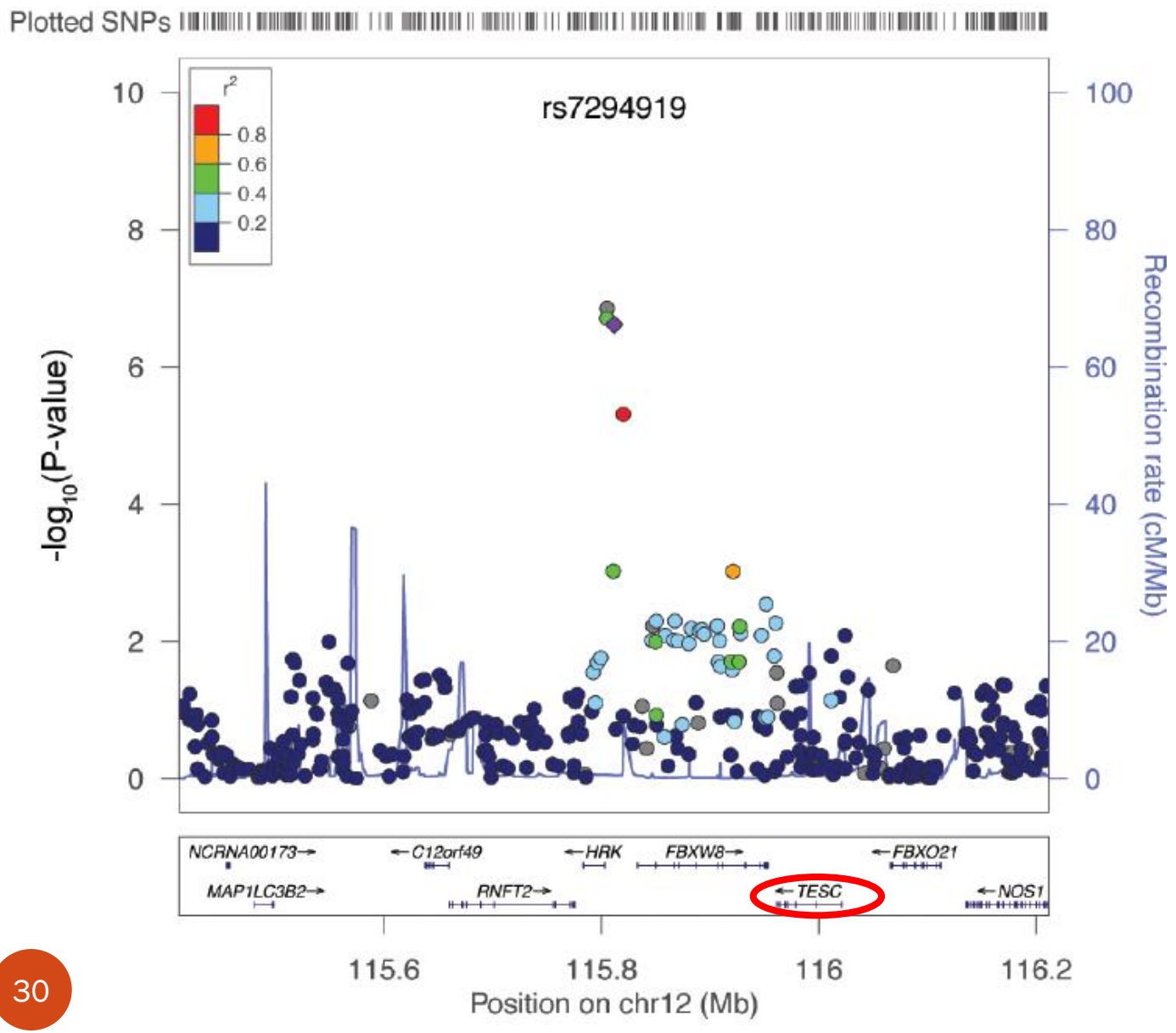
Results ENIGMA MA: hippcampal volume



- **All subjects**
- **Controlled for ICV**
- **Fixed Effects MA p= 2.42 x 10^{-7}**

- **Associated with decreased hippocampal volume of 47.6 mm^3 or 1.2% of the average hippocampal volume per risk allele**

Results ENIGMA MA: hippcampal volume



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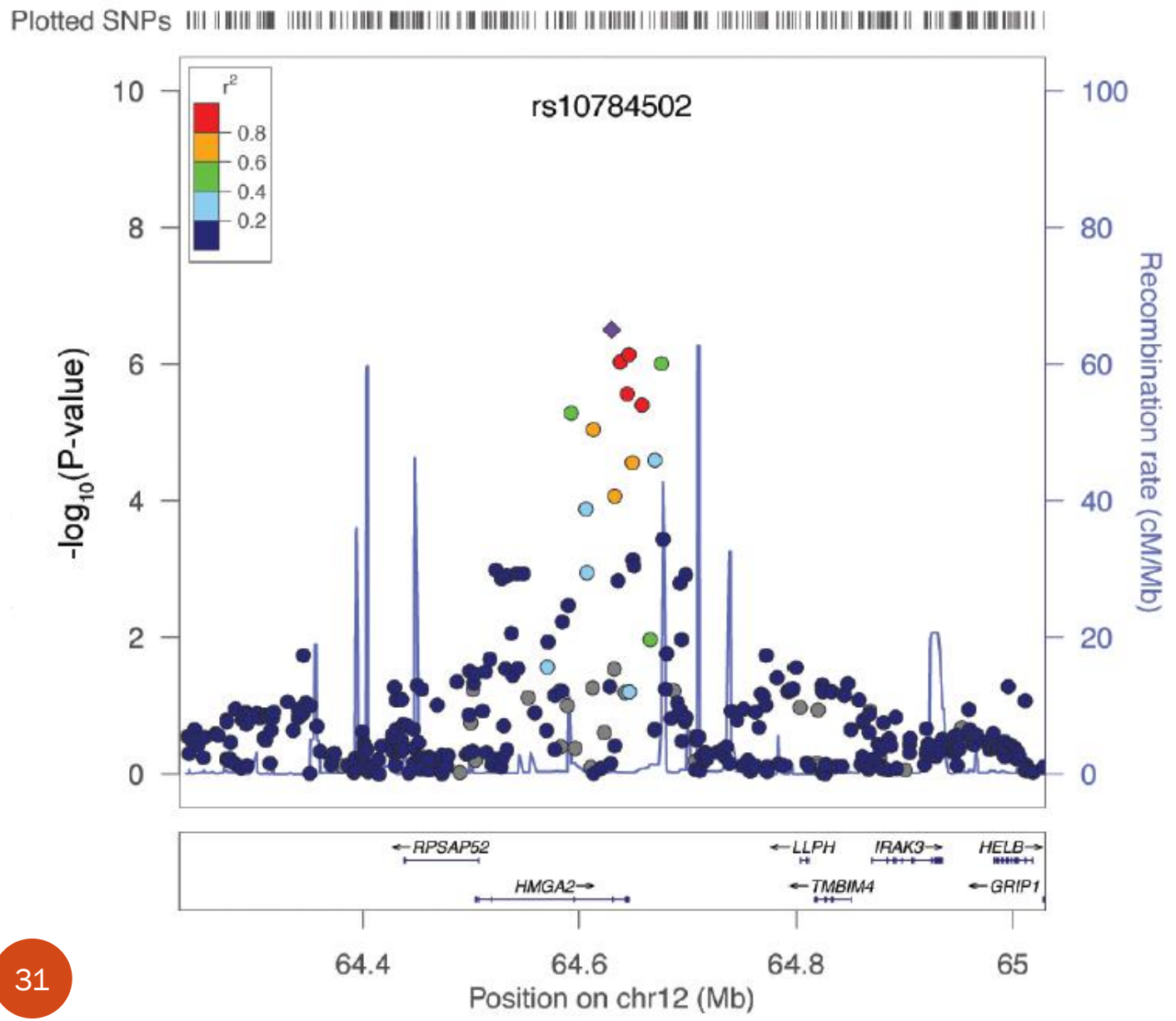
- **Expression level in brain associated with SNP**

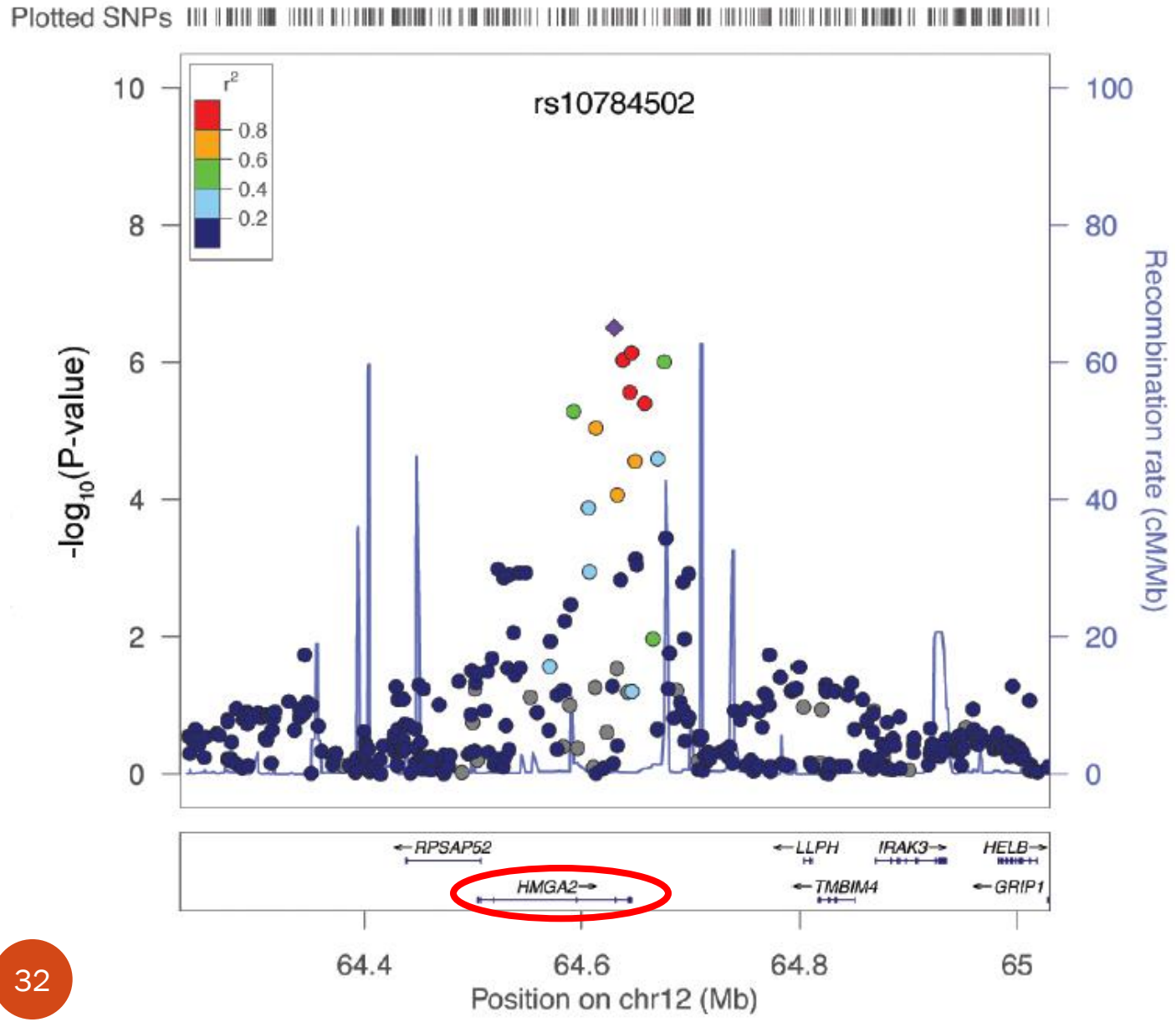
Results ENIGMA MA: intracranial volume



- **Healthy subjects**
- **Fixed Effects MA p= 3.14 x 10^{-7}**

- **Associated with 9,006.7 mm^3 larger intracranial volume, or 0.58% of intracranial volume per risk allele**

Results ENIGMA MA: intracranial volume



- **Healthy subjects**
- **Fixed Effects MA p= 3.14 x 10^{-7}**

- **Associated with 9,006.7 mm^3 larger intracranial volume, or 0.58% of intracranial volume per risk allele**

- **Expression in brain linked with SNP**
- **SNP also associated with IQ**
- **Known height gene**
- **Height genes also affect ICV**

nature genetics

Full text access provided

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NATURE GENETICS | LETTER

Identification of common variants associated with human hippocampal and intracranial volumes

Stein JL, Medland SE, Vasquez AA, Hibar DP, Senstad RE, Winkler AM, Toro R, Appel K, Bartecek R, Bergmann Ø, Bernard M, Brown AA, Cannon DM, Chakravarty MM, Christoforou A, Domin M, Grimm O, Hollinshead M, Holmes AJ, Homuth G, Hottenga JJ, Langan C, Lopez LM, Hansell NK, Hwang KS, Kim S, Laje G, Lee PH, Liu X, Loth E, Lourdusamy A, Mattingsdal M, Mohnke S, Maniega SM, Nho K, Nugent AC, O'Brien C, Papmeyer M, Pütz B, Ramasamy A, Rasmussen J, Rijpkema M, Risacher SL, Roddey JC, Rose EJ, Ryten M, Shen L, Sprooten E, Strengman E, Teumer A, Trabzuni D, Turner J, van Eijk K, van Erp TG, van Tol MJ, Wittfeld K, Wolf C, Woudstra S, Aleman A, Alhusaini S, Almasy L, Binder EB, Brohawn DG, Cantor RM, Carless MA, Corvin A, Czisch M, Curran JE, Davies G, de Almeida MA, Delanty N, Depondt C, Duggirala R, Dyer TD, Erk S, Fagerness J, Fox PT, Freimer NB, Gill M, Göring HH, Hagler DJ, Hoehn D, Holsboer F, Hoogman M, Hosten N, Jahanshad N, Johnson MP, Kasperaviciute D, Kent JW Jr, Kochunov P, Lancaster JL, Lawrie SM, Liewald DC, Mandl R, Matarin M, Mattheisen M, Meisenzahl E, Melle I, Moses EK, Mühleisen TW, Nauck M, Nöthen MM, Olvera RL, Pandolfo M, Pike GB, Puls R, Reinvang I, Rentería ME, Rietschel M, Roffman JL, Royle NA, Rujescu D, Savitz J, Schnack HG, Schnell K, Seiferth N, Smith C, Steen VM, Valdés Hernández MC, Van den Heuvel M, van der Wee NJ, Van Haren NE, Veltman JA, Völzke H, Walker R, Westlye LT, Whelan CD, Agartz I, Boomsma DI, Cavalleri GL, Dale AM, Djurovic S, Drevets WC, Hagoort P, Hall J, Heinz A, Jack CR Jr, Foroud TM, Le Hellard S, Macciardi F, Montgomery GW, Poline JB, Porteous DJ, Sisodiya SM, Starr JM, Sussmann J, Toga AW, Veltman DJ, Walter H, Weiner MW; Alzheimer's Disease Neuroimaging Initiative; EPIGEN Consortium; IMAGEN Consortium; Saguenay Youth Study Group, Bis JC, Ikram MA, Smith AV, Gudnason V, Tzourio C, Vernooij MW, Launer LJ, DeCarli C, Seshadri S; Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium, Andreassen OA, Apostolova LG, Bastin ME, Blangero J, Brunner HG, Buckner RL, Cichon S, Coppola G, de Zubicaray GI, Deary IJ, Donohoe G, de Geus EJ, Espeseth T, Fernández G, Glahn DC, Grabe HJ, Hardy J, Hulshoff Pol HE, Jenkinson M, Kahn RS, McDonald C, McIntosh AM, McMahon FJ, McMahon KL, Meyer-Lindenberg A, Morris DW, Müller-Myhsok B, Nichols TE, Ophoff RA, Paus T, Pausova Z, Penninx BW, Potkin SG, Sämann PG, Saykin AJ, Schumann G, Smoller JW, Wardlaw JM, Weale ME, Martin NG, Franke B, Wright MJ, Thompson PM.

Nature Genetics **44**, 552–561 (2012) | doi:10.1038/ng.2250

Received 06 September 2011 | Accepted 19 March 2012 | Published online 15 April 2012

About | News & Events | References | Ongoing Projects

Members | Protocols | EnigmaVis

Enhancing Neuro Imaging Genetics through Meta-Analysis

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

About News & Events References Ongoing Projects

Members Protocols EnigmaVis

Enhancing Neuro Imaging Genetics t gh Meta-Analysis

Twin Res Hum Genet. 2012 June ; 15(3): 414–418. doi:10.1017/thg.2012.17.

EnigmaVis: online interactive visualization of genome-wide association studies of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium

Nic M. Novak[1], Jason L. Stein[1], Sarah E. Medland[2], Derrek P. Hibar[1], Paul M. Thompson[1], and Arthur W. Toga[1]

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

ENIGMA

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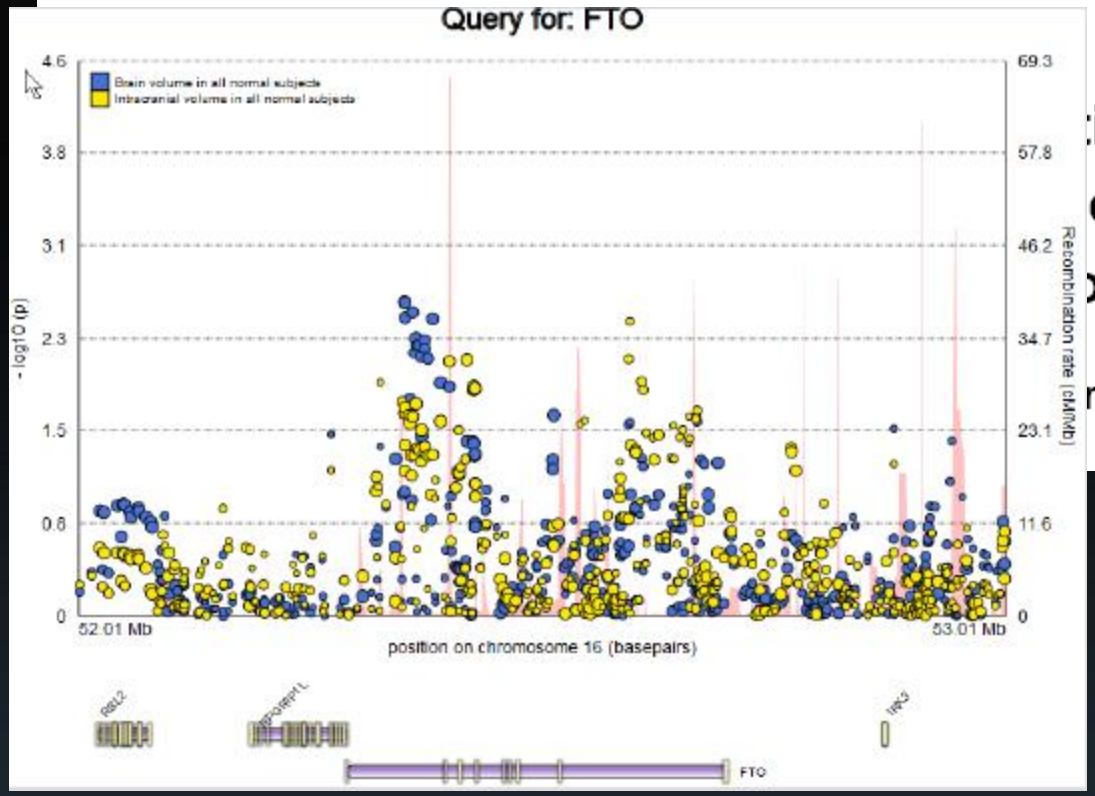
Enhancing Neuro Imaging Genetics t[illegible]gh Meta-Analysis

Twin Res Hum Genet. 2012 June ; 15(3): 414–418. doi:10.1017/thg.2012.17.



[illegible]ion of genome-wide
[illegible]eurolmaging Genetics
[illegible]ortium

[illegible]rek P. Hibar[1], Paul M. Thompson[1],

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

nature genetics

Nature Genetics 44

Bis JC, DeCarli C, Smith AV, van der Lijn F, Crivello F, Fornage M, Debette S, Shulman JM, Schmidt H, Srikanth V, Schuur M, Yu L, Choi SH, Sigurdsson S, Verhaaren BF, DeStefano AL, Lambert JC, Jack CR Jr, Struchalin M, Stankovich J, Ibrahim-Verbaas CA, Fleischman D, Zijdenbos A, den Heijer T, Mazoyer B, Coker LH, Enzinger C, Danoy P, Amin N, Arfanakis K, van Buchem MA, de Bruijn RF, Beiser A, Dufouil C, Huang J, Cavalieri M, Thomson R, Niessen WJ, Chibnik LB, Gislason GK, Hofman A, Pikula A, Amouyel P, Freeman KB, Phan TG, Oostra BA, Stein JL, Medland SE, Vasquez AA, Hibar DP, Wright MJ, Franke B, Martin NG, Thompson PM; Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium, Nalls MA, Uitterlinden AG, Au R, Elbaz A, Beare RJ, van Swieten JC, Lopez OL, Harris TB, Chouraki V, Breteler MM, De Jager PL, Becker JT, Vernooij MW, Knopman D, Fazekas F, Wolf PA, van der Lugt A, Gudnason V, Longstreth WT Jr, Brown MA, Bennett DA, van Duijn CM, Mosley TH, Schmidt R, Tzourio C, Launer LJ, Ikram MA, Seshadri S; Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. **Common variants at 12q14 and 12q24 are associated with hippocampal volume. Nat Genet. 2012 Apr 15;44(5):545-51.**

Taal HR, St Pourcain B, Thiering E, Das S, Mook-Kanamori DO, Warrington NM, Kaakinen M, Kreiner-Møller E, Bradfield JP, Freathy RM, Geller F, Guxens M, Cousminer DL, Kerkhof M, Timpson NJ, Ikram MA, Beilin LJ, Bønnelykke K, Buxton JL, Charoen P, Chawes BL, Eriksson J, Evans DM, Hofman A, Kemp JP, Kim CE, Klopp N, Lahti J, Lye SJ, McMahon G, Mentch FD, Müller-Nurasyid M, O'Reilly PF, Prokopenko I, Rivadeneira F, Steegers EA, Sunyer J, Tiesler C, Yaghootkar H; Cohorts for Heart and Aging Research in Genetic Epidemiology Consortium, Breteler MM, Decarli C, Breteler MM, Debette S, Fornage M, Gudnason V, Launer LJ, van der Lugt A, Mosley TH Jr, Seshadri S, Smith AV, Vernooij MW; Early Genetics & Lifecourse Epidemiology Consortium, Blakemore AI, Chiavacci RM, Feenstra B, Fernandez-Banet J, Grant SF, Hartikainen AL, van der Heijden AJ, Iñiguez C, Lathrop M, McArdle WL, Mølgaard A, Newnham JP, Palmer LJ, Palotie A, Pouta A, Ring SM, Sovio U, Standl M, Uitterlinden AG, Wichmann HE, Vissing NH, DeCarli C, van Duijn CM, McCarthy MI, Koppelman GH, Estivill X, Hattersley AT, Melbye M, Bisgaard H, Pennell CE, Widen E, Hakonarson H, Smith GD, Heinrich J, Jarvelin MR, Jaddoe VW; Early Growth Genetics Consortium. **Common variants at 12q15 and 12q24 are associated with infant head circumference. Nat Genet. 2012 Apr 15;44(5):532-8.**

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This same data was recently re-analysed
- Higher N, imputed to 1000 Genomes

ENIGMA-CHARGE Collaboration (N=26,378)

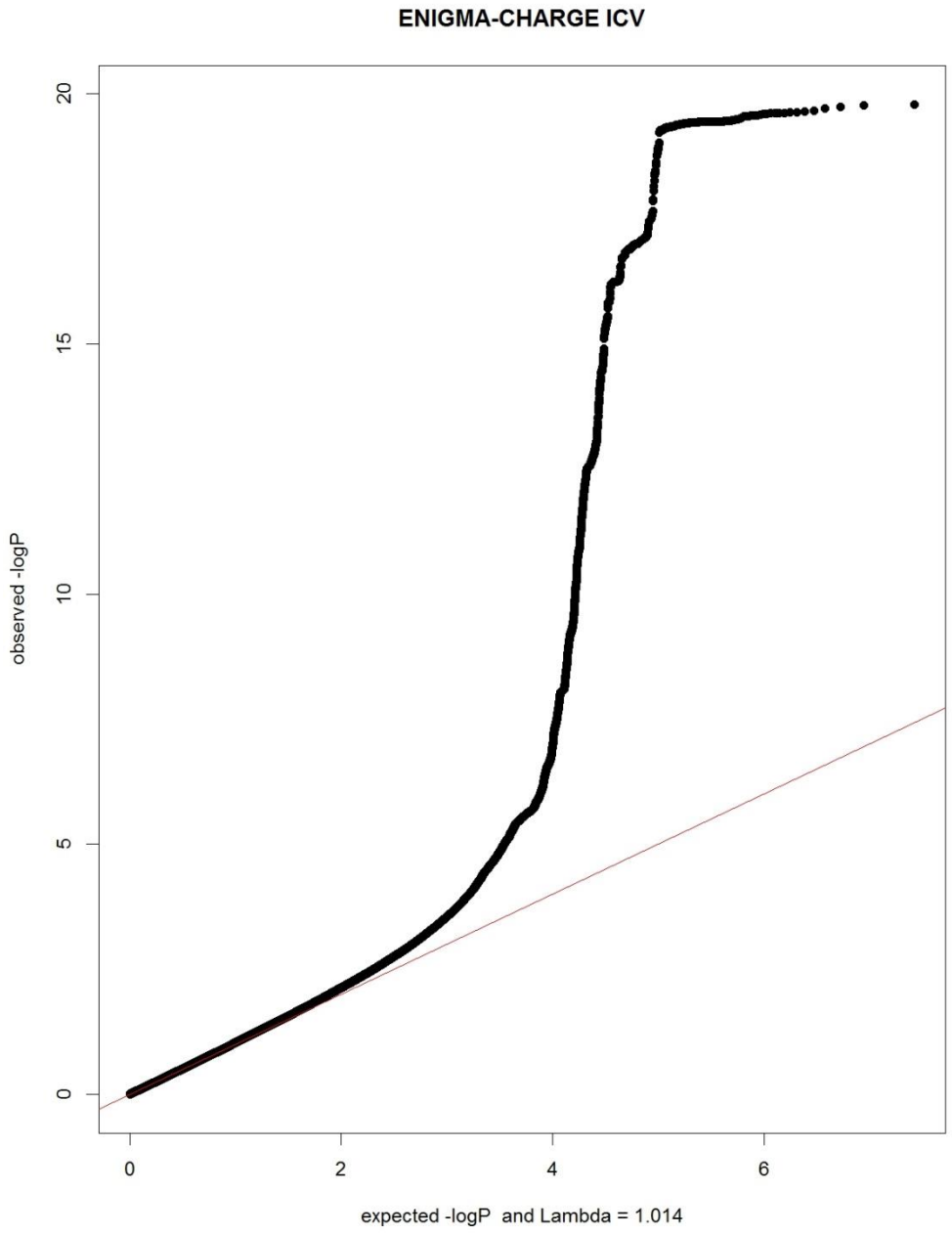
HV & ICV GWAS MA Results

EMBARGOED

N=26,378; several GW-hits, $p \sim 10^{-10}$-10^{-23}

CHARGE-ENIGMA Intracranial volume (ICV) – QQ plot

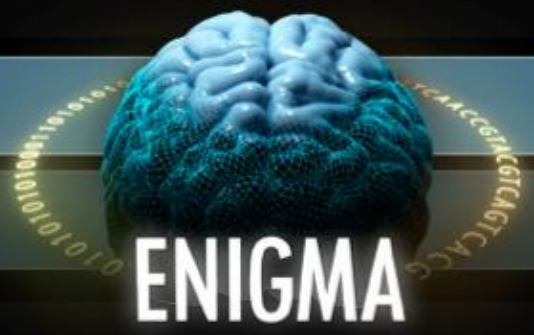
Functional characterization of top hits underway



Next ENIGMA project

Which genes contribute to the volume of subcortical brain structures?

Caudate nucleus, pallidum, putamen, thalamus, nucleus accumbens, amygdala



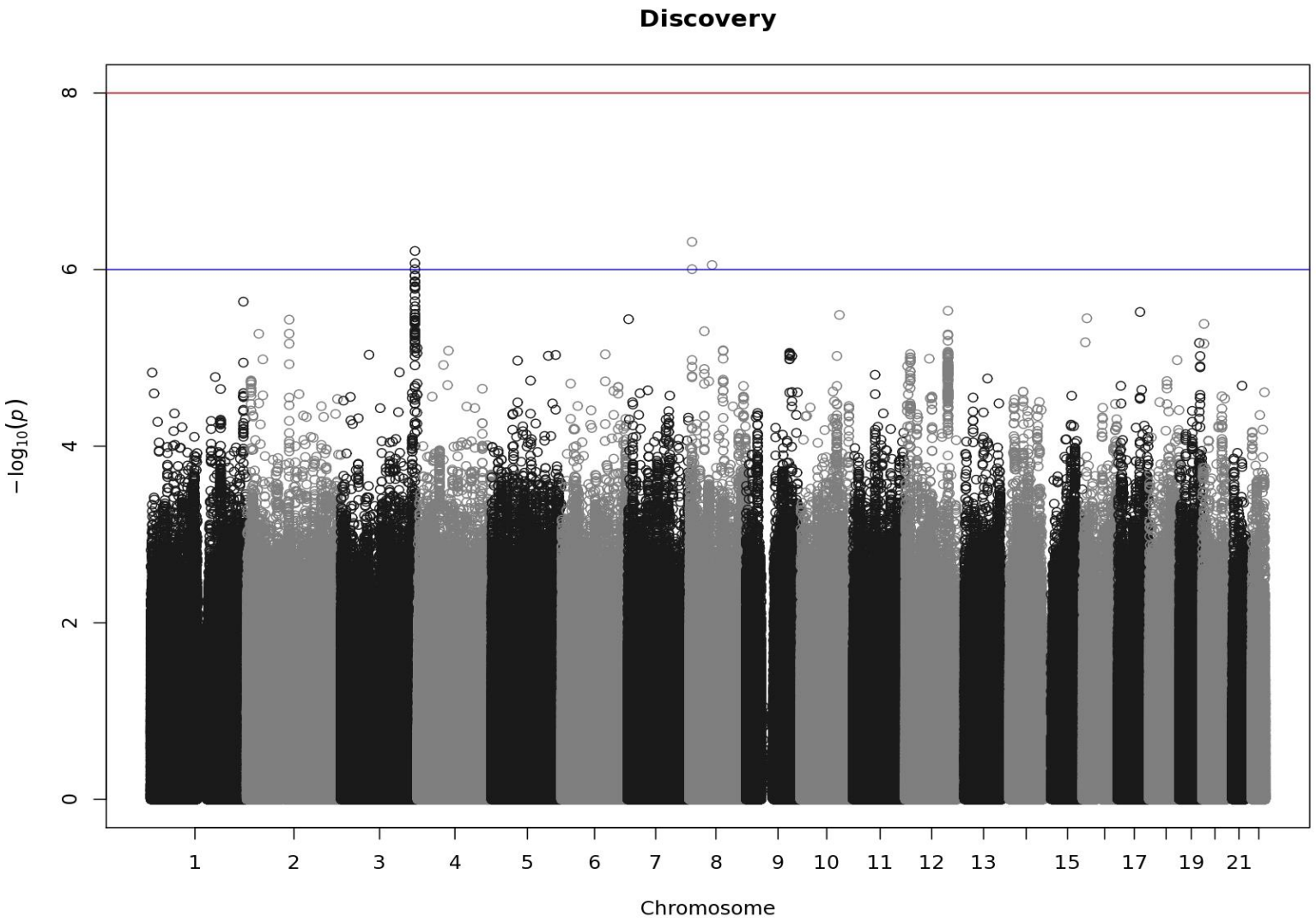
ENIGMA2 Preliminary Results

- Discovery Sample only (N=11,740)

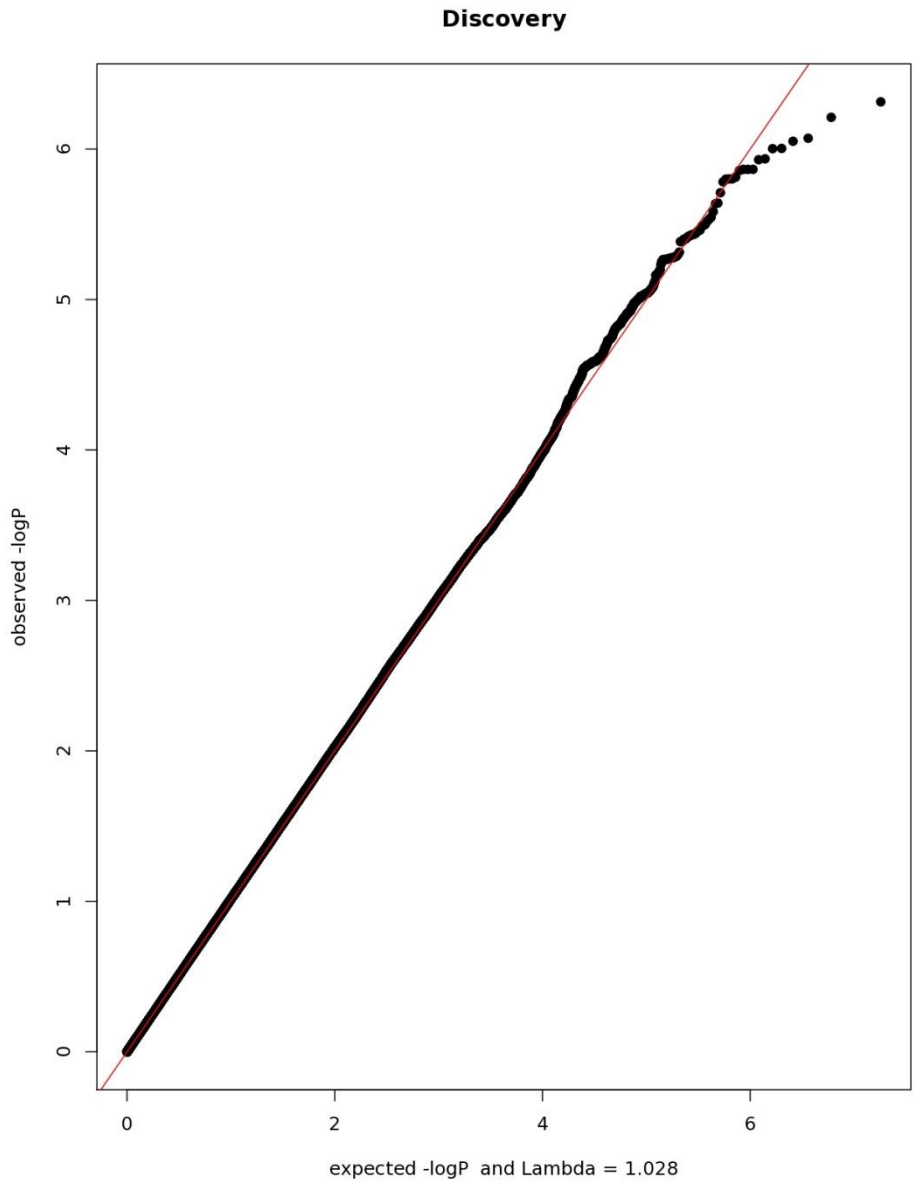
May 14 2013

By Oct 2013 – 32 cohorts; N=16,500+

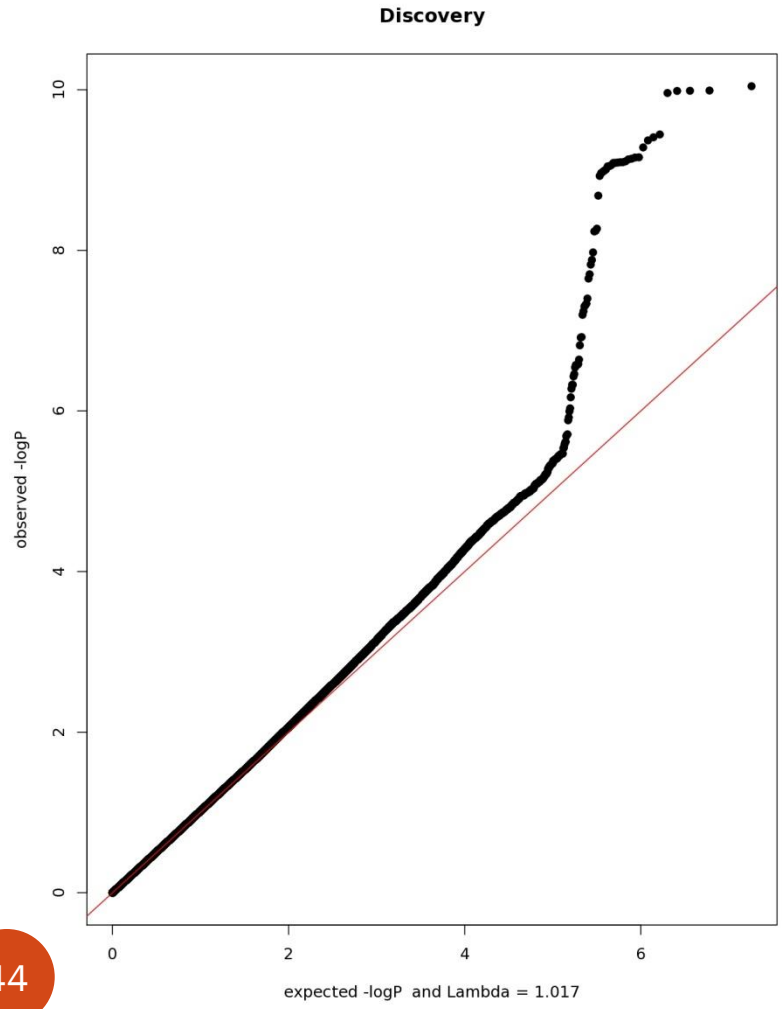
Accumbens (small structure) – not much

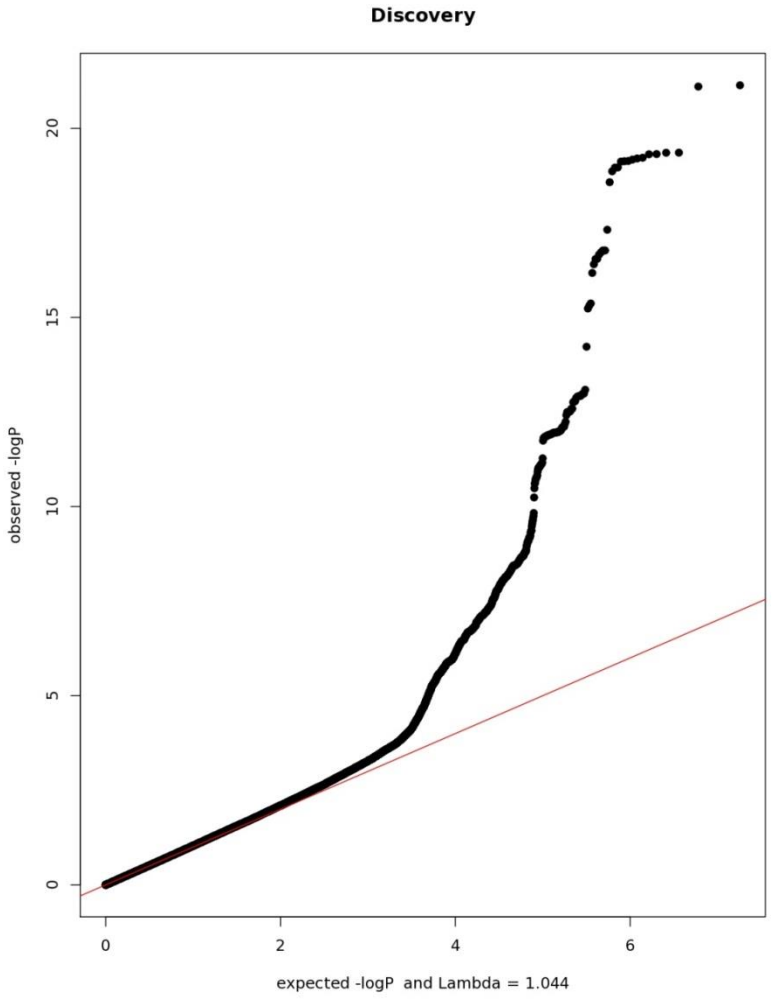


Accumbens – small structure, not much



Other subcortical structures– very strong hits; prior hits confirmed; several new ones





Are the GWAS-derived genes for brain volume also involved in brain disease?

Which brain volumes are relevant?

ENIGMA Studies of Disease Working Groups

Meta-analyzing data worldwide

ENIGMA-SZ
Dr. Jessica Turner (USA)

ENIGMA-BPD
Dr. Ole Andreassen (Oslo, Norway)

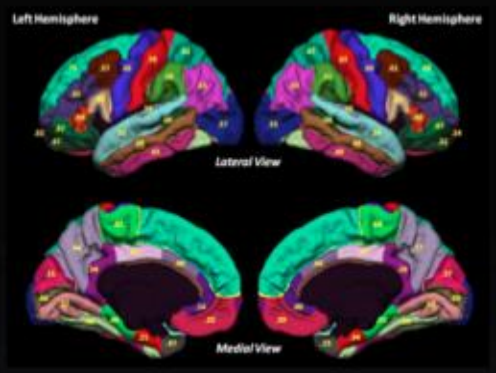
ENIGMA-MDD
Dr. Dick Veltman (Netherlands)

ENIGMA-ADHD
Dr. Barbara Franke (Netherlands)

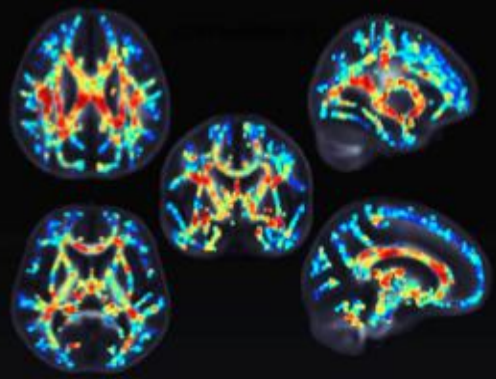
ENIGMA

ENIGMA Studies of Disease

1. Compute brain measures from scans
   - harmonized protocol for image analysis + QC; 125 institutions



Anatomical MRI:
Cortical+ subcortical volumes;
FreeSurfer / FSL



DTI:
FA, MD for Tracts and ROIs
Defined on ENIGMA-DTI template

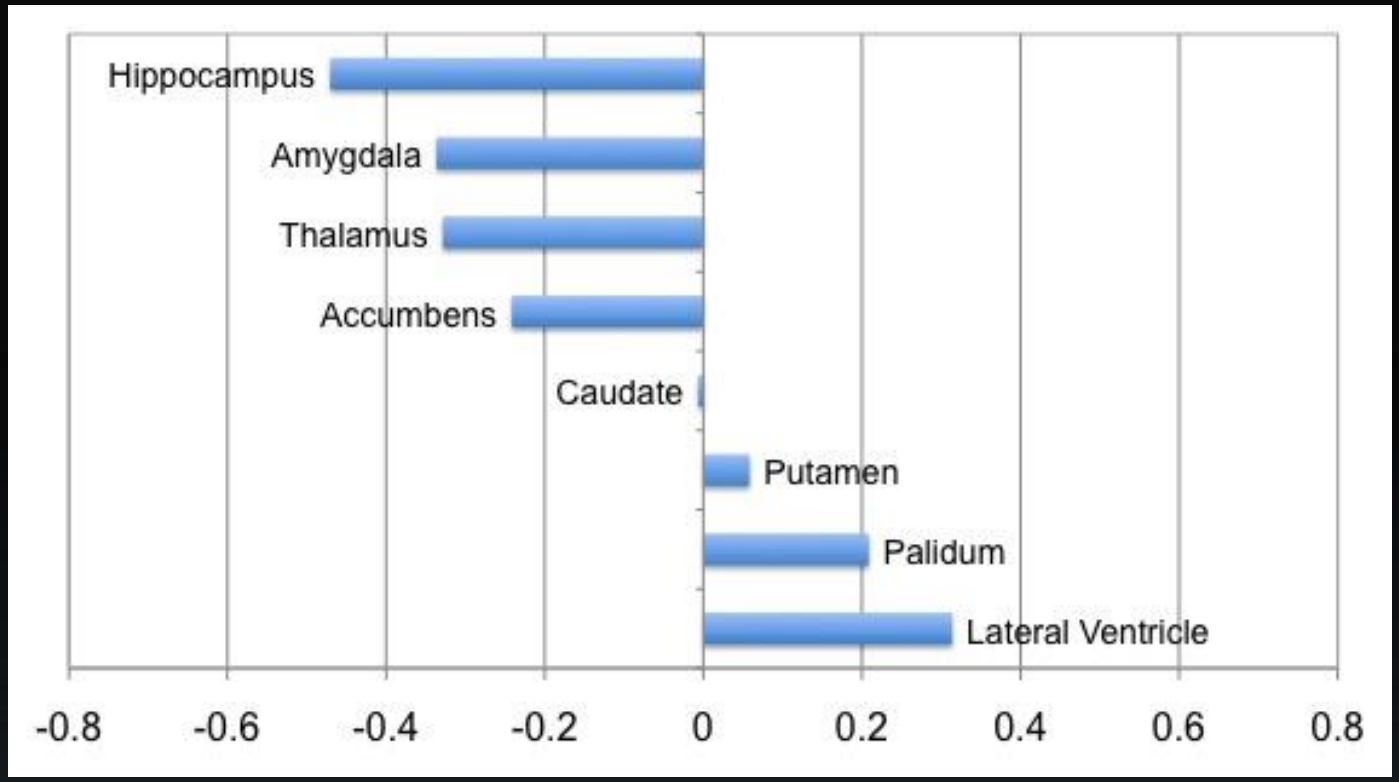
2. What are the patient vs. control differences for each brain measure?
   - which brain measures best distinguish patients from controls

3. Meta-analysis: combine effects across sites: each site's "vote" depends on the sample size
   - make sure effects are reproducible, boosts power to pick up effects no site could pick on its own

ENIGMA

ENIGMA-Schizophrenia Working Group

Lead by Jessica Turner



$N_{cases} = 2047$

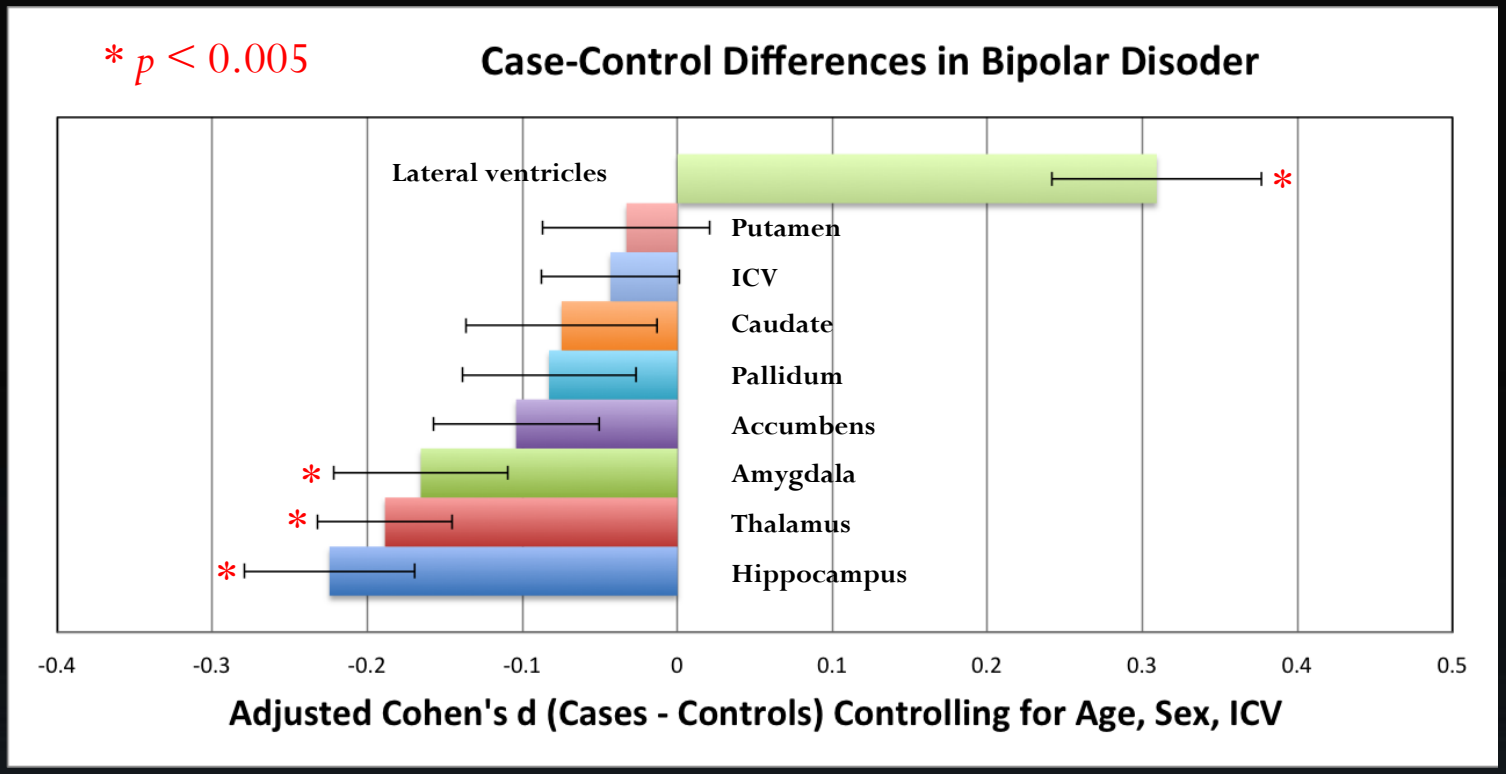
$N_{controls} = 2477$

Cohen's d for brain volume in schizophrenia

Theo G. M. van Erp*, Derrek P. Hibar*, Jerod Rasmussen, Ole A. Andreassen, Unn K. Haukvik, Ingrid Agartz, Steven G. Potkin, Hilleke Hulshoff-Pol, Roel Ophoff, Neeltje E. M. van Haren, Oliver Gruber, [illegible]d Krämer, Stefan Erhlich, Johanna Hass, Lei Wang, Kathryn Alpert, Godfrey D. Pearlson, David [illegible]n, Paul M. Thompson*, Jessica A. Turner*, for the **ENIGMA-Schizophrenia Working Group.**

ENIGMA-Bipolar Disorder Working Group

Lead by Ole Andreassen



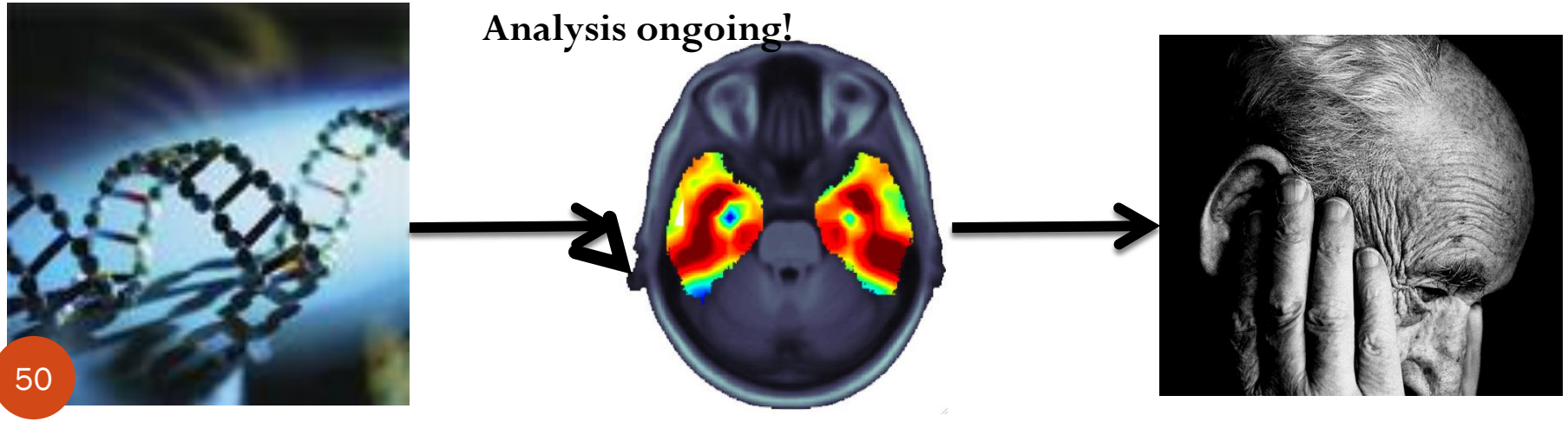
$N_{cases} = 1149$

$N_{controls} = 1523$

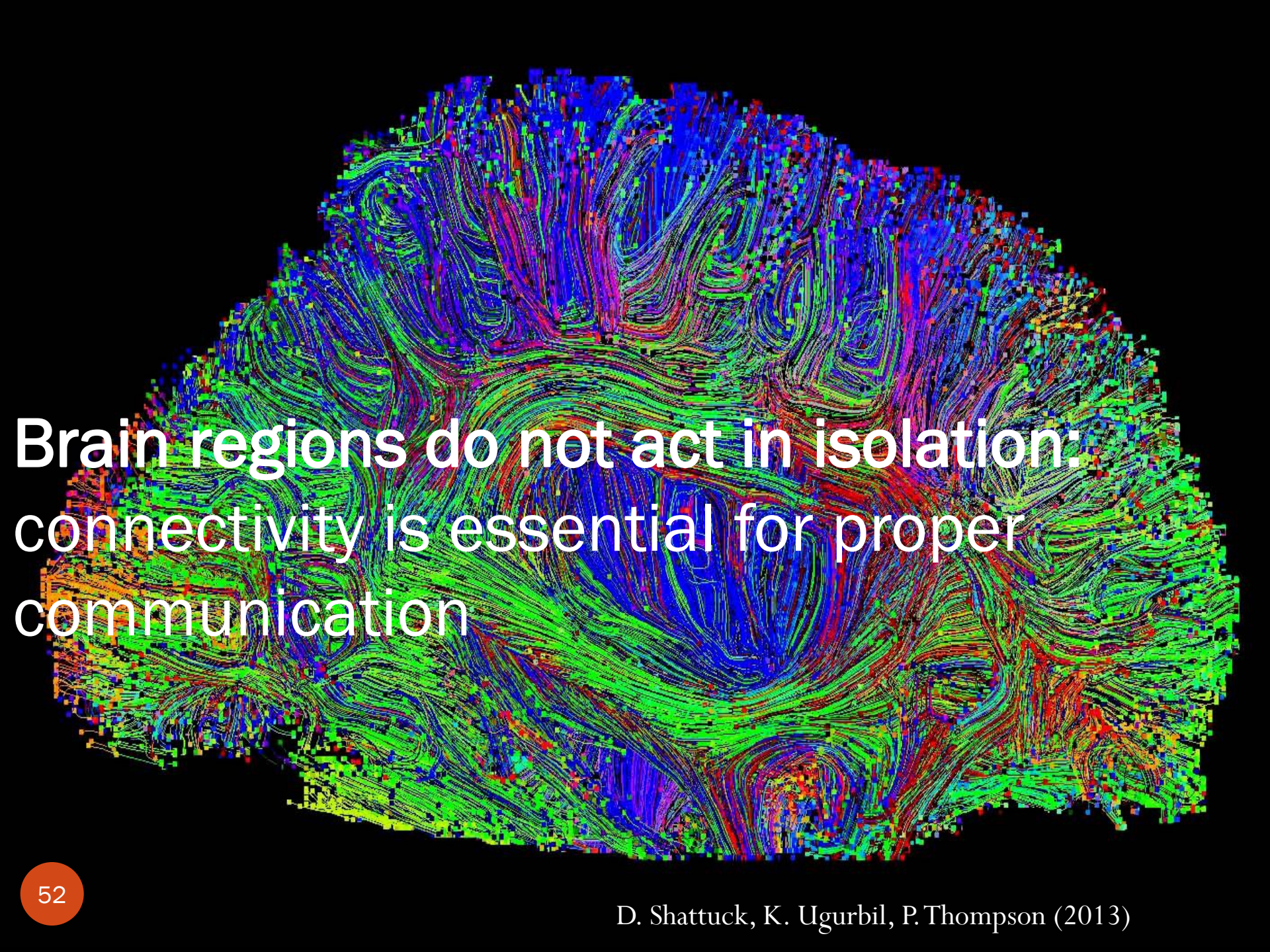
Derrek P. Hibar, Lars T. Westlye, Theo G. M. van Erp, Jerod Rasmussen, Jessica A. Turner, Unn K. Haukvik, Ingrid Agartz, Oliver Gruber, Bernd Krämer, Benny Lindberg, Carl Johan Ekman, Mikael Landen, Allison Nugent, Gonzalo Laje, Francis McMahon, Scott Fears, Carrie Bearden, Nelson Freimer, David Glahn, Colm McDonald, Dara Cannon, Mary Phillips, Stephen Strakowski, Caleb Alder, Sophia Frangou, Paul M. Thompson, Ole A. Andreassen
for the ENIGMA-Bipolar Disorder Working Group

ENIGMA2-PGC2-SCZ Collaboration: Do genetic variants which create risk for changes in brain structure also create risk for schizophrenia?

1. Globally demonstrate if genetic variants affecting the structure of the brain also create risk for psychiatric illness
2. Specifically find any specific genetic variants that create both changes in brain structure and risk for psychiatric illness
3. Give biological relevance to PGC hits (which structures are affected)
4. Determine the validity of the endophenotype concept for subcortical structural MRI measures and schizophrenia



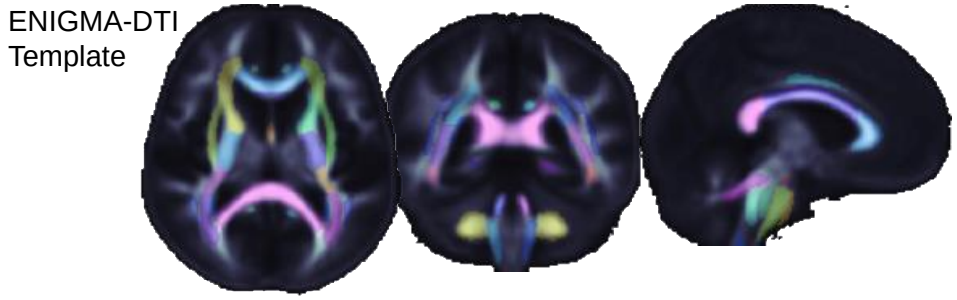
Transition Page

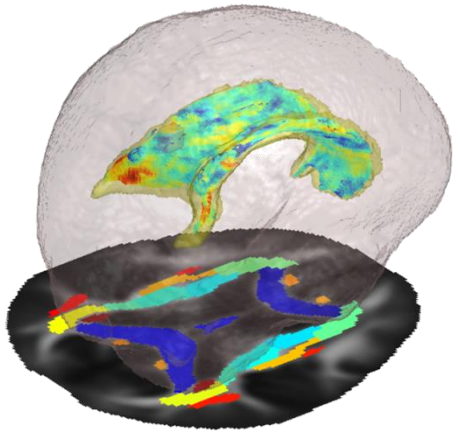


D. Shattuck, K. Ugurbil, P. Thompson (2013)

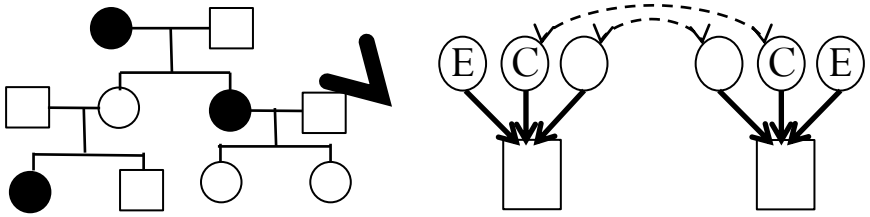
ENIGMA-DTI

1. Create a common template
   - 100 healthy adult subjects from each of 4 sites around the world
2. Find mean white matter fiber integrity values in the full brain and 14 standard tracts of interest along the WM skeleton





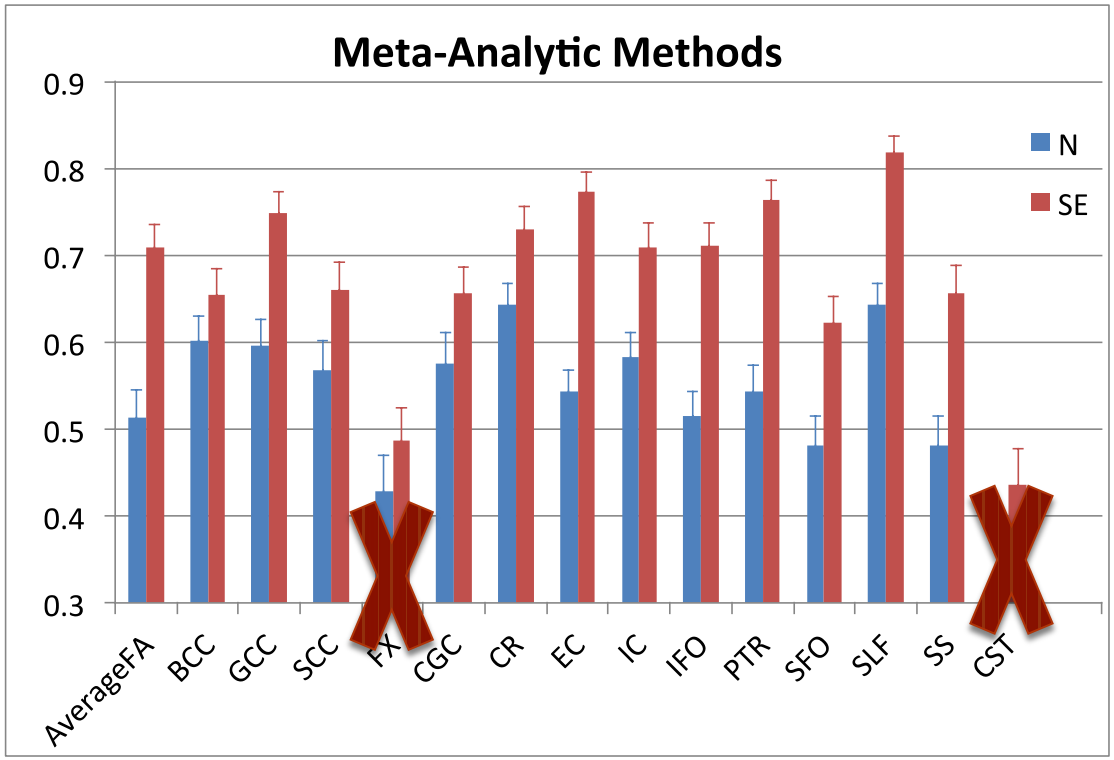
3. Multi-site heritability analysis
   - Are heritability measures stable and reliable across cohorts in regions
   - If not, then they are not good targets for multi-site GWAS-MA



Jahanshad & Kochunov et al, NIMG 2013

Multi-site heritability analysis

- 5 sites DIFFERENT: **Family structures** (twins/pedigrees) / **Image acquisition** methods / **Age groups** (only children/only elderly/wide range) / **Ethnicities** (European/Mexican-American)

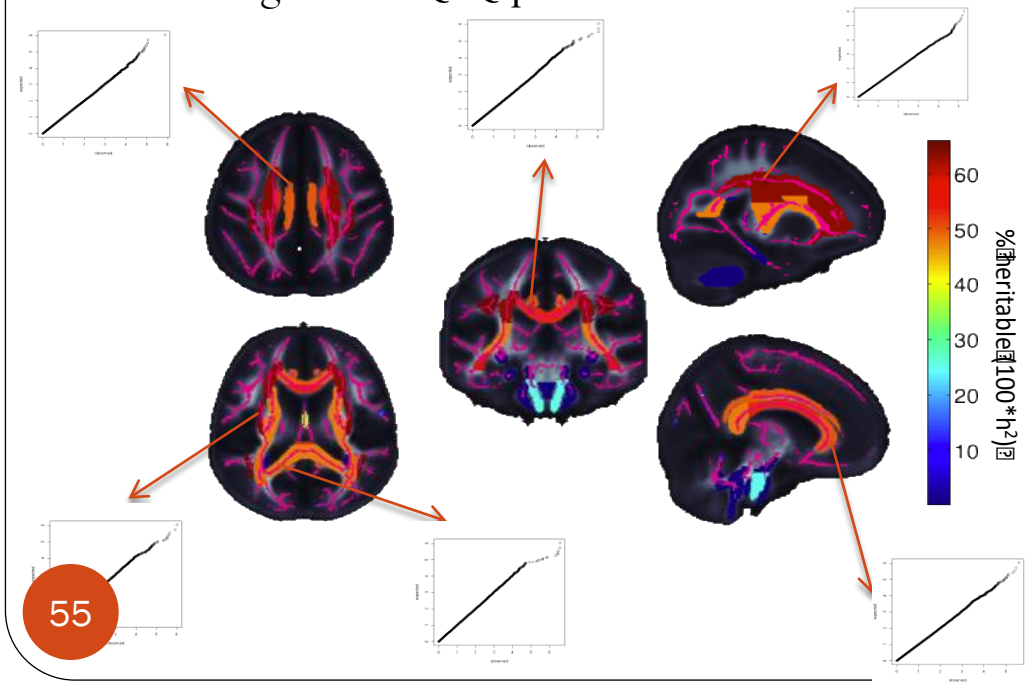


- Compare 2 meta-analysis approaches
  - Weight by N and SE
- 13/15 regions found to be highly reliable and heritable in all cohorts

Kochunov & Jahanshad et al, submitted

GWAS to be conducted on full brain and 12 regional WM integrity values

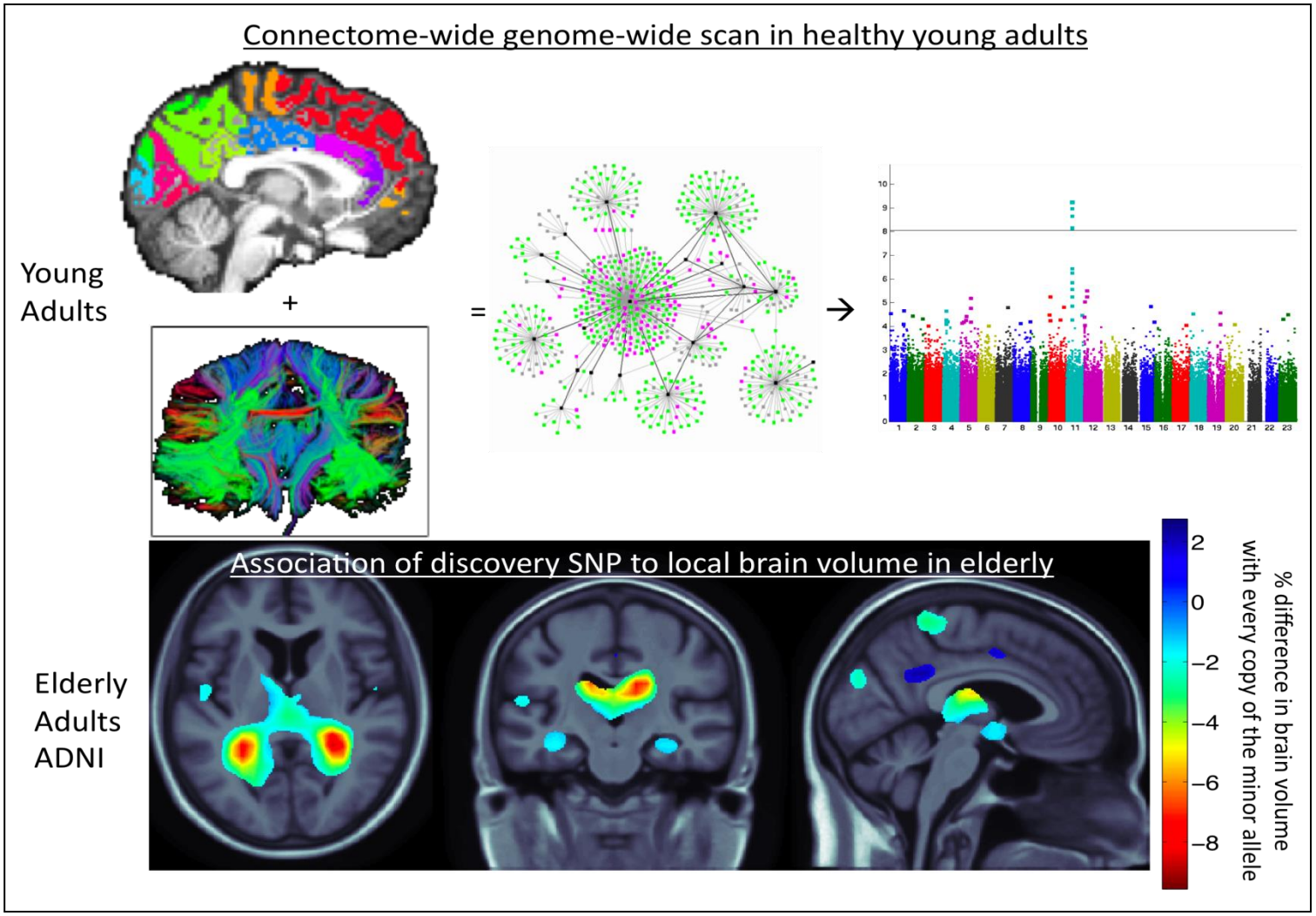
Single –site Q-Q plots



- 20+ sites interested
- 8000+ images available

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

Genome-Wide Screen of the Human Connectome discovers an Alzheimer risk gene (DTI)



Discovery sample – Young Adults
Replication sample – ADNI

Neda Jahanshad/Paul Thompson, **PNAS** 2013

Acknowledgments

Jason L Stein[1,127], Sarah E Medland[2–4,127], Alejandro Arias Vasquez[5–7,127], Derrek P Hibar[1,127], Rudy E Senstad[1], Anderson M Winkler[8,9], Roberto Toro[10–12], Katja Appel[13,14], Richard Bartecek[15], Ørjan Bergmann[16], Manon Bernard[17], Andrew A Brown[16,18], Dara M Cannon[19], M Mallar Chakravarty[20], Andrea Christoforou[22,23], Martin Domin[24], Oliver Grimm[25], Marisa Hollinshead[26,27], Avram J Holmes[28], Georg Homuth[29], Jouke-Jan Hottenga[29], Camilla Langan[29], Lorna M Lopez[30,31], Narelle K Hansell[2], Kristy S Hwang[1,32], Sungeun Kim[33,34], Gonzalo Laje[35], Phil H Lee[36,37], Xinmin Liu[35,38], Eva Loth[39], Anbarasu Lourdusamy[39], Morten Mattingsdal[16,40], Sebastian Mohnke[41], Susana Muñoz Maniega[30,42,43], Kwangsik Nho[33,44], Allison C Nugent[45], Carol O'Brien[46,47], Martina Papmeyer[48], Benno Pütz[49], Adaikalavan Ramasamy[50], Jerod Rasmussen[51], Mark Rijpkema[7,52], Shannon L Risacher[33], J Cooper Roddey[53], Emma J Rose[46,47], Mina Ryten[54], Li Shen[33,34], Emma Sprooten[48], Eric Strengman[55,56], Alexander Teumer[28], Daniah Trabzuni[54,57], Jessica Turner[58], Kristel van Eijk[55,56], Theo G M van Erp[51], Marie-Jose van Tol[59–61], Katharina Wittfeld[13], Christiane Wolf[49], Saskia Woudstra[62], Andre Aleman[61], Saud Alhusaini[63], Laura Almasy[64], Elisabeth B Binder[45], David G Brohawn[36], Rita M Cantor[65], Melanie A Carless[64], Aiden Corvin[46,47], Michael Czisch[49], Joanne E Curran[64], Gail Davies[31], Marcio A A de Almeida[64], Norman Delanty[63,66], Chantal Depondt[67], Ravi Duggirala[64], Thomas D Dyer[64], Susanne Erk[41], Jesen Fagerness[36], Peter T Fox[68], Nelson B Freimer[65], Michael Gill[46,47], Harald H H Göring[64], Donald J Hagler[20], David Hoehn[49], Florian Holsboer[49], Martine Hoogman[5,7,71,72], Norbert Hosten[24], Neda Jahanshad[1], Matthew P Johnson[64], Dalia Kasperaviciute[73], Jack W Kent Jr[64], Peter Kochunov[69,74], Jack L Lancaster[69], Stephen M Lawrie[48], David C Liewald[30], René Mandl[15], Mar Matarin[73], Manuel Mattheisen[75–77], Eva Meisenzahl[78], Ingrid Melle[16,79], Eric K Moses[64], Thomas W Mühleisen[75,76], Matthias Nauck[80], Markus M Nöthen[75,76,81], Rene L Olvera[82], Massimo Pandolfo[67], G Bruce Pike[83], Ralf Puls[24], Ivar Reinvang[84,85], Miguel E Renteria[2,86], Marcella Rietschel[25], Joshua L Roffman[87], Natalie A Royle[30,42,43], Dan Rujescu[78], Jonathan Savitz[45,87], Hugo G Schnack[15], Knut Schnell[88,89], Nina Seiferth[41], Colin Smith[90], Vidar M Steen[22,23], Maria C Valdés Hernández[30,42,43], Martijn Van den Heuvel[15], Nic J van der Wee[59,60], Neeltje E M Van Haren[15], Joris A Veltman[5], Henry Völzke[91], Robert Walker[90], Lars T Westlye[84], Christopher D Whelan[63], Ingrid Agartz[16,92], Dorret I Boomsma[29], Gianpiero L Cavalleri[63], Anders M Dale[93,70], Srdjan Djurovic[16,93], Wayne C Drevets[45,87], Peter Hagoort[7,52,72], Jeremy Hall[48], Andreas Heinz[41], Clifford R Jack Jr[94], Tatiana M Foroud[34,95], Stephanie Le Hellard[22,23], Fabio Macciardi[51], Grant W Montgomery[2], Jean Baptiste Poline[96], David J Porteous[30,97], Sanjay M Sisodiya[73], John M Starr[30,98], Jessika Sussmann[48], Arthur W Toga[1], Dick J Veltman[62], Henrik Walter[41,89], Michael W Weiner[99–102], the Alzheimer's Disease Neuroimaging Initiative (ADNI)[103], EPIGEN Consortium[103], IMAGEN Consortium[103], Saguenay Youth Study Group (SYS)[103], Joshua C Bis[104], M Arfan Ikram[105–107], Albert V Smith[108,109], Vilmundur Gudnason[108,109], Christophe Tzourio[110,111], Meike W Vernooij[105–107], Lenore J Launer[112], Charles DeCarli[113,114], Sudha Seshadri[113,115,116], Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium[103], Ole A Andreassen[16,79], Liana G Apostolova[1,32], Mark E Bastin[30,42,43,117], John Blangero[64], Han G Brunner[5], Randy L Buckner[26,27,37,68], Sven Cichon[75,76,118], Giovanni Coppola[32,119], Greig I de Zubicaray[86], Ian J Deary[30,31], Gary Donohoe[46,47], Eco J C de Geus[29], Thomas Espeseth[84,85,120], Guillén Fernández[7,52,71], David C Glahn[8,9], Hans J Grabe[13,121], John Hardy[54], Hilleke E Hulshoff Pol[15], Mark Jenkinson[122], René S Kahn[15], Colm McDonald[20], Andrew M McIntosh[48], Francis J McMahon[35], Katie L McMahon[123], Andreas Meyer-Lindenberg[25], Derek W Morris[46,47], Bertram Müller-Myhsok[49], Thomas E Nichols[122,124], Roel A Ophoff[15,65], Tomas Paus[21], Zdenka Pausova[17], Brenda W Penninx[59,60,62,125], Steven G Potkin[51], Philipp G Sämann[49], Andrew J Saykin[33,34,95], Gunter Schumann[39], Jordan W Smoller[36,37], Joanna M Wardlaw[30,42,43], Michael E Weale[50], Nicholas G Martin[2,126], Barbara Franke[5–7,127], Margaret J Wright[2,128] & Paul M Thompson[1,126] for the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium[126]

307 ENIGMA Co-Authors and PIs, IMAGEN, MooDs, Many Participating Consortia

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*Alejandro Arias Vasquez, Donders Institute, NL

*Derrek Hibar, IGC

*Neda Jahanshad, IGC

….

Nick Martin, QIMR

Margie Wright, QIMR

Barbara Franke, Donders Institute, NL

Paul Thompson, IGC

ENIGMA Working Groups:

ENIGMA1, ENIGMA2

ENIGMA-DTI

ENIGMA-SZ, BPD, MDD, ADHD, [22q, HIV, Addiction, OCD],

PGC2-SCZ