The genetics of brain structure and function

Nick Martin
Queensland Institute
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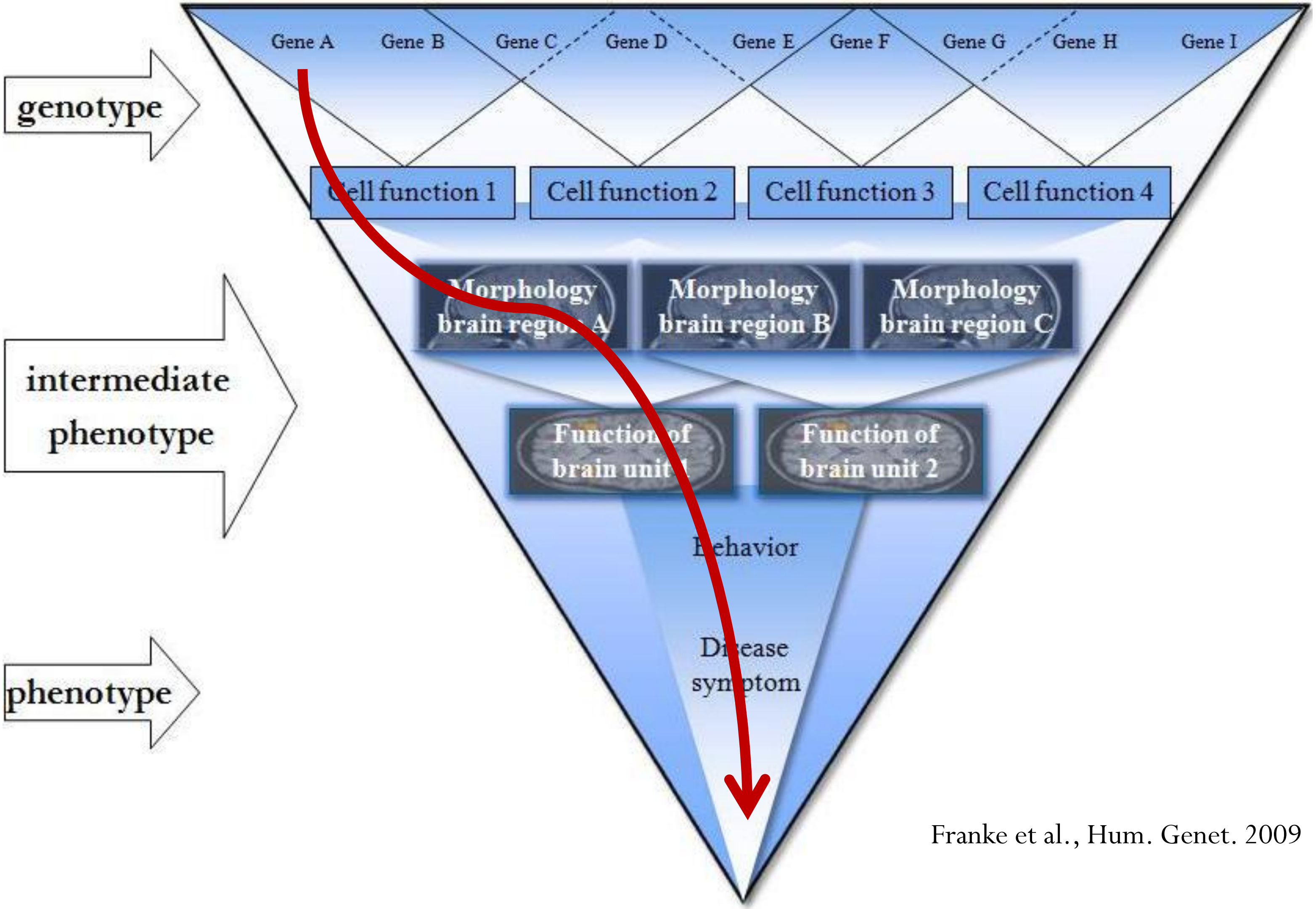
Brisbane

(edits Sarah Medland)

Pathways from gene to disease



Franke et al., Hum. Genet. 2009

Heritability of brain structure and function and its relation to cognition

QLD Twin Imaging Study (QTIMS)

Australia
Greig de Zubicaray (UQ)
Nick Martin (QIMR)
Katie McMahon (UQ)
Margie Wright (QIMR)

USA
Paul Thompson (UCLA)
Arthur Toga (UCLA)

Xavier Castellanos (NYU)
Mike Millham (NYU)

- Supported by NIH (2007-2012) and NHMRC (2008-2013)

Data Acquisition

4 Tesla MRI scanner

Wesley Hospital

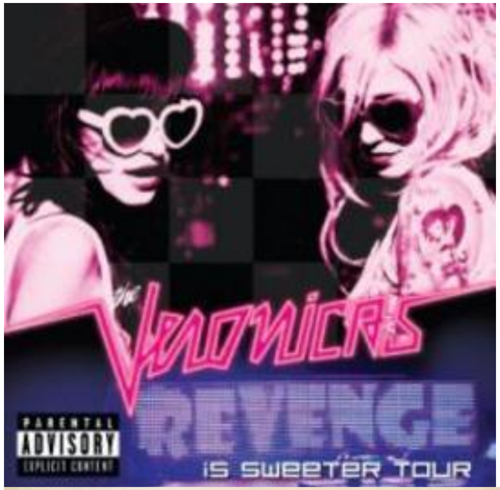
Brisbane, Australia

Structural MRI

Functional MRI (fMRI) - n-back working memory task; resting state

Diffusion Tensor Imaging(DTI)


BRUKER
MedSpec 4T


The Veronicas
REVENGE
IS SWEETER TOUR
PARENTAL ADVISORY EXPLICIT CONTENT


THE VERONICAS
LOLITA

Sample

- **1089 twins/sibs from 611 families (tested 2007-12)**
  - **Aged 18-30yrs; 62% females; all right handed**
  - **Includes 401 complete twin pairs (173 MZ, 227 DZ)**
  - **And 287 single twins/ non-twin siblings**
  - **80 twins/sibs were retested ~3 months later**
  - **Most participated in the cognition study at age 16y**
  - **All GW genotyped(Illumina 610k/core+exome 720k)**
- **Plus 156 younger twins**
    - **36 pairs at age 12 years**
    - **42 pairs at age 16 years**

Cognitive Battery:

- Extensive battery of cognitive tests **<u>at 16 yrs</u>**
- 3.5 hr in-person assessment
- Short battery of cognitive tests at MRI if no cognitive testing available at 16 yrs

current, old, new

Psychometric IQ
- Full-scale IQ (MAB)
- Verbal ability (info, arith, vocab)
- Performance ability (spatial, obj ass)
- WAIS digit span/symb, LNS, matrix

Processing speed
- Inspection time
- Reaction time
- N200 latency
- P300 latency

Working memory (DRT, nBack)
- Performance accuracy
- P300 amplitude
- Slow wave amplitude

Relational Complexity
- N-term, Latin square, Sentence

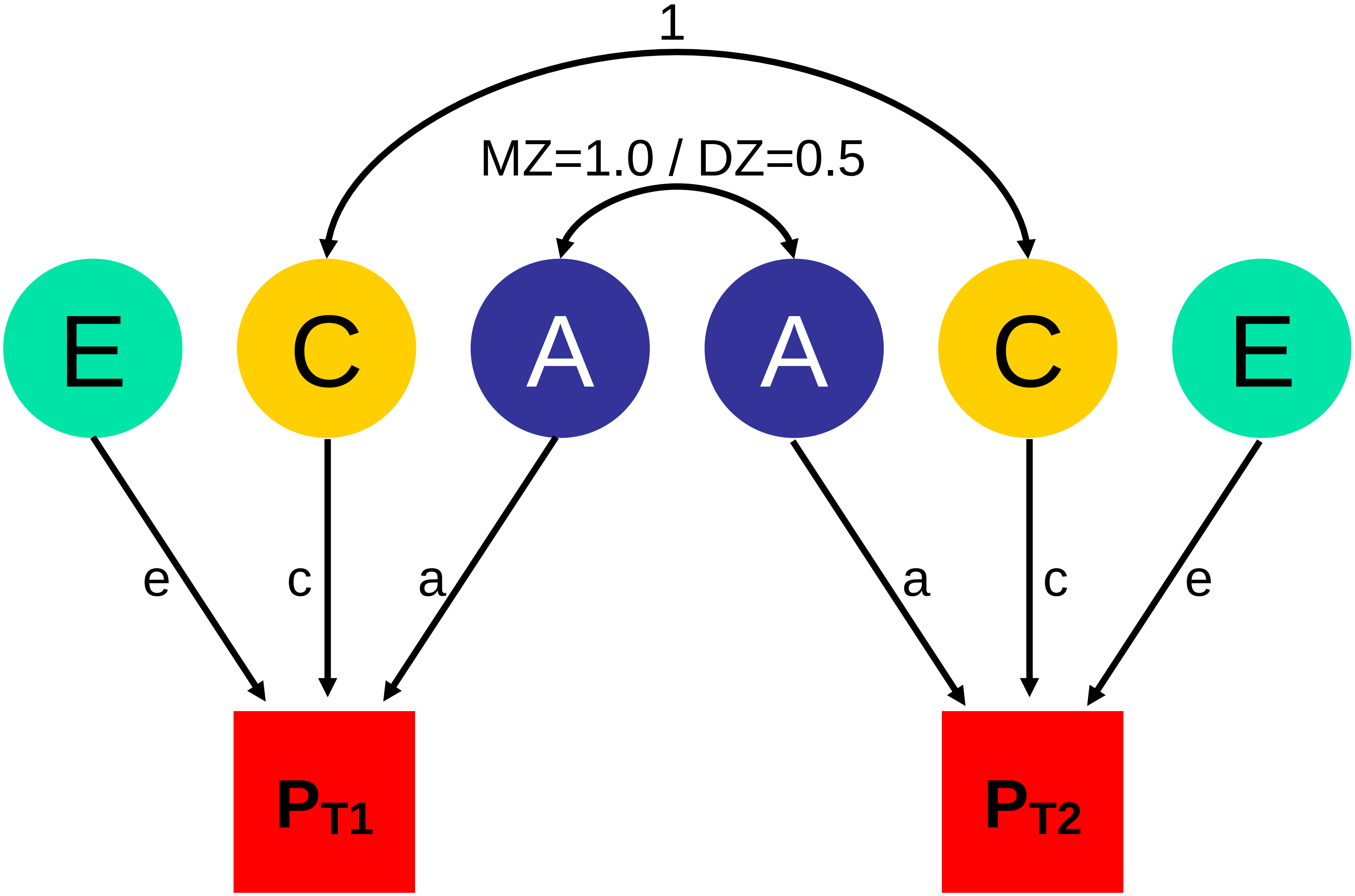
Psychophysiological
- alpha frequency
- EEG power
- EEG coherence

Academic achievement
- Queensland Core Skills

Reading
- NART
- Schonell
- CORE reading and spelling

Genetics of brain structure

ACE Model for twin data

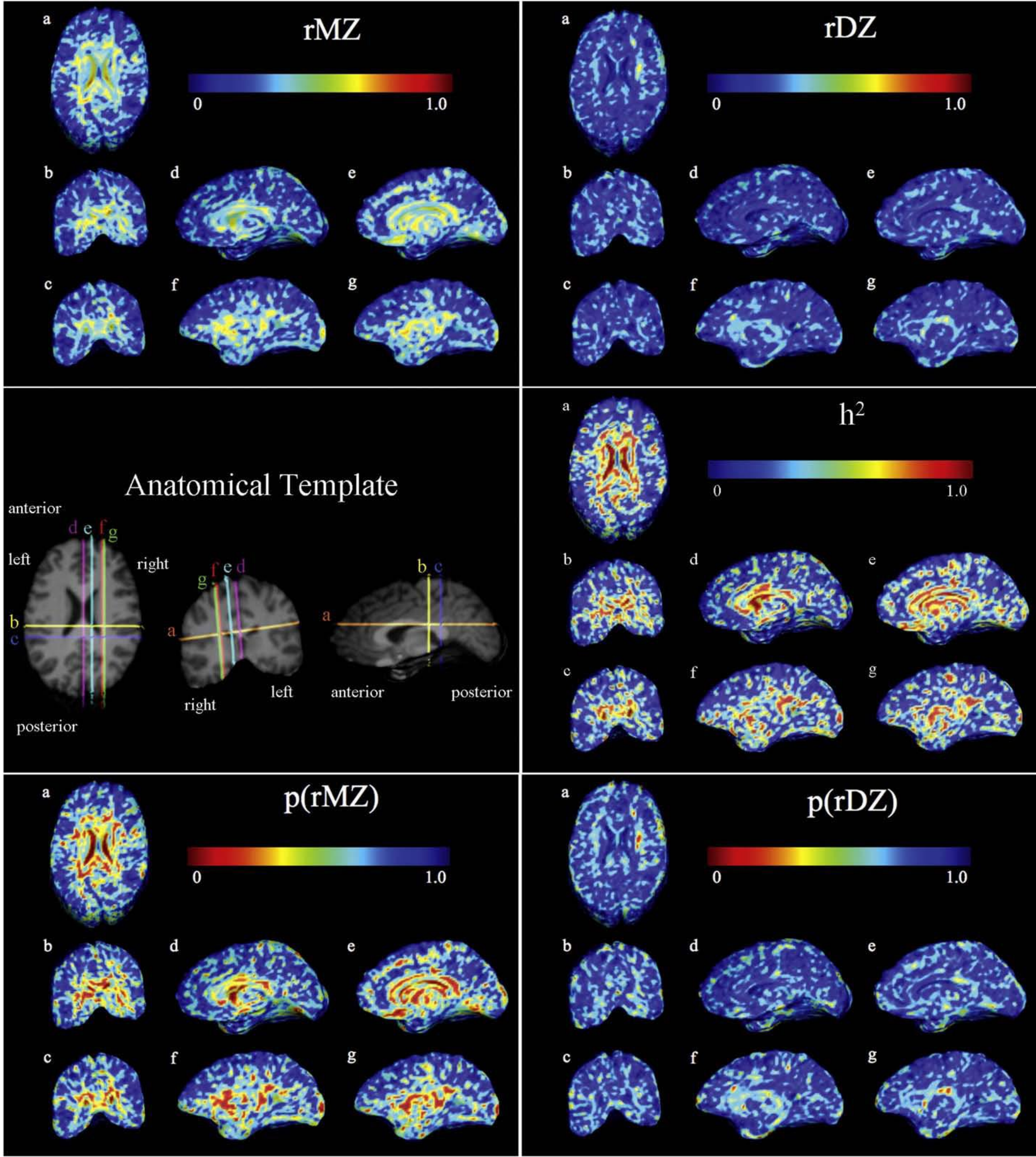


For neuroimaging phenotypes
we can fit the ACE model to
every voxel –
up to 2M. Very computer
intensive!

MZ twins show greater resemblance in morphometry than DZ twins

Heritability:-

- 20% in white matter
- 75% in subcortical structures (corpus callosum, ventricles)
- 20–40% in basal ganglia, thalamus
- 50% occipital lobes
- voxelwise maps define a more detailed spatial pattern for the different influences

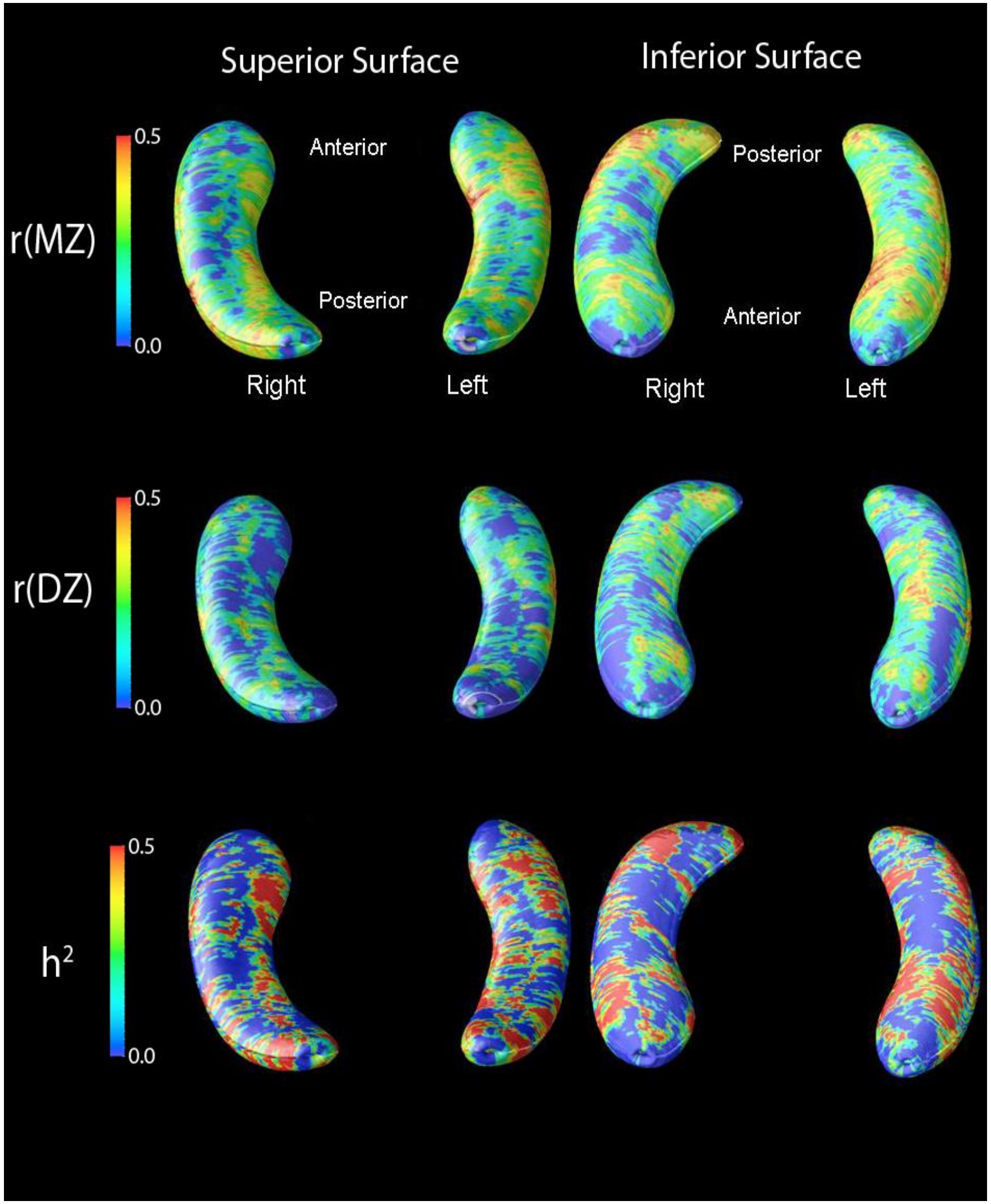


Neuroimage 48:37- 49, 2009

3D profile of genetic influences on the hippocampus

- 81 MZ & 44 DZ twin pairs
- maps show hotspots of genetic influence
- substantial variance due to unique environment - hippocampus is highly plastic, adapting in response to individual experiences
- confirms previous studies - h^2 of hippocampal vol.~40-69%

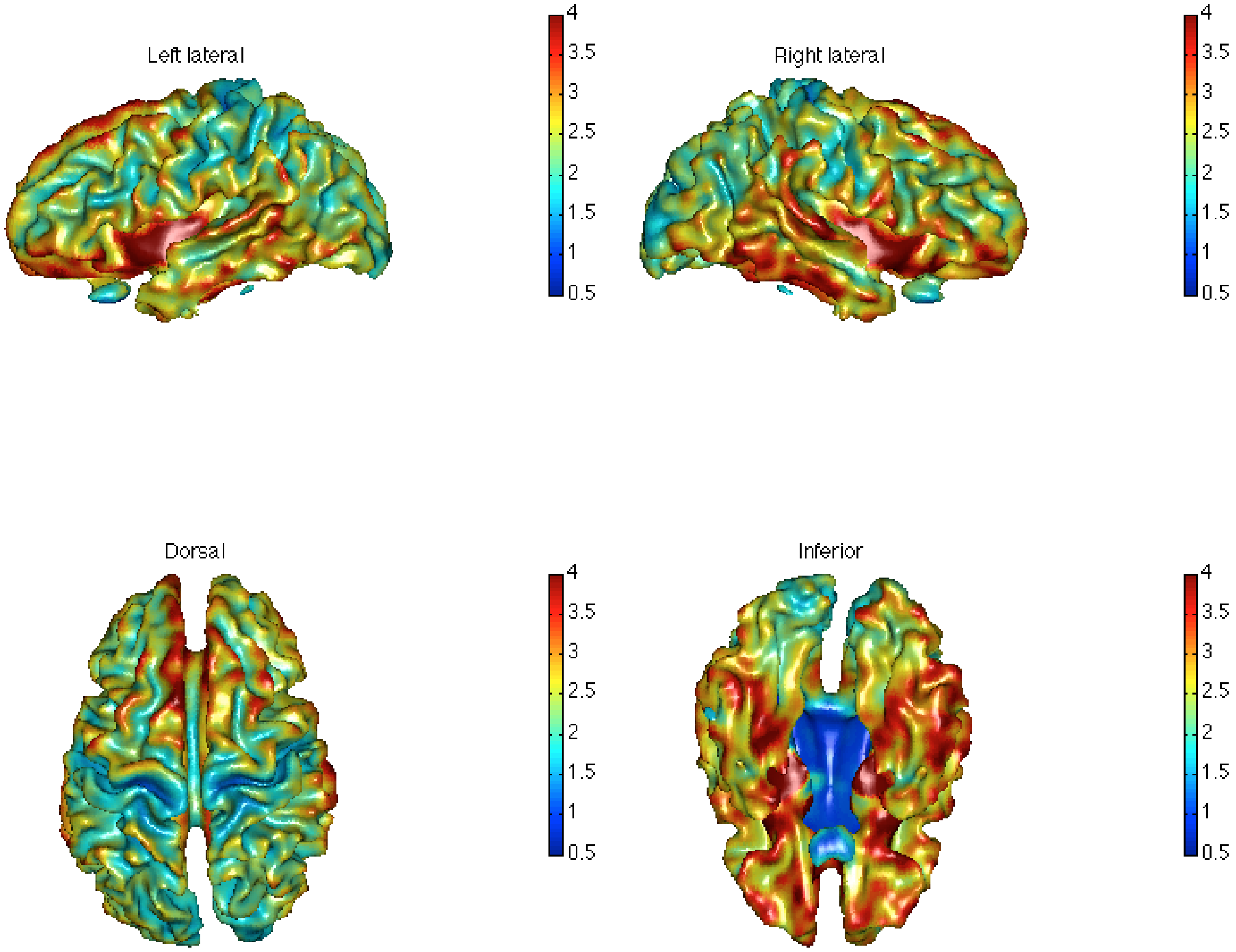
(Peper et al. Human Brain Mapping, 2007; Sullivan et al. Hippocampus, 2001)



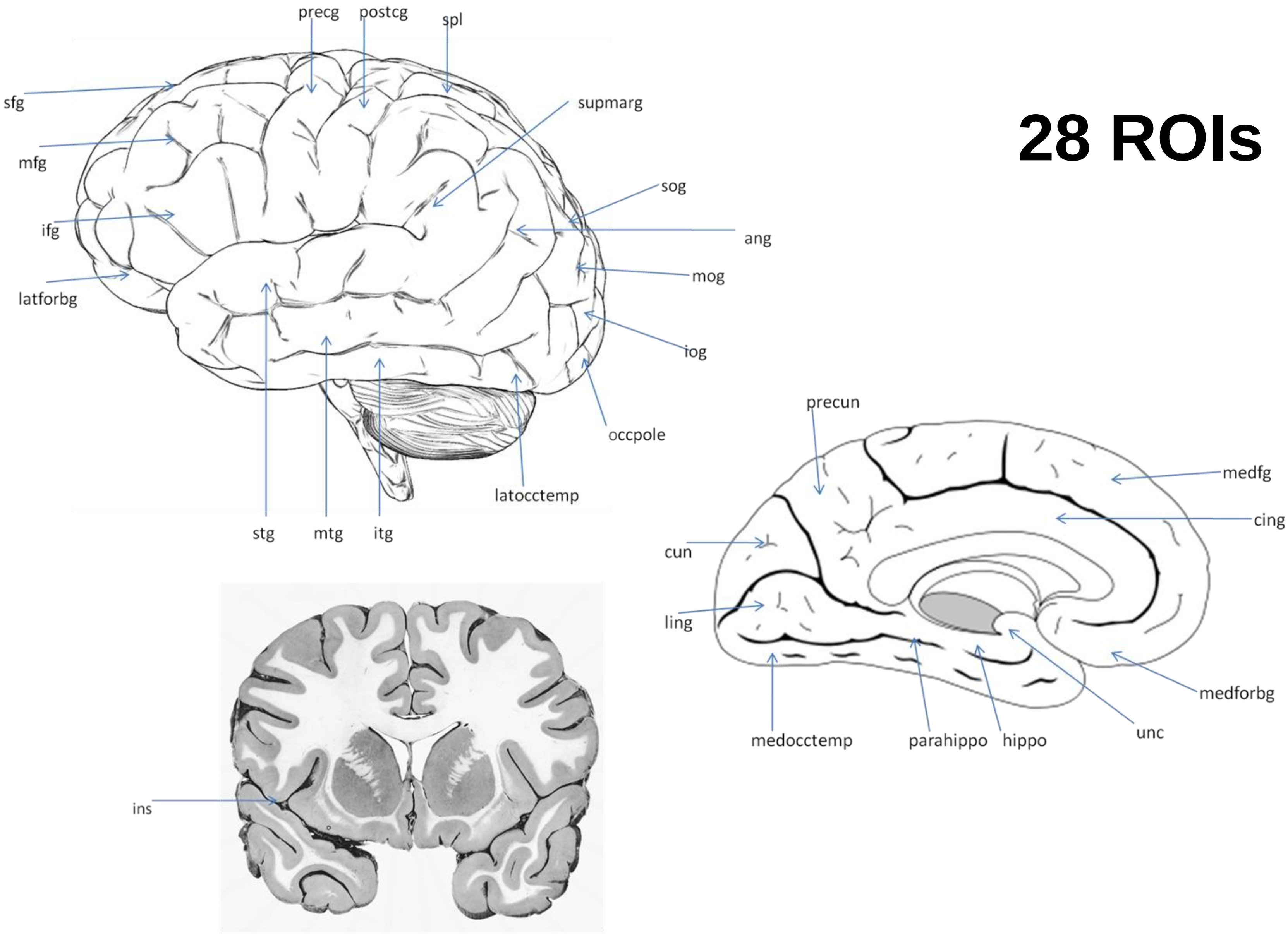
Heritability of cortical thickness (CT)

- Research has shown that patterns of cortical thinning is associated with diseases such as schizophrenia, bipolar, depression, and Alzheimer’s.
- In this study, we estimated the heritability of cortical thickness from 28 regions of interest (ROIs).
- Genome-wide association (GWA) scans were performed on each ROI in order to identify variants associated with the thickness of the cortex.

Voxel-by-voxel CT brain map for one individual



28 ROIs


precg
postcg
spl
sfg
supmarg
mfg
sog
ifg
ang
mog
latforbg
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latocctemp
stg
mtg
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medocctemp
parahippo
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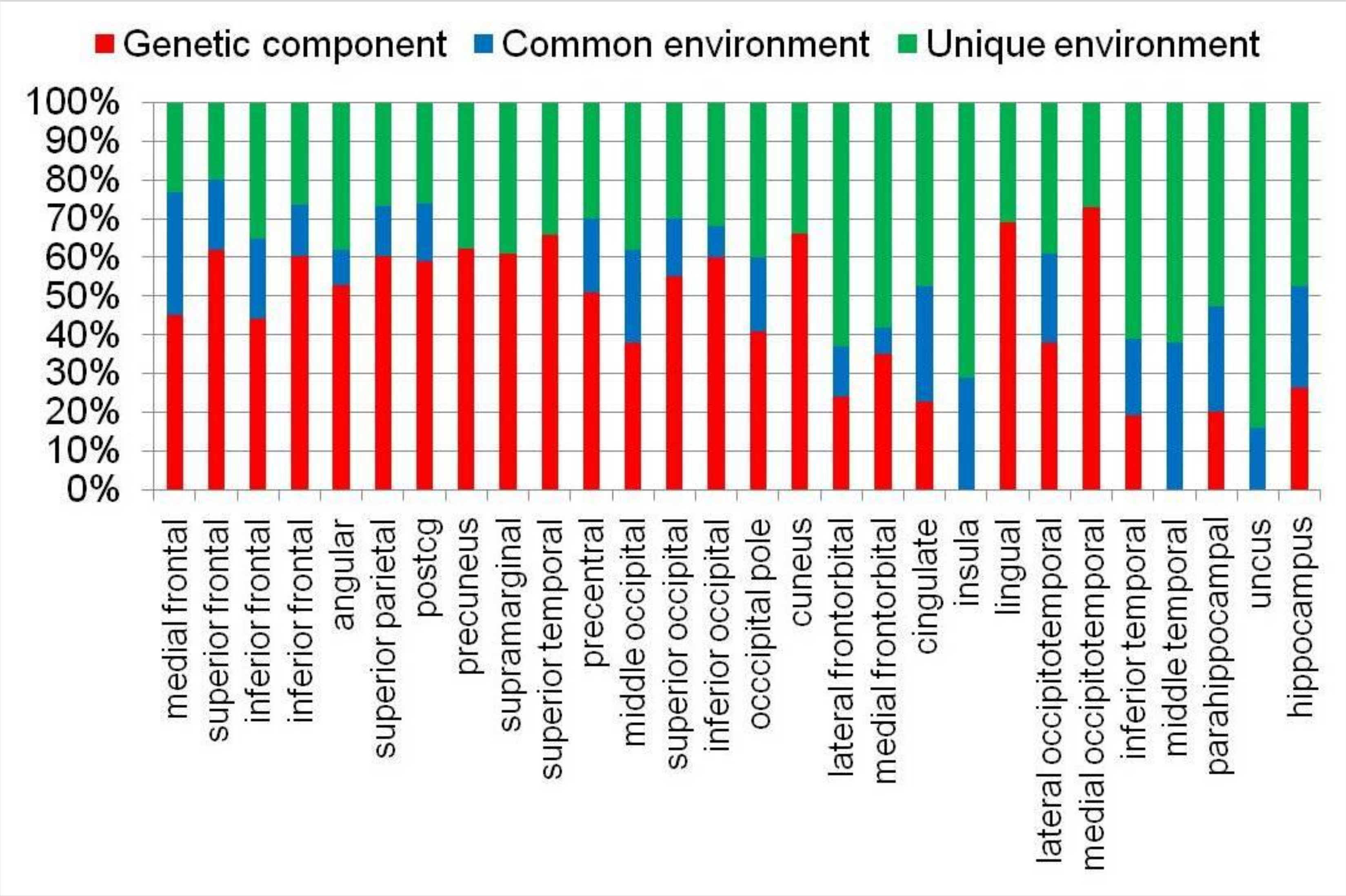
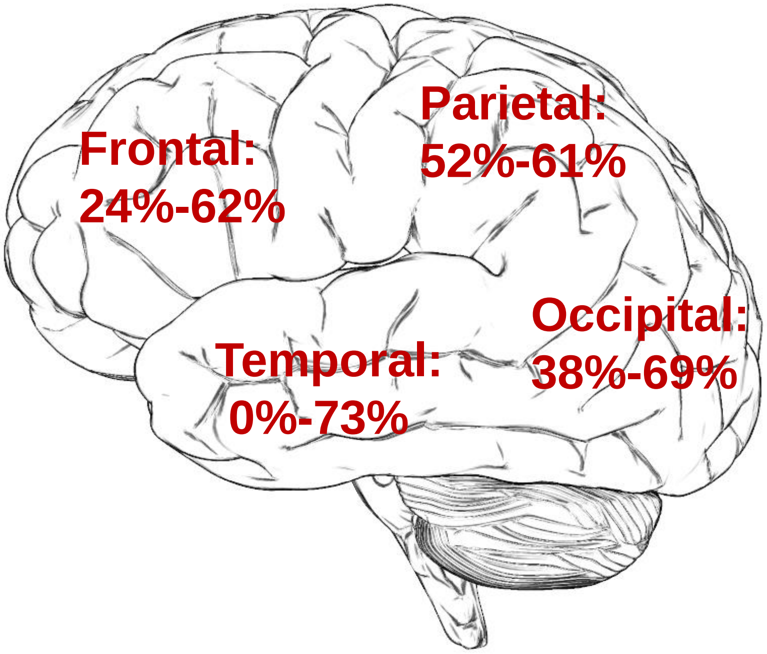
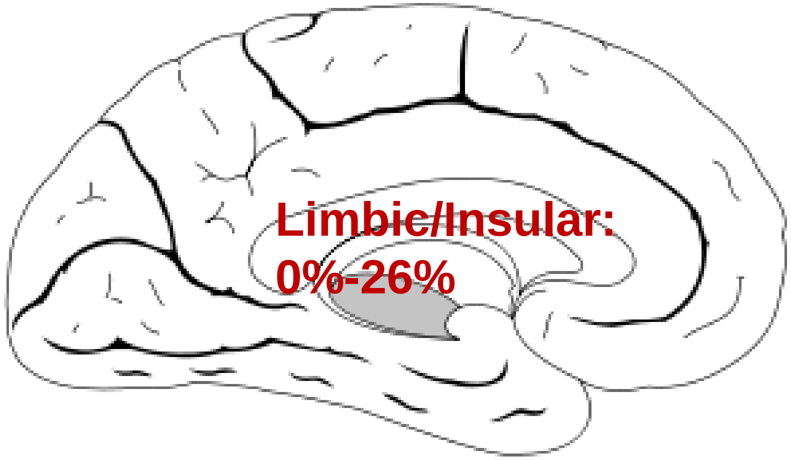
ins

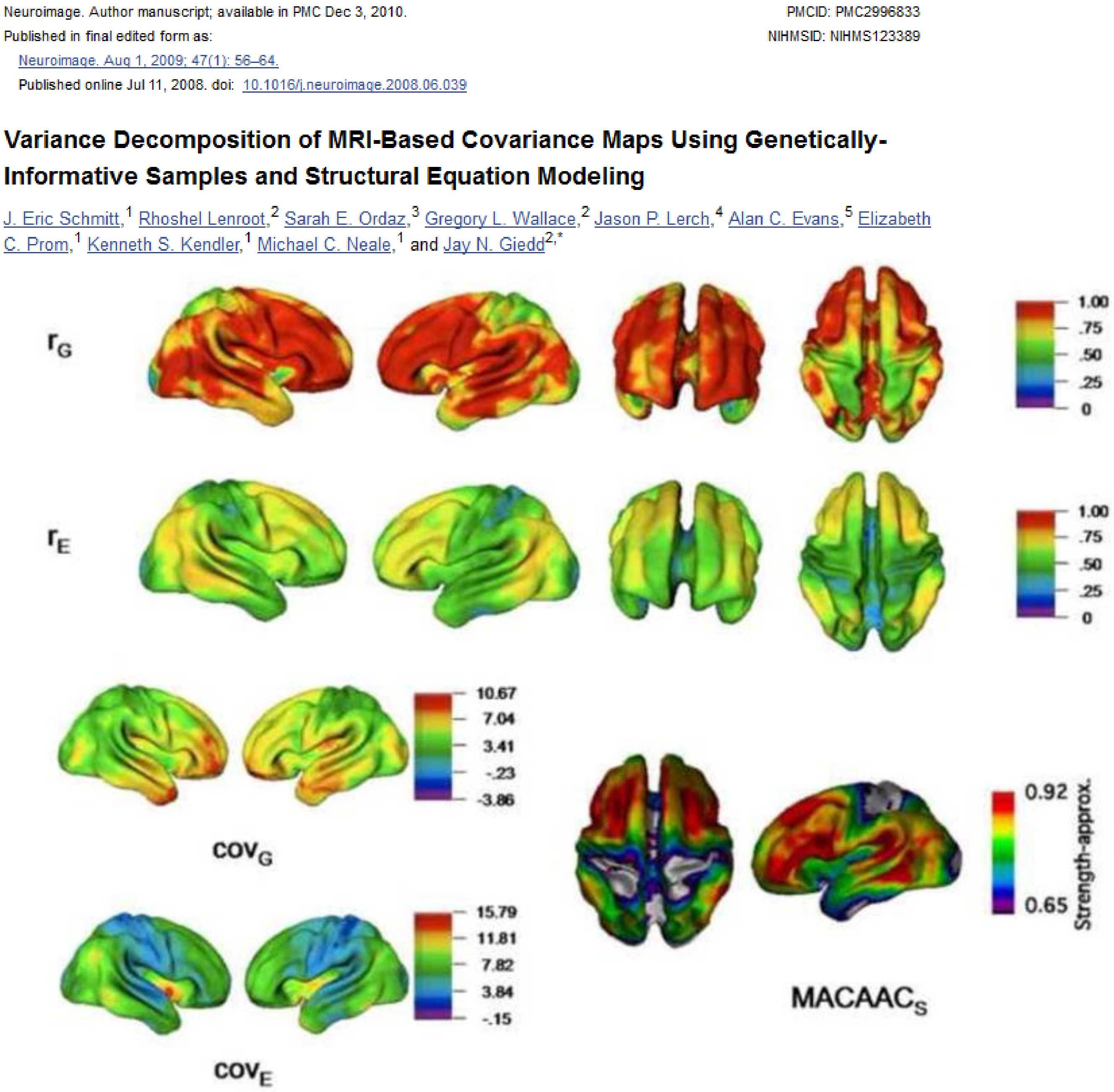
Variance components estimates on CT



Heritability ranges by lobe







Neuroimage. Author manuscript; available in PMC Dec 3, 2010.
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Neuroimage. Aug 1, 2009; 47(1): 56–64.

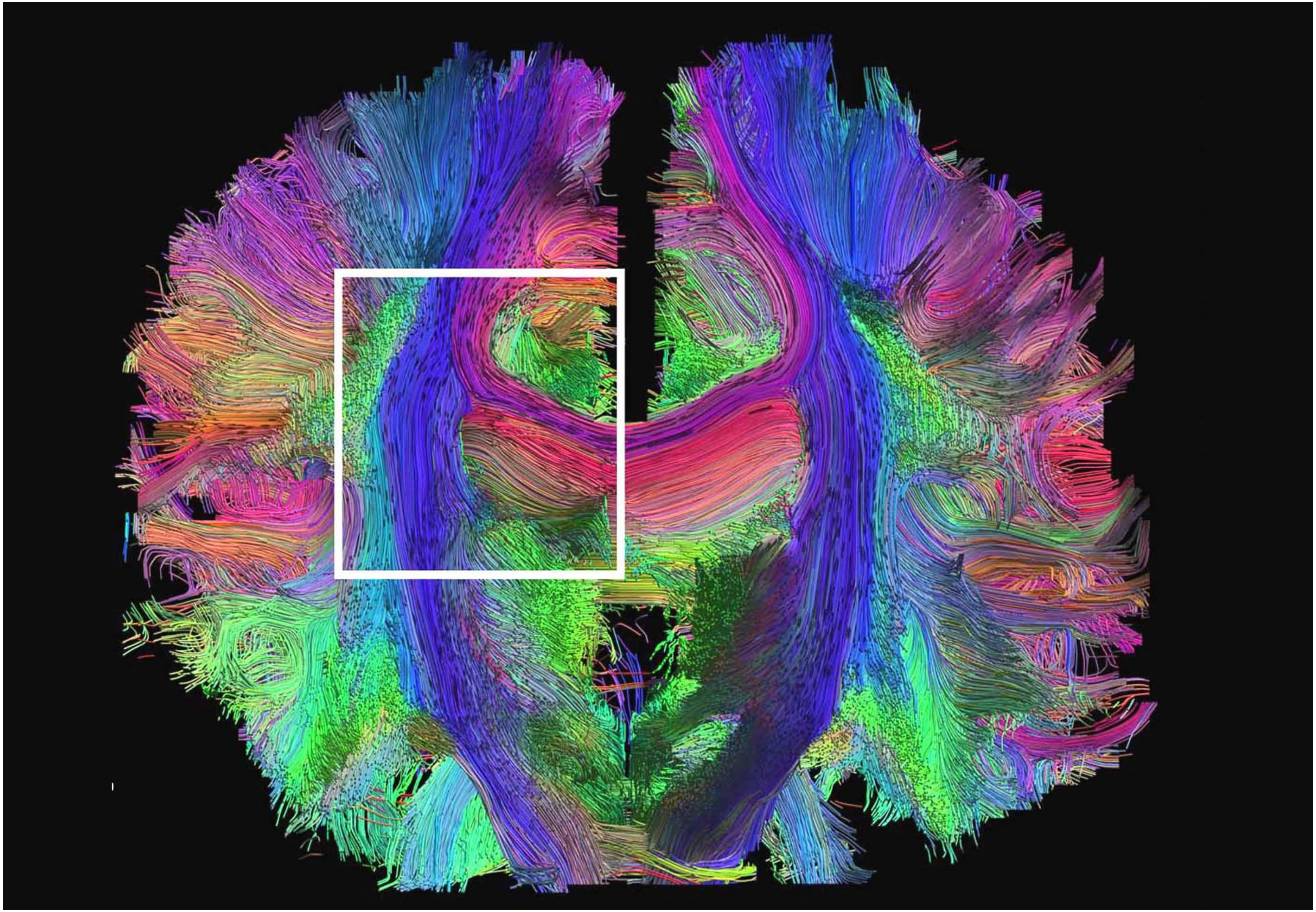
doi: 10.1016/j.neuroimage.2008.06.039

PMCID: PMC2996833
NIHMSID: NIHMS123389

Variance Decomposition of MRI-Based Covariance Maps Using Genetically-Informative Samples and Structural Equation Modeling

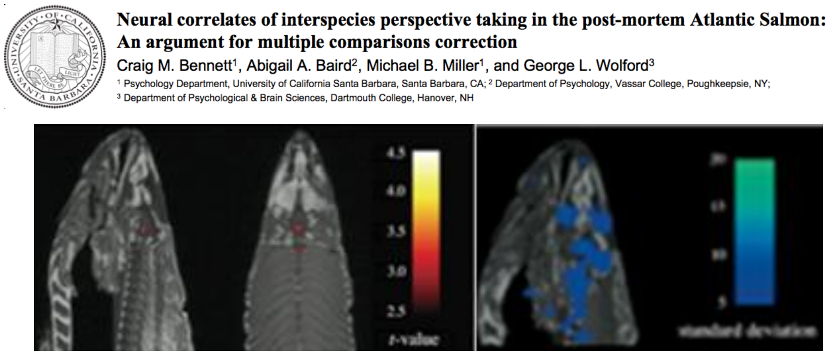
J. Eric Schmitt,[1] Rhoshel Lenroot,[2] Sarah E. Ordaz,[3] Gregory L. Wallace,[2] Jason P. Lerch,[4] Alan C. Evans,[5] Elizabeth C. Prom,[1] Kenneth S. Kendler,[1] Michael C. Neale,[1] and Jay N. Giedd[2,*]

Genetics of brain connectivity



Challenges in Neuro Imaging Genetics

- **Scope and scale of studies**
  - Small N & candidate approaches
- **Strong hypotheses re effect sizes**
  - Common variants with large effects...
- **Data harmonization**
- **Multiple testing**



Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction

Craig M. Bennett[1], Abigail A. Baird[2], Michael B. Miller[1], and George L. Wolford[3]

[1] Psychology Department, University of California Santa Barbara, Santa Barbara, CA; [2] Department of Psychology, Vassar College, Poughkeepsie, NY; [3] Department of Psychological & Brain Sciences, Dartmouth College, Hanover, NH

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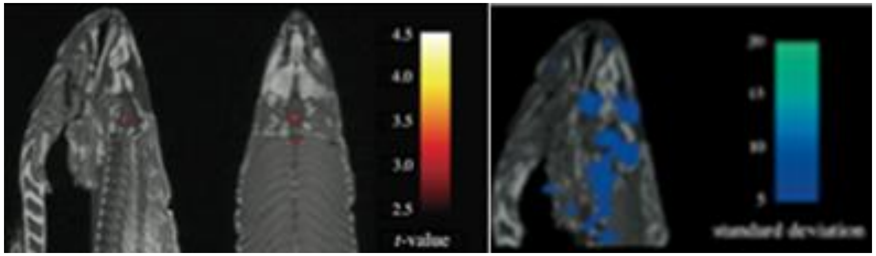
Journal of Serendipitous and Unexpected Results

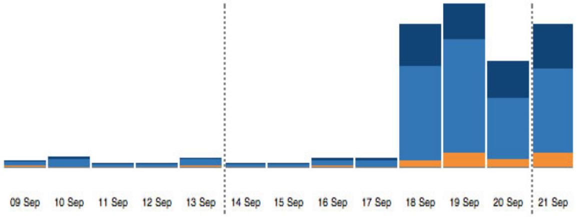
Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Proper Multiple Comparisons Correction

Craig M. Bennett [1*], Abigail A. Baird [2], Michael B. Miller [1] and George L. Wolford [3]



Subject. One mature Atlantic Salmon (Salmo salar) participated in the fMRI study. The salmon was approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning.

Task. The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence. The salmon was asked to determine what emotion the individual in the photo must have been experiencing.



NEUROSCIENCE PRIZE: Craig Bennett, Abigail Baird, Michael Miller, and George Wolford [USA], for demonstrating that brain researchers, by using complicated instruments and simple statistics, can see meaningful brain activity anywhere — even in a dead salmon.

REFERENCE: "Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction," Craig M. Bennett, Abigail A. Baird, Michael B. Miller, and George L. Wolford, poster, 15th Annual Meeting of the Organization for Human Brain Mapping, San Francisco, CA, June 2009.

REFERENCE: "Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Multiple Comparisons Correction," Craig M. Bennett, Abigail A. Baird, Michael B. Miller, and George L. Wolford, Journal of Serendipitous and Unexpected Results, vol. 1, no. 1, 2010, pp. 1-5.

ATTENDING THE CEREMONY: Craig Bennett, Abigail Baird, Michael Miller, and George Wolford

White matter integrity
DTI - diffusion tensor images

i) 30 gradient directions (27 high b values and 3 b=0 repetitions)

ii)105 gradient directions (94 high b-values and 11 b=0 repetitions)

Fractional Anisotropy (FA) = White Matter integrity

FA=0 – isotropic - in areas where water diffuses freely

FA=1 – anisotropic- in highly myelinated WM fibres

Genetic Influences on White Matter Integrity (FA)

- genetic factors explain 75 - 90% of the variance in FA in almost all white matter regions *Chiang et al. 2009 J Neurosci. 29: 2212-24*

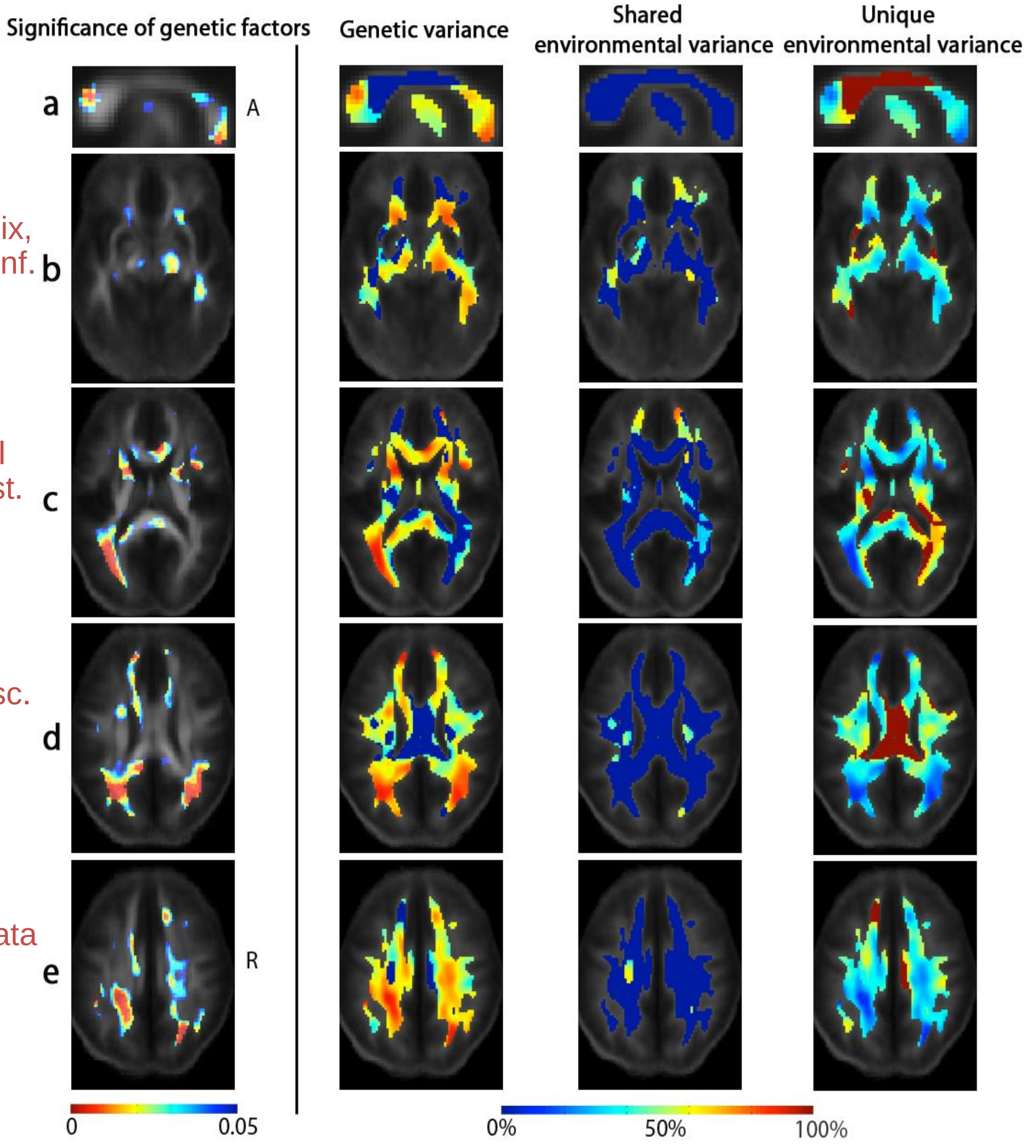
splenium &
part of CC

L cerebral peduncle, fornix,
R inf. longitudinal fasc. / inf.
fronto-occipital fasc.

Anterior internal
capsule & L post.
thalamic / optic
radiation

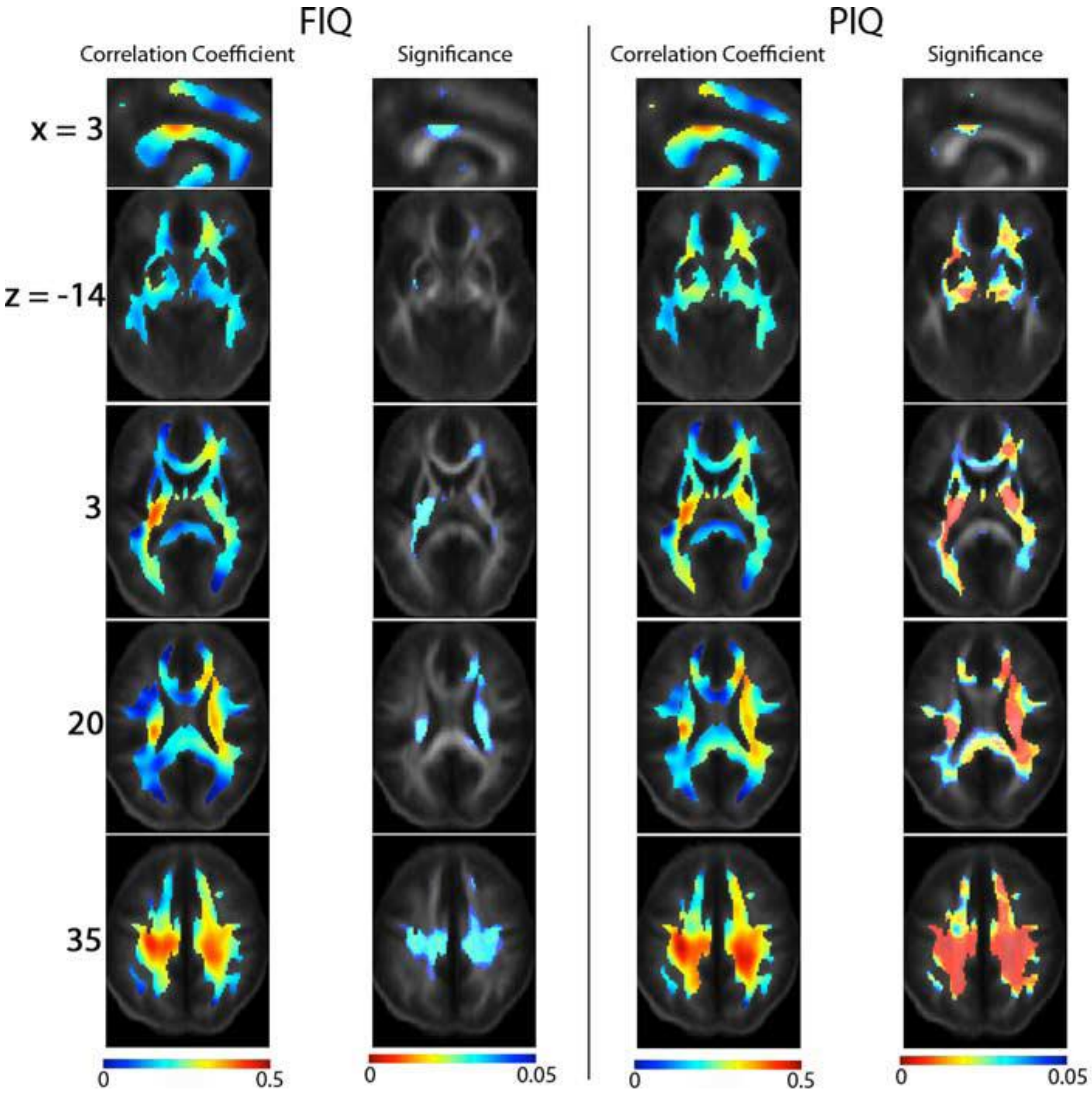
sup. longitudinal fasc.

sup. & post. corona radiata



White matter integrity correlated with IQ

- correlated with PIQ
- r = 0.3 - 0.4



Chiang et al. 2009

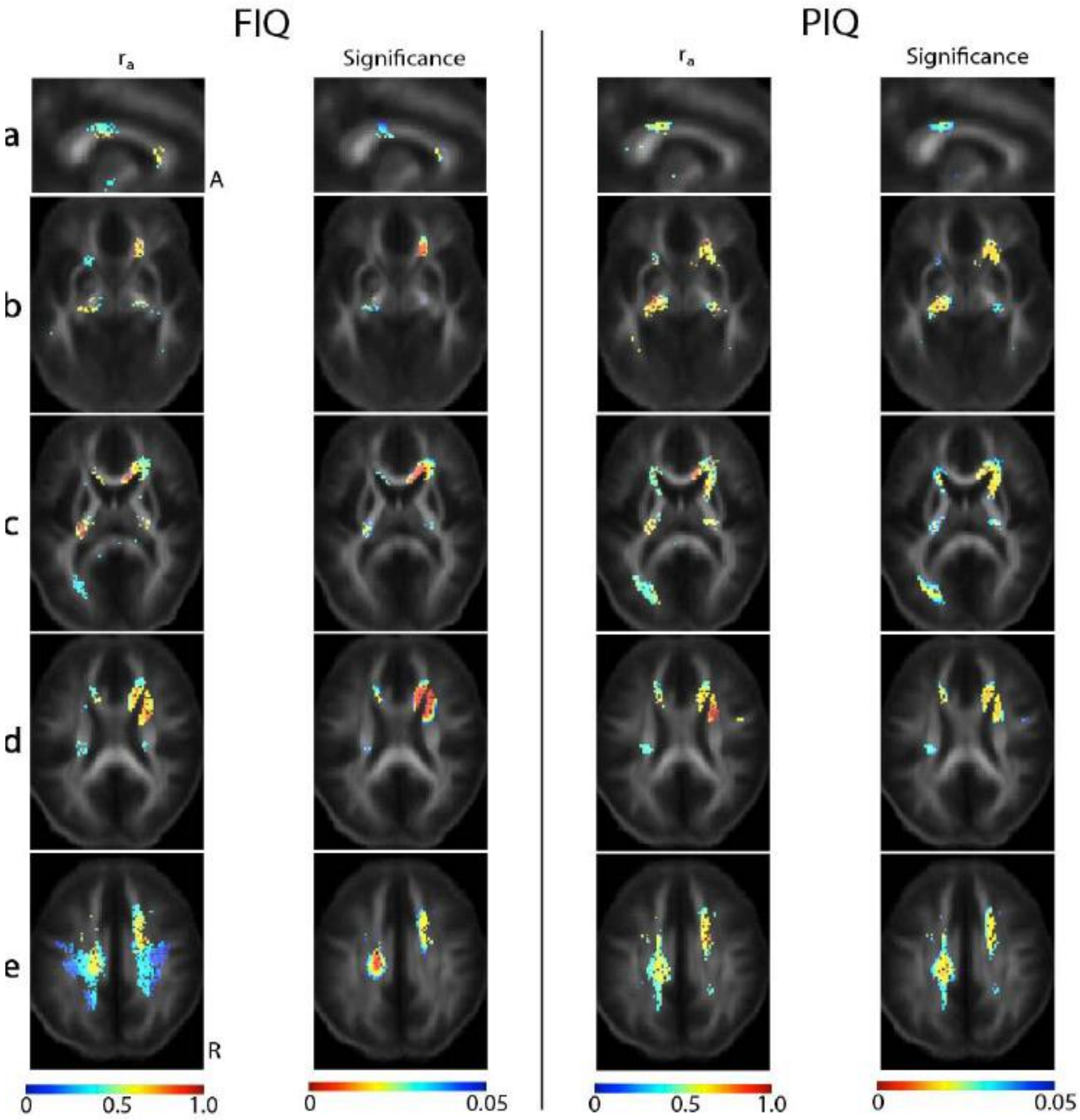
J Neurosci. 29: 2212-24

Genetic correlation of white matter integrity (FA) with IQ

- Genes (partly) moderate the correlation between fibre integrity and IQ common physiological mechanism

Chiang et al. 2009

J Neurosci. 29: 2212-24

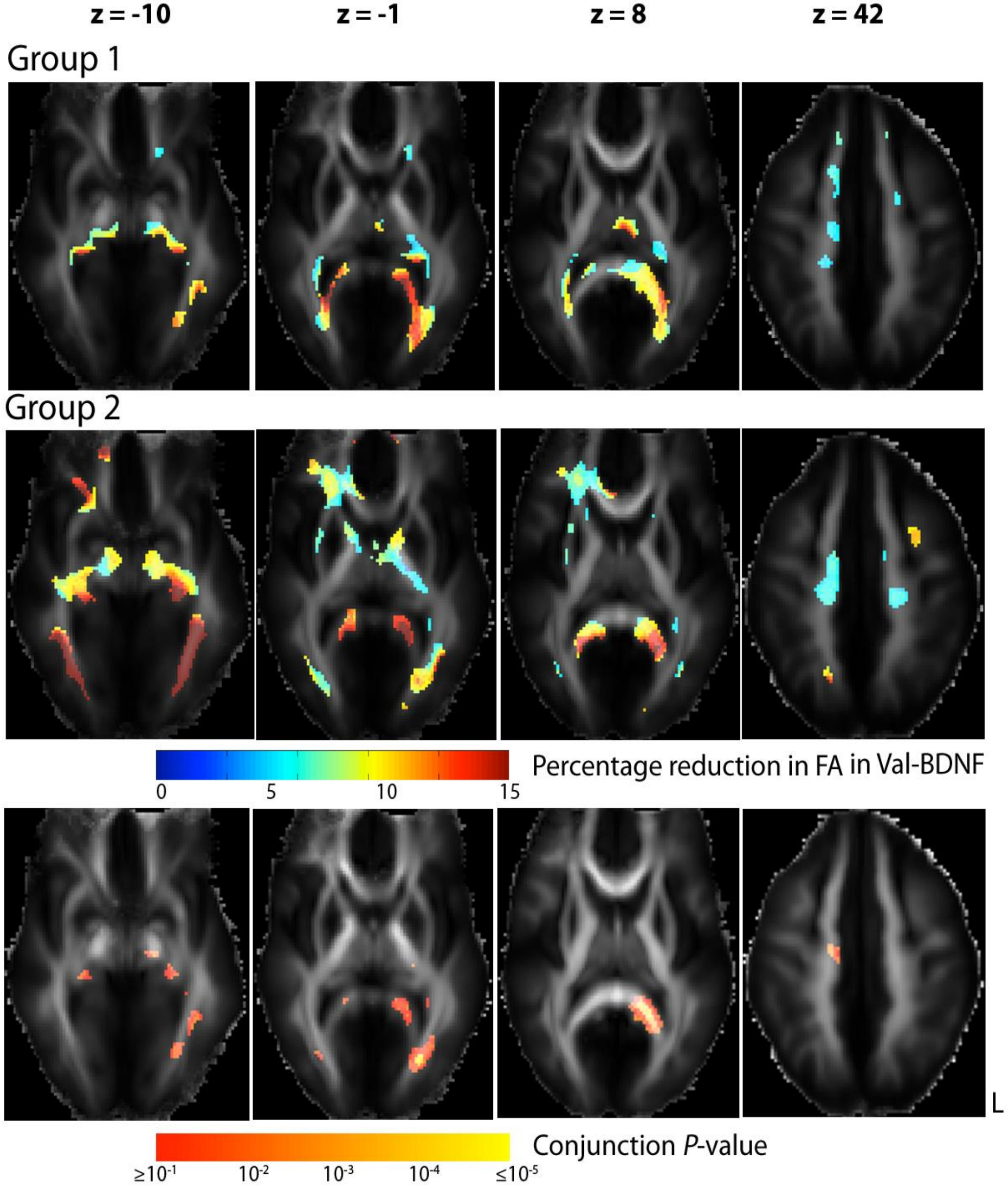


BDNF Val66Met polymorphism effects on white matter

Group 1: 99M /135F (110 fam)
age: 23.7±1.9 years.

Group 2: 89M /132F (128 fam)
age: 23.7±2.2 years

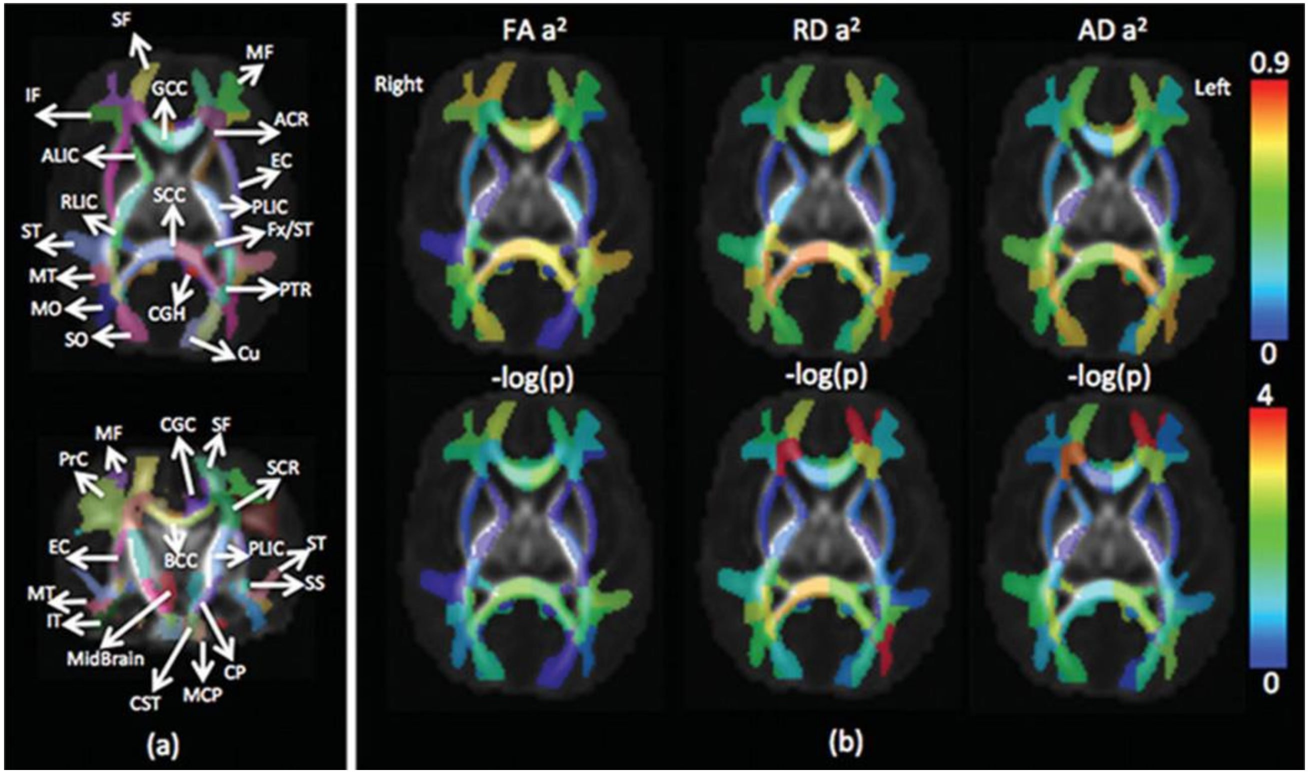
- Val allele associated with up to 15% reduction in FA in major fiber tracts (splenium of the corpus callosum, left optic radiation)
- replicated in both samples



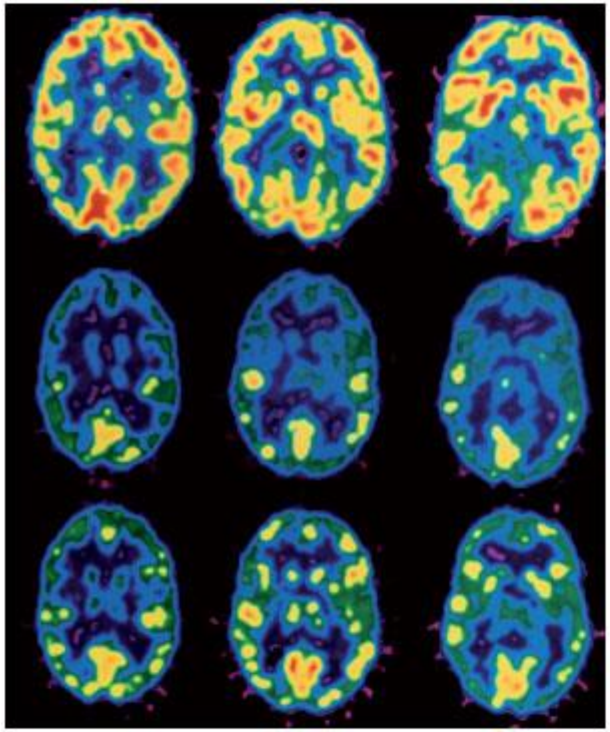
Twin Res Hum Genet. 2012 Jun;15(3):336-50. doi: 10.1017/thg.2012.14.

White matter heritability using diffusion tensor imaging in neonatal brains.

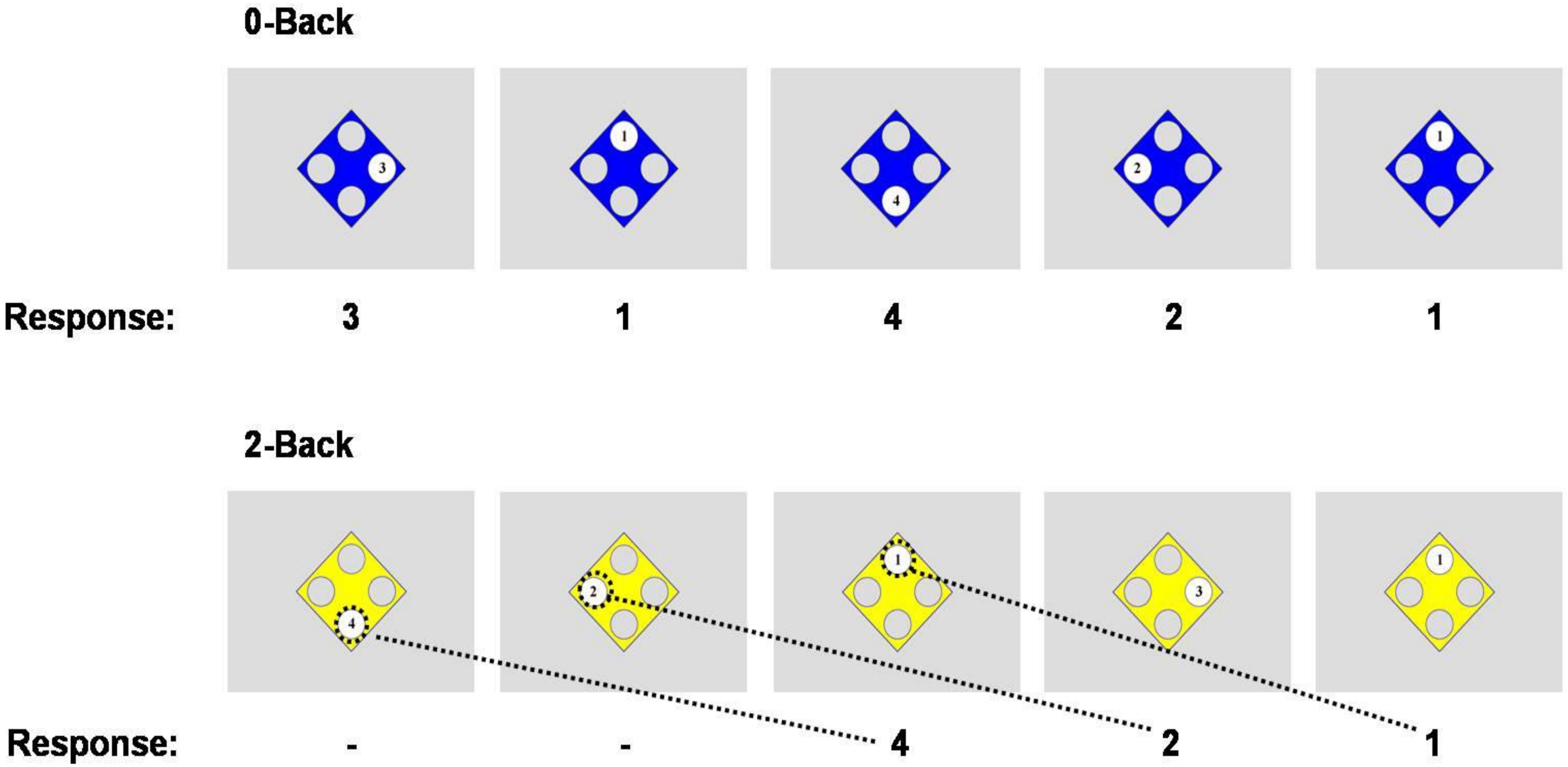
Geng X[1], Prom-Wormley EC, Perez J, Kubarych T, Styner M, Lin W, Neale MC, Gilmore JH.



Genetics of brain function

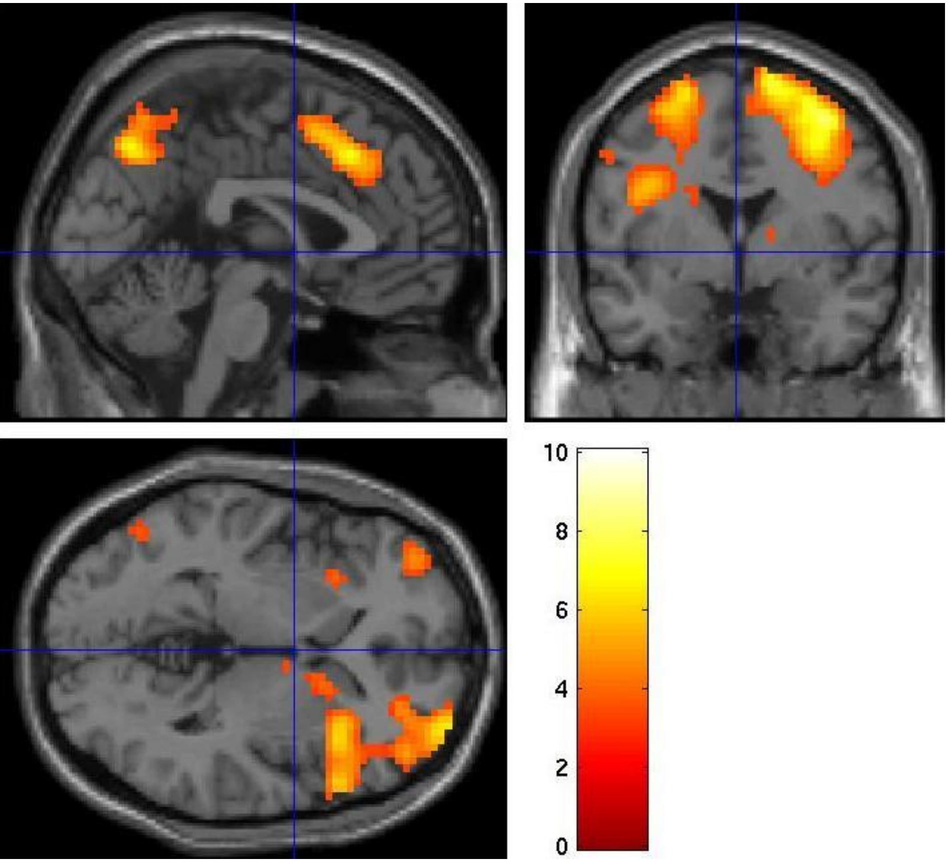


BOLD fMRI during *n*-back working memory task

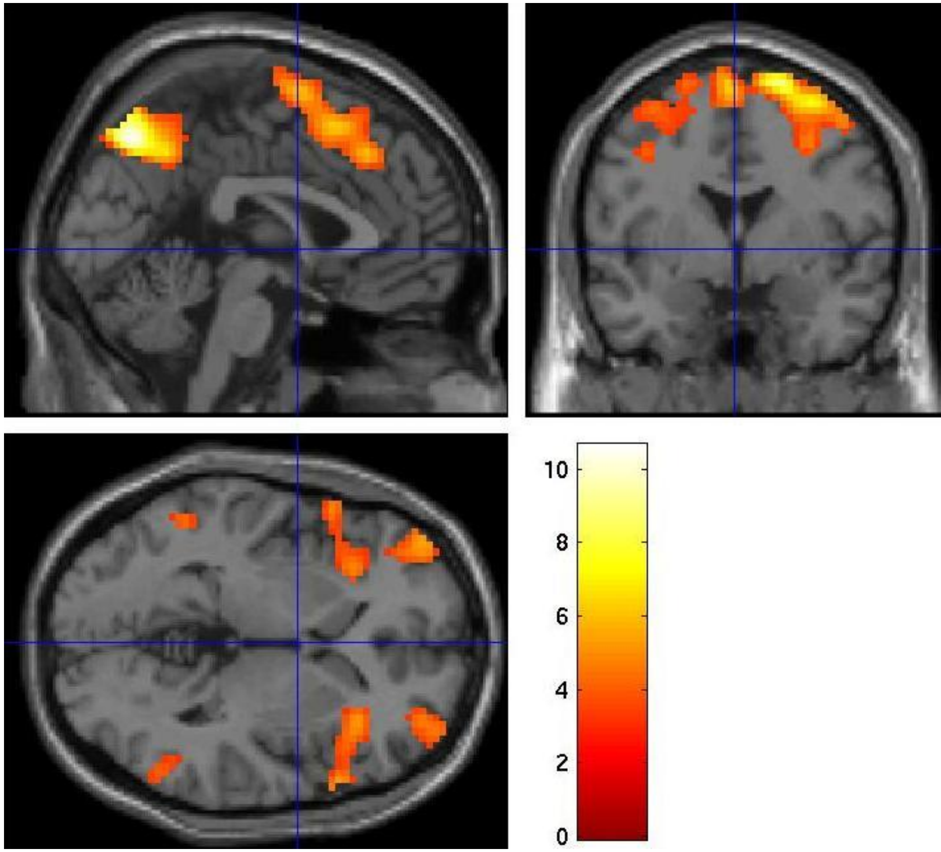


MZ co-twins showing similar brain activation patterns during the N-back task

Twin 1

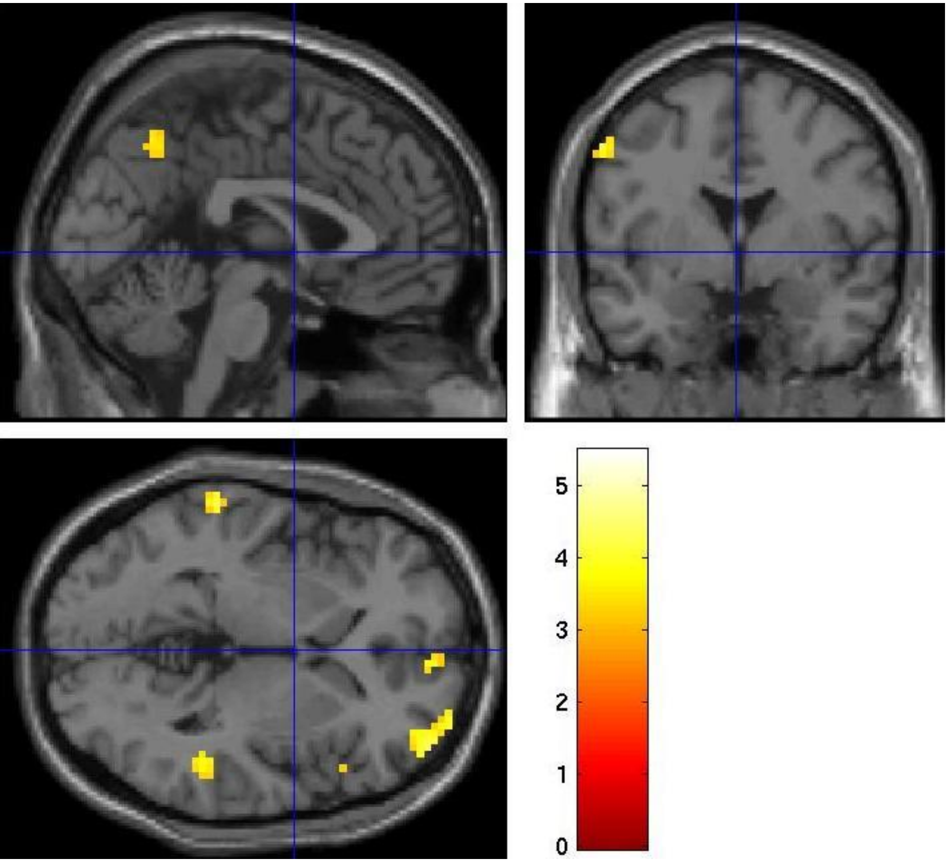


Twin 2

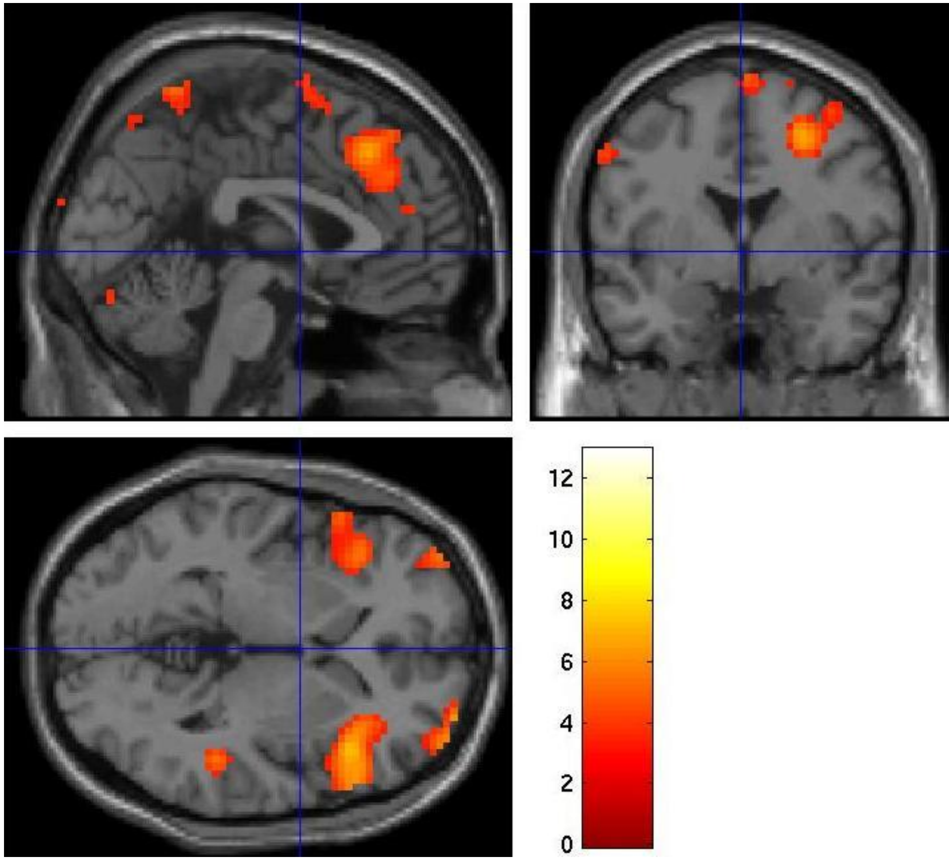


DZ co-twins showing different brain activation patterns during the N-back task

Twin 1



Twin 2



fMRI during **working memory**

fMRI study of 315 twins

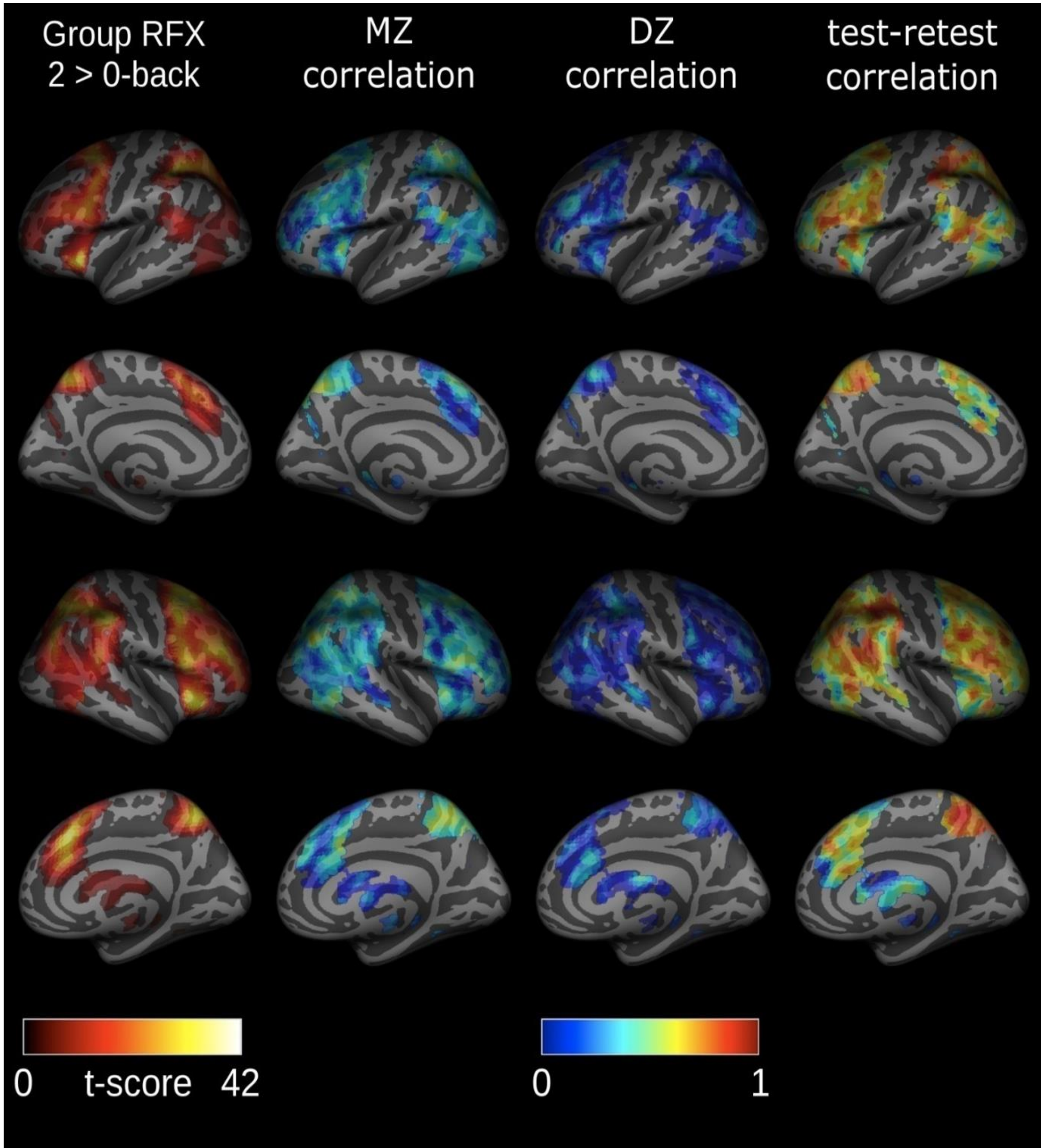
- 74 MZ pairs (29M/45F)
- 63 DZ pairs (11M /27F /25MF)
- 41 unpaired subjects

- voxel analysis

  Blokland et al. J Neurosci. 2011

- regions of interest analysis (N=75 pairs)

Blokland et al. 2008 Biol. Psychology

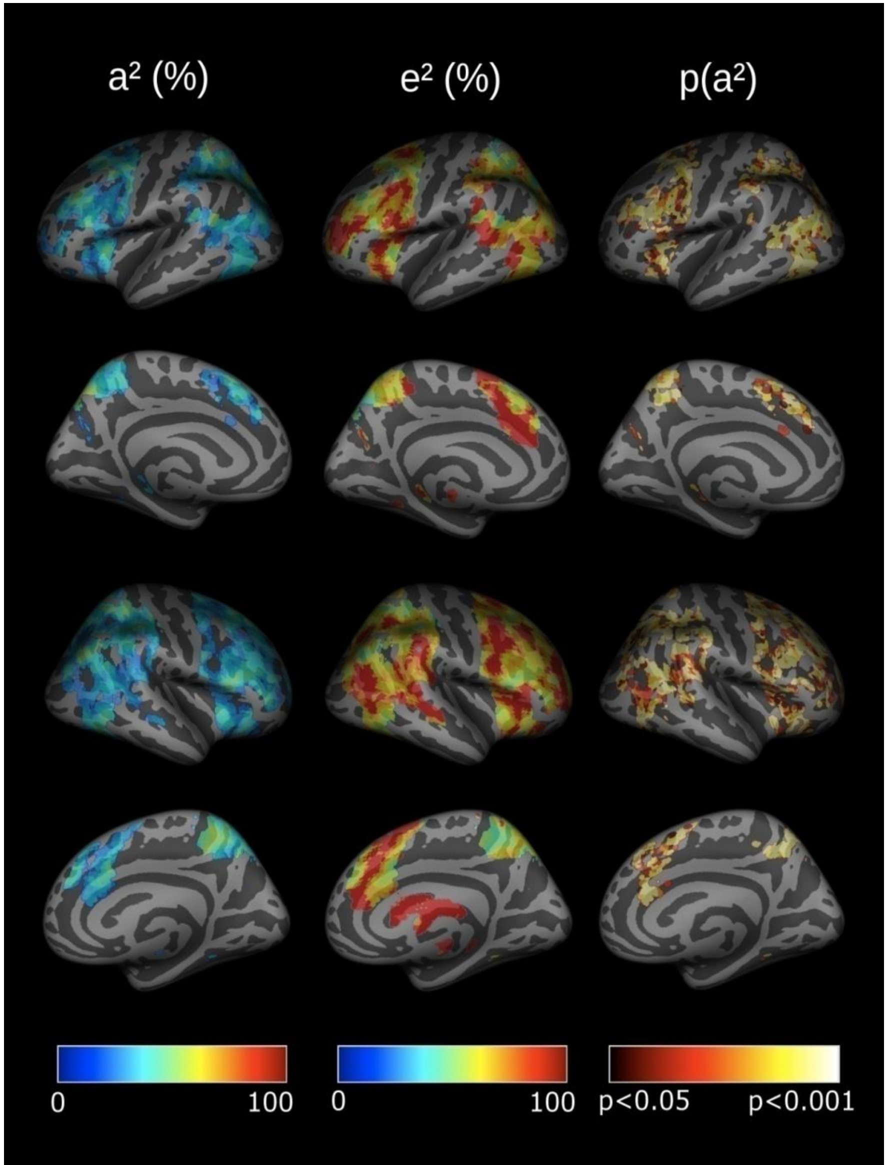


Maps showing genetic influences on brain activation during working memory

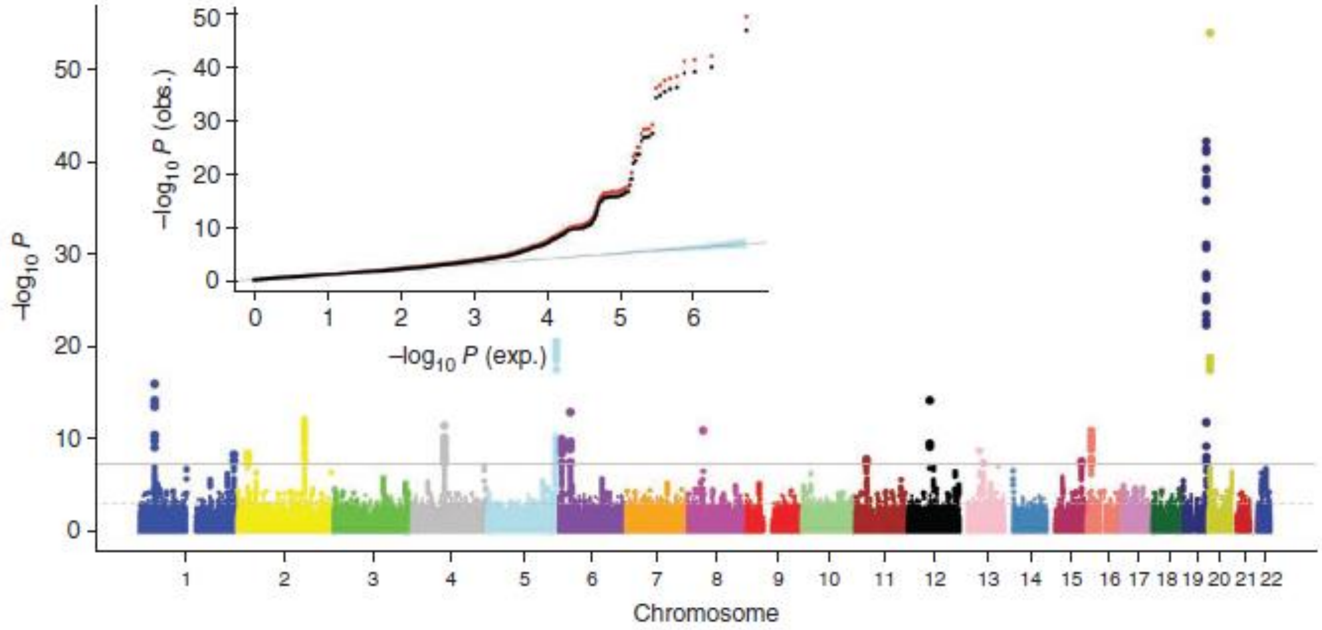
- significant genetic influences on WM related brain activation, especially in frontal and parietal brain regions

- genetic influences highest in the parietal lobe (60-70%)

- sizeable unique environmental effects - NOT all measurement error (reliability = 0.7 – 0.9 in most activated areas)



GWAS for neuroimaging phenotypes



GWAS of brain volumes (ADNI sample)

Alzheimer's Disease Neuroimaging Iniative (ADNI)
- mixed sample of healthy controls, MCI, AD

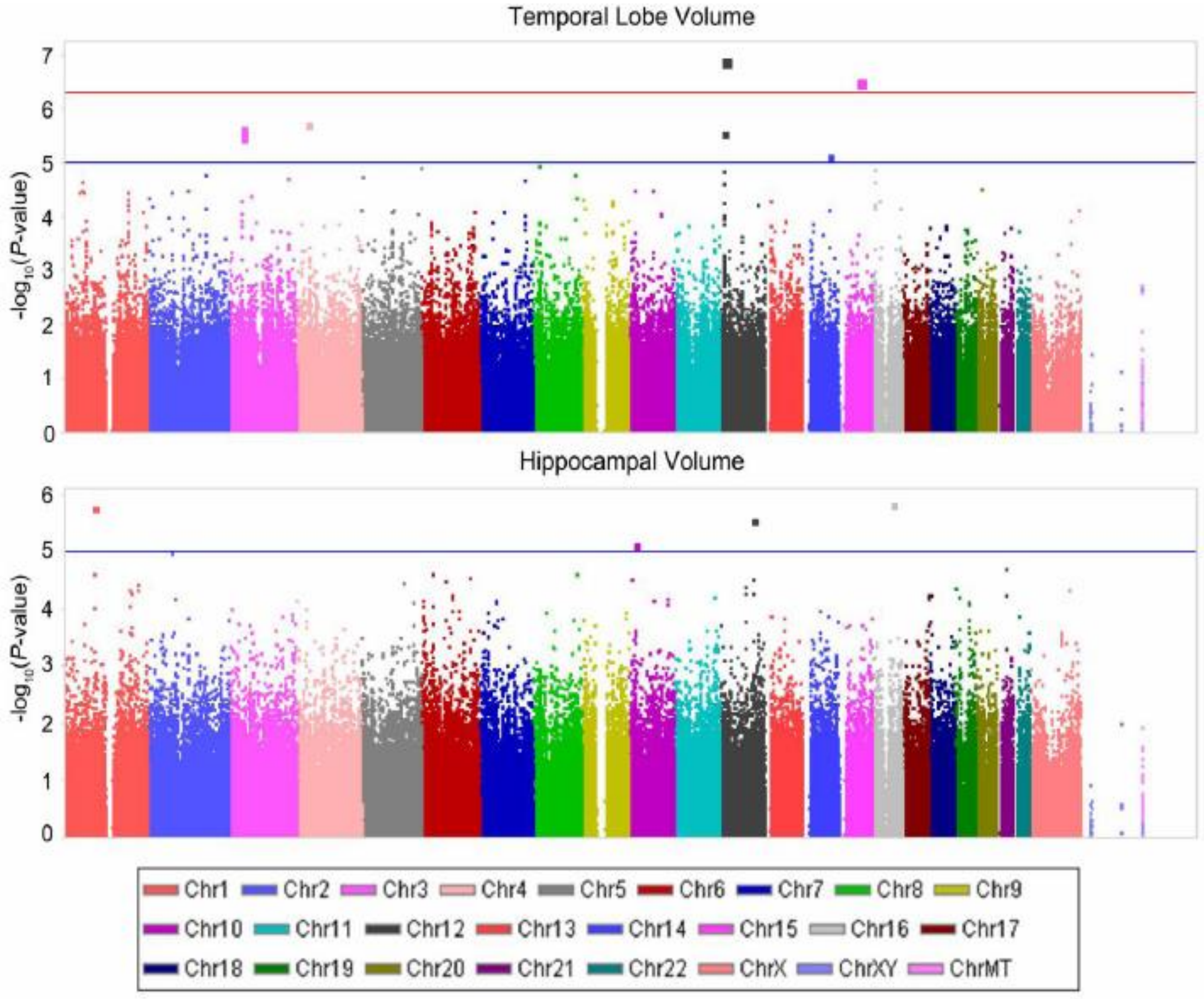
N = 742 (temporal)
N = 698 (hippo)

610K Illumina SNP

Genome –wide evidence or support - chrm. 12

Lower temporal lobe vols were most assoc. with a common variant in GRIN2B .

Risk allele over-represented in AD and MCI vs elderly controls



Temporal Lobe Volume

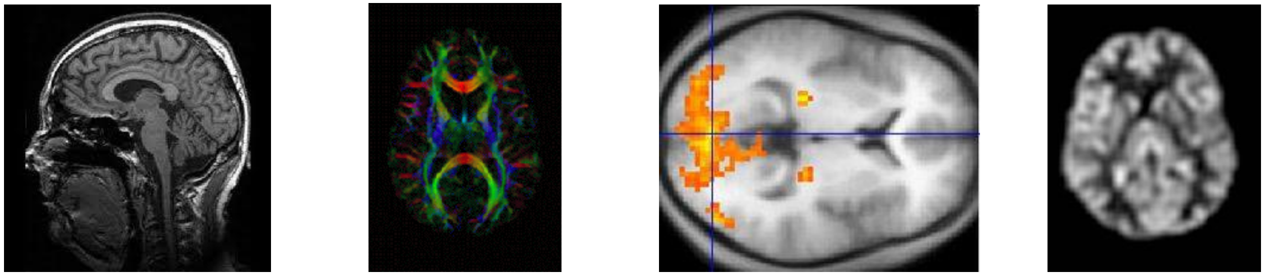
Hippocampal Volume

Stein et al. Neuroimage, 2010

Enhancing Neuroimaging Genetics through Meta-Analysis

ENIGMA

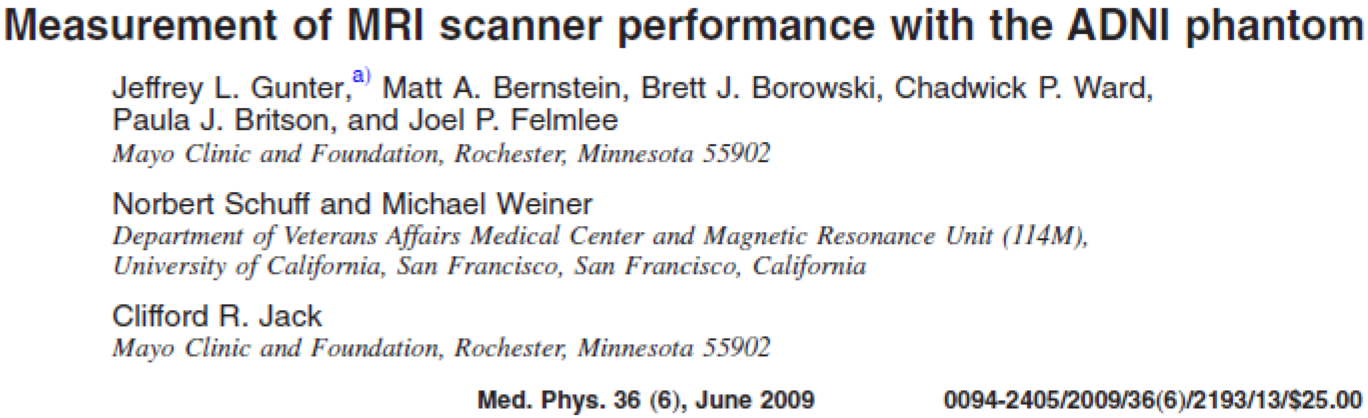
- Drawing together groups conducting brain imaging studies
  - both patient and population samples
  - with MRI, DTI, fMRI, and ASL
  - with or collecting GWAS data
- Predominantly imaging groups moving into genetics



Meta not Mega analysis

- 3 main reasons (in order of increasing importance)
  - Cultural Barriers
  - Practical constraints
    - Size of data
    - Processing time
  - Scientific obstacles
    - Insurmountable phenotypic heterogeneity?

Insurmountable phenotypic heterogeneity



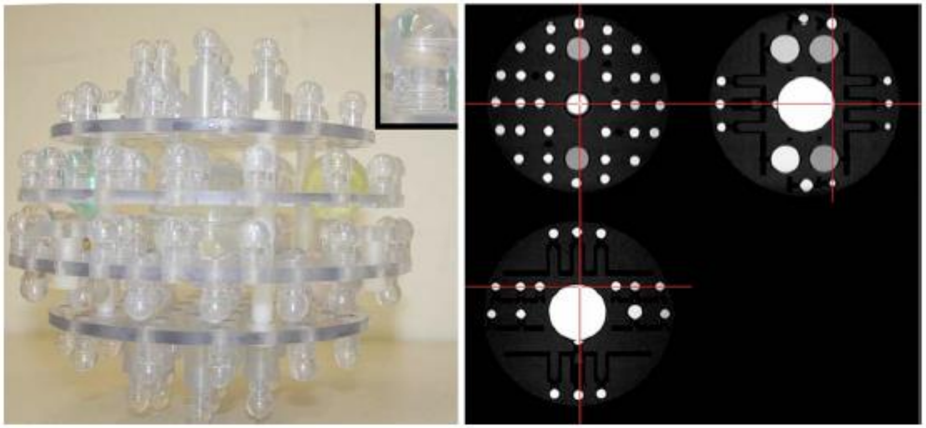
Measurement of MRI scanner performance with the ADNI phantom

Jeffrey L. Gunter,[a] Matt A. Bernstein, Brett J. Borowski, Chadwick P. Ward,
Paula J. Britson, and Joel P. Felmlee
Mayo Clinic and Foundation, Rochester, Minnesota 55902

Norbert Schuff and Michael Weiner
Department of Veterans Affairs Medical Center and Magnetic Resonance Unit (114M), University of California, San Francisco, San Francisco, California

Clifford R. Jack
Mayo Clinic and Foundation, Rochester, Minnesota 55902

Med. Phys. 36 (6), June 2009 **0094-2405/2009/36(6)/2193/13/$25.00**



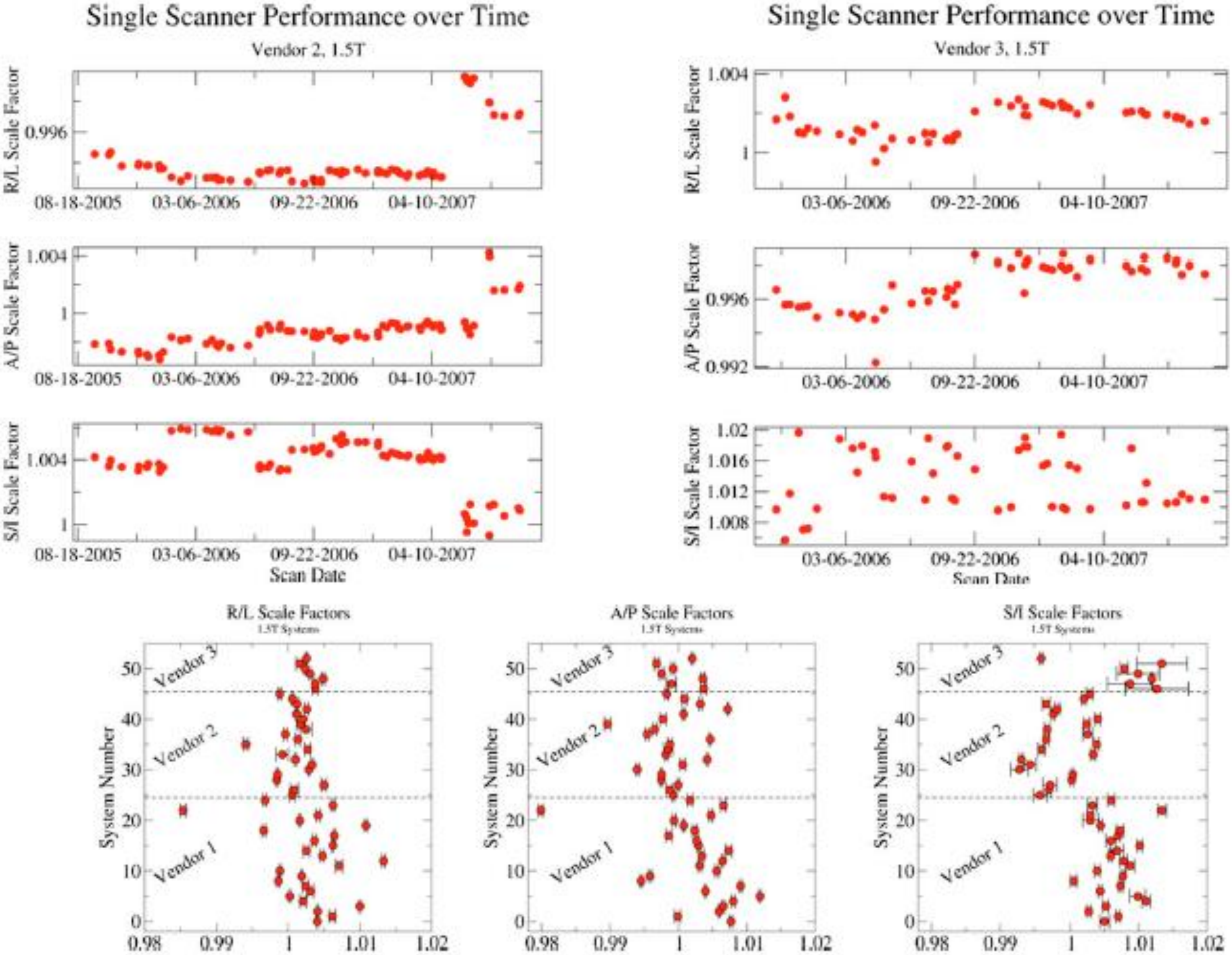
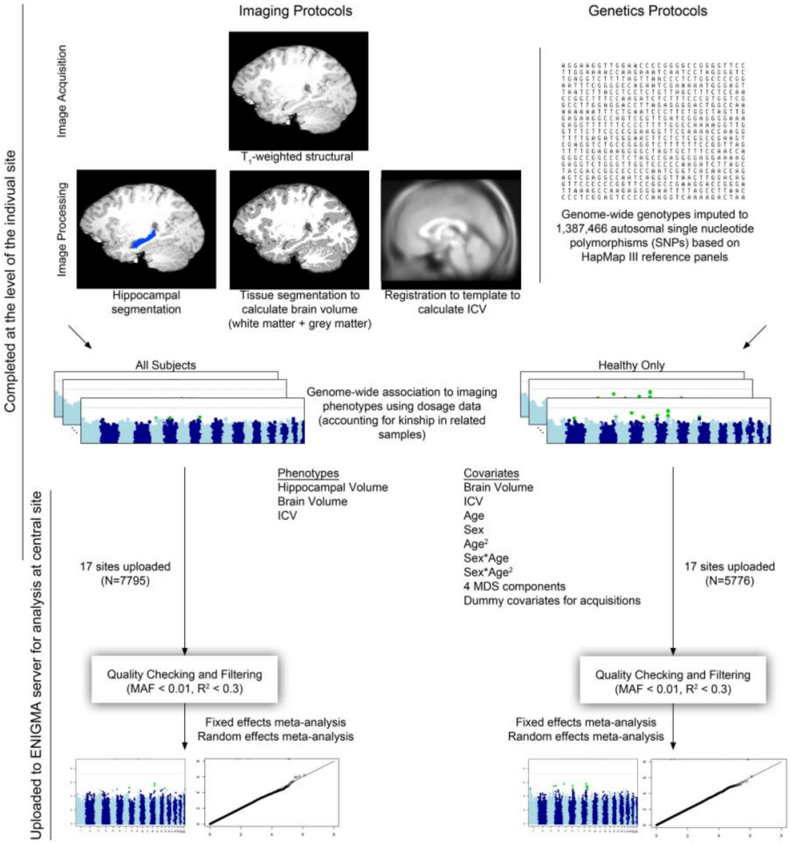


FIG. 8. Summary of scanner performance for more than 2200 phantom scans. A pooled-variance approach is used to estimate the stability of gradient performance factoring out discrete changes generally due to scanner recalibration. Symbols are plotted at the mean scale value over all values, and error bars indicate the square root of the pooled variance. System number is an arbitrary enumeration. R/L calibration appears less consistent across scanners for vendor 1 than for other vendors. The S/I per scanner error bars for vendor 3 are much larger than for other vendors and other directions. Scanners from vendor 2 are from two different models and the data are clustered by model in the S/I mean scale factors.


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

Protocols



Completed at the level of the indivual site

Uploaded to ENIGMA server for analysis at central site

Imaging Protocols

Image Acquisition

T_1-weighted structural

Image Processing

Hippocampal segmentation

Tissue segmentation to calculate brain volume (white matter + grey matter)

Registration to template to calculate ICV

Genetics Protocols

Genome-wide genotypes imputed to 1,387,466 autosomal single nucleotide polymorphisms (SNPs) based on HapMap III reference panels

All Subjects

Healthy Only

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, $R^2 < 0.3$)

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

Fixed effects meta-analysis
Random effects meta-analysis

Fixed effects meta-analysis
Random effects meta-analysis

- FSL FIRST/ FREESURFER
- HapMap III
- Full sample vs healthy controls only

FIRST v1.2

FMRIB's Integrated Registration and Segmentation Tool

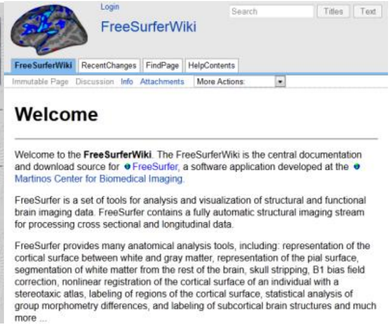
Subcortical brain segmentation using Bayesian shape & appearance models.

Contents

Introduction - References - Segmentation - Vertex Analysis - Models - Advanced Usage

Introduction

FIRST is a model-based segmentation/registration tool. The shape/appearance models used in FIRST are constructed from manually segmented images provided by the Center for Morphometric Analysis (CMA), MGH, Boston. The manual labels are parameterized as surface meshes and modelled as a point distribution model. Deformable surfaces are used to automatically parameterize the volumetric labels in terms of meshes; the deformable surfaces are constrained to preserve vertex correspondence across the training data. Furthermore, normalized intensities along the surface normals are sampled and modelled. The shape and appearance model is based on multivariate Gaussian assumptions. Shape is then expressed as a mean with modes of variation (principal components). Based on our learned models, FIRST searches through linear combinations of shape modes of variation for the most probable shape instance given the observed intensities in your T1 image.



Welcome

Welcome to the **FreeSurferWiki**. The FreeSurferWiki is the central documentation and download source for FreeSurfer, a software application developed at the Martinos Center for Biomedical Imaging.

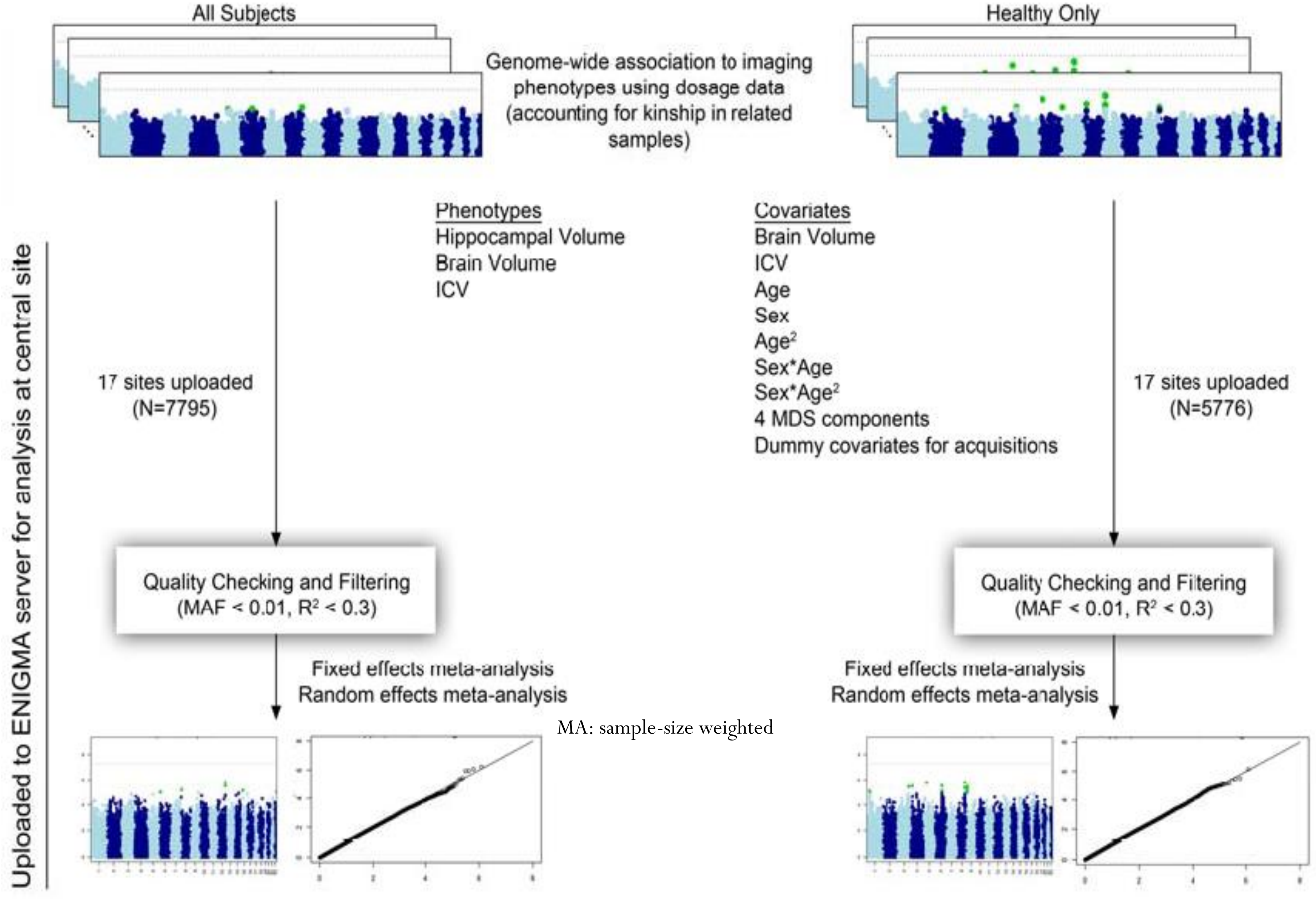
FreeSurfer is a set of tools for analysis and visualization of structural and functional brain imaging data. FreeSurfer contains a fully automatic structural imaging stream for processing cross sectional and longitudinal data.

FreeSurfer provides many anatomical analysis tools, including: representation of the cortical surface between white and gray matter, representation of the pial surface, segmentation of white matter from the rest of the brain, skull stripping, B1 bias field correction, nonlinear registration of the cortical surface of an individual with a stereotaxic atlas, labeling of regions of the cortical surface, statistical analysis of group morphometry differences, and labeling of subcortical brain structures and much more ...

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 ($MAF < 0.01$, $R^2 < 0.3$)

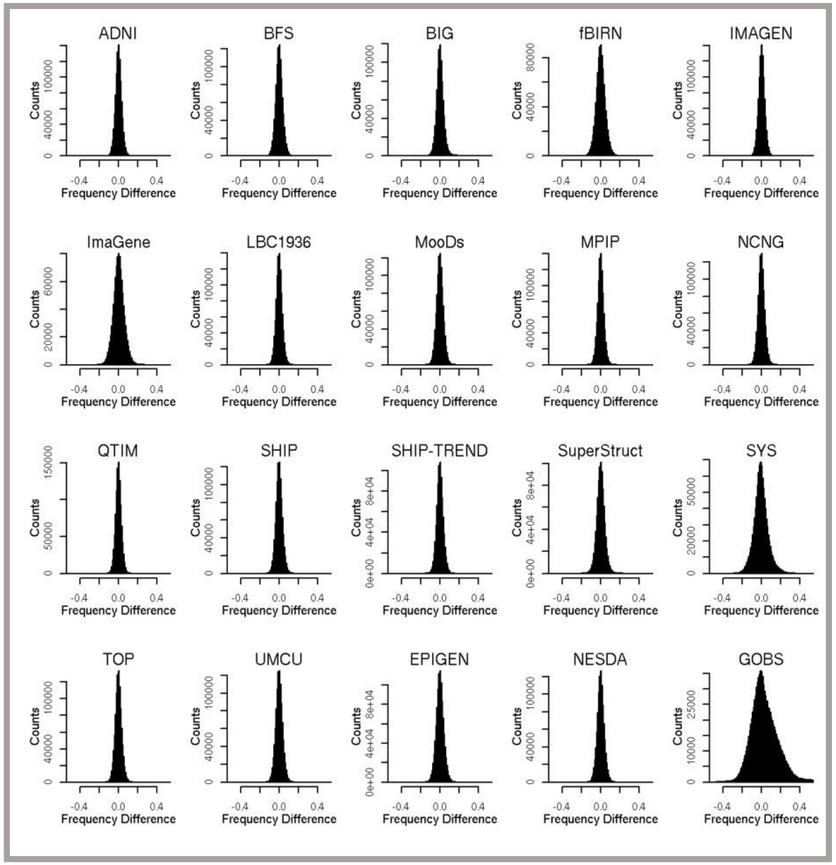
Quality Checking and Filtering ($MAF < 0.01$, $R^2 < 0.3$)

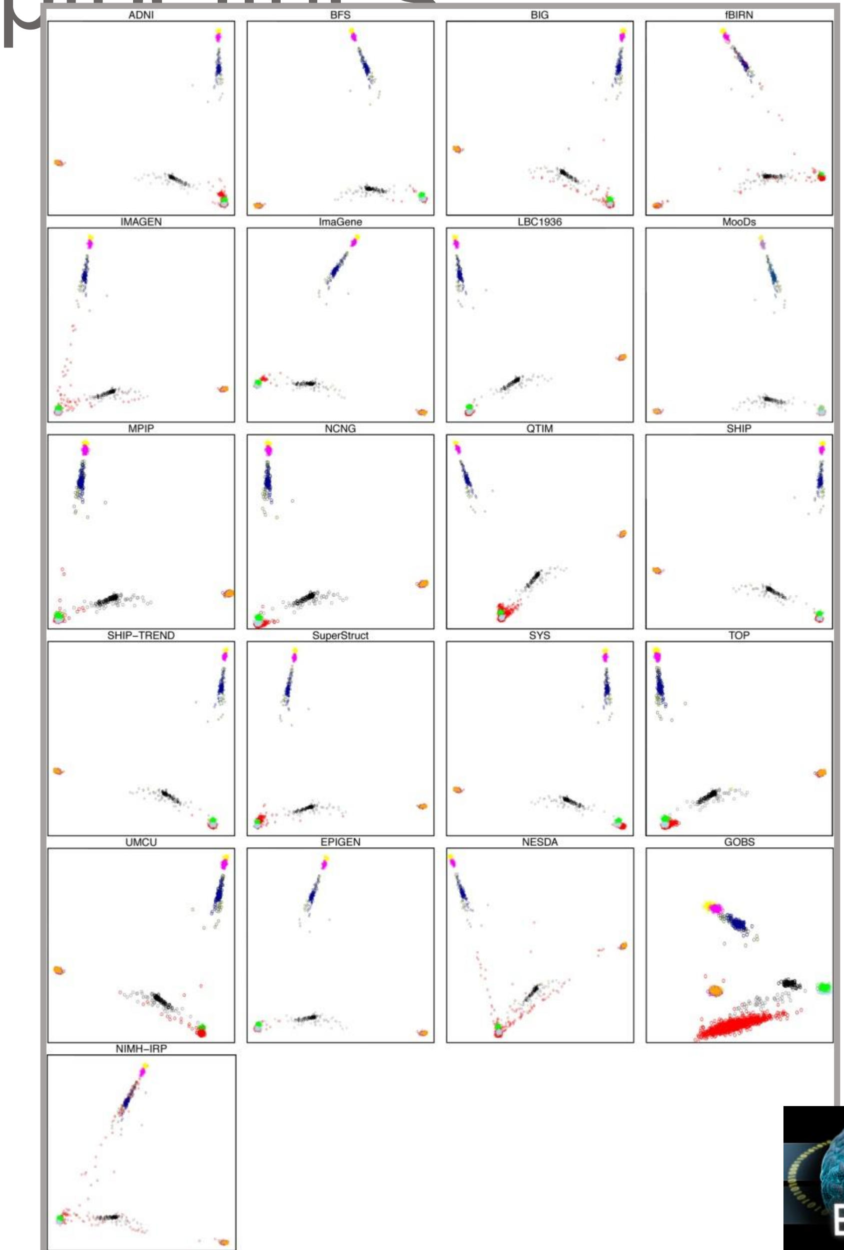
Fixed effects meta-analysis
Random effects meta-analysis

Fixed effects meta-analysis
Random effects meta-analysis

MA: sample-size weighted

Custom built QC pipelines





QC protocols

Add the current folder containing all of the required scripts to Matlab's path.

Select: File -> Set Path -> Add Folder -> {OK} -> {Save} -> {Close}

In the Matlab console window change directories to the folder with all of your FSL FIRS
data.

```
cd /enigma/first/data/
```

Make a directory to store all of the QC output.

```
mkdir /enigma/first/QC/
```

The script we want to run is called make_pngsFSL.m with the following parameters:

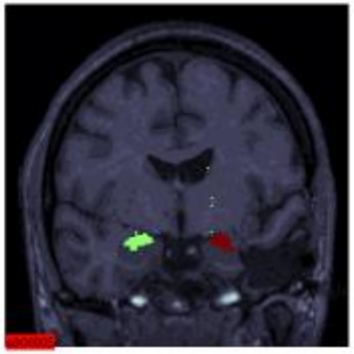
make_pngsFSL(output_directory, subject_name, select_segmentations_image, select_

We want to set 'subject_name' such that 'subject_name' + 'select_segmentations_ima
full name of the registered segmentation label files we just made with flirt (e.g.
subj1_brain_first12_all_fast_firstseg_std.nii.gz) and similarly for 'select_mri_image' we
the full name of the registered MRI scan outputted by FIRST (e.g. subj1_brain_ to_std_

In Matlab we can do:

```
a=dir('subj*.nii'); %Choose this so that it selects
%your original subject MRI files
for x = 1:size(a,1)
    [c,b,d]=fileparts(a(x,1).name);
    %if your original data files are in .nii.gz format you need
    %to remove both extensions
    %uncomment this next command to do it
    %[c,b,d]=fileparts(b);
    try
        make_pngsFSL('/enigma/first/QC/', b, ['/enigma/first/data/',
b, '_to_std_sub.nii.gz'], ['/enigma/first/data/', b,
'_first12_all_fast_firstseg_std.nii.gz']);
    end
    display(['Done with subject: ', num2str(x), ' of ',
num2str(size(a,1))]);
end
%Note that you may have to change '_to_std_sub.nii.gz'
% or '_first12_all_fast_firstseg_std.nii.gz' if
% Your files are named following a different convention
```

The make_pngFSL script should take approximately 5 minutes/subject and will output a series of *.png image files separated by individual subject folders.



You can increase the size of each individual picture so that they are easier to see:

Type -> "Ctrl" and "+"

the subject ID info

e -> "s"

e "Down" or "Up" arrow on the keyboard scrolls through each of your subjects. Using the
'Right" arrow takes you to a new slice view for that same set of subjects.

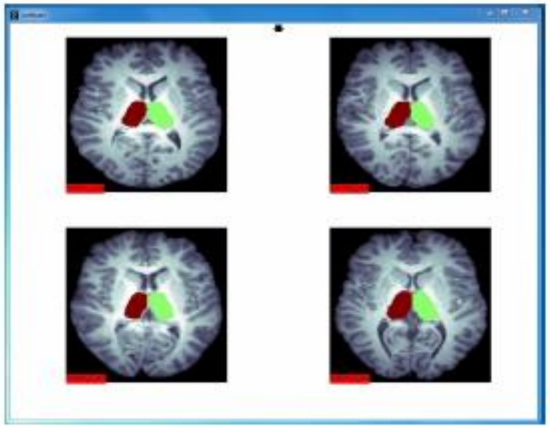
the LandRvolumes.csv file we created in Step 2 in your favorite spreadsheet software (e.g.
xcel), you can find any bad subjects and mark either its left or right Thalamus value with an
r or upper case X is fine).

**an determine the laterality (left or right) in your image by referencing the color of the
ed label indicates the RIGHT structure and the green label indicates the LEFT.**

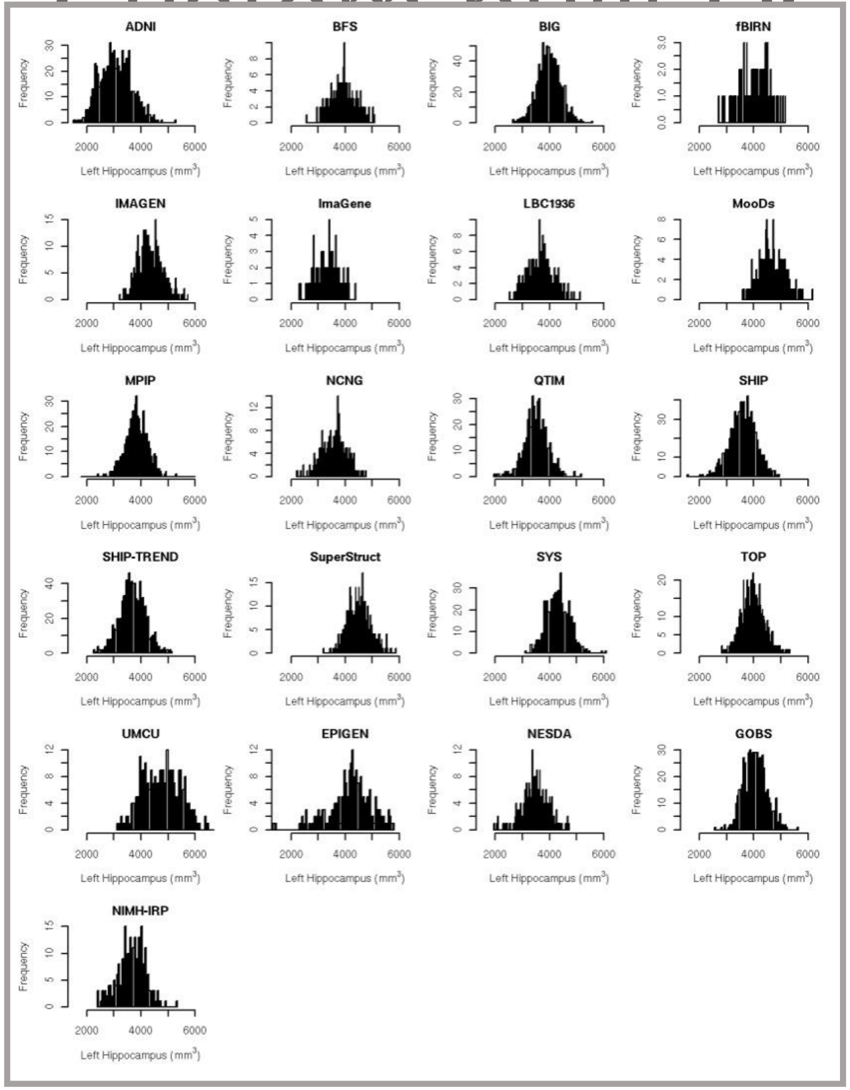
**e users have noticed while QC'ing the images generated in Matlab that it can sometimes
ages with colored pixels scatter around the image. These additional pixels can be safely
ee Figure 2 below for an example).**

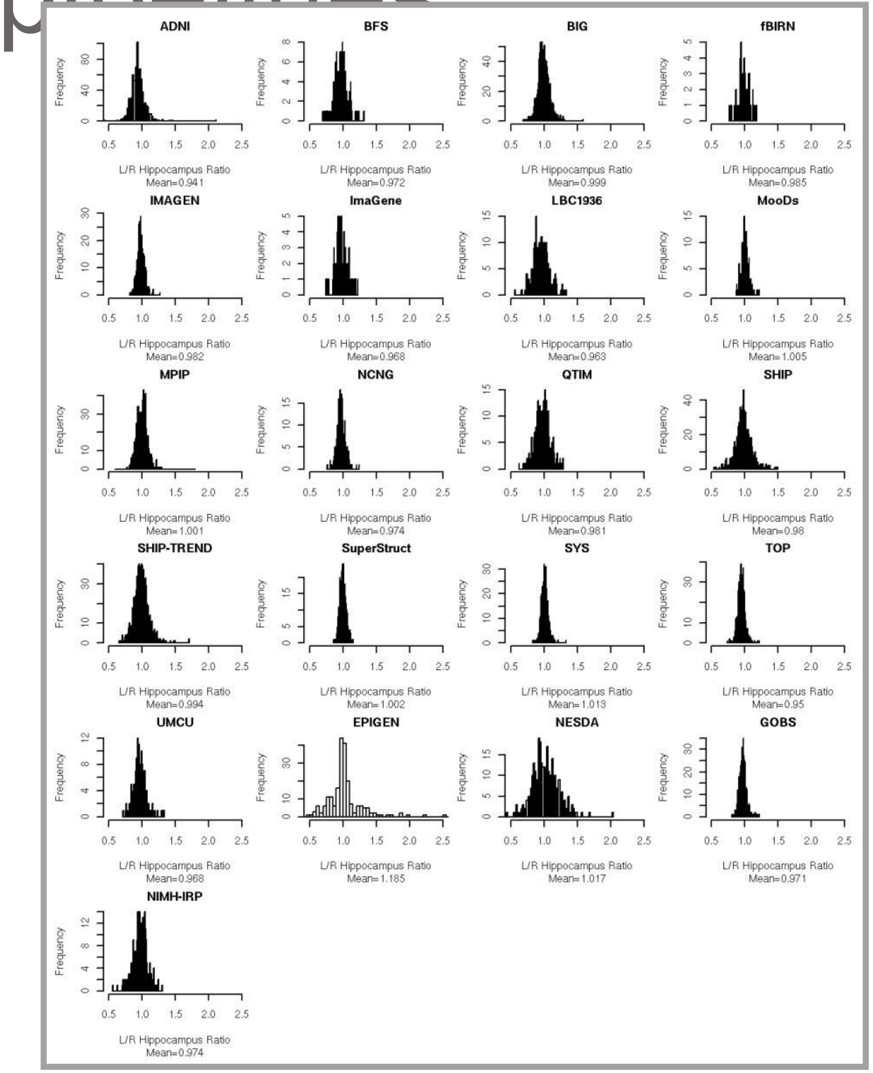
Repeat this process for the remaining 6 structures and save the LandRvolumes.csv file for use in the association testing steps.

Figure 1:

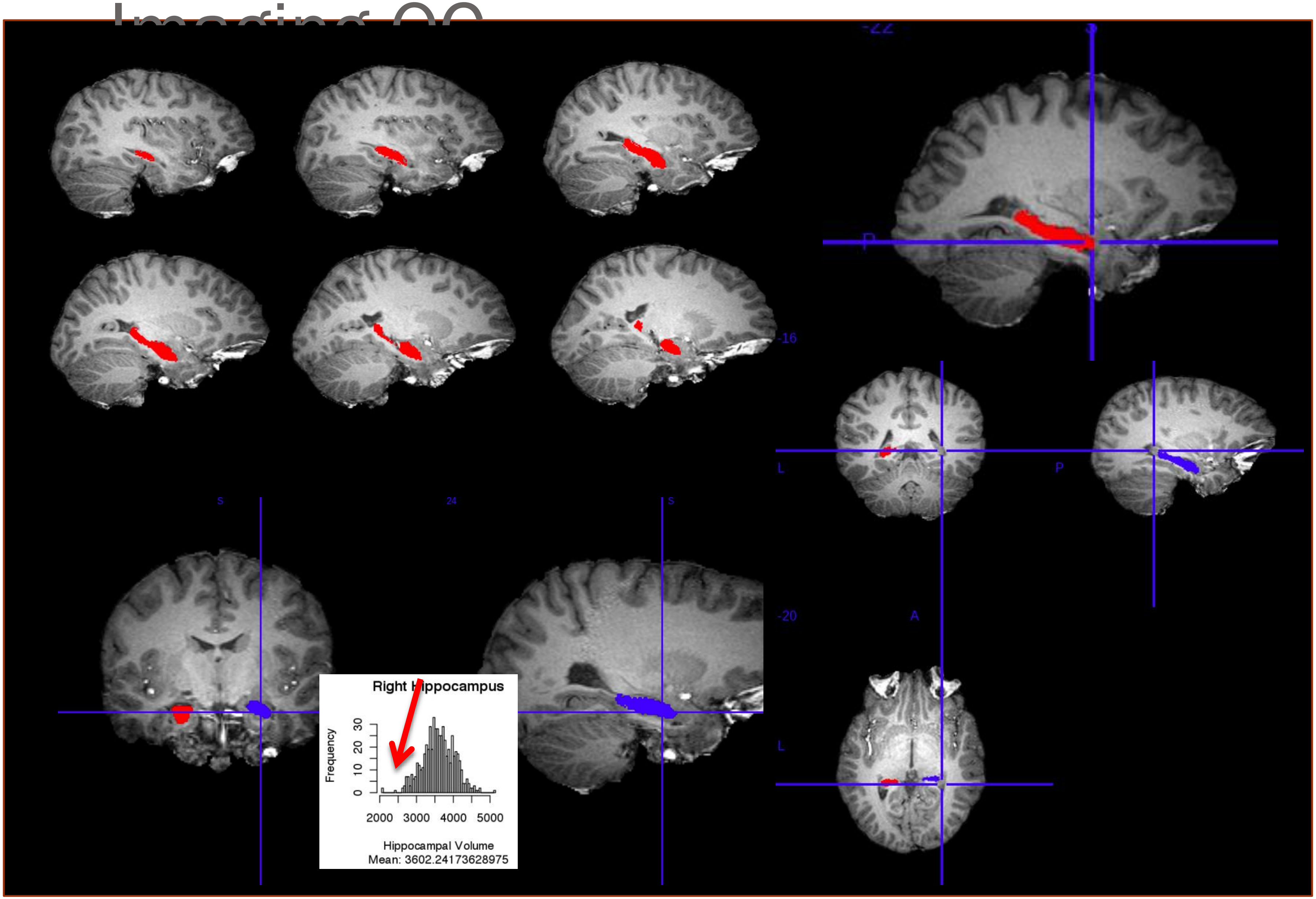


Custom built QC pipelines

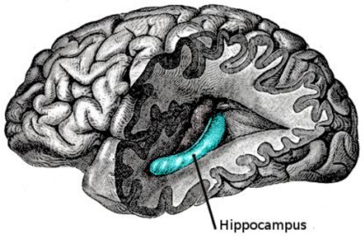




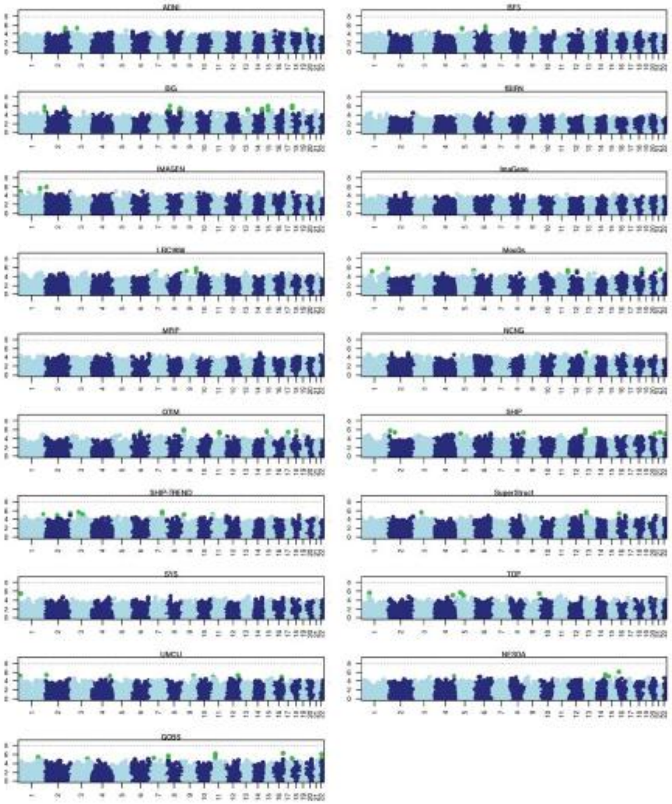
Imaging QC


-22
S
P
-16
L
P
S
24
S
-20
A
L
Right Hippocampus
Frequency
0
10
20
30
2000
3000
4000
5000
Hippocampal Volume
Mean: 3602.24173628975

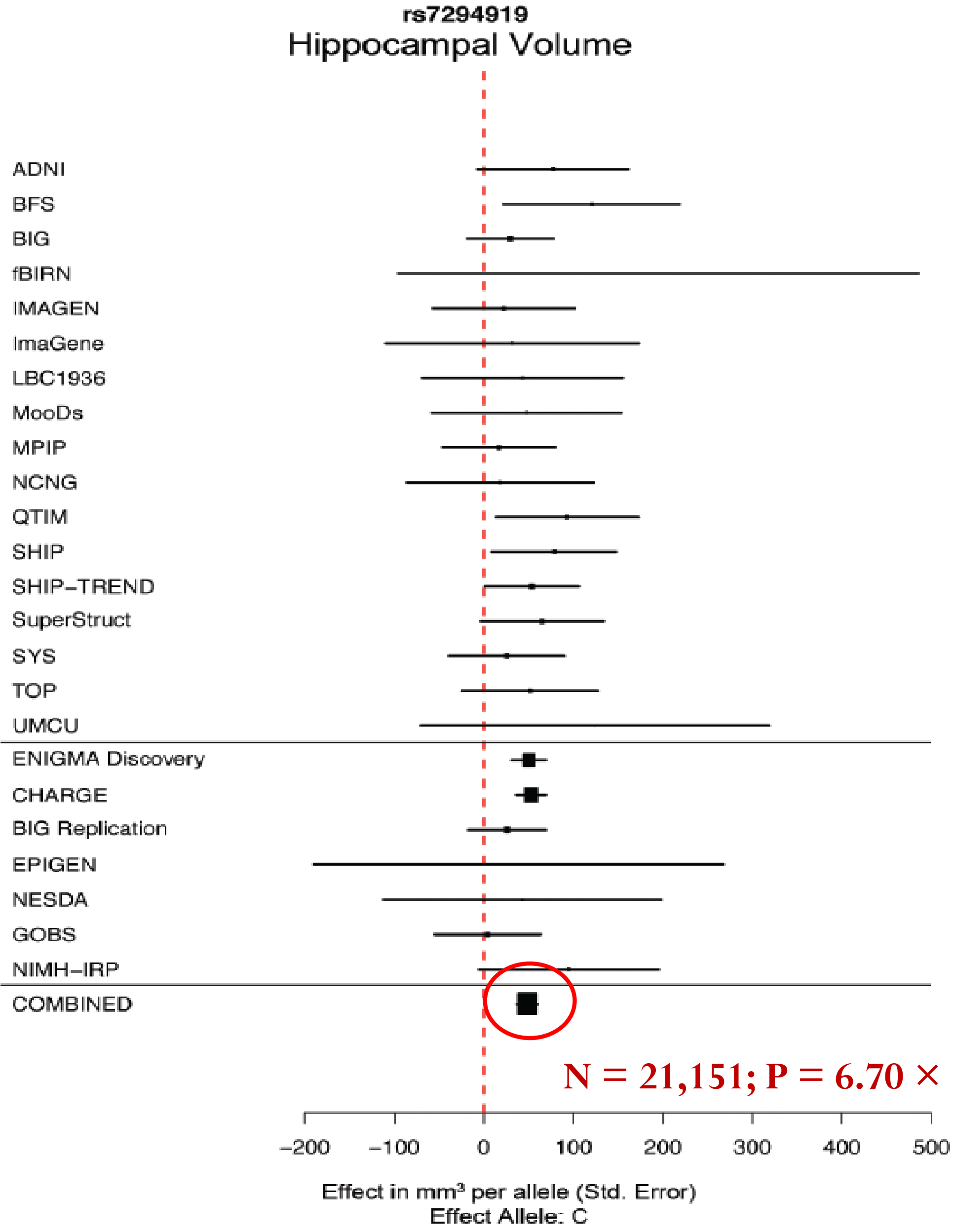
Did the consortium approach work?



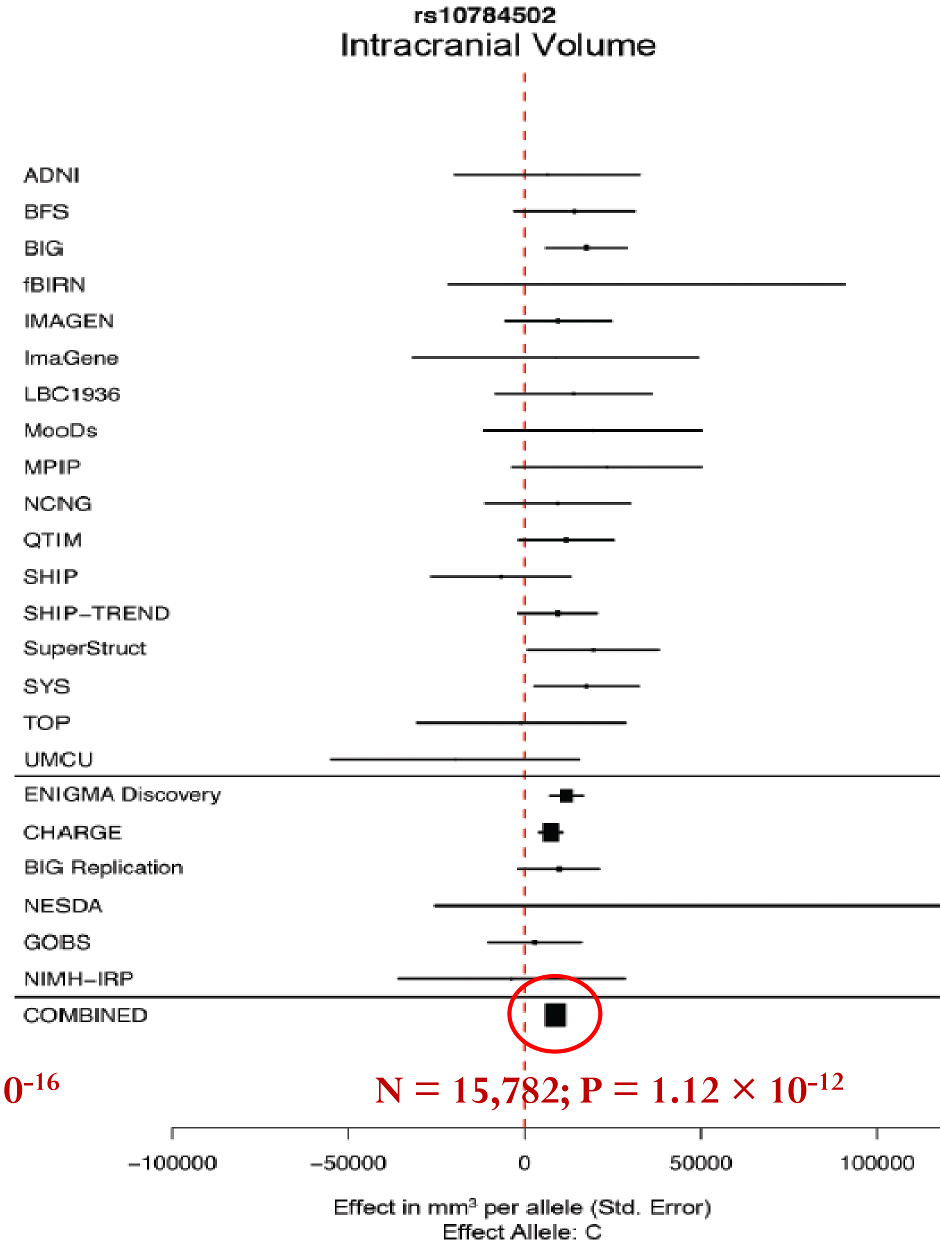
- All studies underpowered
- Within ‘normals’ no sig results in any individual study
- 206 authors vs effect of 22 underpowered null papers on the literature?



First ENIGMA project: the findings



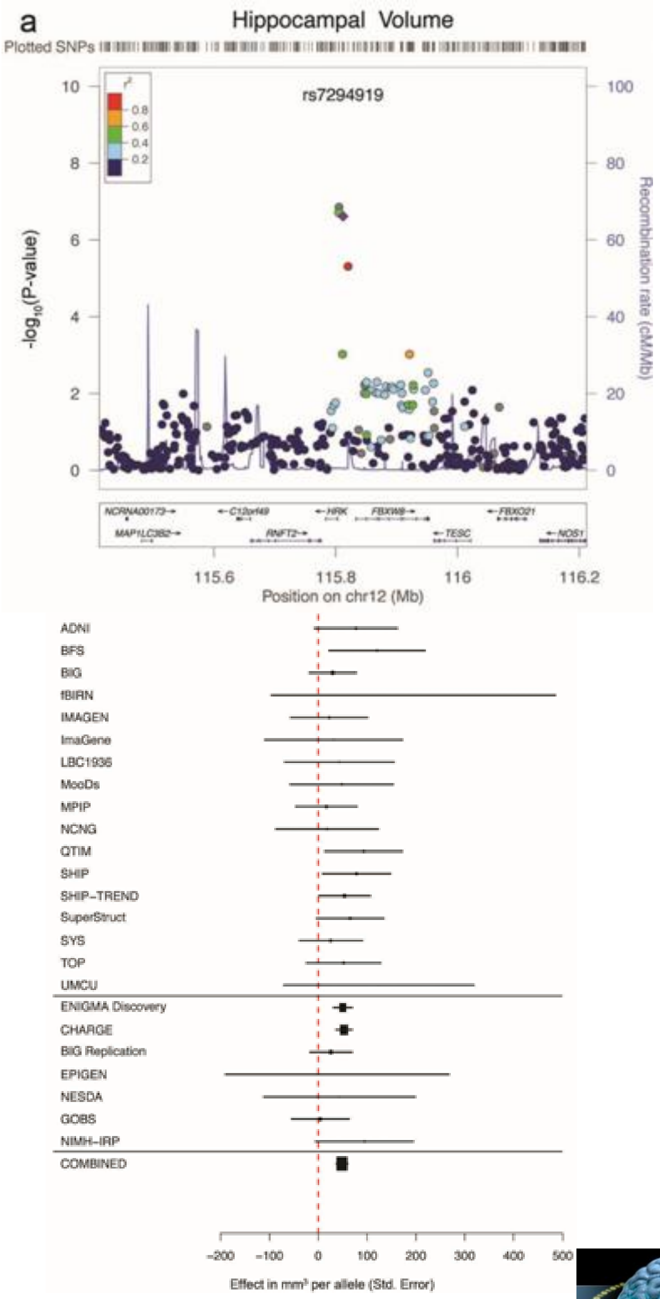
N = 21,151; P = 6.70 × 10^{-16}



N = 15,782; P = 1.12 × 10^{-12}

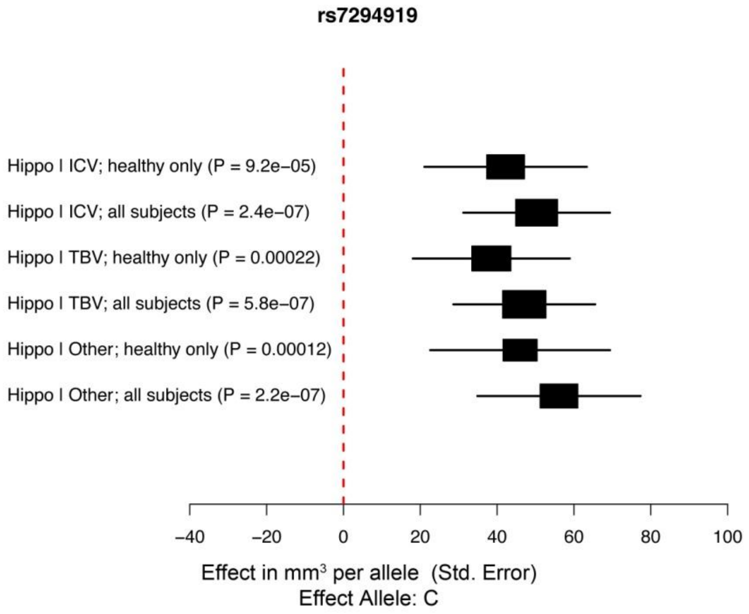
Hippocampal Volume

- Intergenic region 12q24.22
- between *HRK* and *FBXW8*
- Significant within ENIGMA
- Reciprocal replication with the CHARGE consortium
    - N=20,797; P=3.43x10^{-16} , MAF =.10



Hippocampal Volume

- Signal present in healthy and patient samples
- Independent of brain or head size
- variant is associated with decreased HV of 50.6 mm^3 or 1.3% of the average hippocampal volume per risk allele.

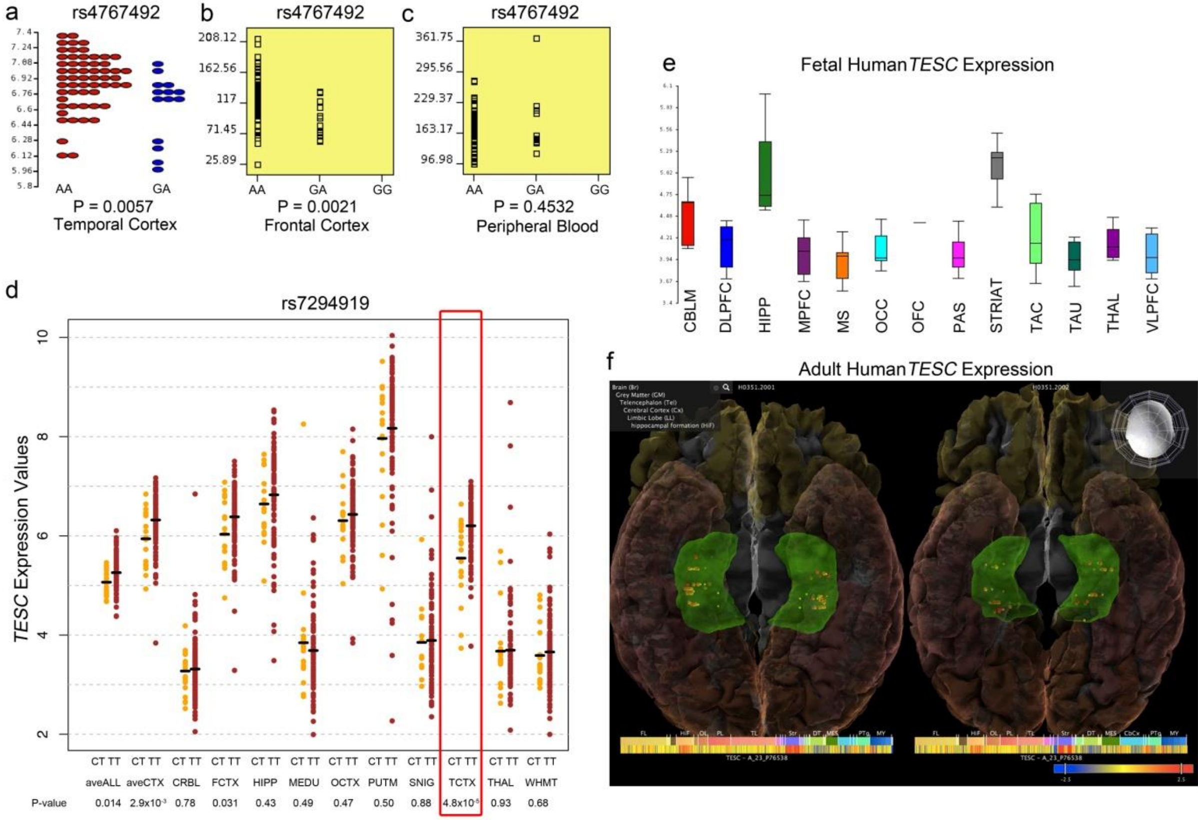


Hippocampal Volume

- *TESC* - *cis* eQTL in brain tissue
- UCL resected temporal lobe
- SNPExpress
- UK Brain Expression Database
- Fetal Brain Expression
- Adult Brain Expression

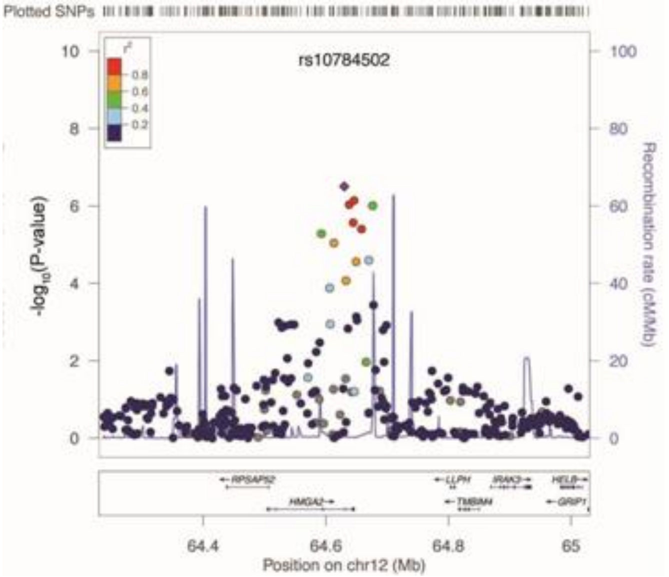
- Notably tissue specific eQTLS

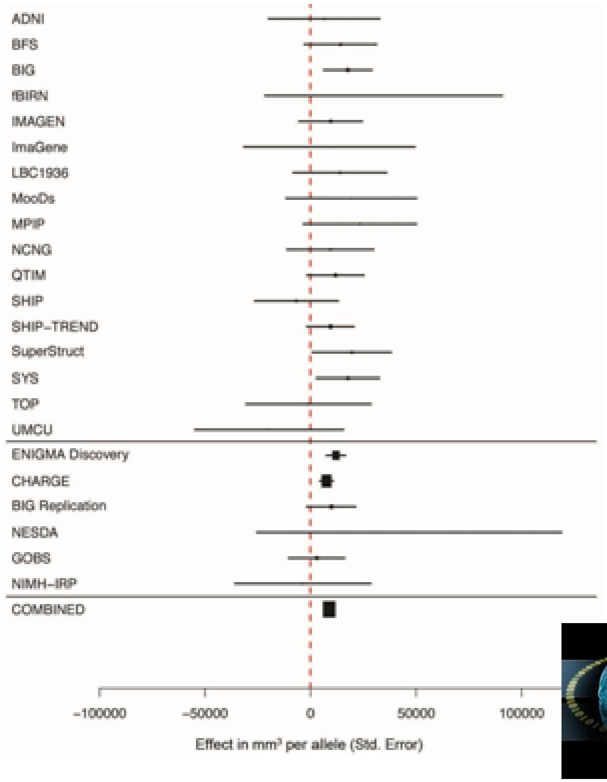
- *cis* eQTLs for *HRK* and *FBXW8* in blood (PBMC)



Intracranial Volume

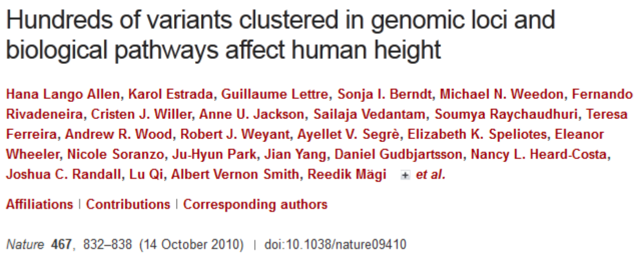
- *HMGA2* 12q14.3
  - rs10784502 intronic SNP near the 3’ UTR
  - high mobility group AT-hook 2 protein
  - chromatin-associated protein that regulates stem-cell renewal
  - role in neural precursor cells
  - Increase of 8637.0 mm^3 or 0.56% of ICV per risk allele
- Replication with the CHARGE consortium
  - *N*=15,622; *P*=8.50x10^{-12}, MAF =.48





Pleiotropic effects?

- *HMGA2* & rs10784502 previously associated with height

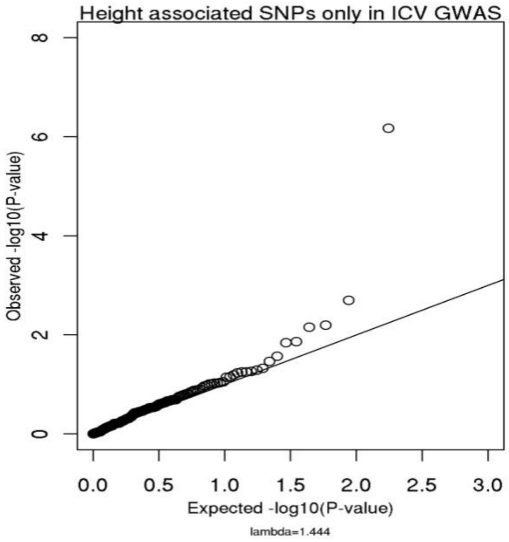


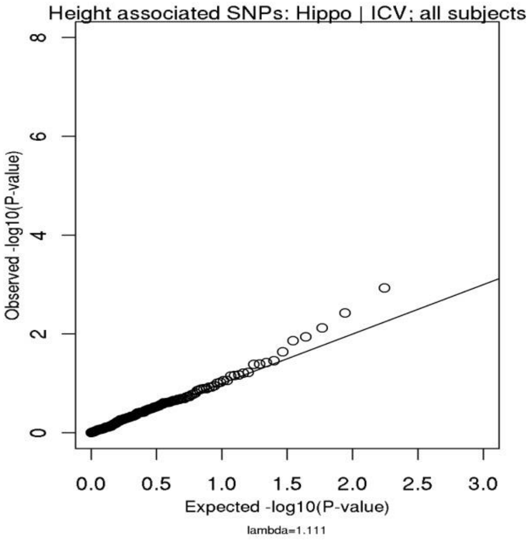
Hundreds of variants clustered in genomic loci and biological pathways affect human height

Hana Lango Allen, Karol Estrada, Guillaume Lettre, Sonja I. Berndt, Michael N. Weedon, Fernando Rivadeneira, Cristen J. Willer, Anne U. Jackson, Sailaja Vedantam, Soumya Raychaudhuri, Teresa Ferreira, Andrew R. Wood, Robert J. Weyant, Ayellet V. Segrè, Elizabeth K. Speliotes, Eleanor Wheeler, Nicole Soranzo, Ju-Hyun Park, Jian Yang, Daniel Gudbjartsson, Nancy L. Heard-Costa, Joshua C. Randall, Lu Qi, Albert Vernon Smith, Reedik Mägi + *et al.*

Affiliations | Contributions | Corresponding authors

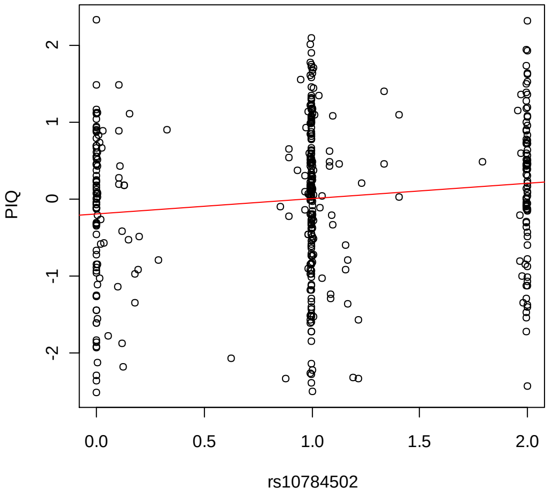
Nature **467**, 832–838 (14 October 2010) | doi:10.1038/nature09410





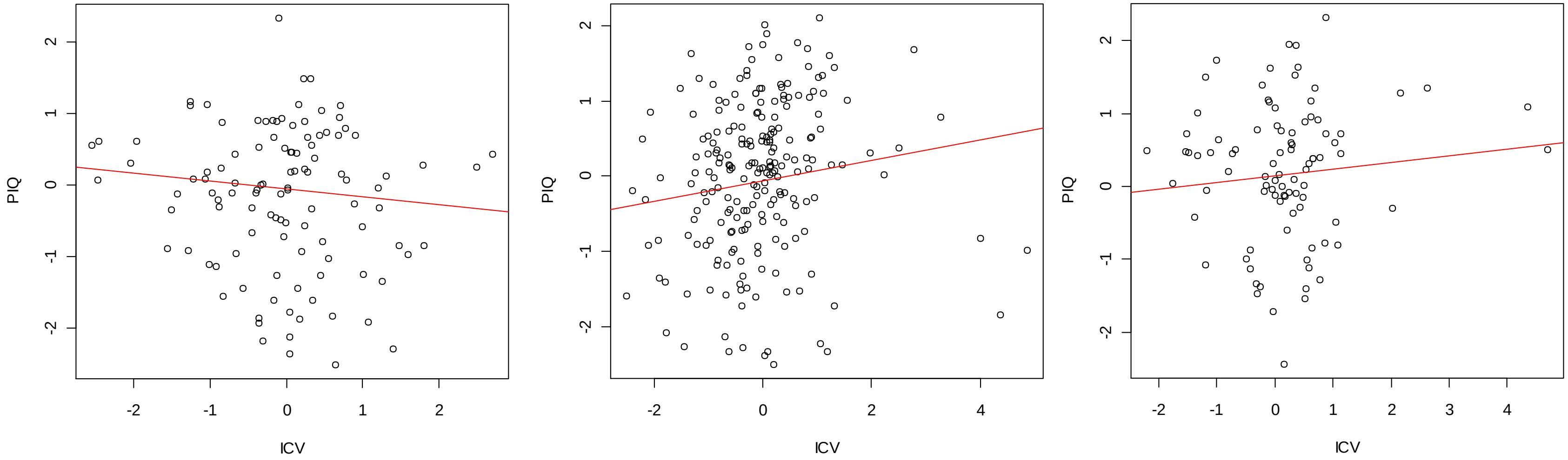
Pleiotropic effects?

- rs10784502 is also associated with PIQ
  - *P*=0.0044



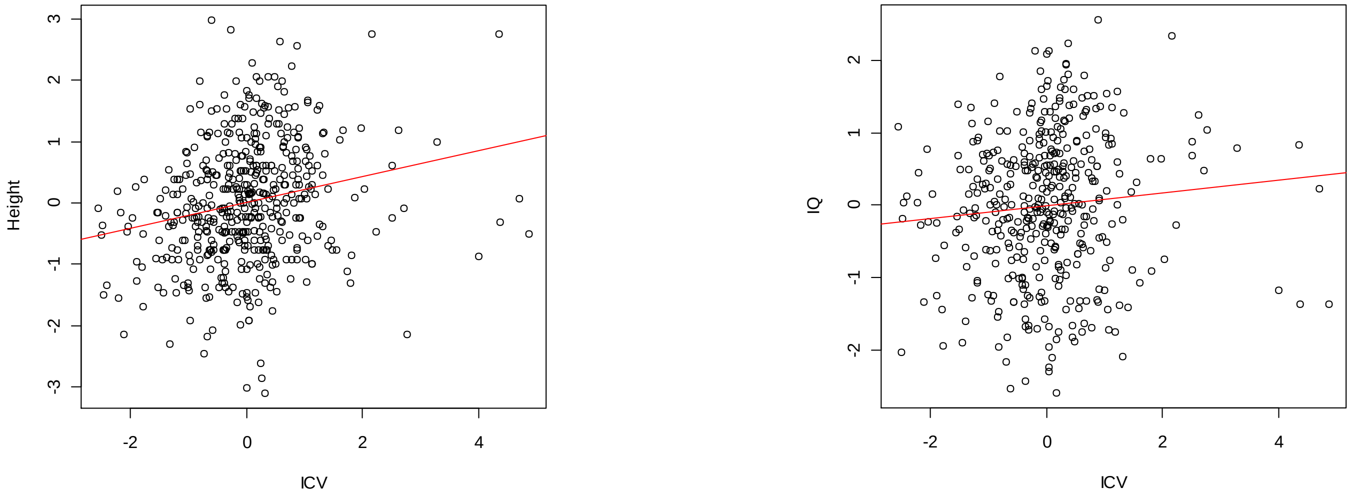
N ‘increasing’ risk alleles

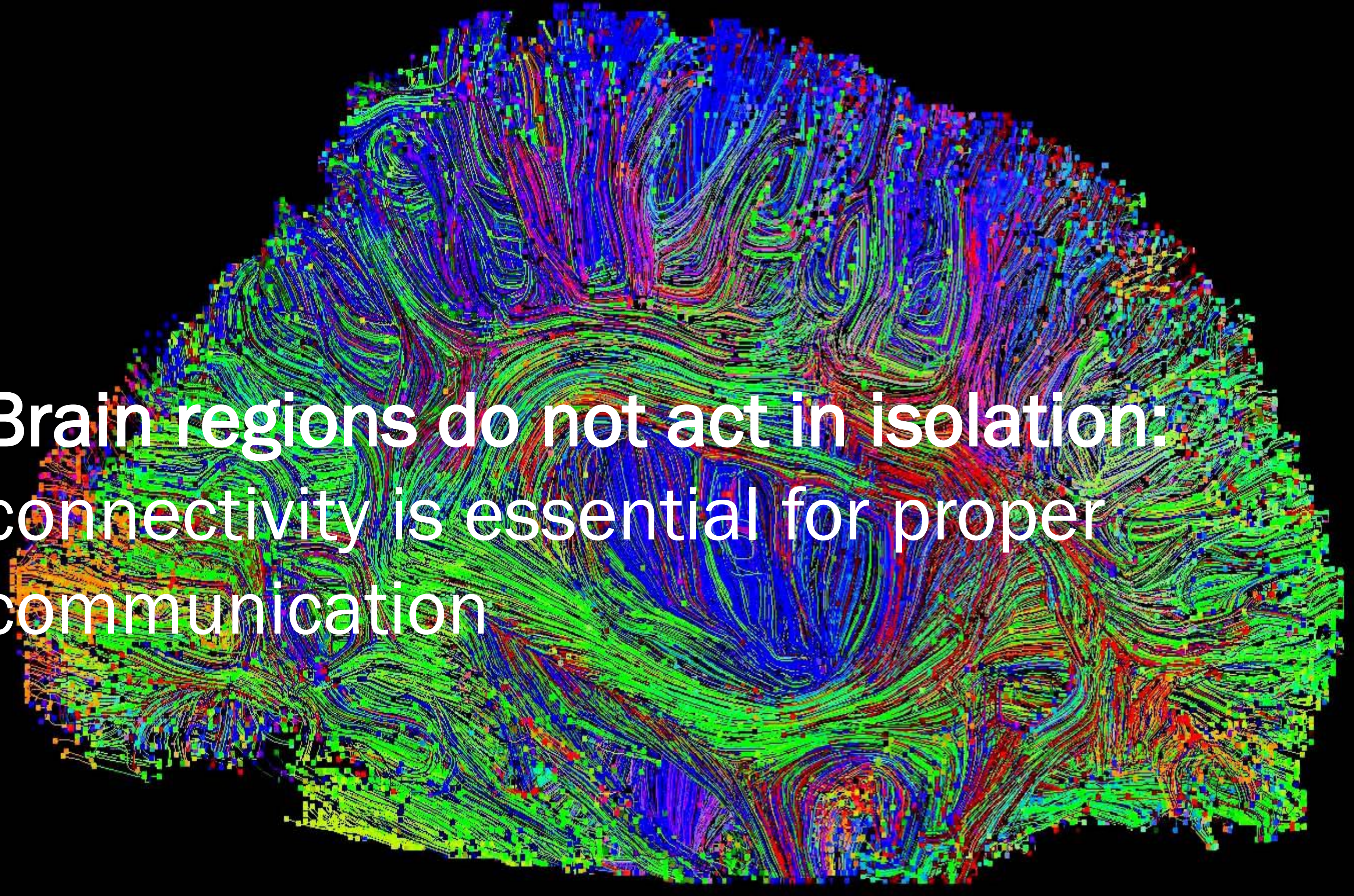
0 1 2



Endophenotypes/Attenuated functional consequences/ Pleiotropy…

- ICV known to correlate with body size and IQ
- Height and IQ correlated r^2 ~4%
  - r^2_G ~1.4%





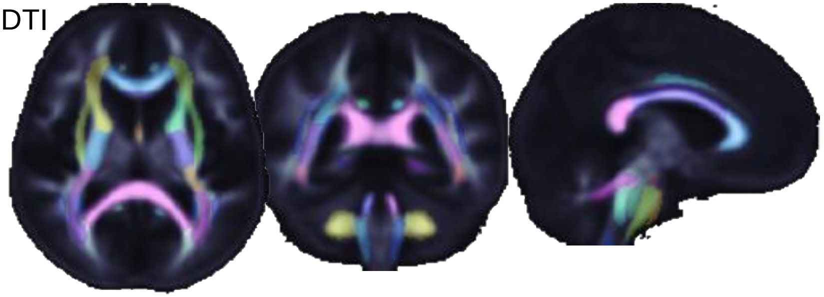
Brain regions do not act in isolation:

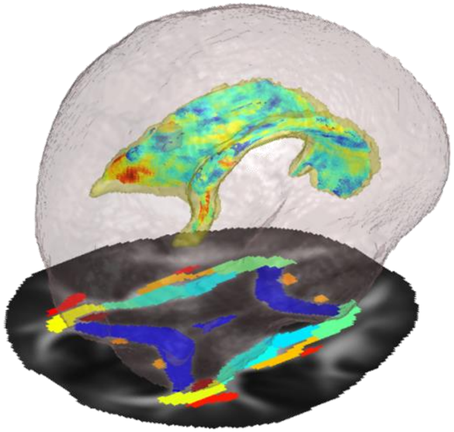
connectivity is essential for proper communication

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

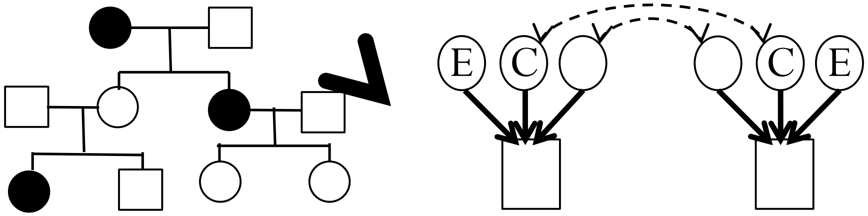
ENIGMA-DTI

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


ENIGMA-DTI
Template



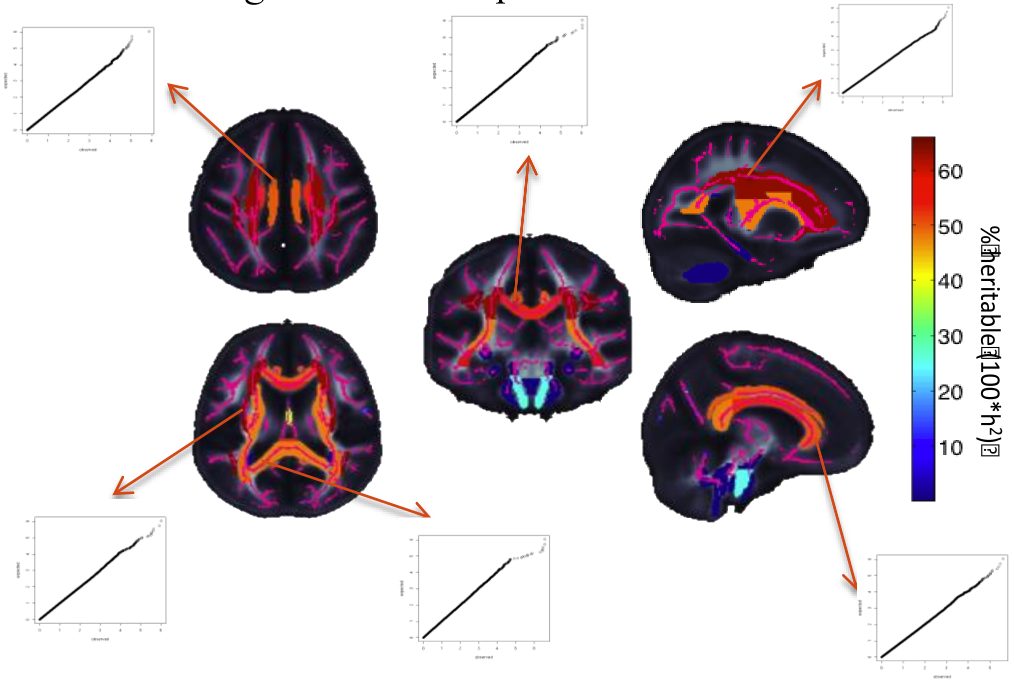
3. Multi-site heritability analysis
   - Are heritability measures stable and reliable across cohorts in regions
   - If not, then they are not good targets for multi-site GWAS-MA



Jahanshad & Kochunov et al, NIMG 2013

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

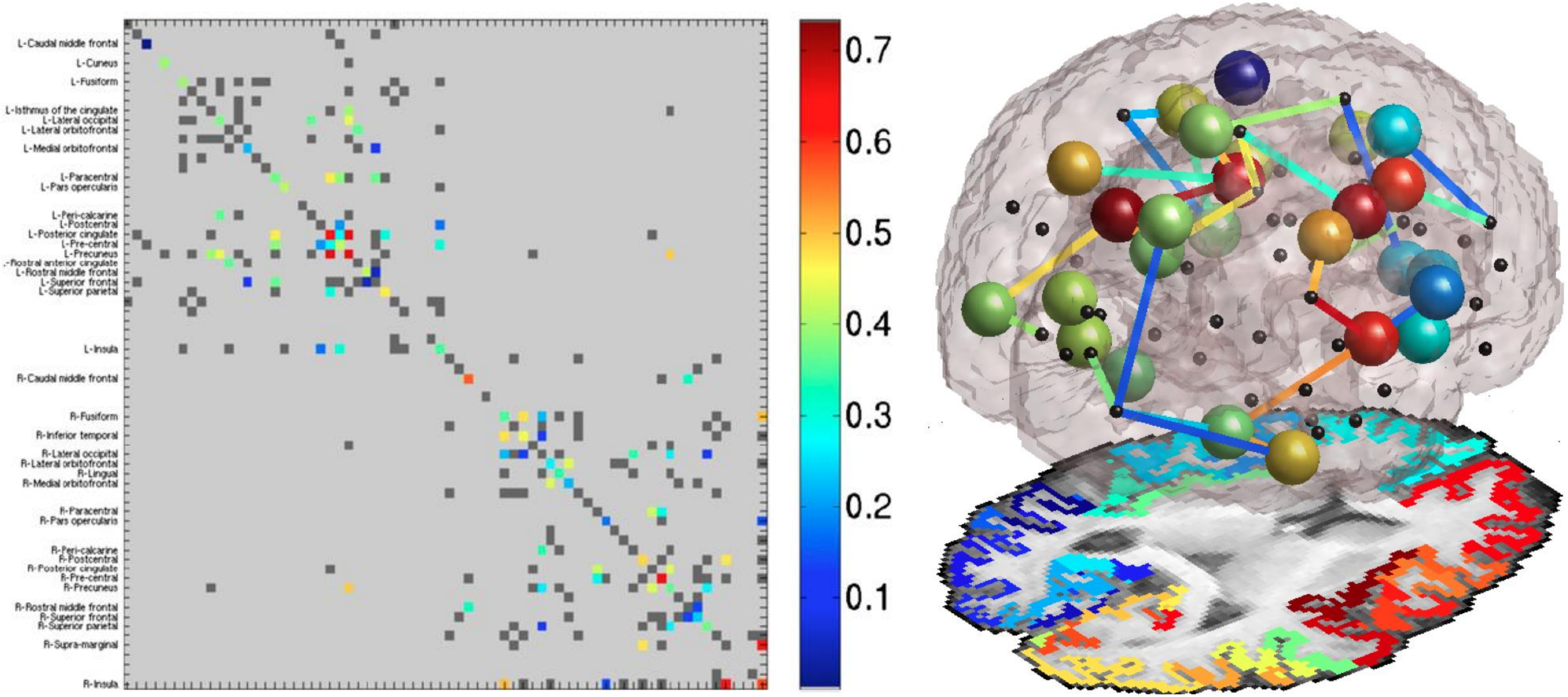
Single –site Q-Q plots



- 20+ sites interested
- 8000+ images available

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

Prioritize the most heritable connections from a comparison of MZ and DZ twins

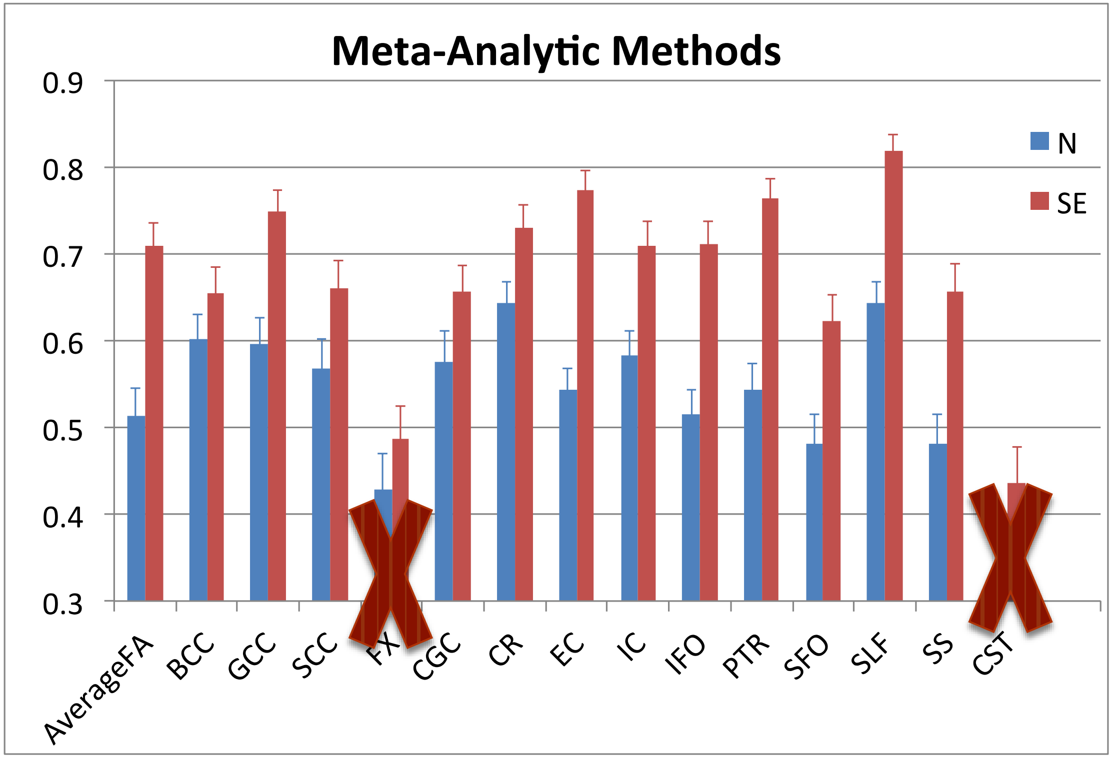


Carry forward the most heritable connections into a full Genome-Wide Screen (GWAS)….

Jahanshad/Thompson, ***PNAS***, March 5 2013

Multi-site heritability analysis

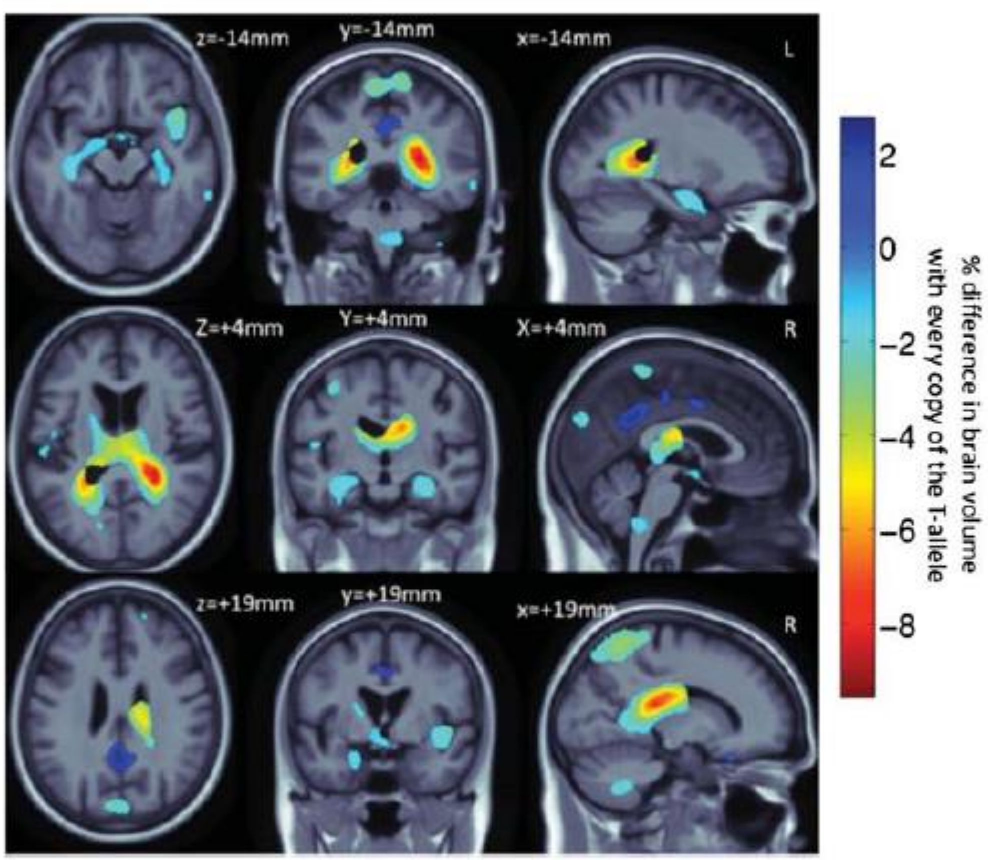
- 5 sites DIFFERENT: **Family structures** (twins/pedigrees) / **Image acquisition** methods / **Age groups** (only children/only elderly/wide range) / **Ethnicities** (European/Mexican-American)



- 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

SPON1 influences regional brain volumes in AD



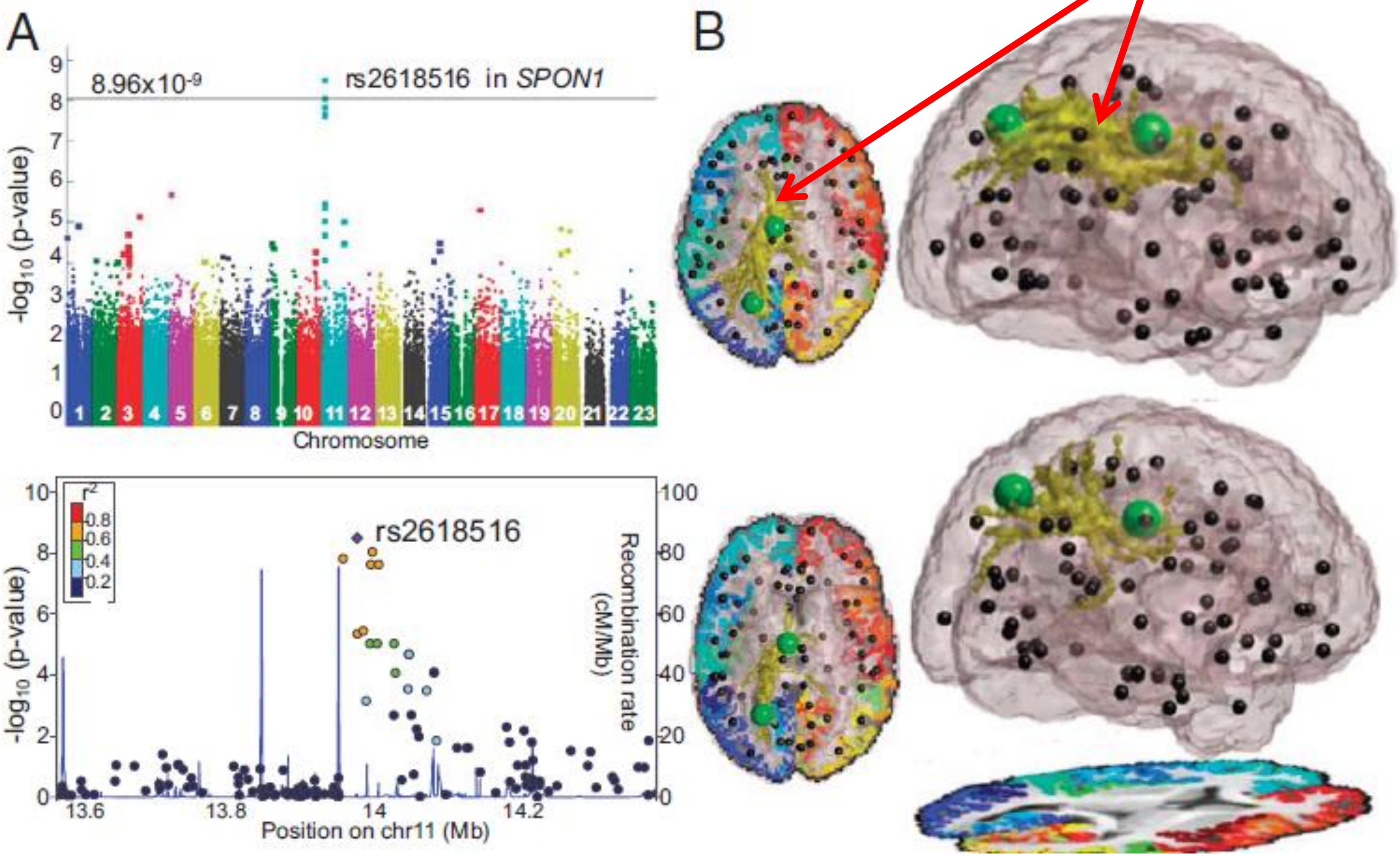
Ventricular regions, particularly surrounding the temporal lobes, were significantly reduced in size, whereas grey matter around the posterior cingulate cortex was increased with each additional copy of the minor T allele at rs2618516.

Older people who carried the connectivity variant had significantly milder dementia scores and risk of AD

PNAS | March 19, 2013 | vol. 110

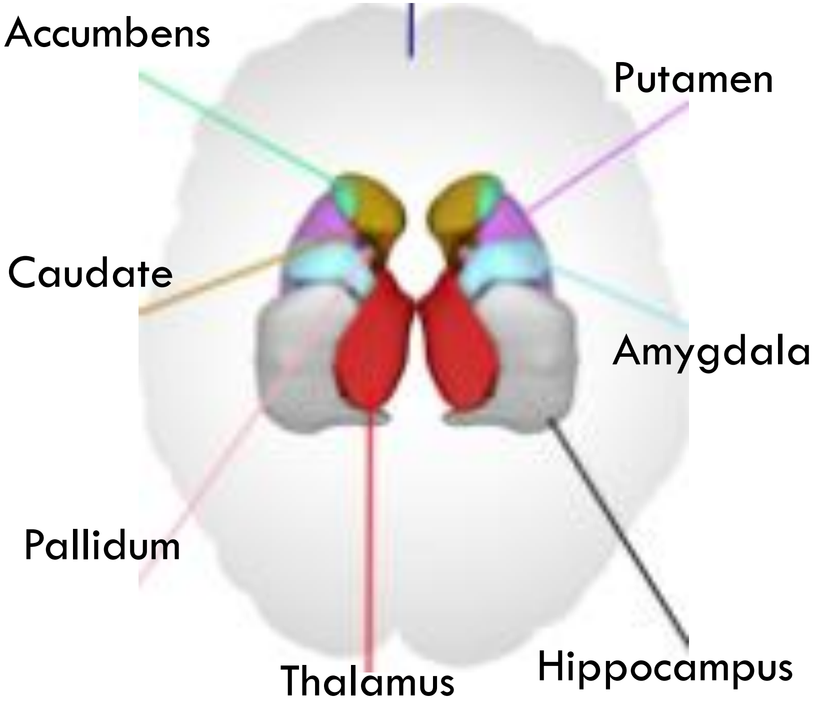
Genome-wide scan of healthy human connectome discovers *SPON1* gene variant influencing dementia severity

Neda Jahanshad[a], Priya Rajagopalan[a], Xue Hua[a], Derrek P. Hibar[a], Talia M. Nir[a], Arthur W. Toga[a], Clifford R. Jac

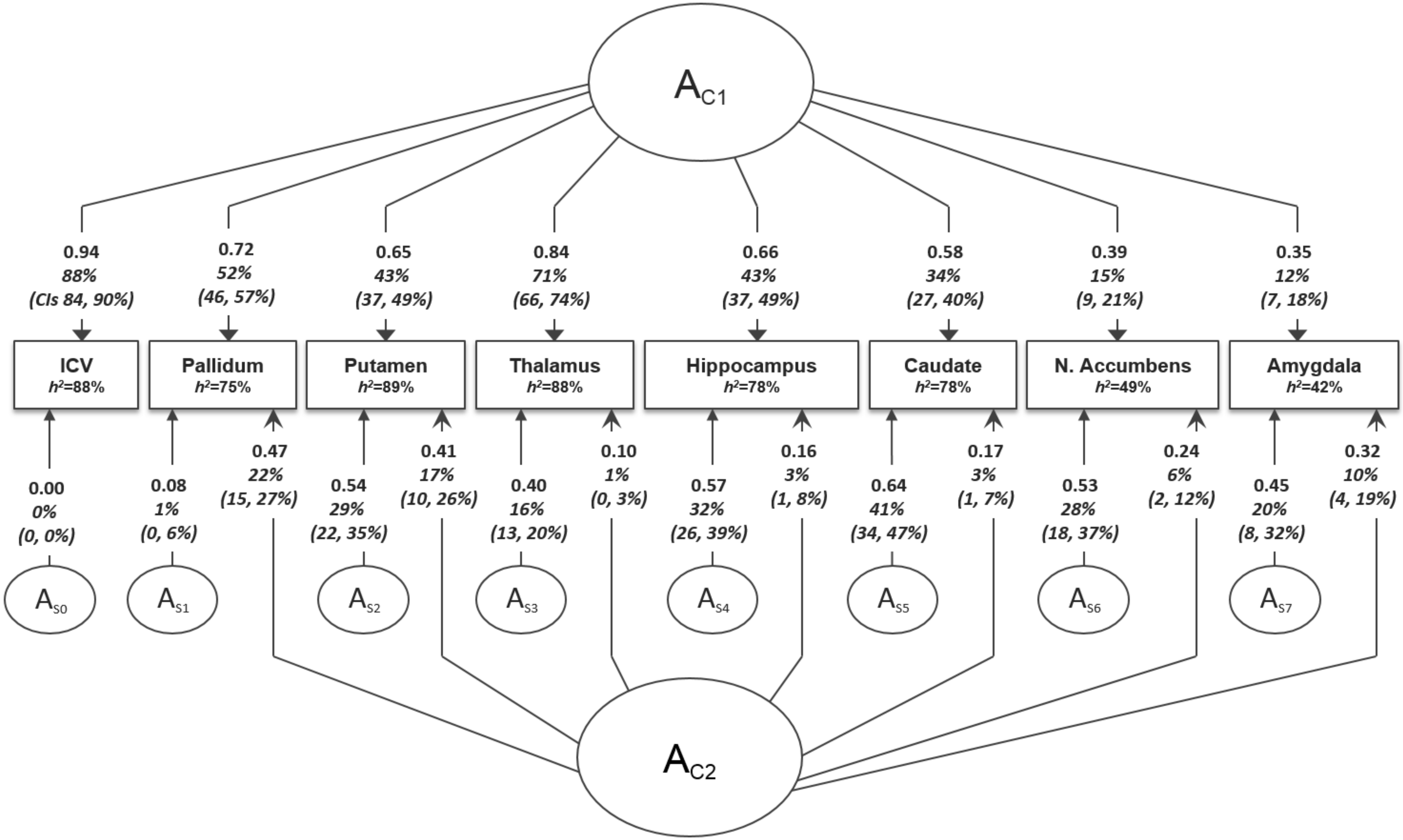


ENIGMA2

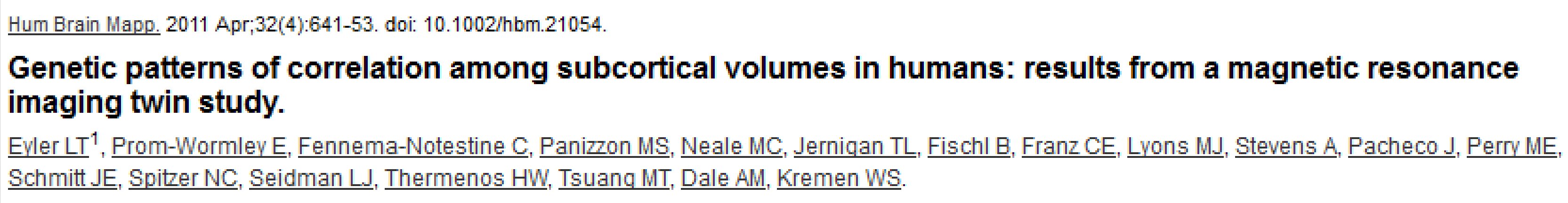
- GWASMA of subcortical region volumes - Caudate, Putamen, Pallidum, Thalamus, Accumbens, Amygdala and Hippocampus
- 29,000 brain scans from 47 centres
- Genetics protocols
  - 1000 Genomes imputation – April 2012 release – minus singletons
  - EUR or ALL-Ethnicities versions



Shared and region-specific genetic factors influence subcortical volumes: multivariate variance component analysis of 1090 twins



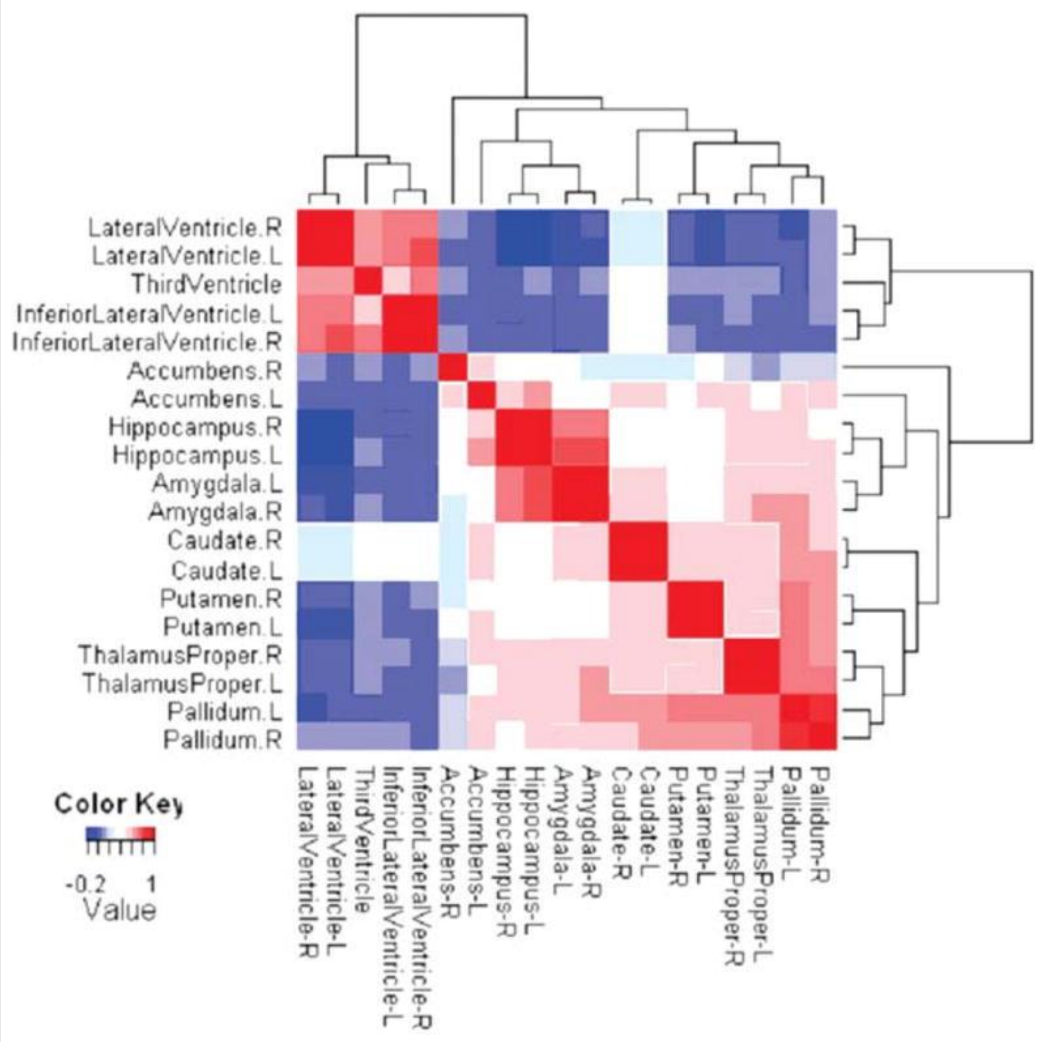
Miguel Renteria



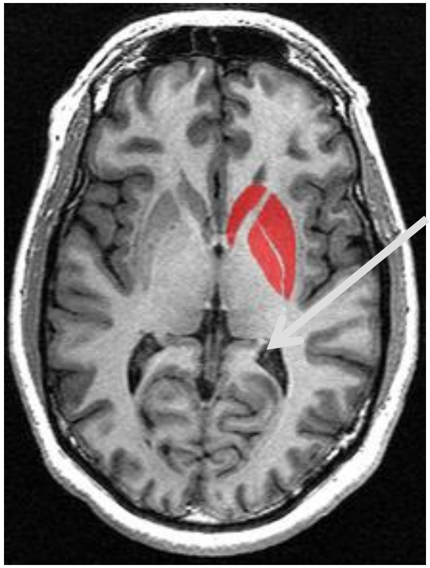
Hum Brain Mapp. 2011 Apr;32(4):641-53. doi: 10.1002/hbm.21054.

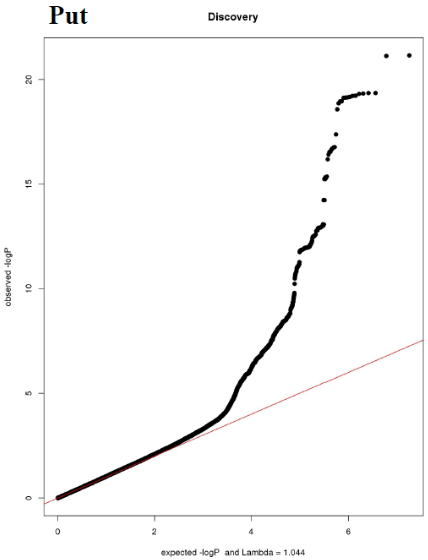
Genetic patterns of correlation among subcortical volumes in humans: results from a magnetic resonance imaging twin study.

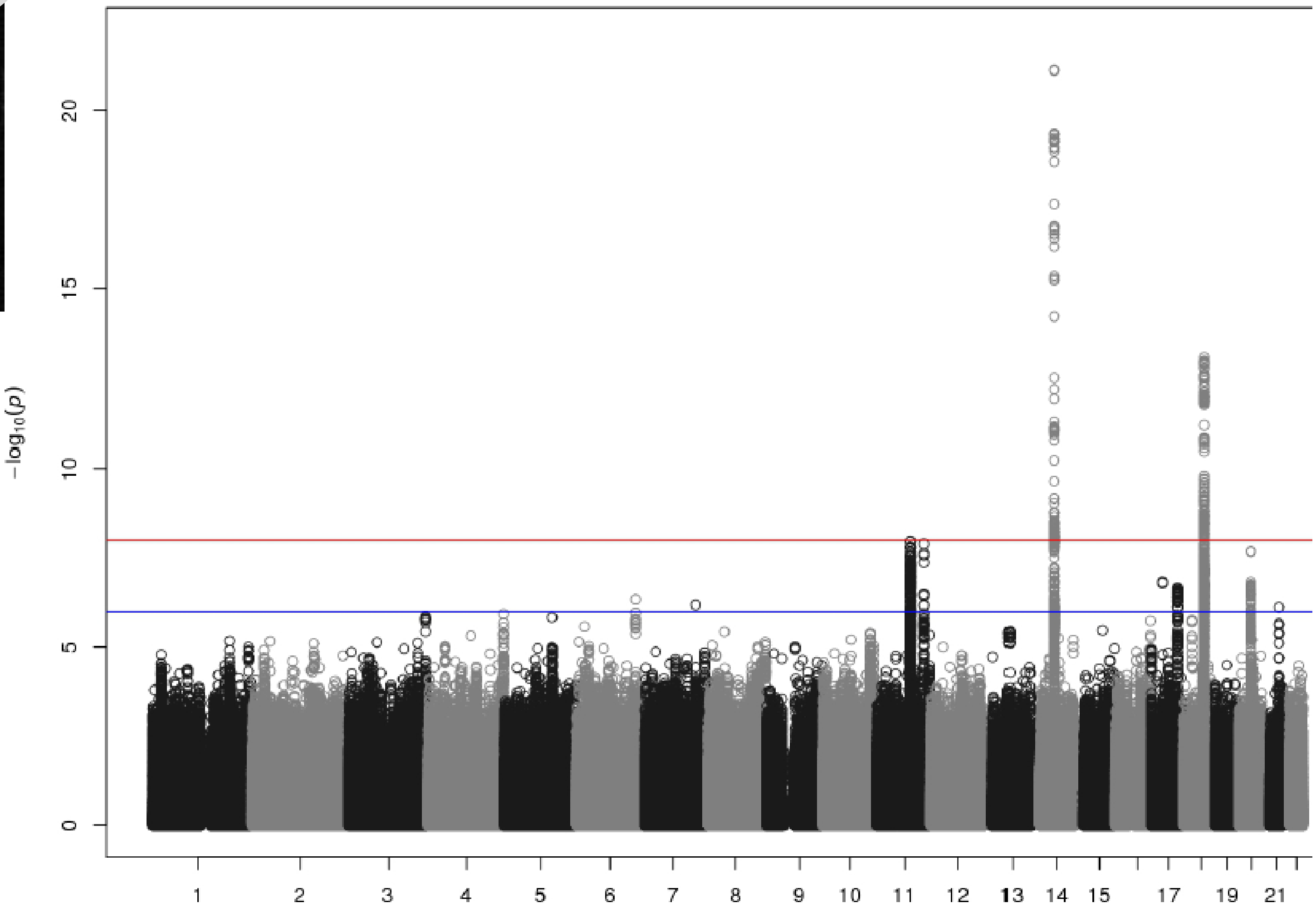
Eyler LT[1], Prom-Wormley E, Fennema-Notestine C, Panizzon MS, Neale MC, Jernigan TL, Fischl B, Franz CE, Lyons MJ, Stevens A, Pacheco J, Perry ME, Schmitt JE, Spitzer NC, Seidman LJ, Thermenos HW, Tsuang MT, Dale AM, Kremen WS.



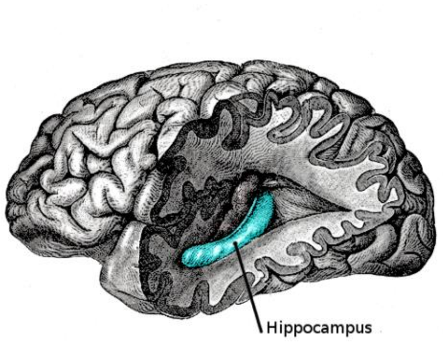
ENIGMA2 preliminary results: Putamen

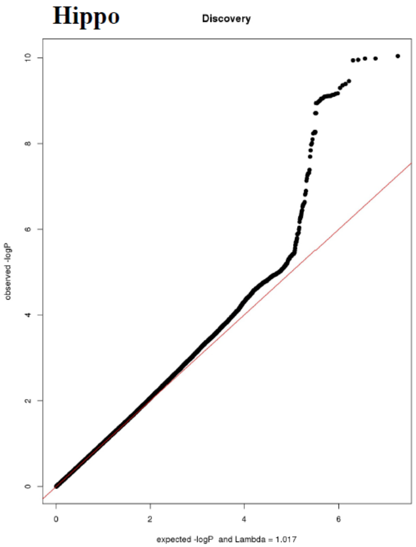


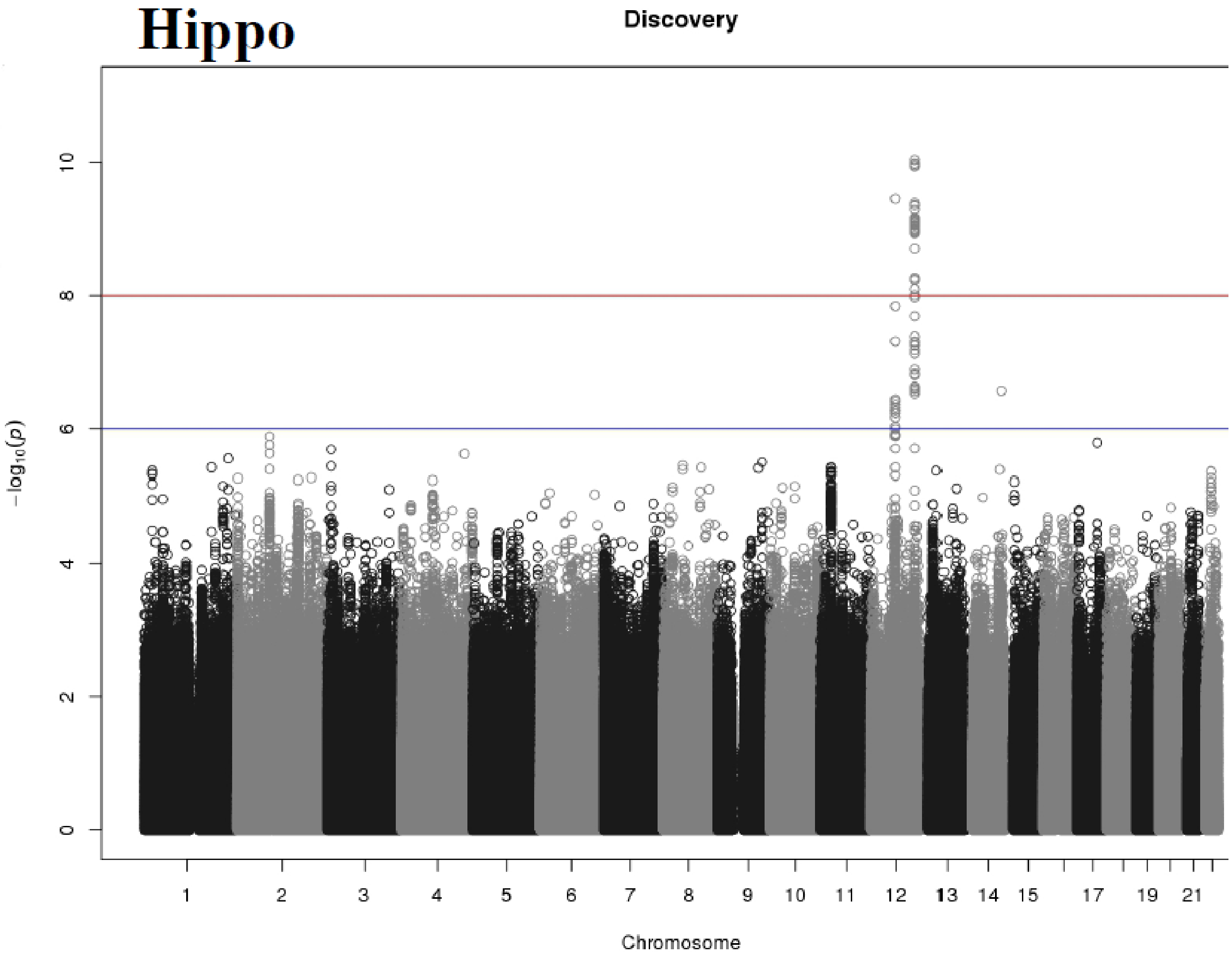




ENIGMA2 preliminary results: Hippocampus

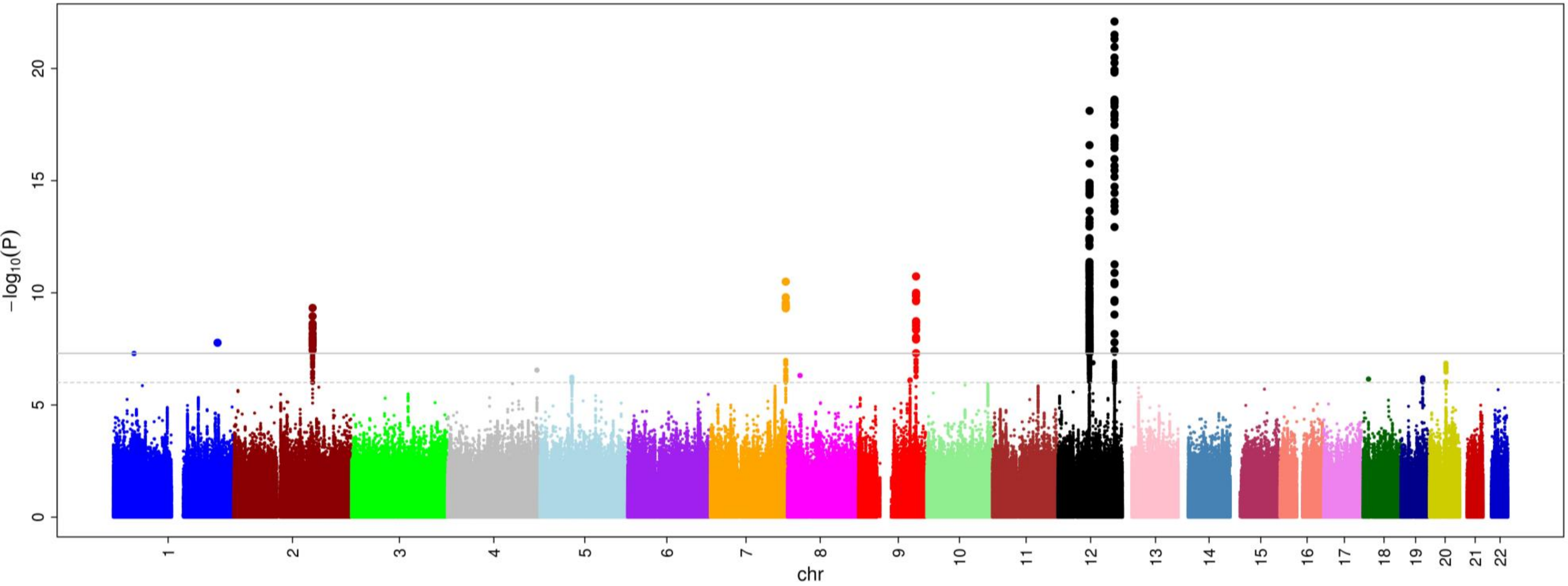






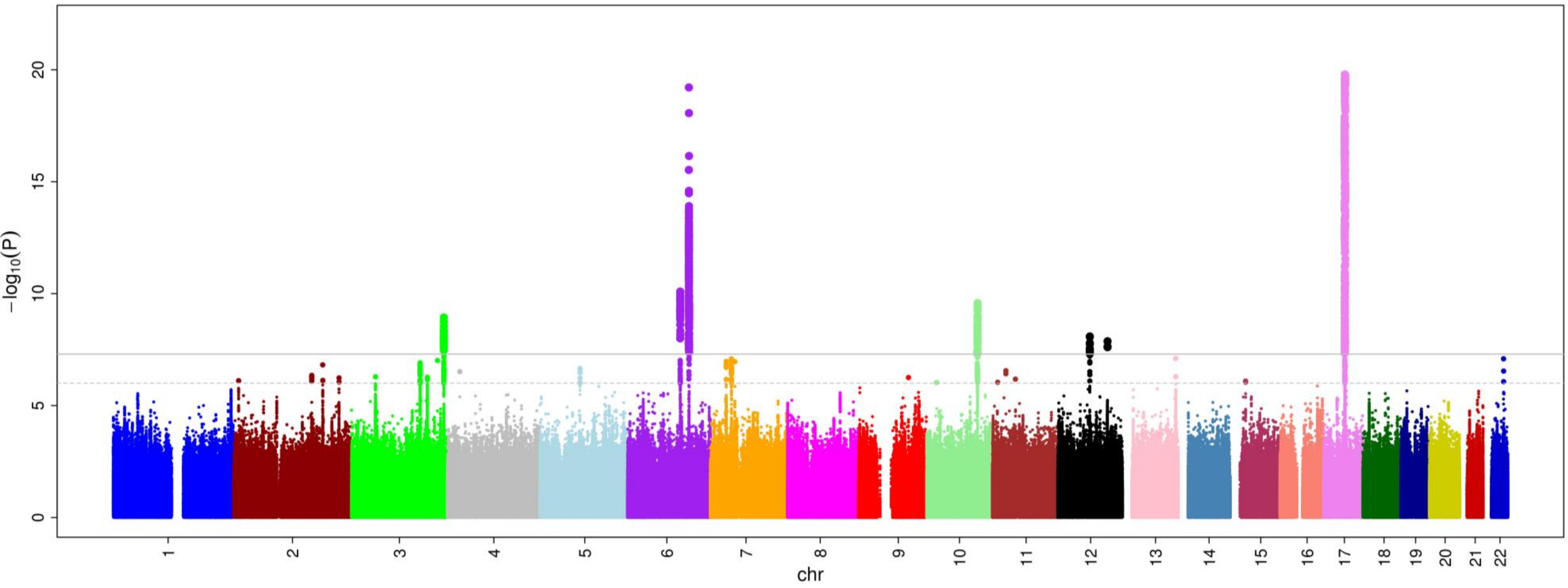
CHARGE-ENIGMA HV – Manhattan plot

N=25,889; several GW-hits, $p \sim 10^{-10}$-10^{-23}



CHARGE-ENIGMA ICV – Manhattan plot

N=26,378; several GW-hits, p~10^{-10}-10^{-20}

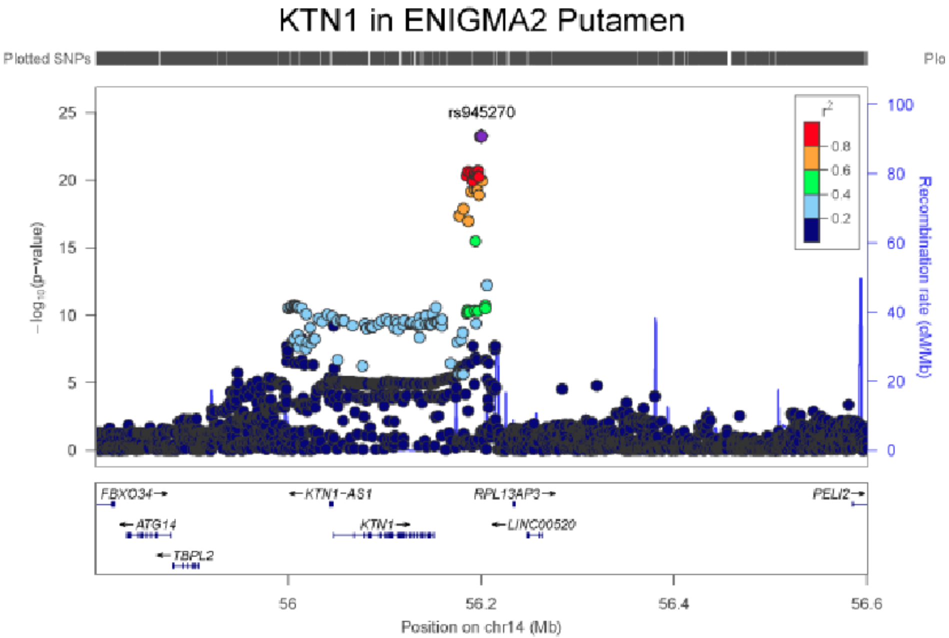


Putamen association (*KTN1, chr 14; $p \sim 10^{-20}$*) is a cross-species QTL

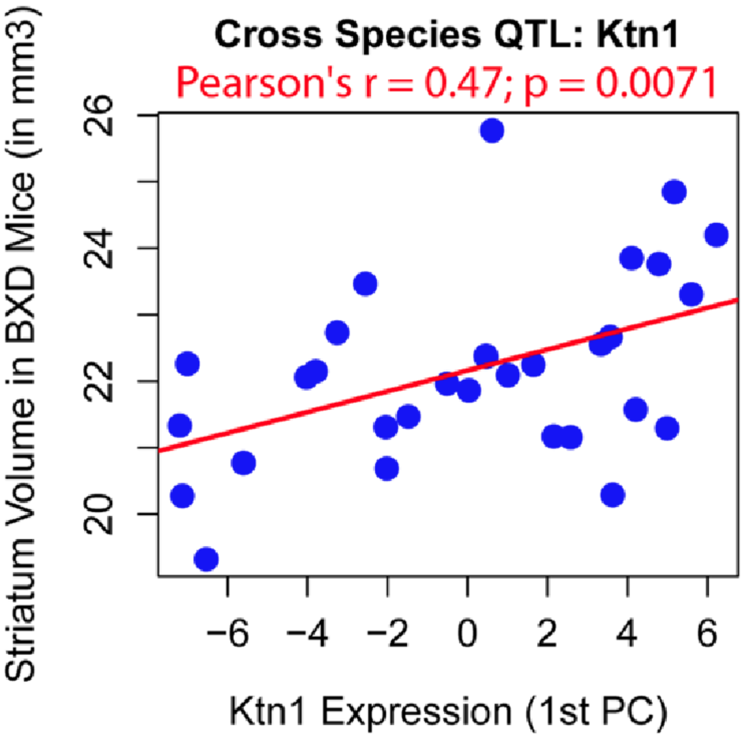
In BXD mice, the expression of this gene predicts putamen volume ($r = 0.47$)

(collaboration: Rob Williams lab, UT Memphis)

HUMANS



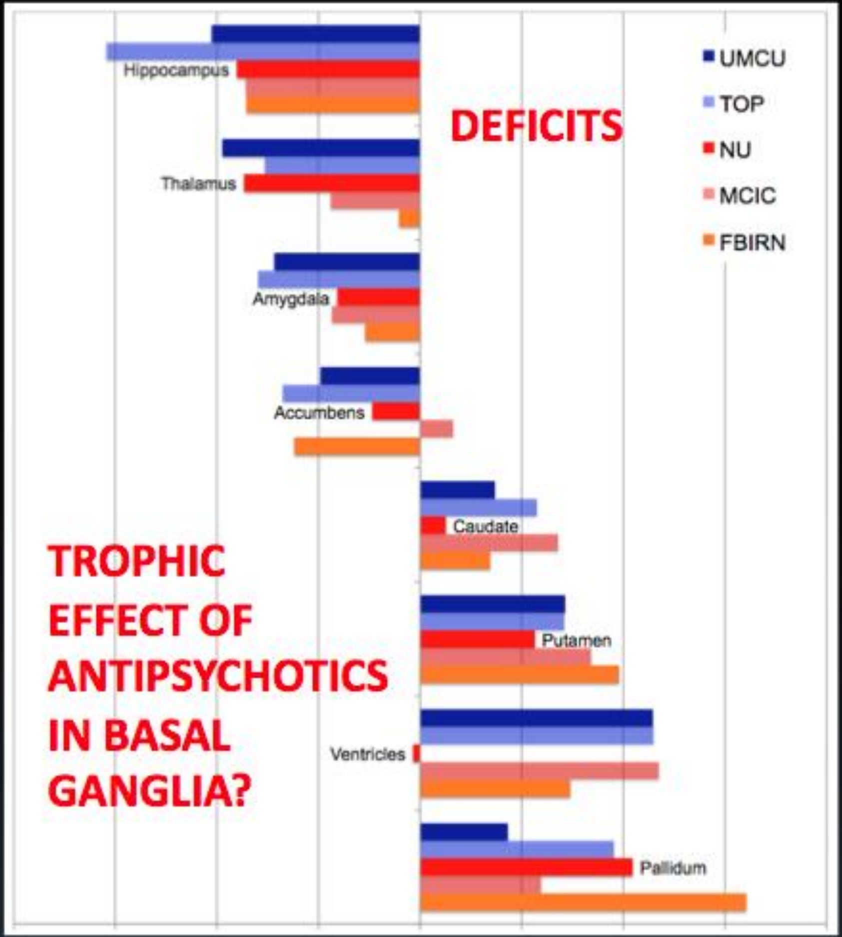
MICE



Development of ENIGMA working groups…

- Phenotypic Meta-Analyses of case control differences in subcortical volumes
  - Schizophrenia, Bipolar, Major Depression, ADHD
  - Where should we look for endo-phenotypes?

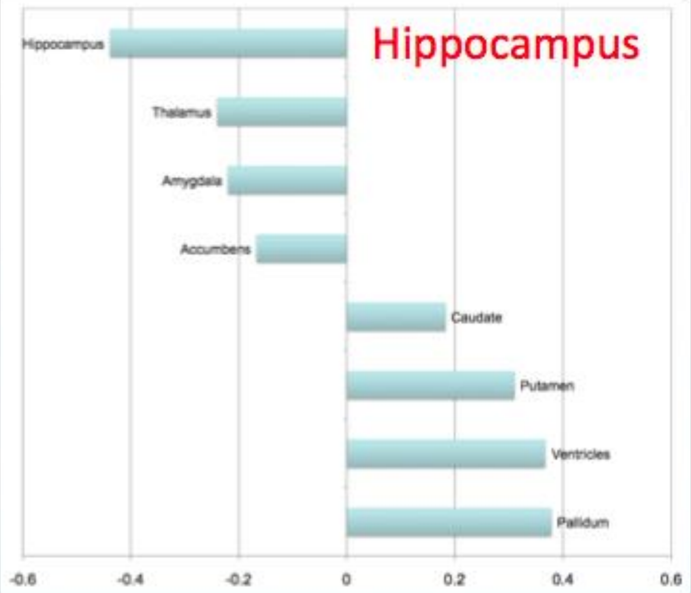
ENIGMA-Schizophrenia Working Group



DEFICITS

TROPHIC EFFECT OF ANTIPSYCHOTICS IN BASAL GANGLIA?

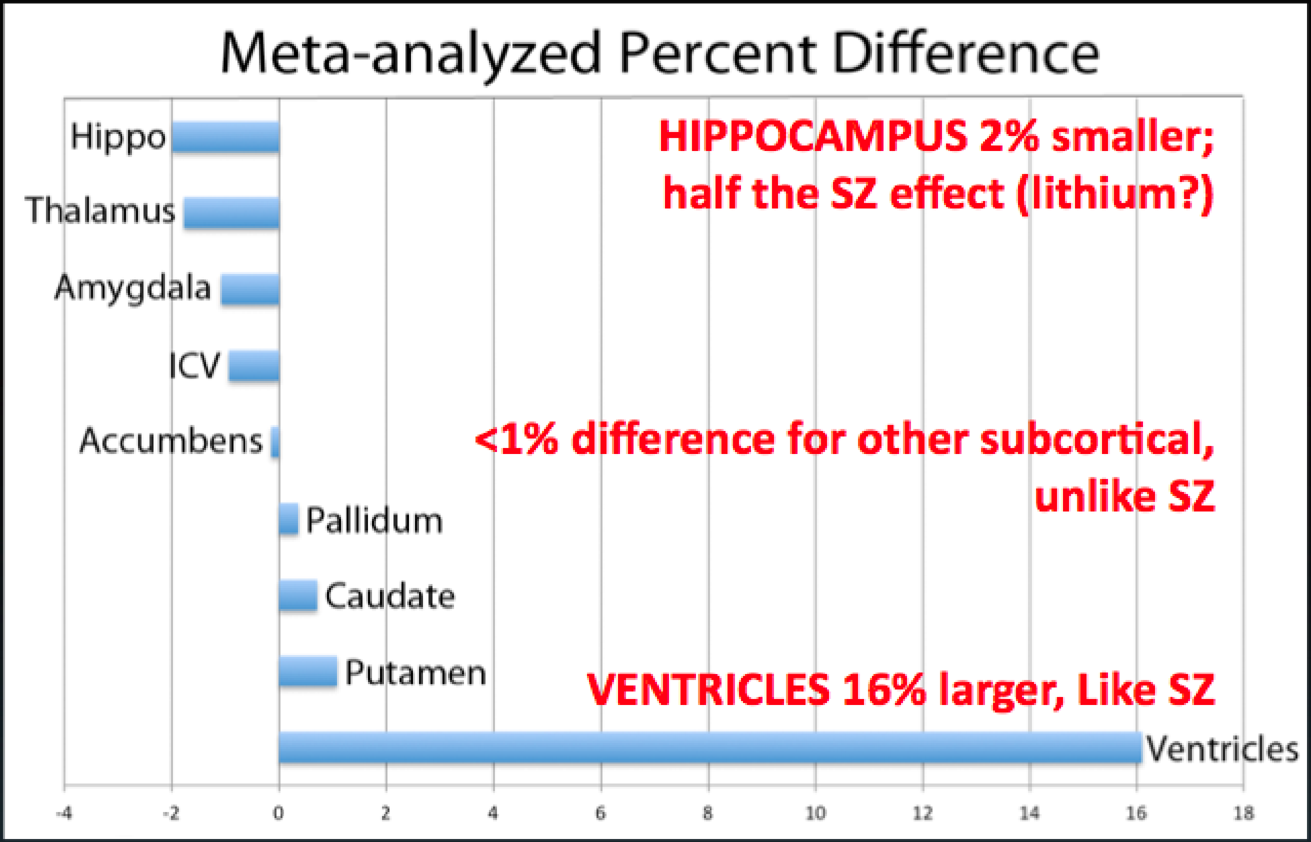
- N=1,686
- Effect size is greatest for hippocampus, not ventricles (ventricles are too variable)



Hippocampus

Theo G. M. van Erp*[1], Derrek P. Hibar*[2], Jerod Rasmussen[1], Ole A. Andreassen[3], Unn K. Haukvik[3,4], Ingrid Agartz[3,4], Steven G. Potkin[1], Hilleke Hulshoff-Pol[5], Roel Ophoff[6], Neeltje E. M. van Haren[5], Oliver Gruber[7], Bernd Krämer[7], Stefan Erhlich[8,9], Johanna Hass[8], Lei Wang[10], Kathryn Alpert[10], Godfrey D. Pearlson[11,12], David Glahn[11,12], Paul M.Thompson*[2], Jessica A. Turner*[11,12], the **ENIGMA-Schizophrenia Working Group**, SOBP (2013).

ENIGMA-Bipolar Disorder Working Group



Meta-analyzed Percent Difference

HIPPOCAMPUS 2% smaller; half the SZ effect (lithium?)

<1% difference for other subcortical, unlike SZ

VENTRICLES 16% larger, Like SZ

- 12 sites participating
- prelim. results from 4
  - 429 BPD patients
  - 484 CTLs

Oct 1 2013:

- 1149 BP patients
- 1523 CTLs

Derrek P. Hibar, 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** (2013). **Meta-analysis of structural brain differences in bipolar disorder: the ENIGMA-Bipolar Disorder Project,** OHBM, Seattle, WA, June 2013.

The ENIGMA Network and active Working Groups:

ENIGMA -2: Subcortical GWAS-MA

Diffusion Tensor Imaging

Shape Analysis

Schizophrenia

Bipolar Disorder

ADHD

22q11.2

Major Depressive Disorder

Addiction

Obsessive Compulsive Disorder

HIV

Arterial Spin Labeling

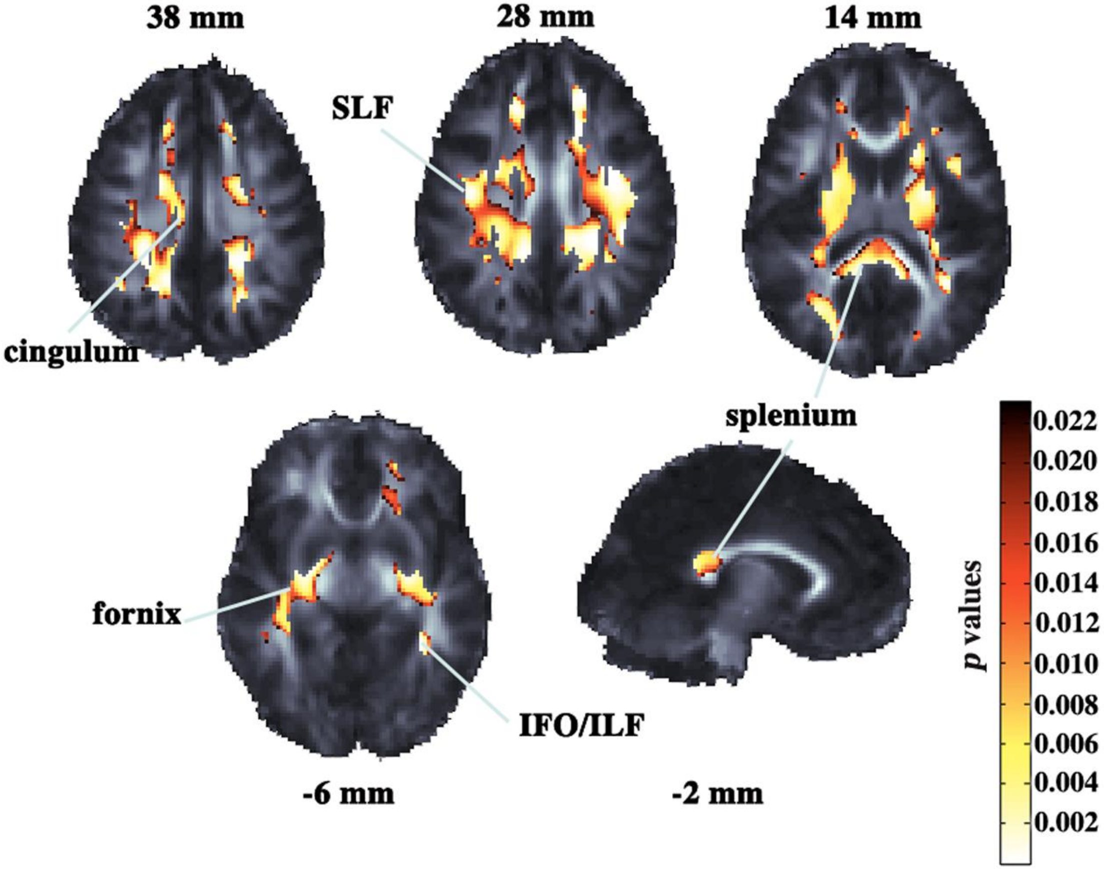
The ENIGMA Network with other Consortia:

ENIGMA + PGC

ENIGMA + CHARGE

…and finally, do gene variants affecting neuroimaging phenotypes also affect risk of psychiatric disease ?

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]

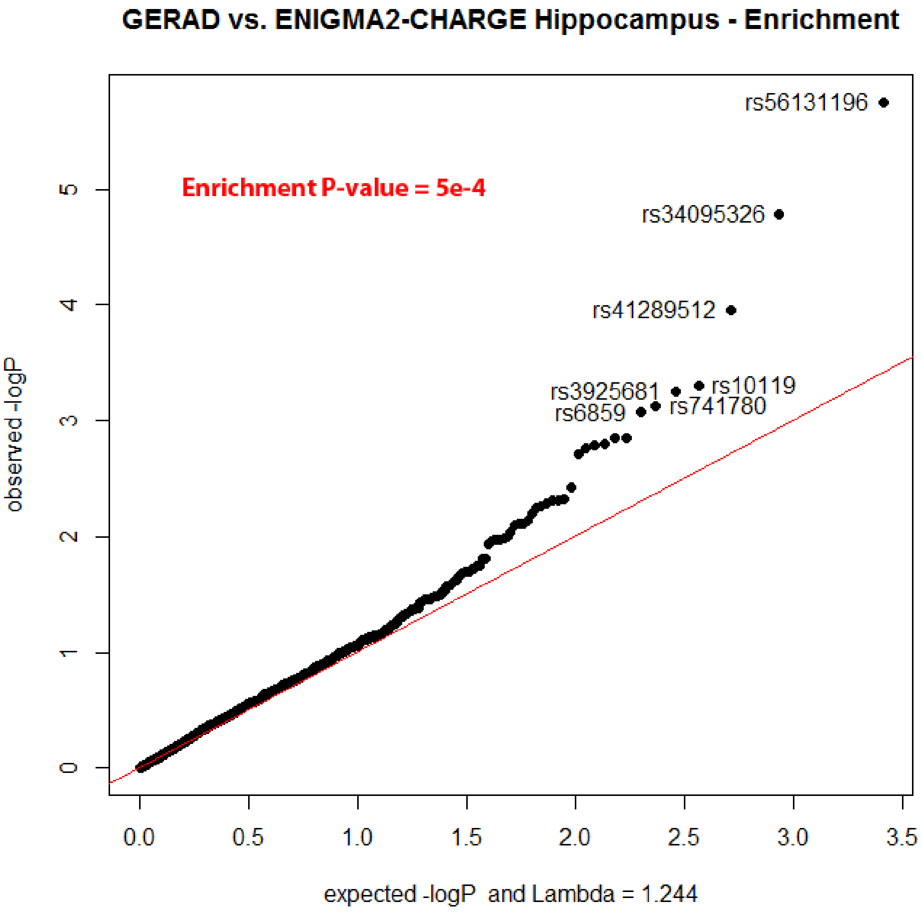


Voxels where *CLU* allele C (at rs11136000) is associated with lower FA after adjusting for age, sex, and kinship in 398 young adults
(68 T/T; 220 C/T; 110 C/C). FDR critical $p = 0.023$. Left hem. on Right

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

Some of ENIGMA's "hippocampal" genes may be Alzheimer's Disease risk genes

GERAD-ENIGMA-CHARGE

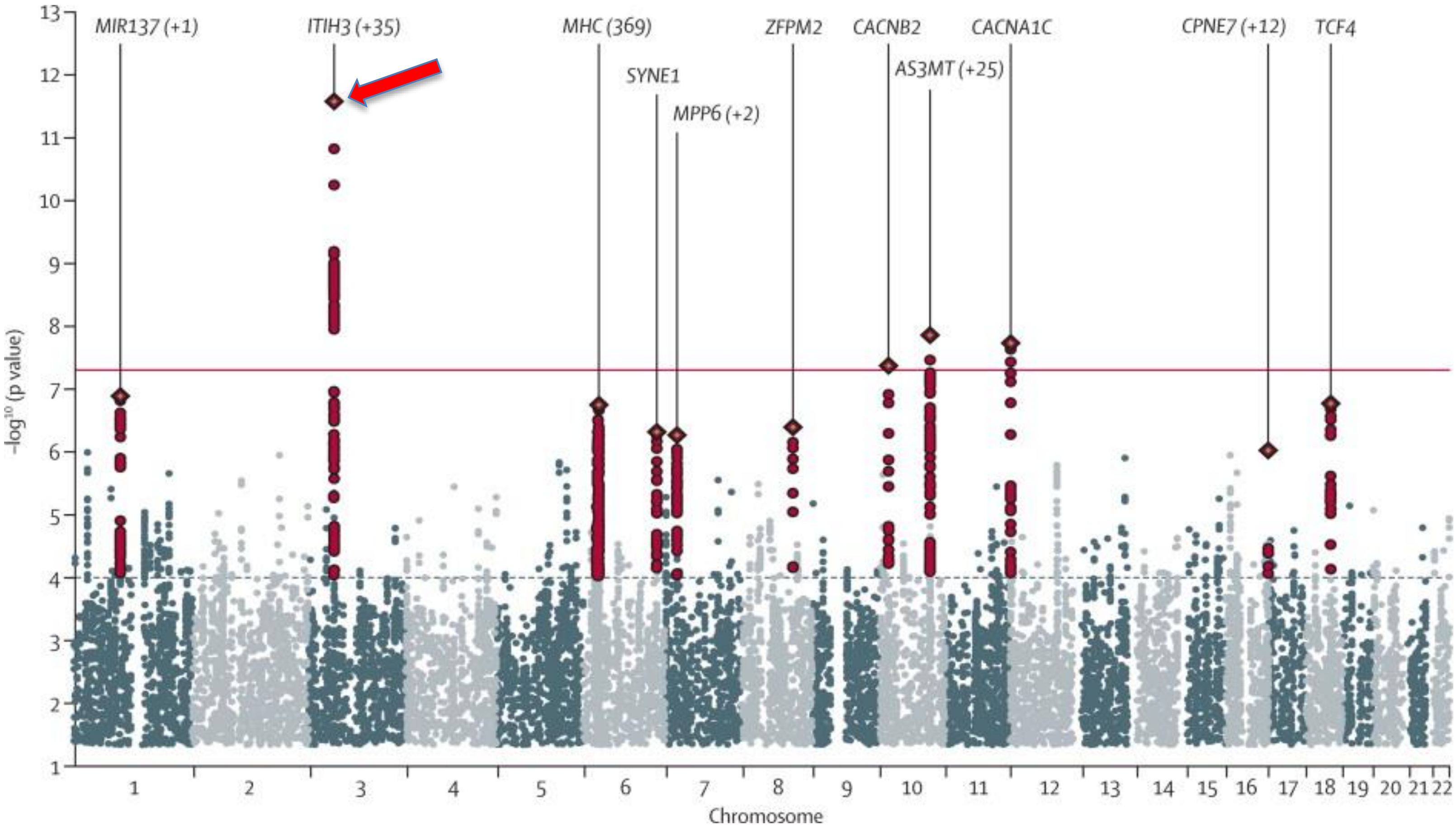


Perhaps you *can* screen images and find disease risk genes

***Genetic & Environmental Risk in AD Consortium**

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

*Cross-Disorder Group of the Psychiatric Genomics Consortium**



www.thelancet.com Vol 381 April 20, 2013

Can PGC Cross Disorder GWAS results predict subcortical structure volumes ?

i.e. are the same SNPs that cause psychiatric disease also affecting brain volumes ?

Results

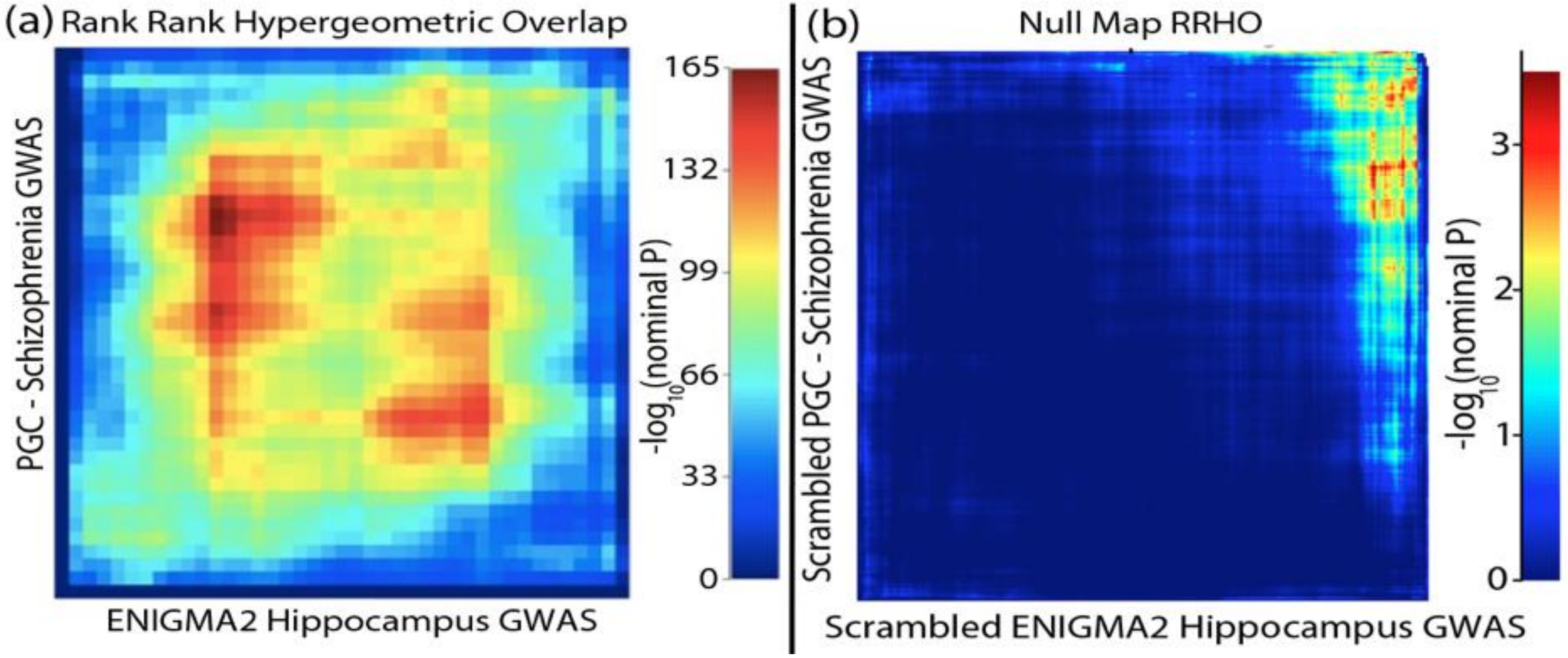
SNPs in the most strongly associated region in PGC's cross-disorder mega-analysis (chr3p21.1) also show low P-values for amygdala and pallidum volumes

SNP ID	Chr:Pos	OR	P-values in PGC-CD	Association P-values in QTIM						
				Caudate	Accumb.	Amygdala	Hippocam	Pallidum	Putamen	Thalamus
rs2535629	3:52808259	0.91	2.5e-12			4.7e-03	0.04	6.3e-04	0.02	6.9e-03
rs3617	3:52808845	0.92	1.4e-11		0.04	5.3e-03		2.6e-04		
rs2071044	3:52822641	0.92	5.5e-11			3.1e-03	0.04	5.0e-04		
rs1075653	3:52800568	1.08	5.9e-09			9.7e-03	0.04	5.9e-03		0.04
rs1076425	3:52800502	1.08	6.7e-09			9.7e-03	0.04	5.9e-03		0.04
rs2071506	3:52801316	1.08	7.1e-09			9.7e-03	0.04	5.8e-03		0.04
rs2239547	3:52830269	1.08	7.1e-09			0.02		0.01		0.02
rs9324	3:52800625	1.08	7.8e-09			9.7e-03	0.04	5.9e-03		0.04
rs2071508	3:52801886	0.93	8.4e-09		0.03	9.7e-03	0.04	5.8e-03		0.04
rs4687657	3:52827578	0.92	8.6e-09			0.02		0.01		0.02
rs4687551	3:52798488	1.08	9.7e-09		0.03	9.7e-03	0.04	5.9e-03		0.04

Next step: ENIGMA → PGC: can brain volume SNPs predict psychiatric disease ?

Are ‘brain-related’ genes also psychiatric risk genes? If so, we could discover new psychiatric risk genes by screening images, and we’d also know what they do.

ENIGMA-PGC2-SZ: SNPs affecting hippocampus DO affect SZ risk ($p=10^{-165}$)



Jason Stein for the ENIGMA-PGC2-SZ Working Group

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