The genetics of DNA methylation and of brain structure and function

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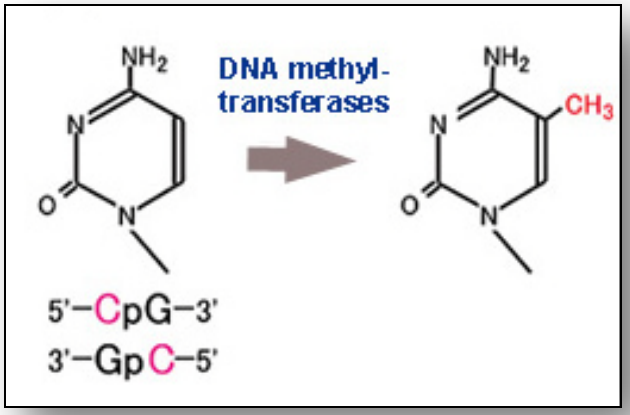
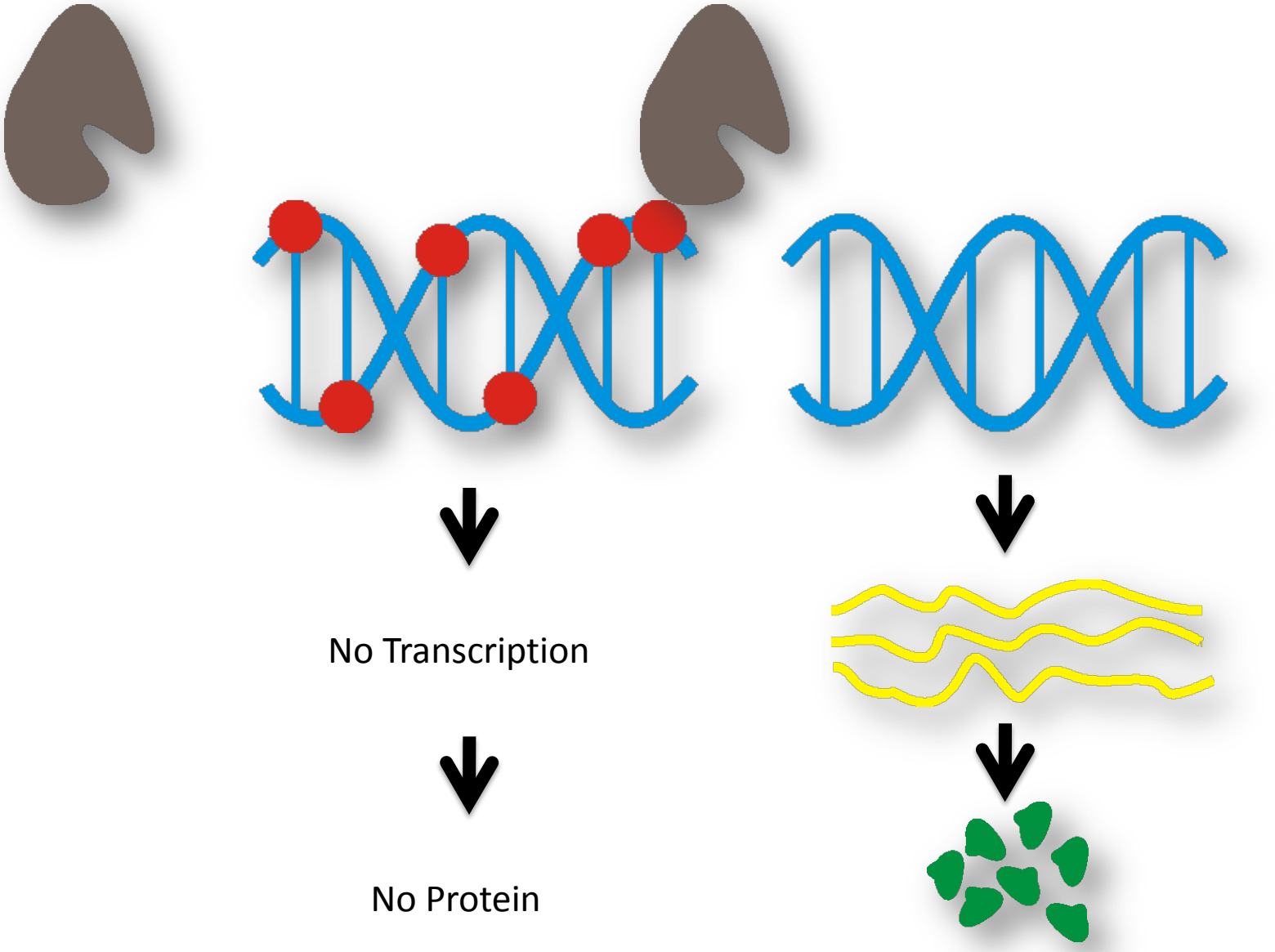
What is Epigenetics?

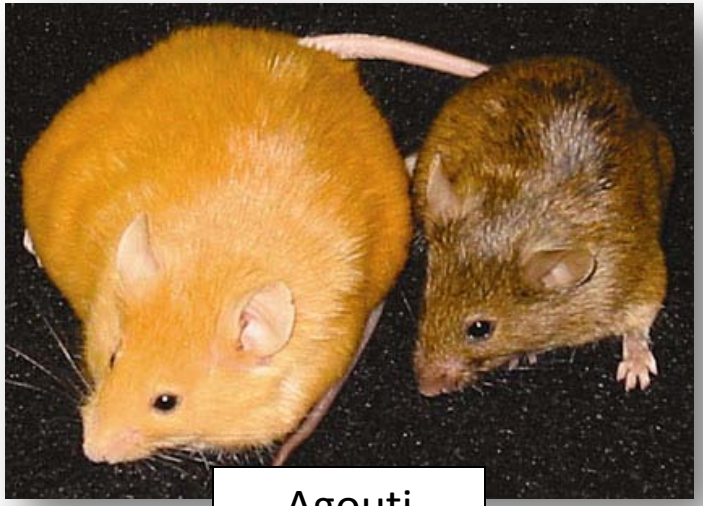
- Heritable, yet reversible, changes in gene function **WITHOUT** changes in the DNA sequence
  - Mediated by DNA methylation, histone modification, siRNA, etc
  - Epigenetic mechanisms are linked
- Degree of methylation is inversely proportional to gene expression
  - CpG island in 60% of promoters
- DNA methylation is considered as primary modification involving transmission



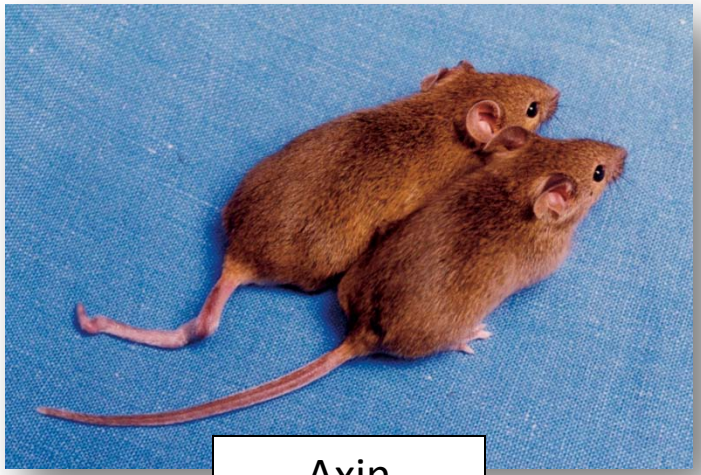
Epigenetic mechanism



Epigenetic Modifiers



Agouti



Axin

- Diet
  - Agouti and Axin
- Stress
  - Maternal behaviour
  - Contextual fear conditioning
- Drugs
  - Methamphetamine
  - Smoking
- Stochasticity
  - Cloned animals
  - De novo methylation
- Hormones, Infections, etc...

Main Genome Wide Techniques for Studying Methylation

27k Illumina methylation array

- Measures methylation of 27k cytosins upstream of 14,000 human genes

450k Illumina methylation array

- Measures methylation of 450k cytosins in the human genome

MeDip-seq

- Sequencing based, genome-wide identification of methylated regions

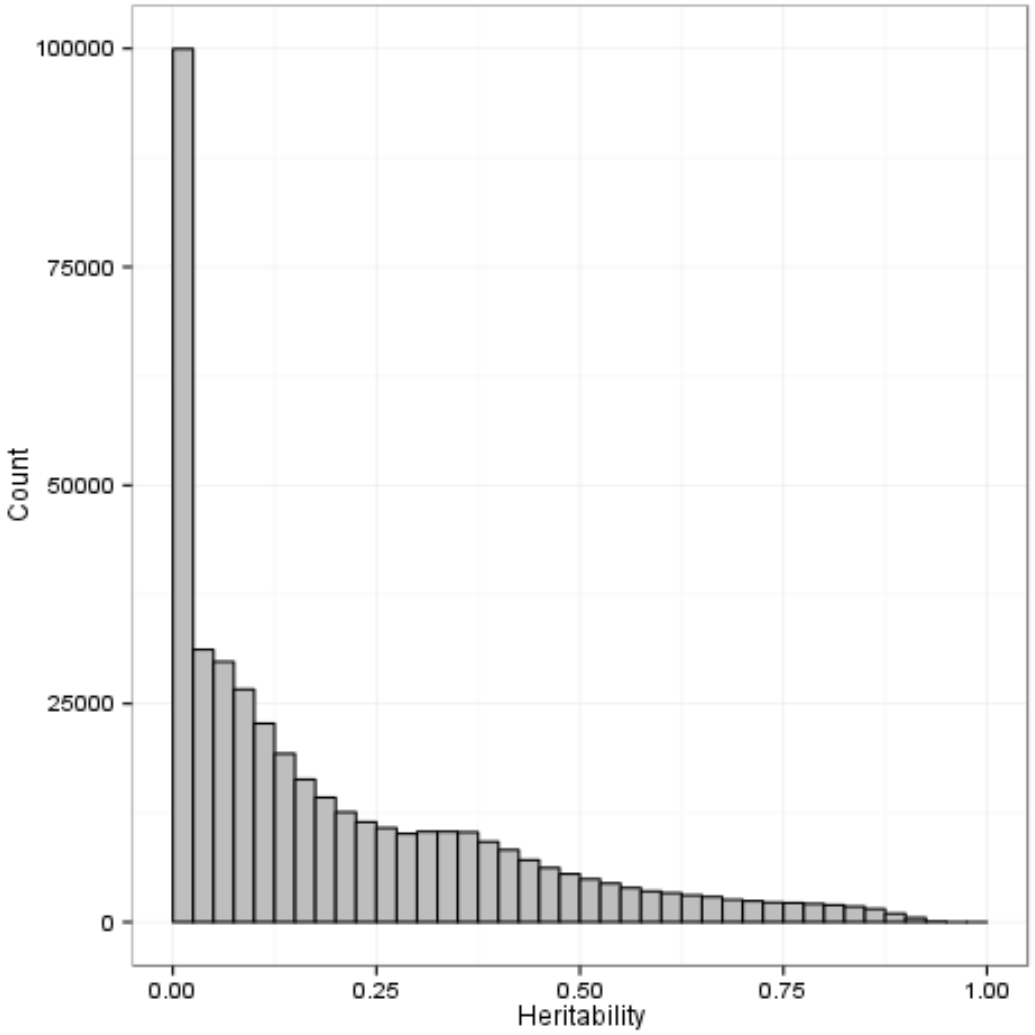
Average correlation across all probes of normalised methylation measurements between relative pairs

Relationship	# Pairs	Correlation	Expected
MZ twin	67	0.200	h^2
DZ twin	111	0.109	$h^2/2$
Sibling	262	0.090	$h^2/2$
Parent – Offspring	362	0.089	$h^2/2$
Parent – Parent	58	0.023	0
Unrelated	187331	-0.002	0

Allan McRae

Distribution of heritability estimates for DNA methylation levels

The average genetic heritability estimate is 0.199. A zero estimate for genetic heritability was observed in 17.1% of cases indicating that genetic heritability results in transgenerational inheritance of DNA methylation for at least 65.8% of probes.



Allan McRae

REVIEW ARTICLE

AMERICAN JOURNAL OF
medical genetics
Neuropsychiatric Genetics

Identical But Not the Same: The Value of Discordant Monozygotic Twins in Genetic Research

Petra J.G. Zwijnenburg,[1]* Hanne Meijers-Heijboer,[1] and Dorret I. Boomsma[2]

[1]Department of Clinical Genetics, VU University Medical Center, Amsterdam, the Netherlands

[2]Department of Biological Psychology, VU University, Amsterdam, the Netherlands

and PubMed. A total number of 2,016 publications were retrieved and reviewed and 439 reports were retained. Discordant MZ twin pairs are informative in respect to variability of phenotypic expression, pathogenetic mechanisms, epigenetics, and post-zygotic mutagenesis and may serve as a model for research on genetic defects. The analysis of single discordant MZ twin pairs may represent an elegant approach to identify genes in inherited disorders.

Am J Med Genet Part B 153B:1134–1149.

Discordant MZ twin design

MZ concordance

for complex disease (heritability) and MZ and DZ twin concordance		
	Probandwise concordance (%)	
	MZ	DZ
Diabetes Type 1 (88%)	**42.9**	7.4
Diabetes Type 2 (64%)	**34**	16
Multiple Sclerosis (25-70%)	**25.3**	5.4
Alzheimer's Disease (48%)	**32.2**	8.7
Parkinson Disease (34%)	**15.5**	11.1
Schizophrenia (81%)	**40.8**	5.3
Major Depresssion (37%)	**31.1**	25.1

Personalized medicine?

Incomplete concordance of MZ twins indicates that a genome cannot predict individual outcome.

Dorret Boomsma

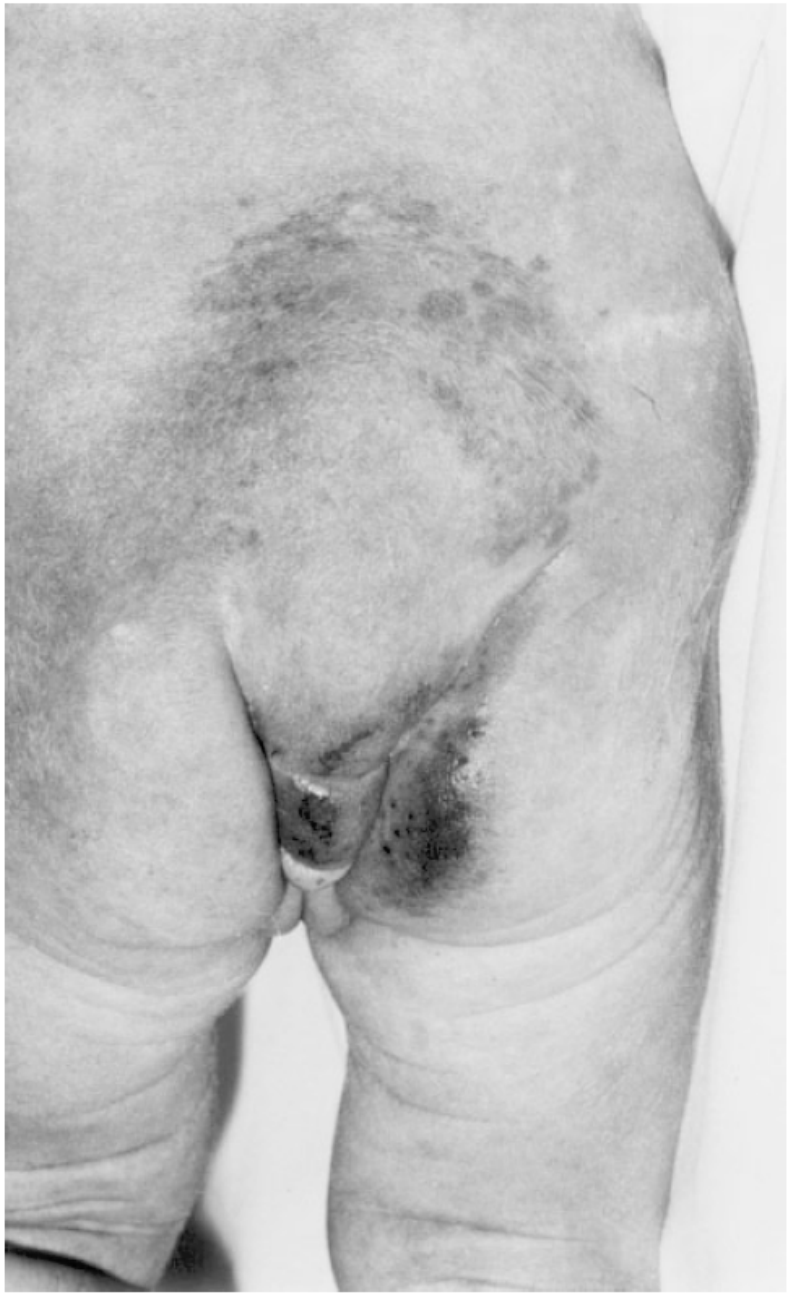


Fig. 1. Patient 1. Soft tumor and abnormal aspect in the lumbosacral area.

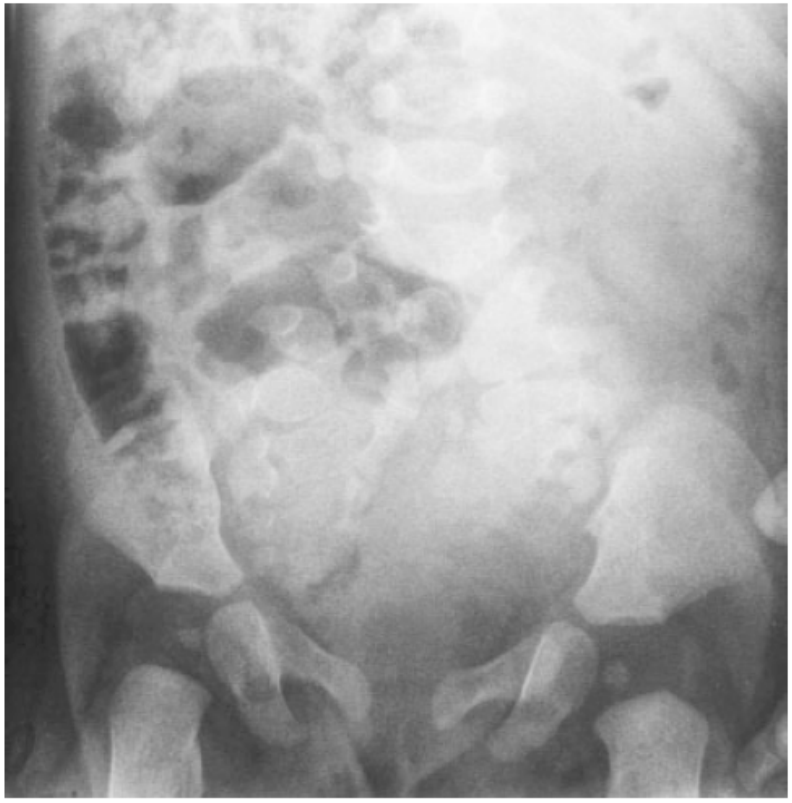
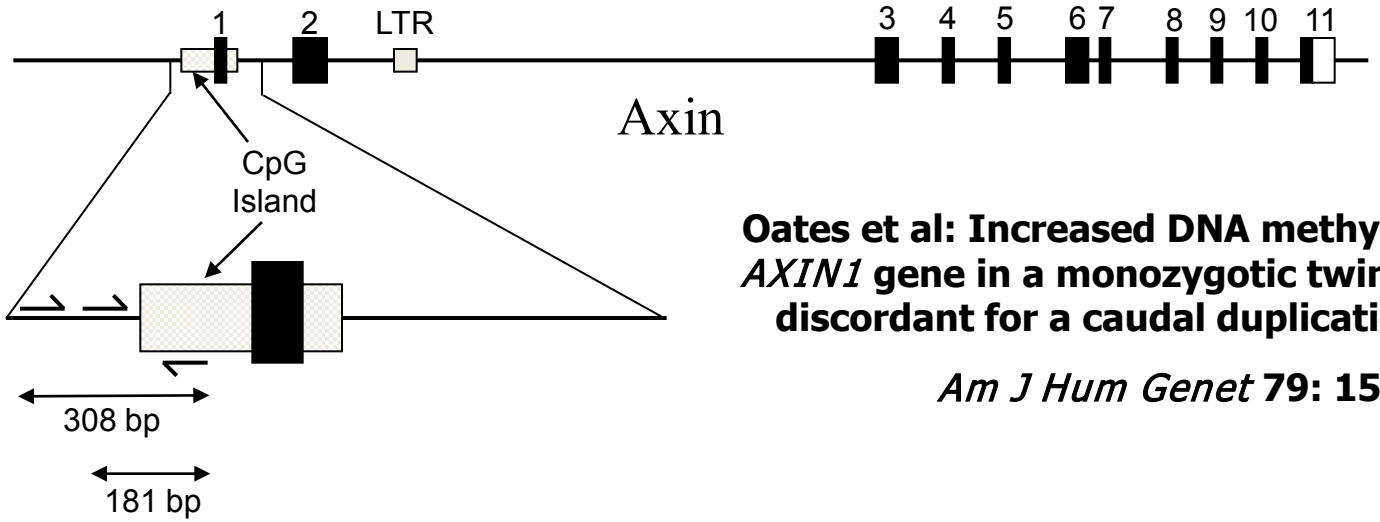


Fig. 2. Patient 1. Radiograph of the vertebral column shows complete duplication of the spine from L4 down.

urethra, a dilated pelvis of the right kidney, bilateral uterus unicornis with normal ovaries, hemivertebrae of thoracic vertebrae 6 and 10, and abnormal curvature of the sacrum. A persistent ductus arteriosus and secundum atrial septum defect was suspected, but results of cardiac investigations at 10 months were normal.

At physical examination for genetic evaluation at 4 months we saw a baby girl with epicanthal folds, but no other minor anomalies. She had a capillary nevus on her left buttock. In the anal region only a dimple was seen. The patient was operated on one day after birth, when a colostomy was made and a fistula connected to the colon

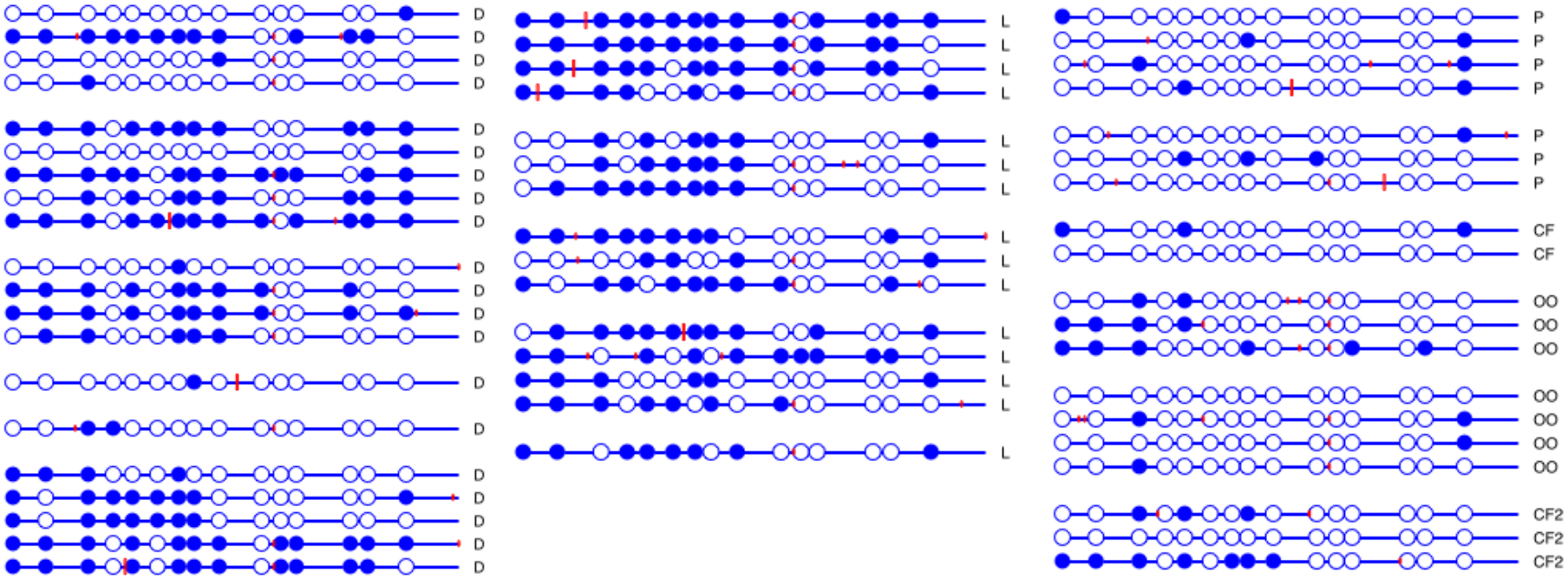
Discordant caudal duplication in MZ twins



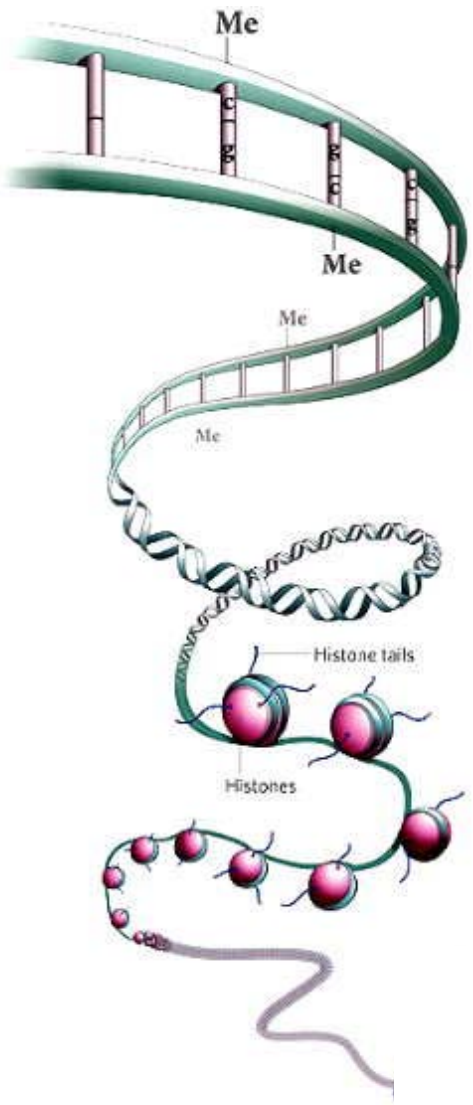
Oates et al: Increased DNA methylation at the *AXIN1* gene in a monozygotic twin from a pair discordant for a caudal duplication anomaly.

***Am J Hum Genet* 79: 155-162, 2006**

Twin 1- unaffected < Twin 2 - affected > Controls [e.g.]



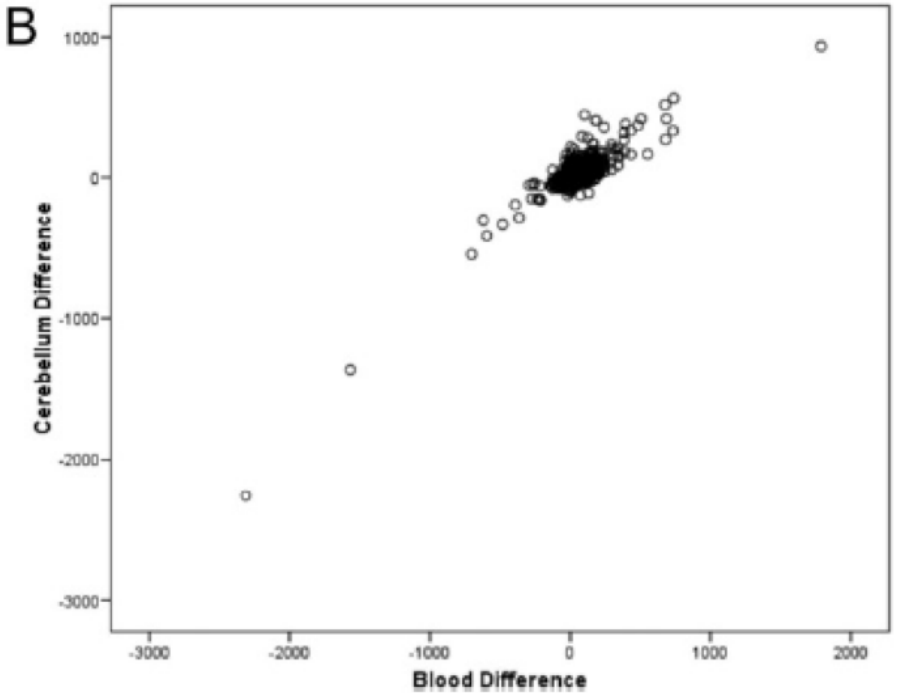
Are there epigenetic factors in depression?

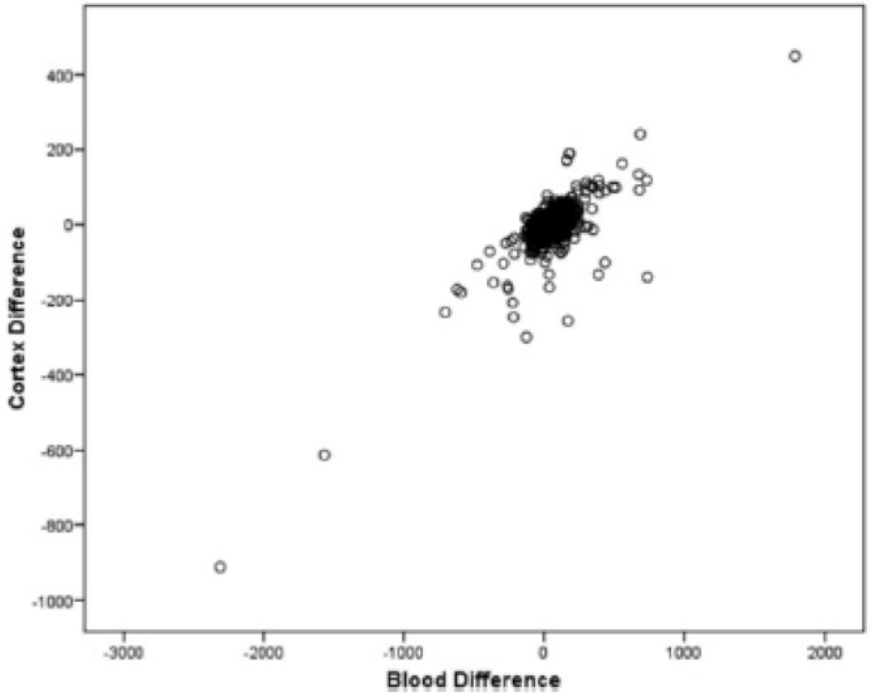


- Modifications of genome other than nucleotide changes that regulate gene expression (e.g. methylation of cytosines, histone modifications, microRNAs,)

Are Blood Samples an Appropriate Surrogate for Brain?

- Brain (cortex and cerebellum) and blood tissue of 2 elderly pairs of twins
- Correlation between blood and brain methylation ~0.7
- So blood DNA is not a perfect surrogate for brain – but it is not useless either!





Davies, Genome Biology, 2012

Study Design

Aims:

- Identify differentially methylated regions associated with MDD

First cohort (Australian cohort):

- 23 MZ twin pairs (Age 25-73)
- Male (7 pairs) and female (16), discordant for MDD

Second cohort (TwinsUK):

- 27 MZ pairs UK Caucasian females, discordant for MDD

Samples:

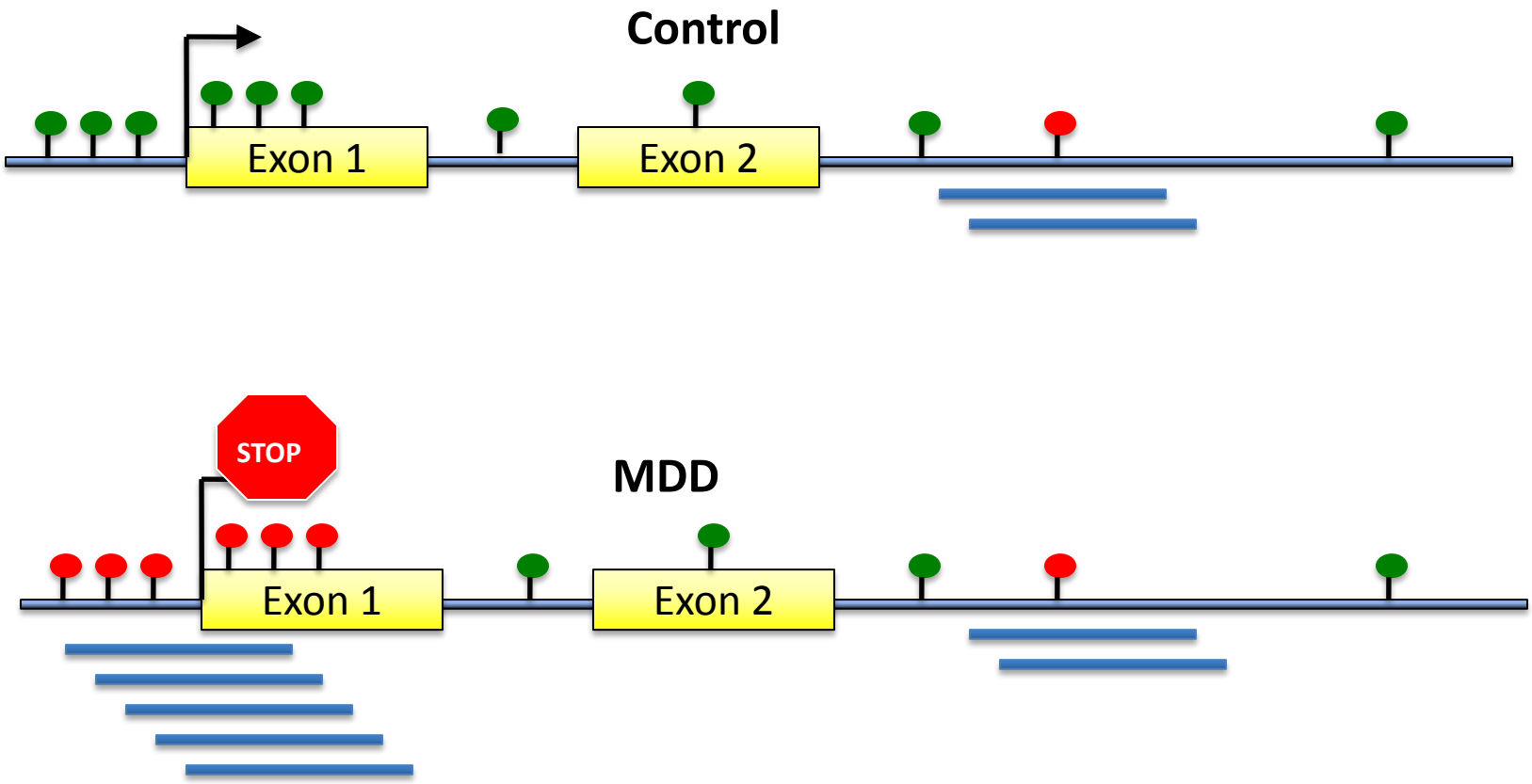
- Blood samples subjected to MeDIP-seq and partially to 27k and/or 450k Illumina methylation arrays

Tim Spector

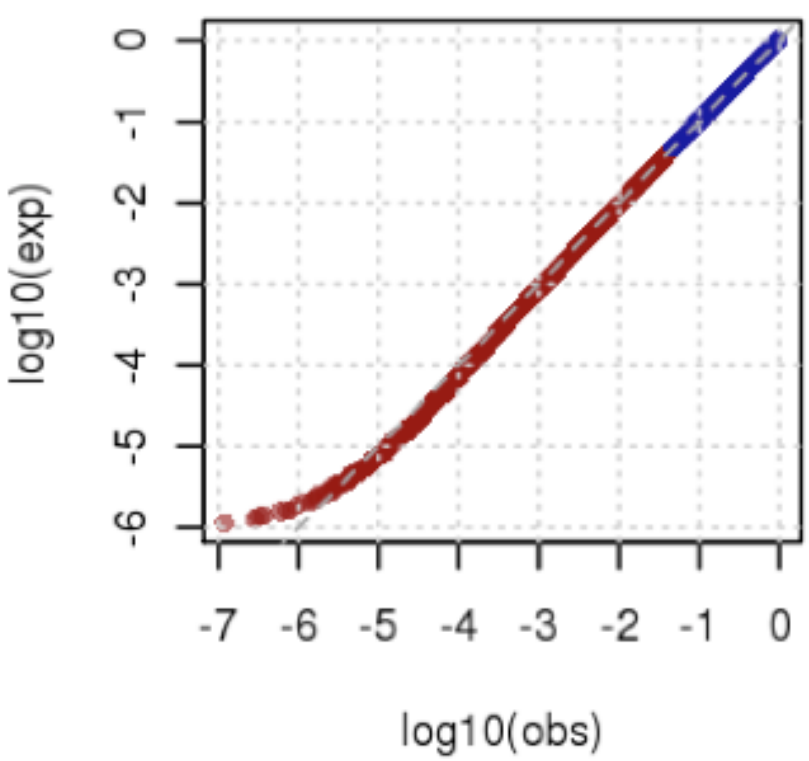
Naomi Wray

Lutz Krause

MeDIP-seq: Identification of Differentially Methylated Regions

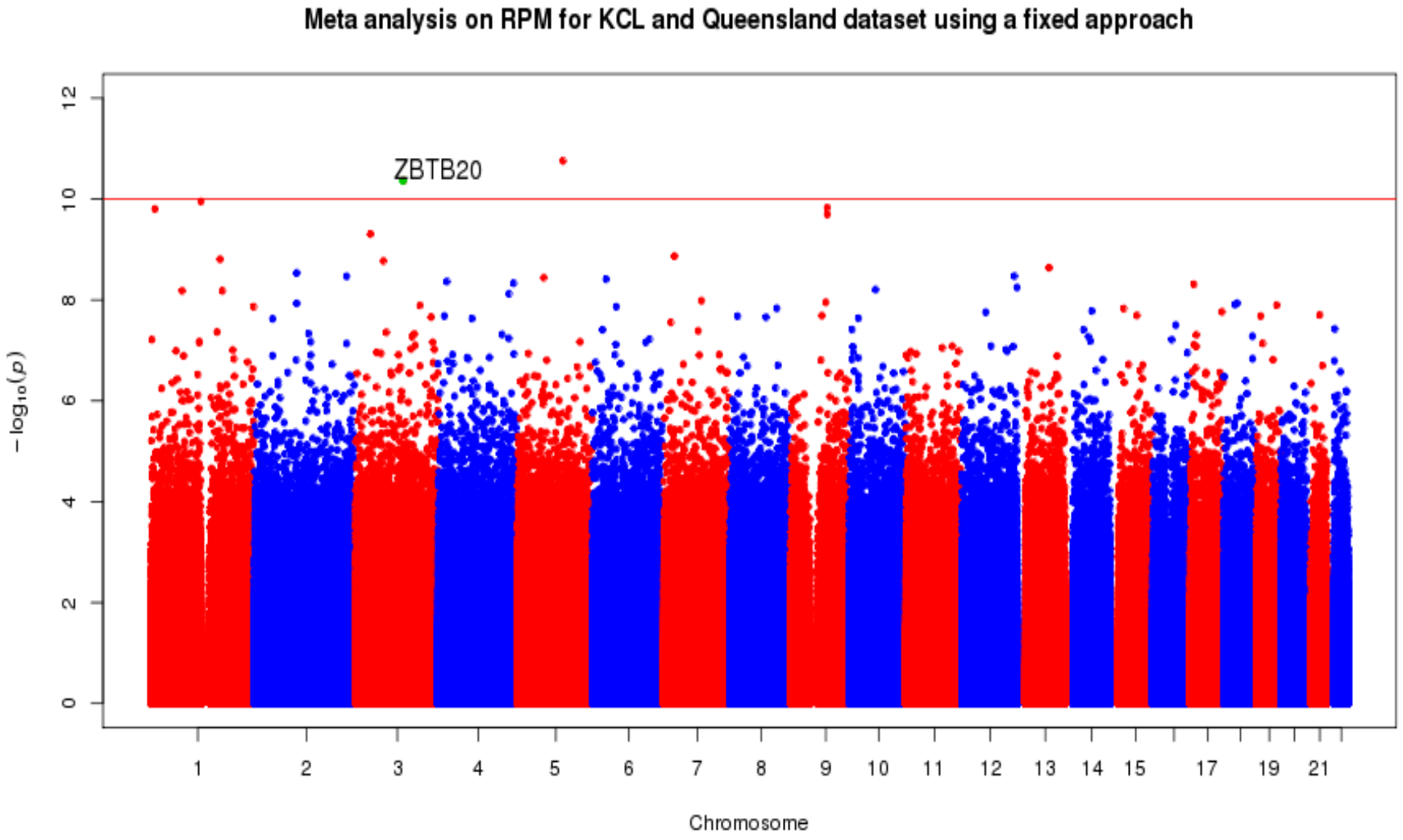


Differentially Methylated Sites in Twins Discordant for MDD



- More changes observed than expected by chance
- Some genomic regions significantly differentially methylated in twins discordant for MDD

Differentially Methylated Sites in Twins Discordant for MDD



ZBTB20

- The region was replicated in an independent sample of age-matched females and showed an increased methylation of 28.2% in the 118 MDD cases compared to the 236 controls (p=0.018).

- Observed methylation changes are not result of anti-depressants

- ZBTB20 shows similar methylation pattern in entorhinal cortex and blood

- A comparison of hippocampal expression data of seven males who died by suicide (cases) and four who died in car accidents (controls) identified a significant lower expression of ZBTB20 in the hippocampus of subjects who died by suicide ($p=4.23 \times 10^{-11}$.)

- ZTBT20 targets hippocampal neurons as well as cerebellum granule cells consistent with our observation of a high ZTBT20 expression in the hippocampal, cerebellum and white matter regions of the brain. Zbtb20 is also crucial for the regionalisation and volume of the archicortex which plays a role in depression.

Gene Expression Analysis Identified 30 Genes Differentially Expressed in MDD

OPEN ACCESS Freely available online

PLoS one

Blood-Based Gene Expression Profiles Models for Classification of Subsyndromal Symptomatic Depression and Major Depressive Disorder

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1 Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, 2 Department of Genetics, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, 3 The Center for Bioinformatics and Institute of Biomedical Sciences, The College of Life Sciences, East China Normal University, Shanghai, China, 4 Shanghai Information Center for Life Sciences, Chinese Academy of Sciences, Shanghai, China

5 of 30 diff. expressed genes also differentially methylated (p<1e-5):

CAB39L	Homo sapiens **calcium binding protein** 39-like (CAB39L), transcript variant 1, mRNA.
IL13RA1	Homo sapiens **interleukin** 13 receptor, alpha 1 (IL13RA1), mRNA.
RGS6	Homo sapiens regulator of **G-protein** signalling 6 (RGS6), transcript variant 3, mRNA.
IL20RB	Homo sapiens **interleukin** 20 receptor beta (IL20RB), mRNA.
IL15RA	Homo sapiens **interleukine** 15 receptor, alpha (IL15RA), transcript variant 1, mRNA.

Enrichment Analysis of Top 200 Differentially Methylated Genes in IPA

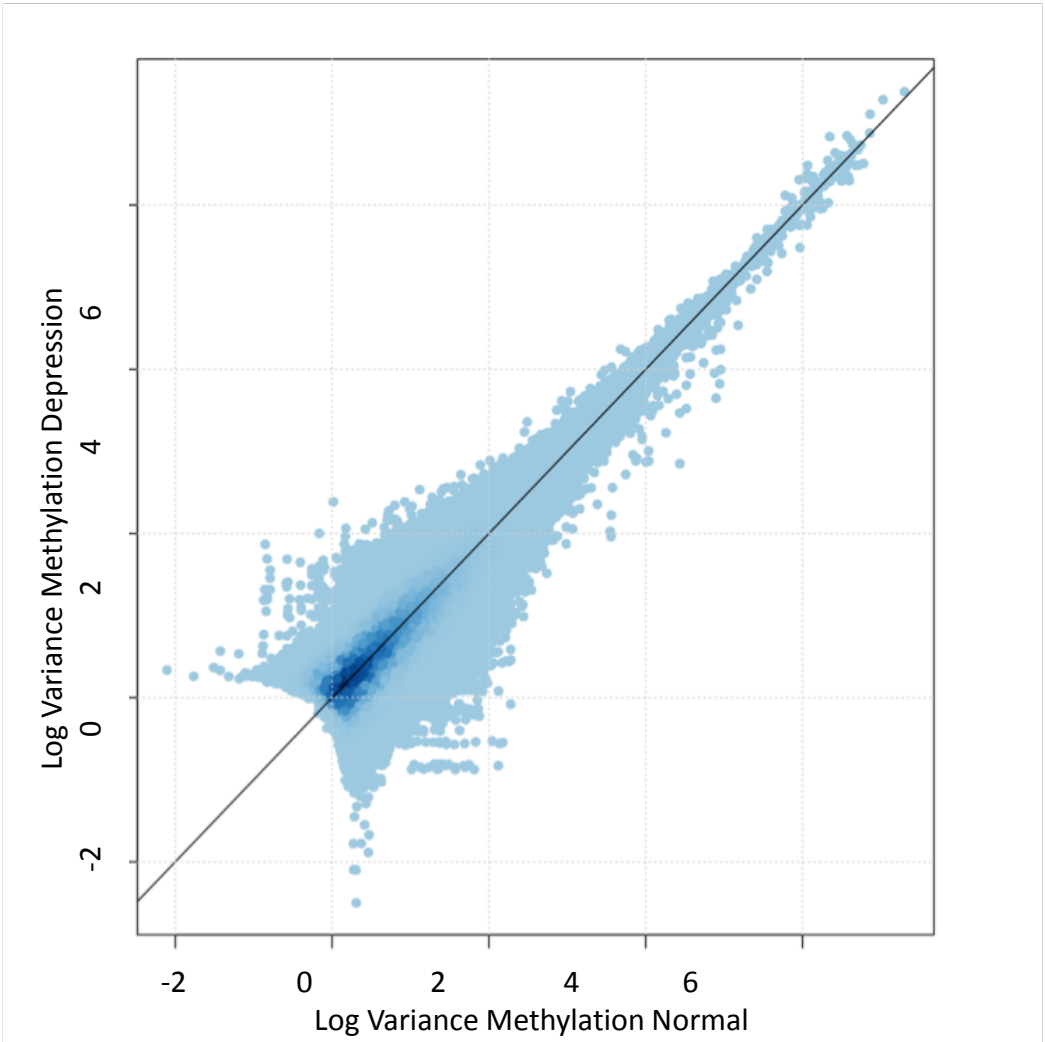
- 81 genes associated with neurological disease
- 87 genes associated with nervous system development

=> Some observed differences relevant

Top Canonical Pathways

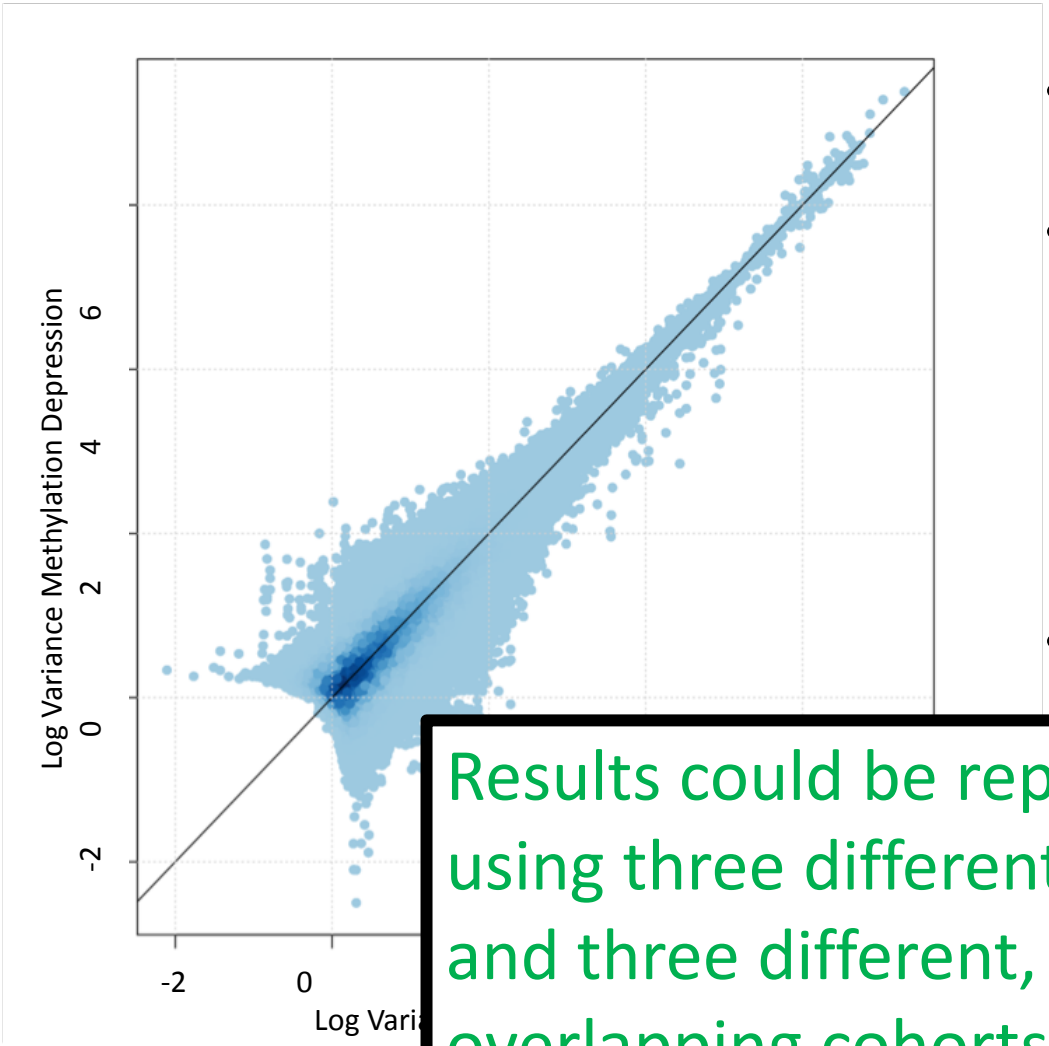
Name	p-value	Ratio
Corticotropin Releasing Hormone Signaling	1.85E-03	4/136 (0.029)
Melatonin Signaling	4.37E-03	3/78 (0.038)
Dopamine-DARPP32 Feedback in cAMP Signaling	6.69E-03	4/183 (0.022)
Neuropathic Pain Signaling In Dorsal Horn Neurons	1.17E-02	3/108 (0.028)
CCR3 Signaling in Eosinophils	1.51E-02	3/126 (0.024)

Variance in Methylation Significantly Higher in Twins With Depression (MeDIP-seq)



- 23 twin pairs discordant for MDD
- Each dot represents one 500bp window, variation in methylation in normal vs. MDD group, measured by MeDIP-seq
- $P=2.2\ e^{-16}$ (Paired, one-tailed Wilcoxon rank test)

Variance in Methylation Significantly Higher in Twins With Depression (MeDIP-seq)



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Results could be reproduced, using three different techniques and three different, partially overlapping cohorts

Conclusions

- Methylation arrays: accurate (high correlation for techical replicates), easy analysis
- MeDIP-seq: genome-wide but data-analysis challenging
- Twin design powerful for identifying methylation differences
- Significant differences in methylation observed for MDD in plausible genes
- Variation in methylation significant higher in MDD twins on a genome wide scale

Epigenetics: the confused epidemiologist's friend.

Davey Smith G Int. J. Epidemiol. 2012;41:303-308

International Journal of Epidemiology

The genetics of brain structure and function

Goal To discover some of the genes and pathways that influence the structure and function of the brain and provide a window into the biological mechanisms leading to mental illness.

- Genetic and environmental factors continuously shape the development of the brain, but the specific variants that predispose us, or protect us against, development of psychiatric disorders are largely unknown.

- QTIMS: acquiring structural and functional brain data as well as cognition and health and well-being, in hundreds of twins.

- With identical (MZ) and non-identical (DZ) twins we are able to disentangle the relative contributions of genetic and environmental factors on brain variation.

- Even in healthy individuals of the same age there is large variation in brain structure and function, some of which is due to genes and some to the environment.

Queensland Twin IMaging Study (QTIMS)

Began June 2007

Target sample ~1400 twins/sibs (20-28yrs; 50% females; R handed)

600 twin pairs (300 MZ, 300 DZ)

200 siblings

Available phenotypes

- Cognition at age 16yrs
- Personality, Health and Well-being

Available genotyping

- GWAS - Illumina 610K SNP chip; >500,000 common genetic variants (SNPs)spread across the entire 23 chromosomes

Multi-modal Imaging - 4 Tesla Bruker Medspec Scanner

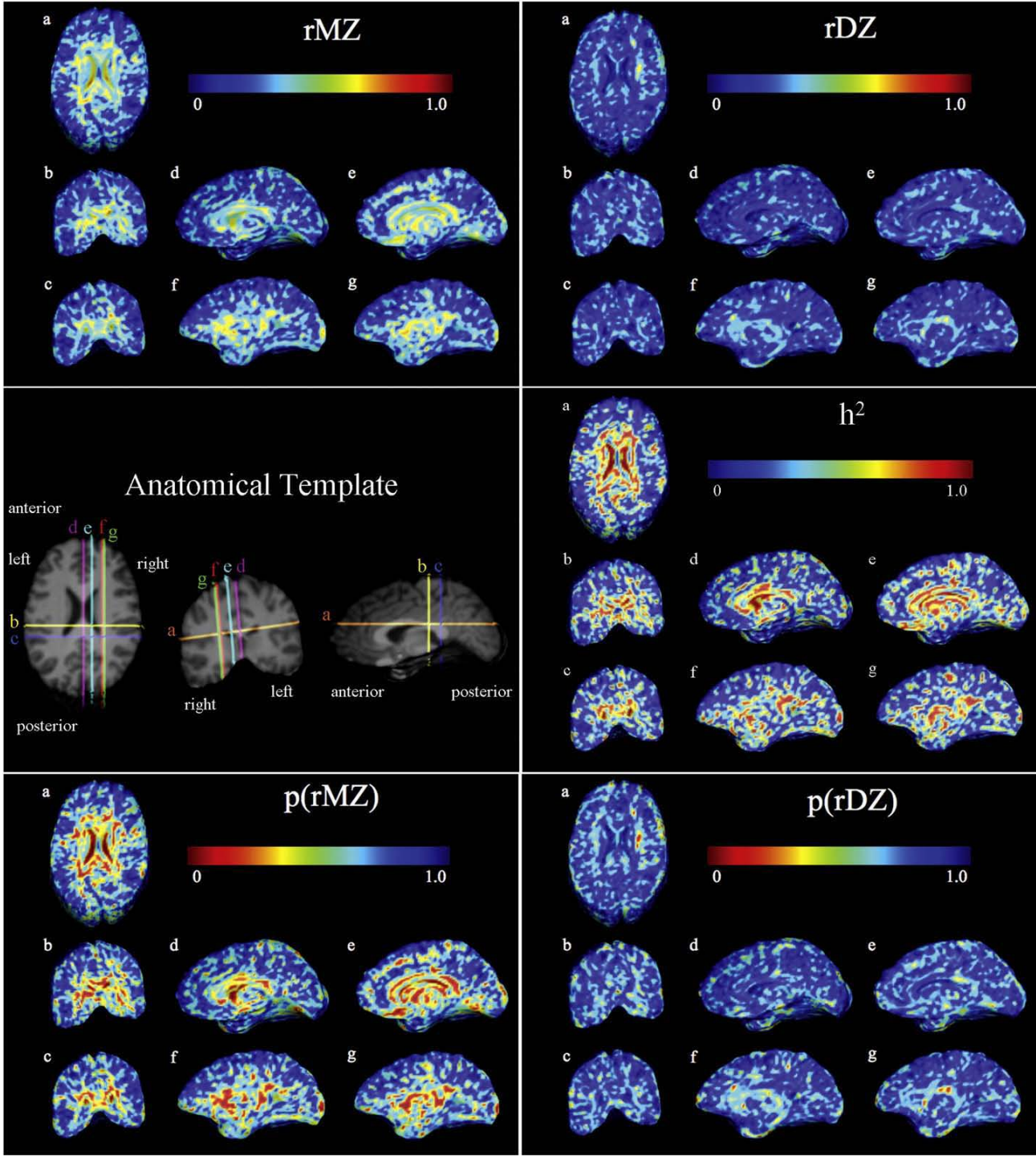
- High resolution anatomic scan
- 30-gradient DTI
- 105-gradient HARDI –DTI scan
- fMRI during rest
- fMRI during n-back task

To Date: ~1000 twins and sibs have been scanned

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

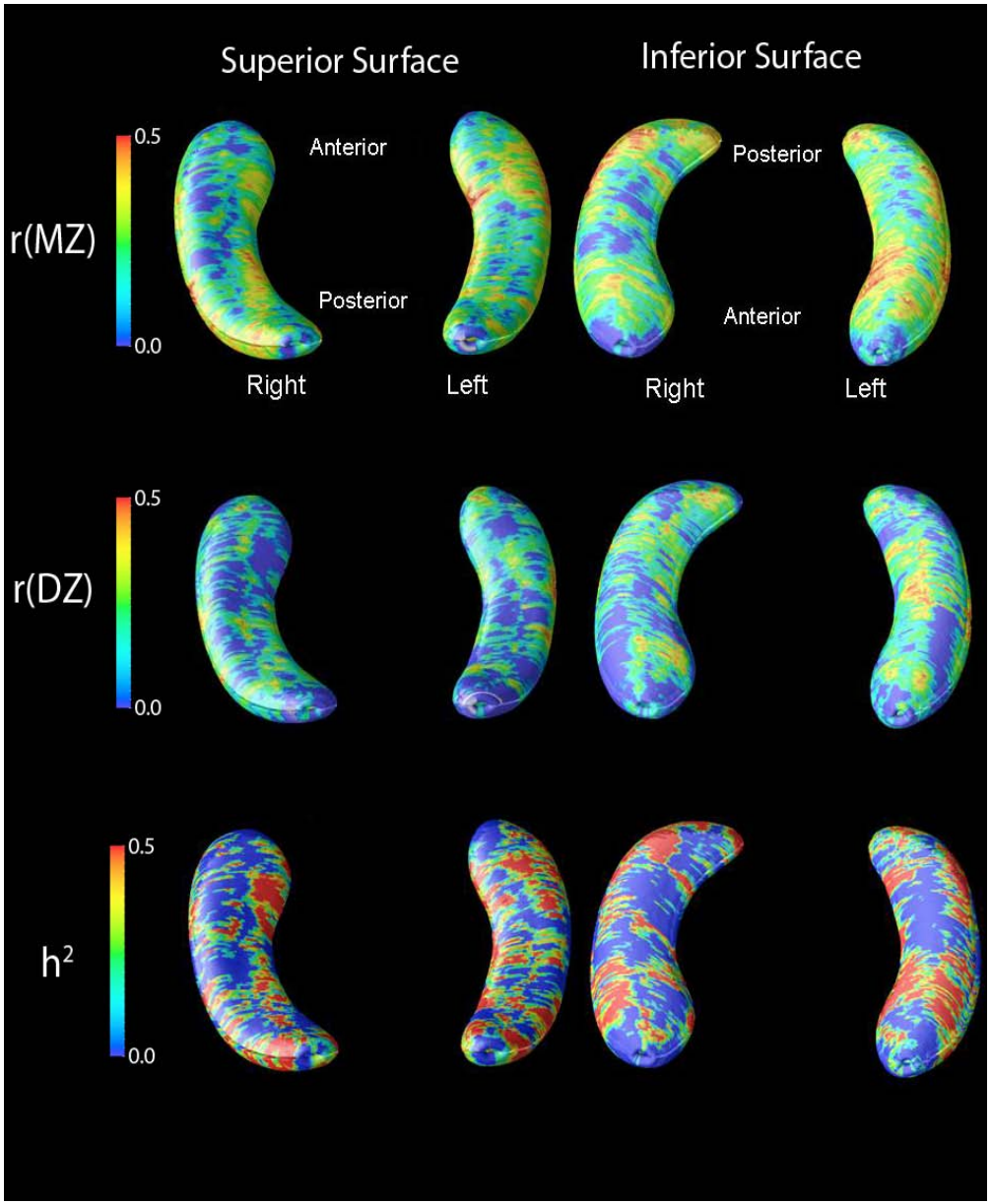


Neuroimage 48:37- 49, 2009

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)

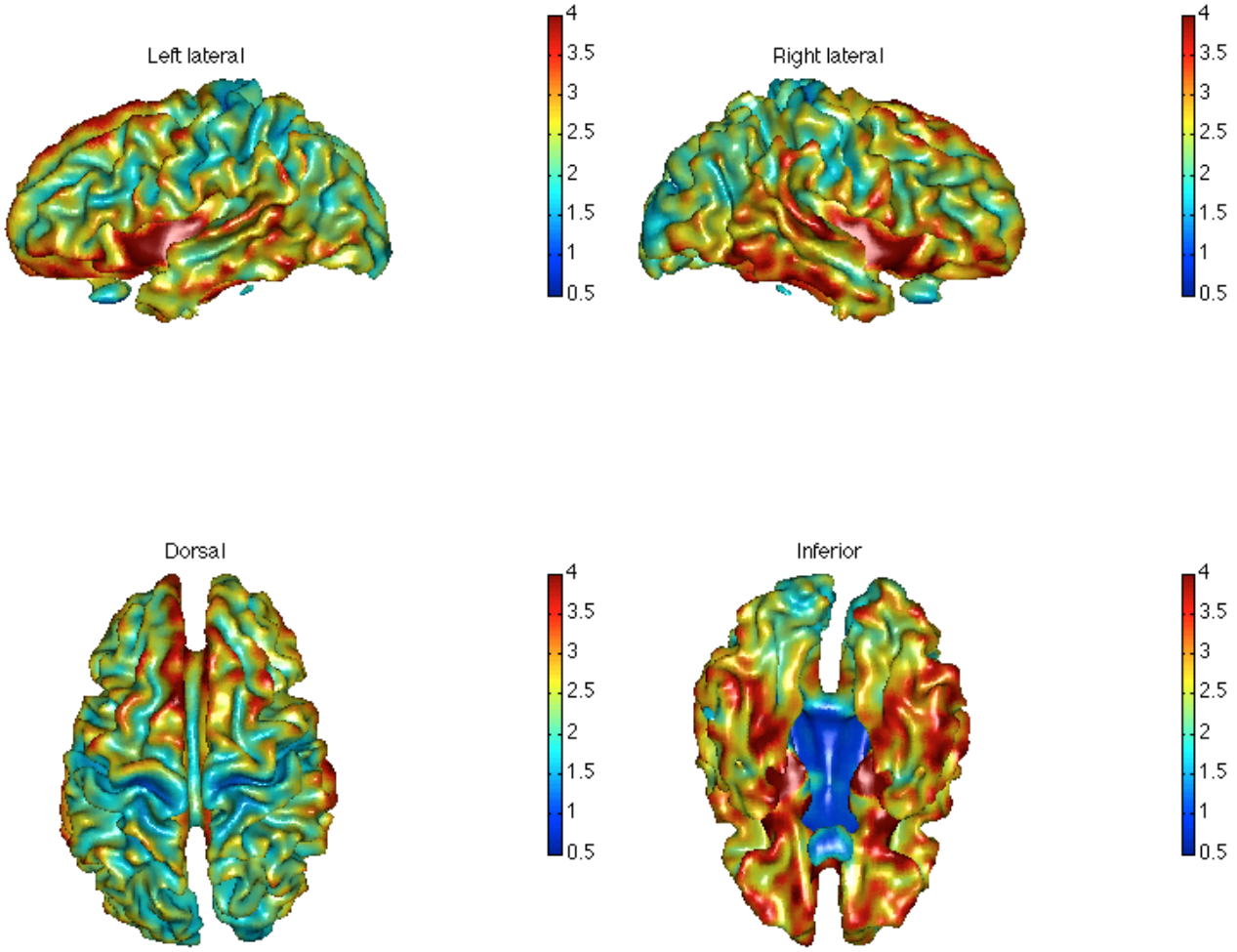


Heritability of cortical thickness (CT)

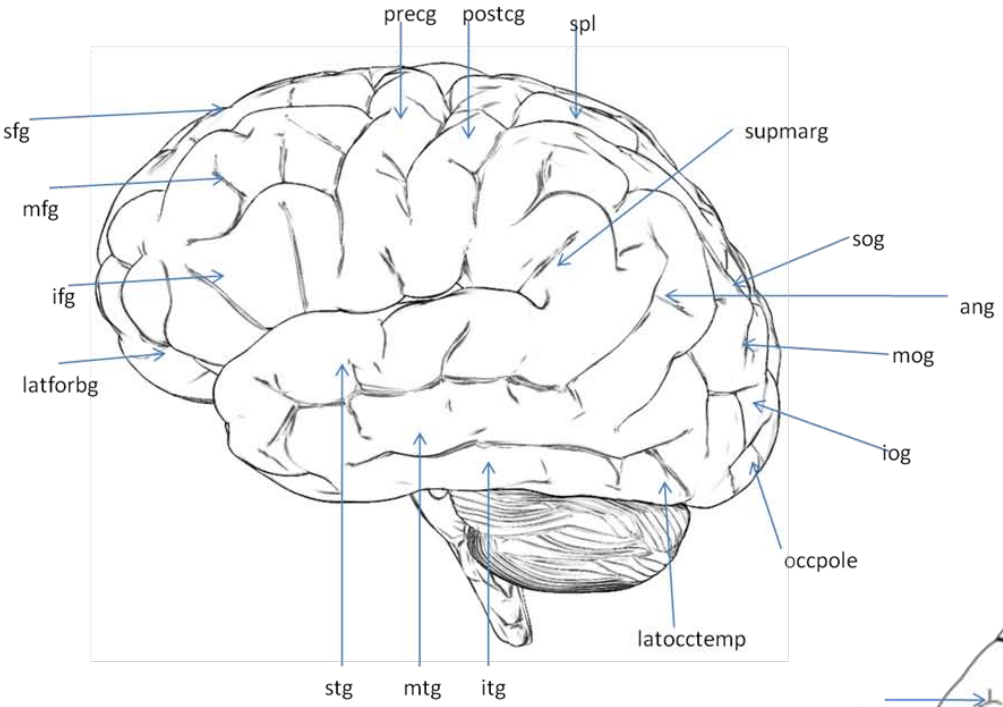
- Research has shown that patterns of cortical thinning is associated with diseases such as schizophrenia, bipolar, depression, and Alzheimer's. Although the brain is thought to be widely heritable, little is still known about the genetic underpinnings of the cerebral cortex and about which genes are likely to be involved.

- 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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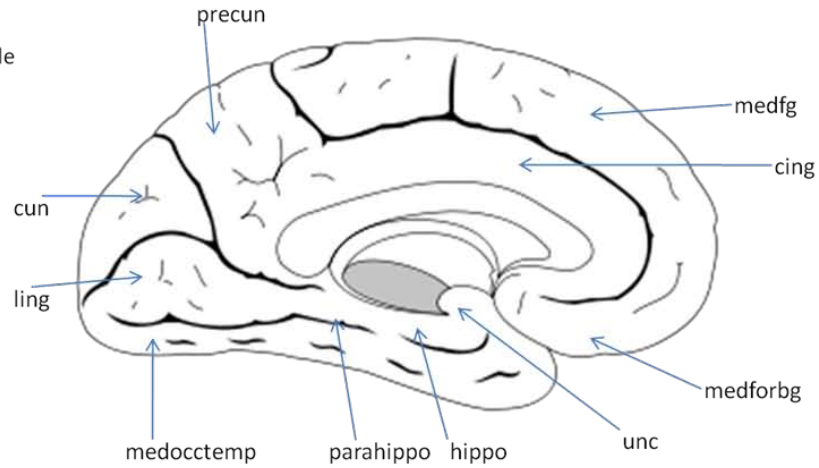
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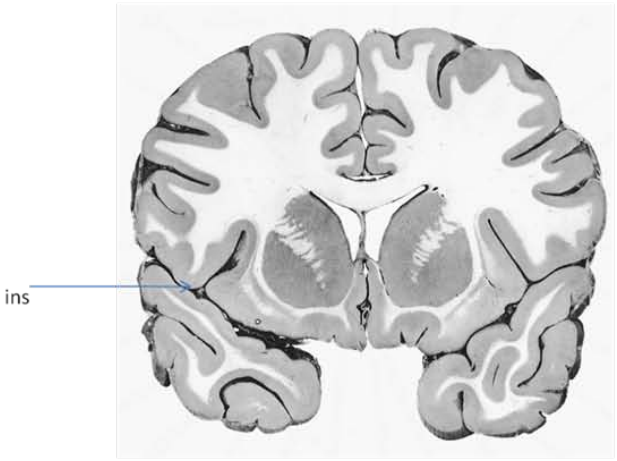
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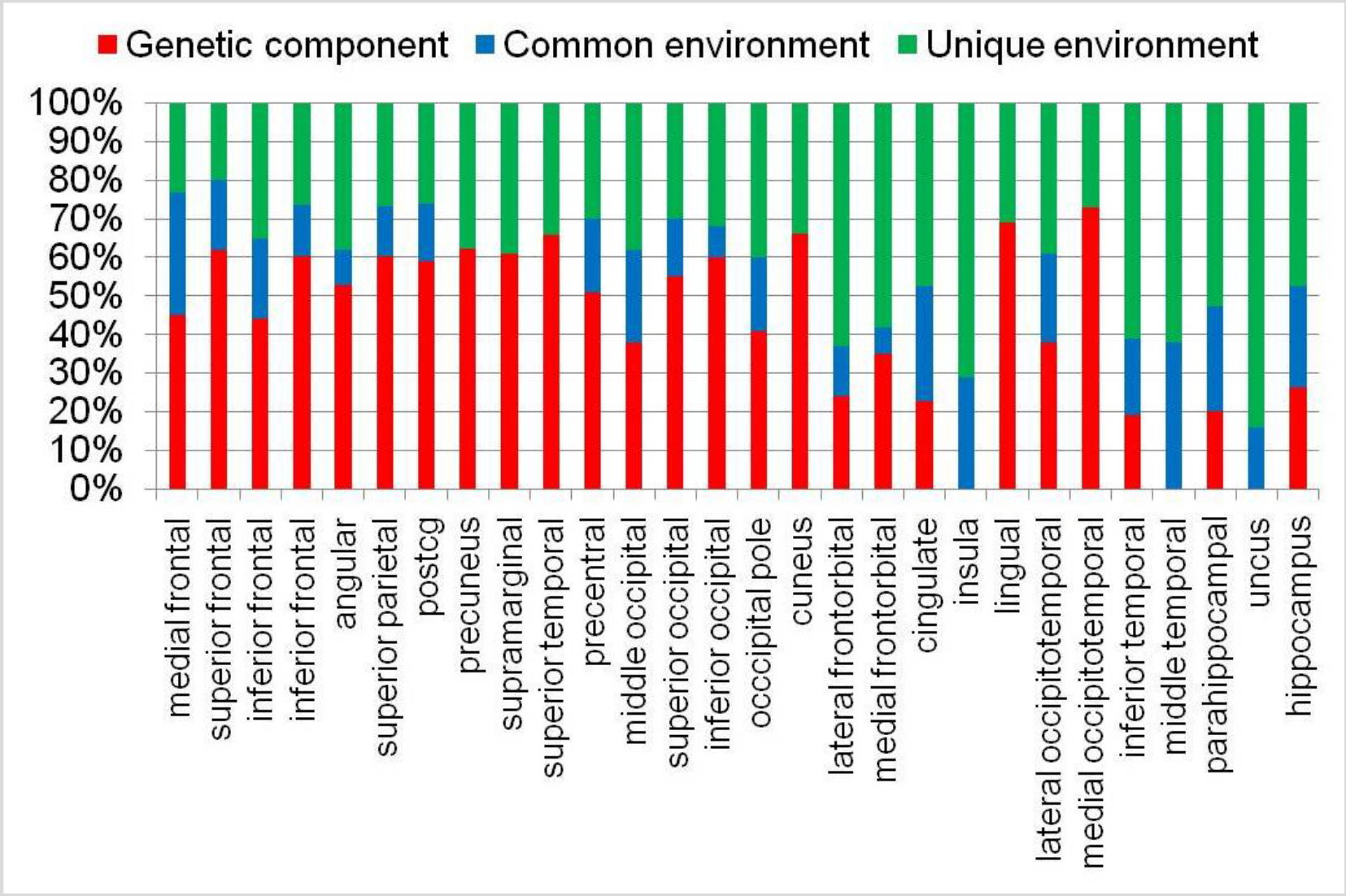
Variance components estimates on CT



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

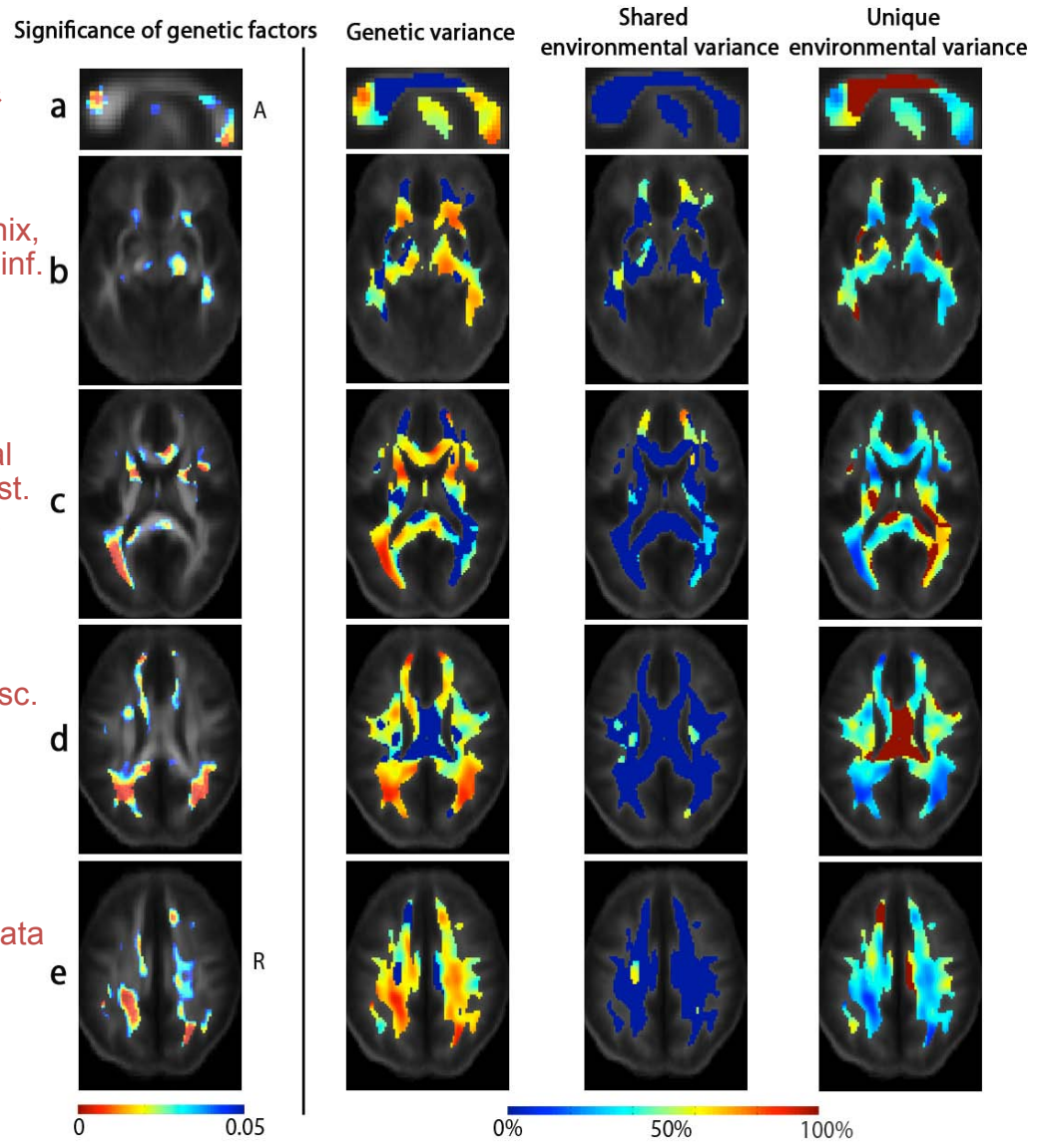
FA=0 – isotropic - in areas where water diffuses freely

FA=1 – anisotropic- in highly myelinated WM fibres

Genetic Influences on White Matter Integrity (FA)

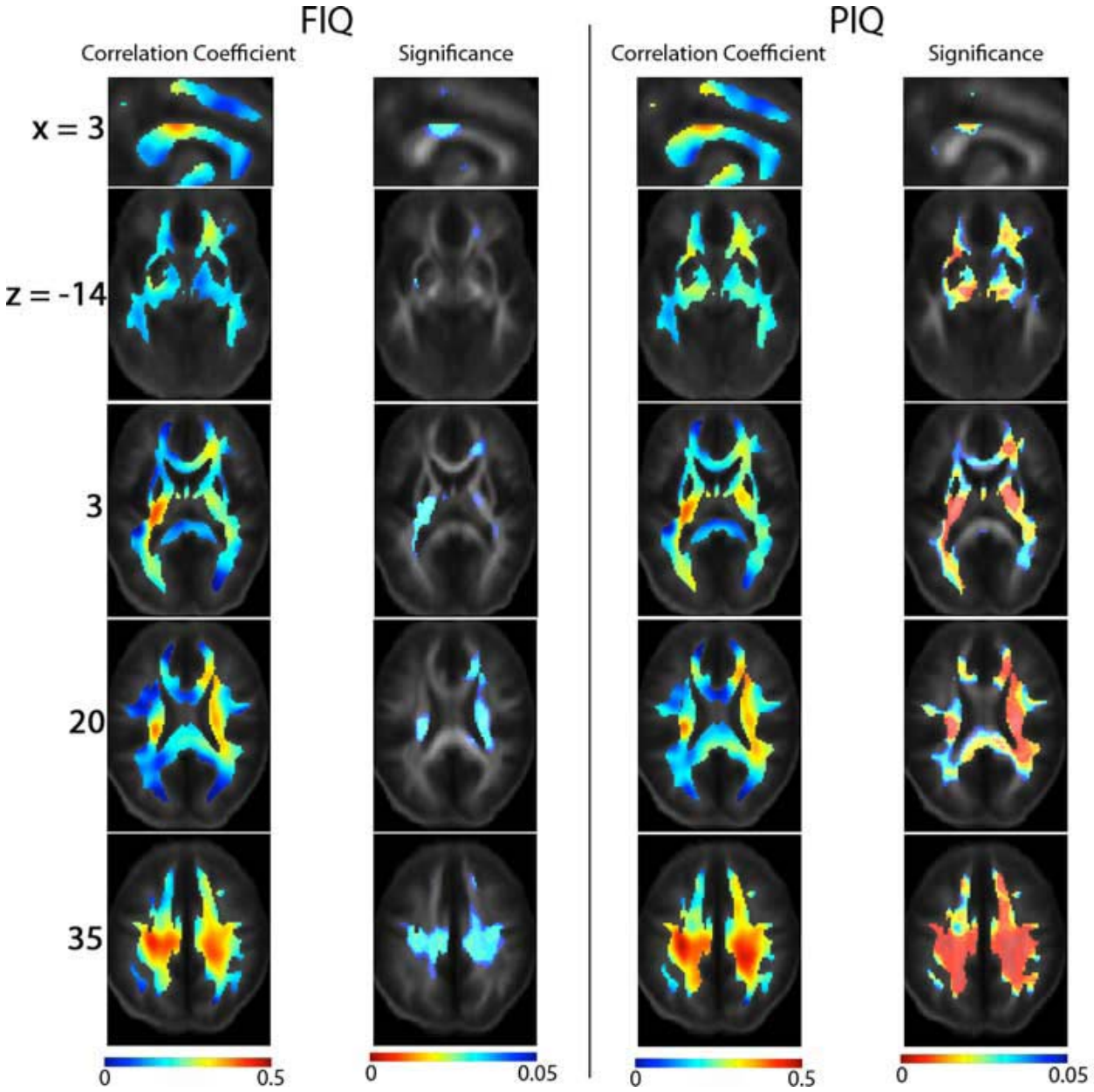
- 23 MZ & 23 DZ pairs
- strong genetic influence in all posterior white matter regions (first column)
- genetic factors explain 75 - 90% of the variance in FA in almost all white matter regions (second column).

Chiang et al. 2009 J Neurosci. 29: 2212-24



White matter integrity correlated with IQ

- correlated with PIQ
- r = 0.3 - 0.4



Chiang et al. 2009

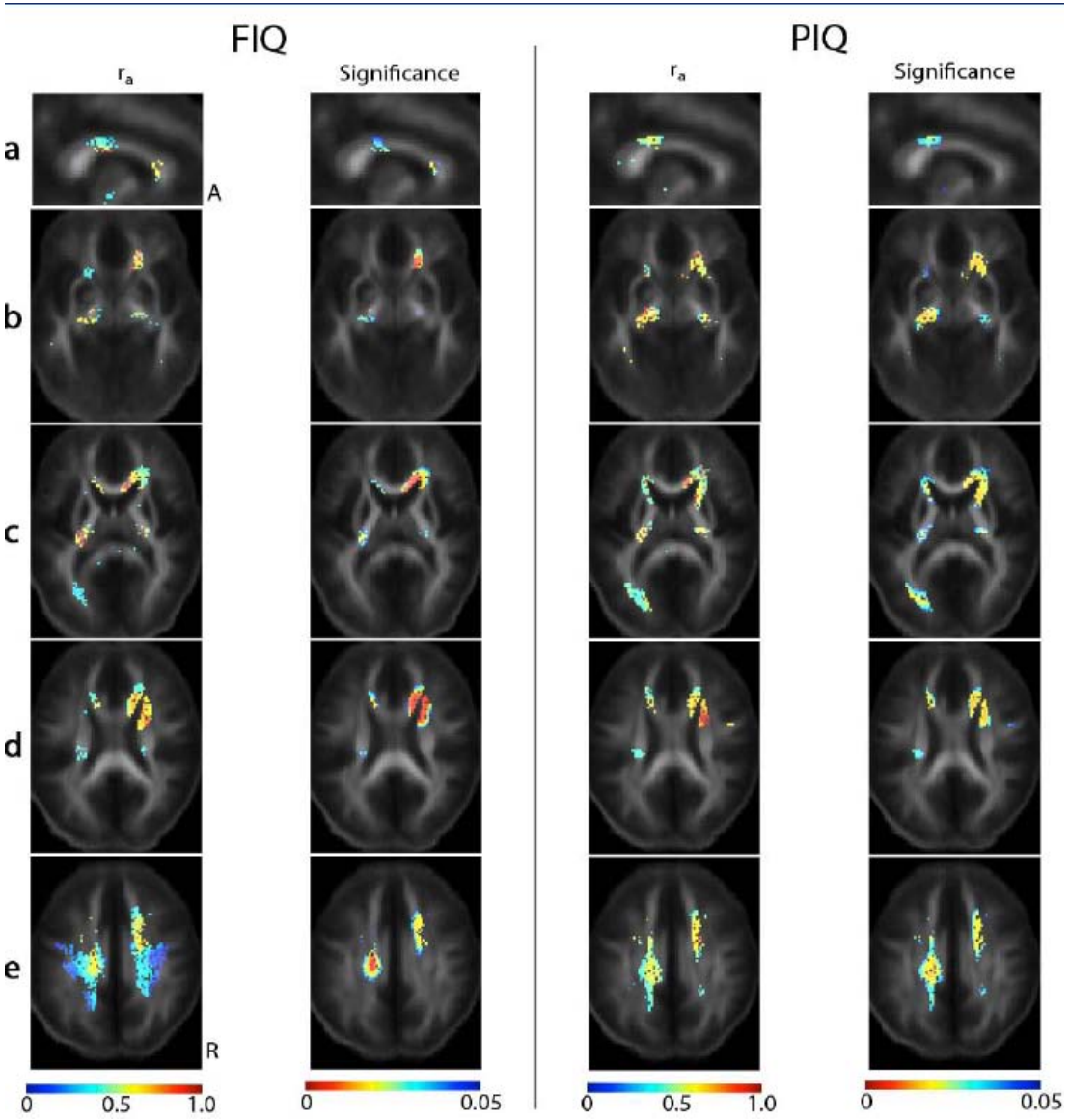
J Neurosci. 29: 2212-24

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



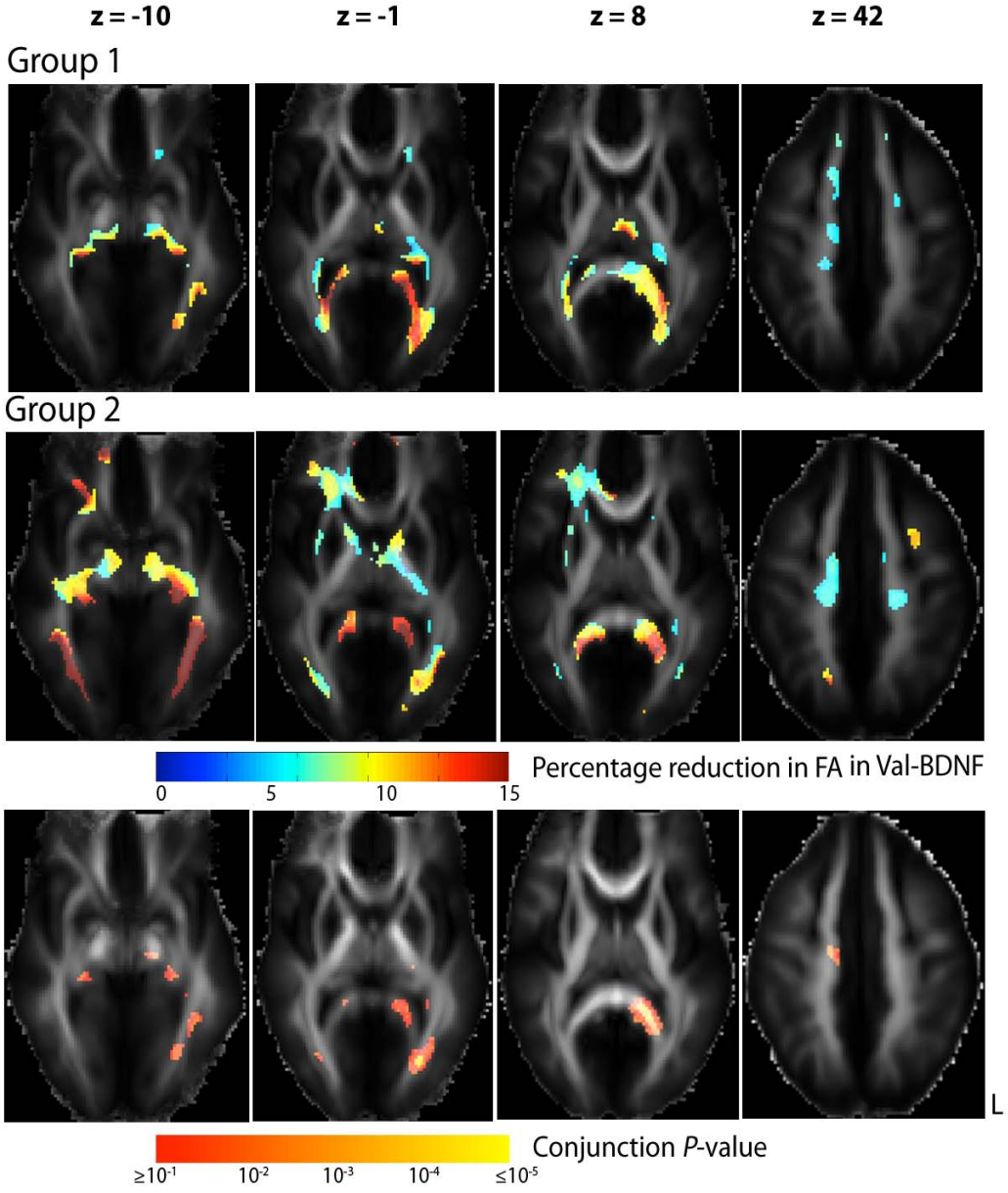
BDNF Val66Met polymorphism effects on white matter

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



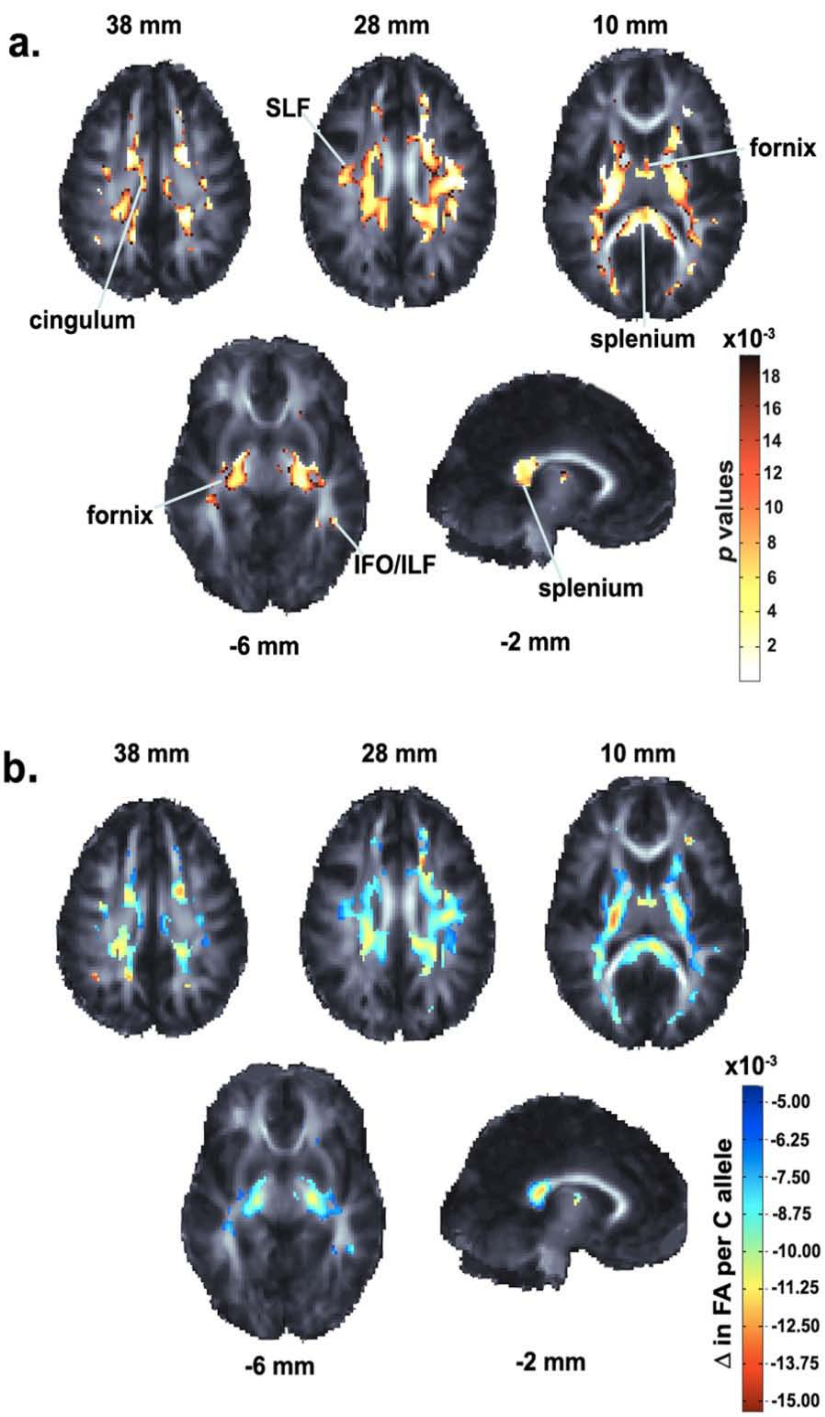
Clusterin (CLU-C) variant is associated with lower white matter integrity (FA)

N =325 (23.5 ± 2.1 years)

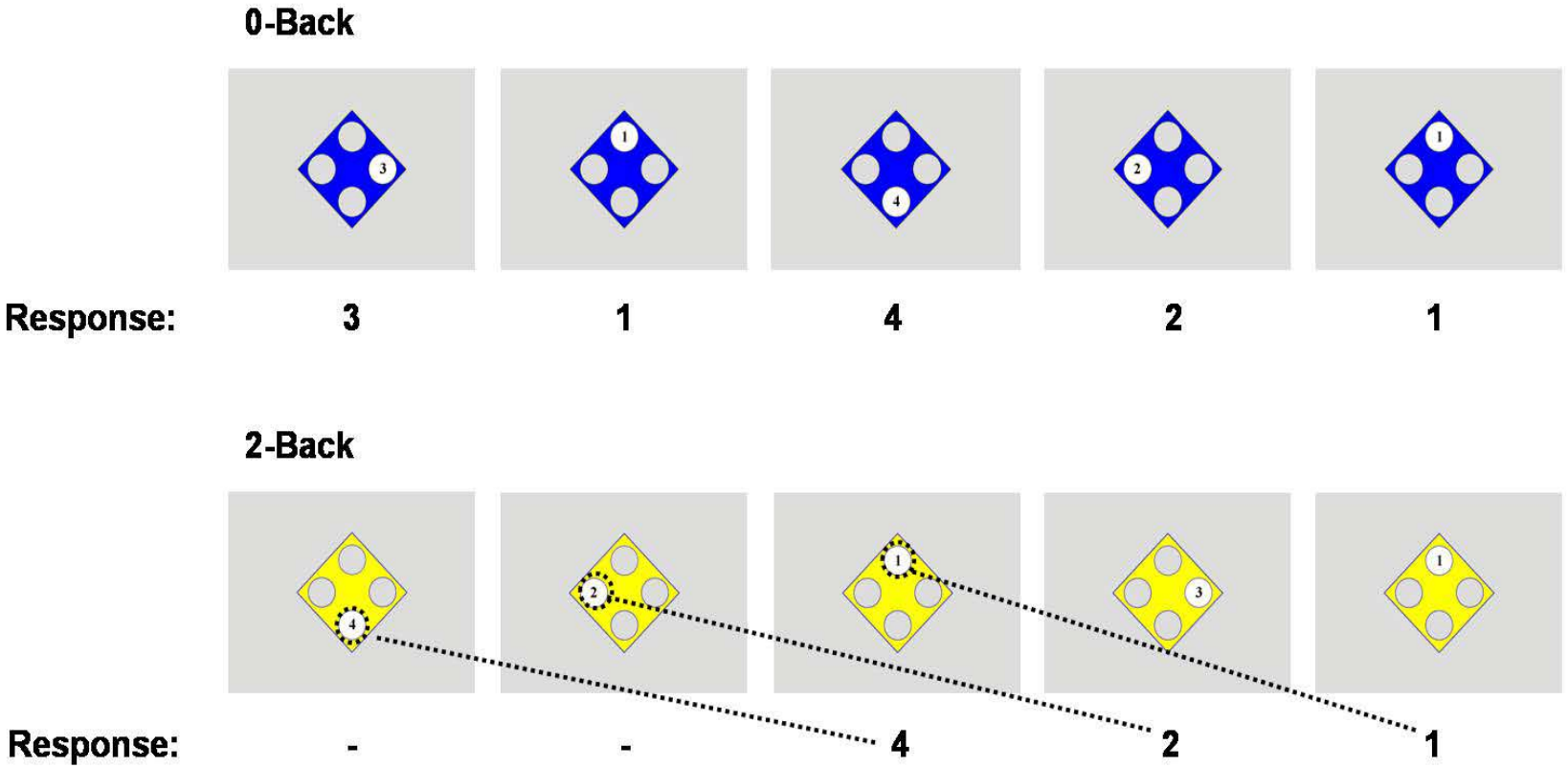
- *CLU*-C increases the lifetime risk for AD ~16%
- approx. 88% of Caucasians carry one copy

Young, healthy carriers of CLU-C show a distinct profile of lower FA in brain regions implicated in AD

Braskie et al. J Neurosci 2011



BOLD fMRI during *n*-back working memory task

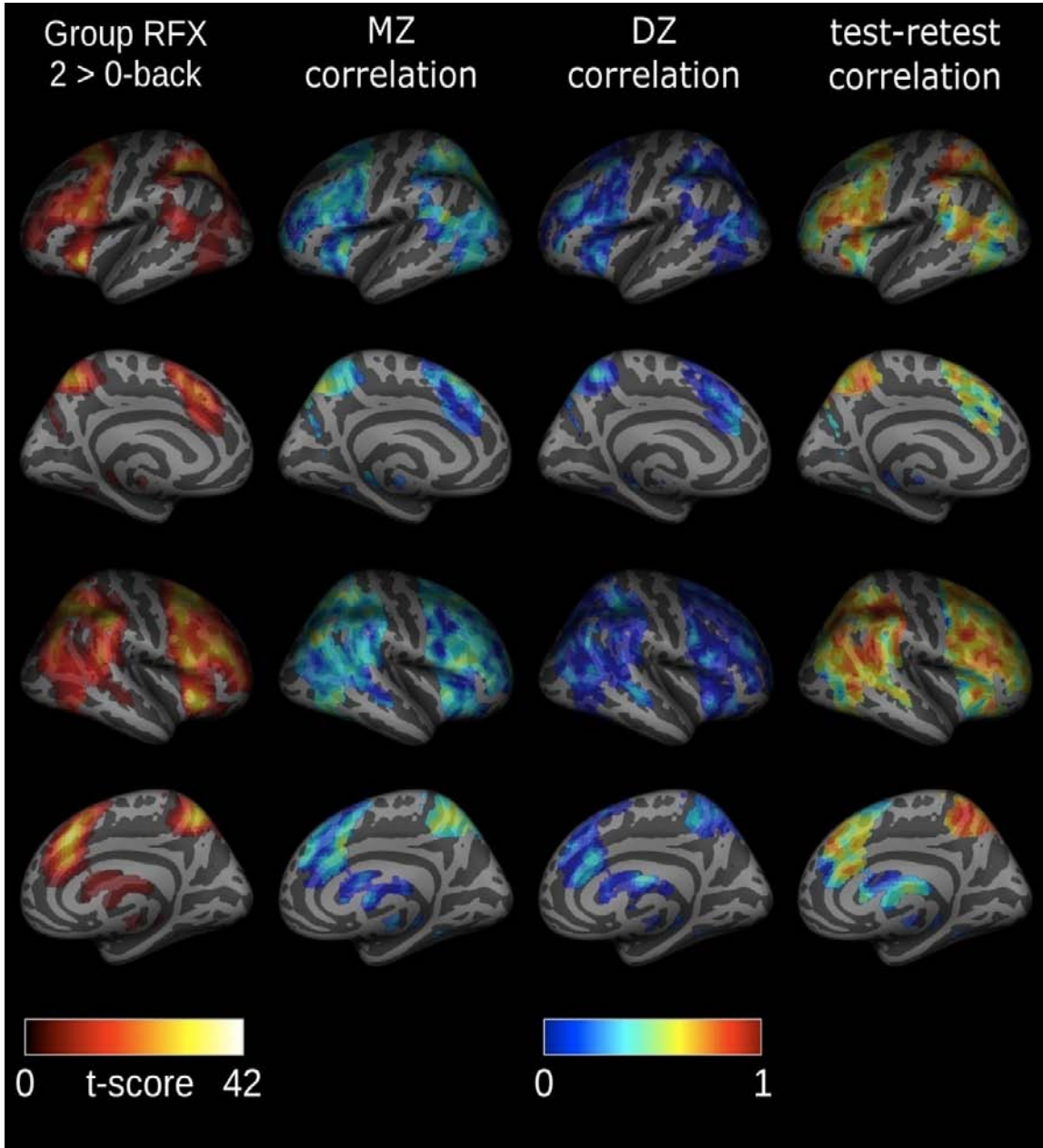


fMRI during **working memory**

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

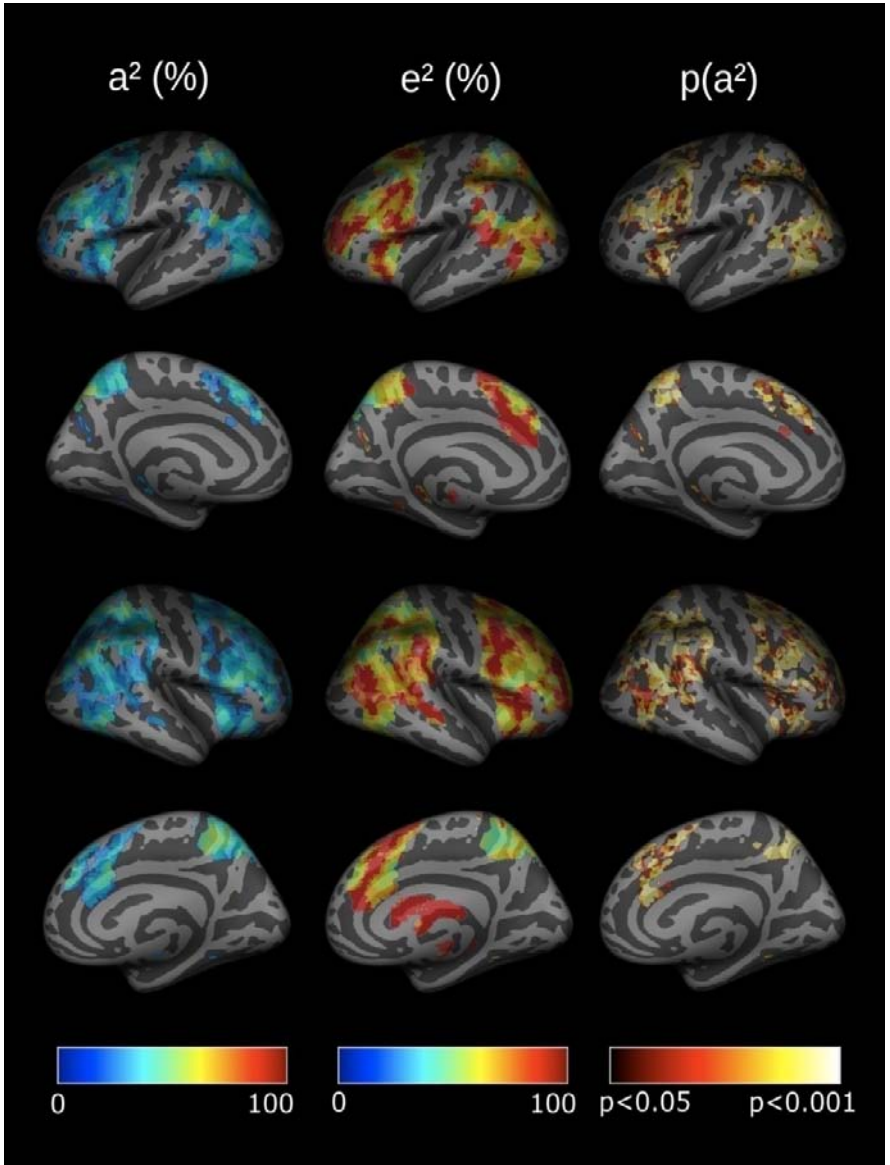


Maps showing genetic influences on brain activation during working memory

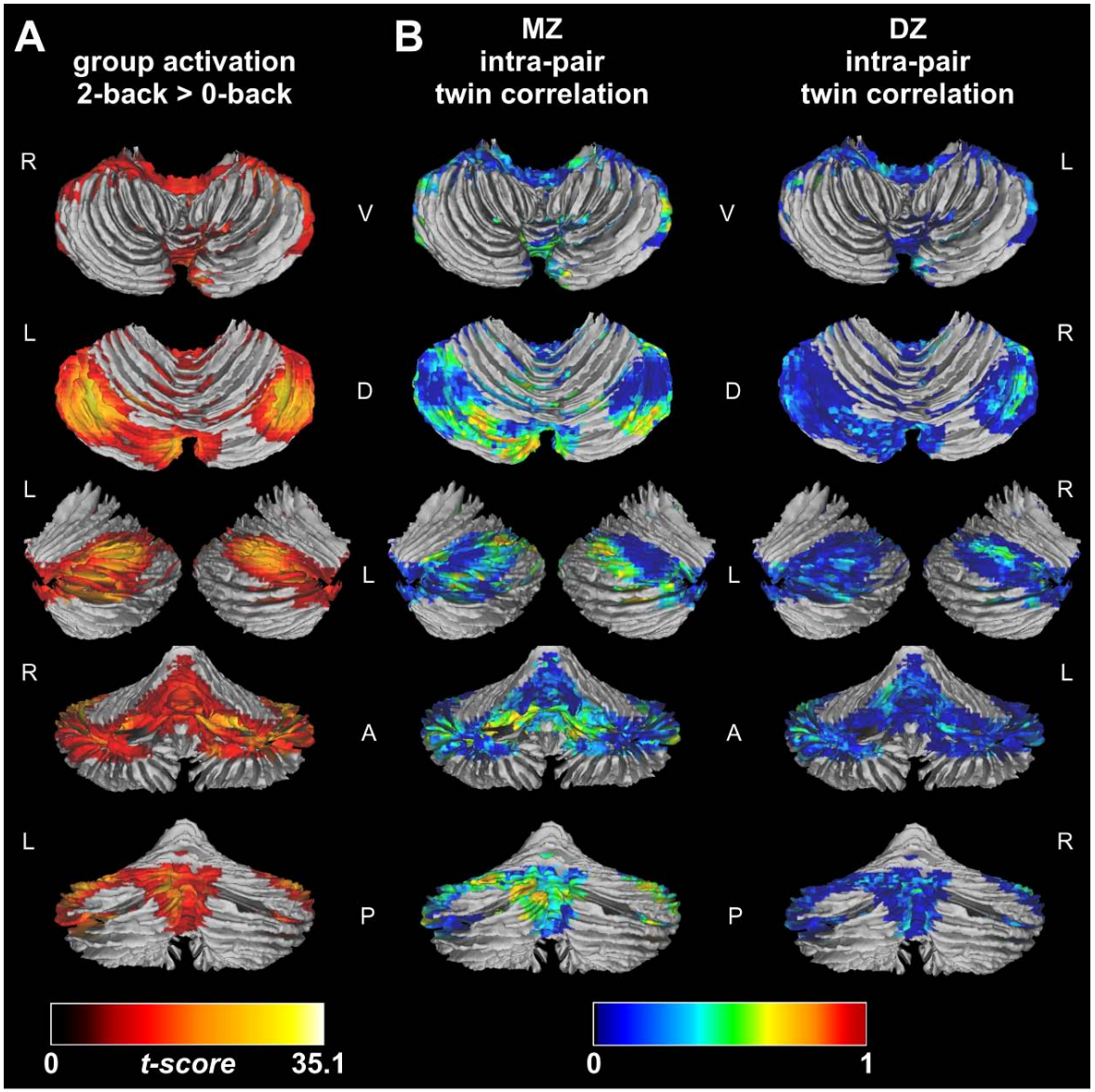
- significant genetic influences on WM related brain activation, especially in frontal and parietal brain regions

- 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)



Cerebellar group activation maps and twin correlations.



GWAS of brain volumes (ADNI sample)

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

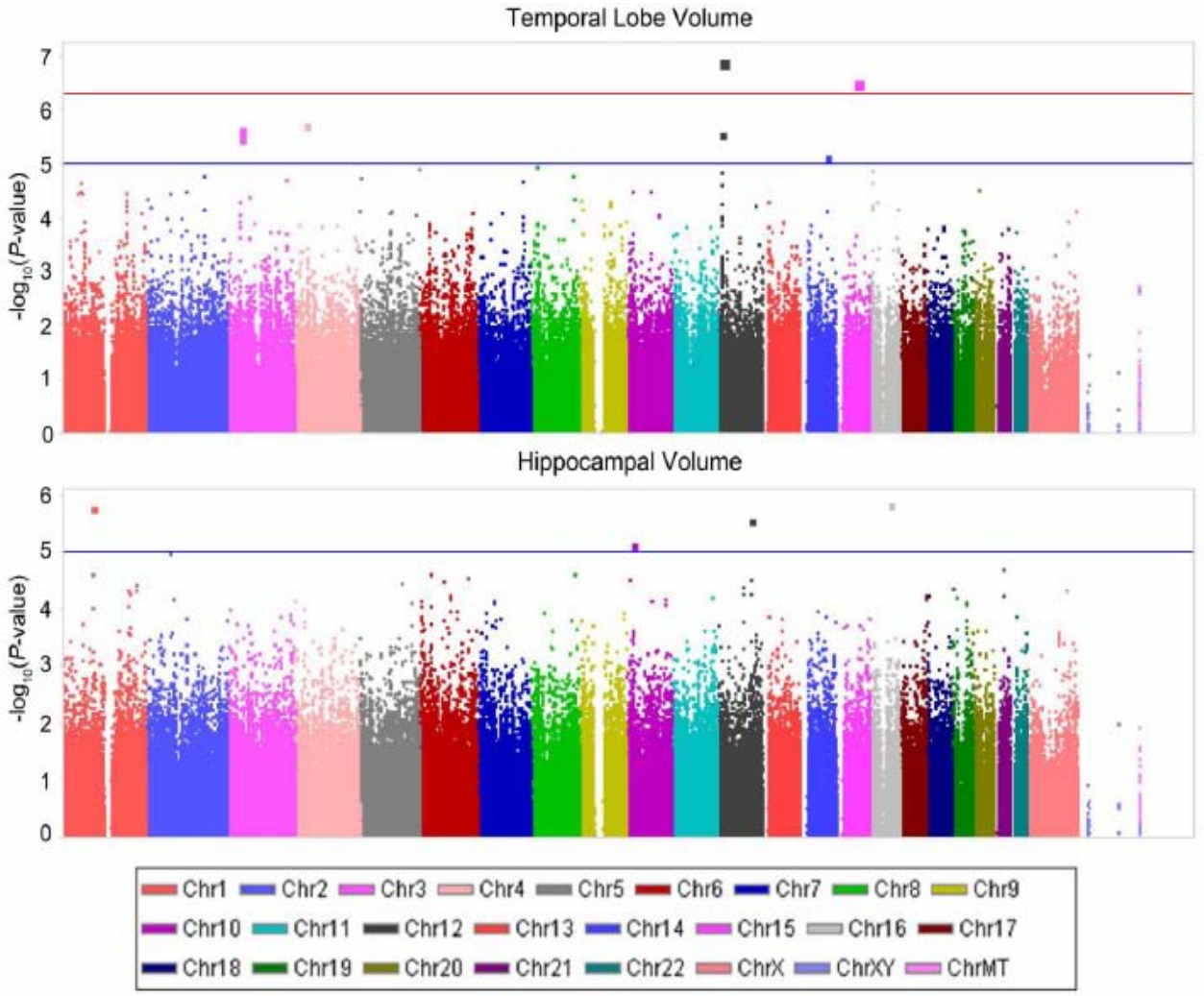
N = 742 (temporal)
N = 698 (hippo)

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

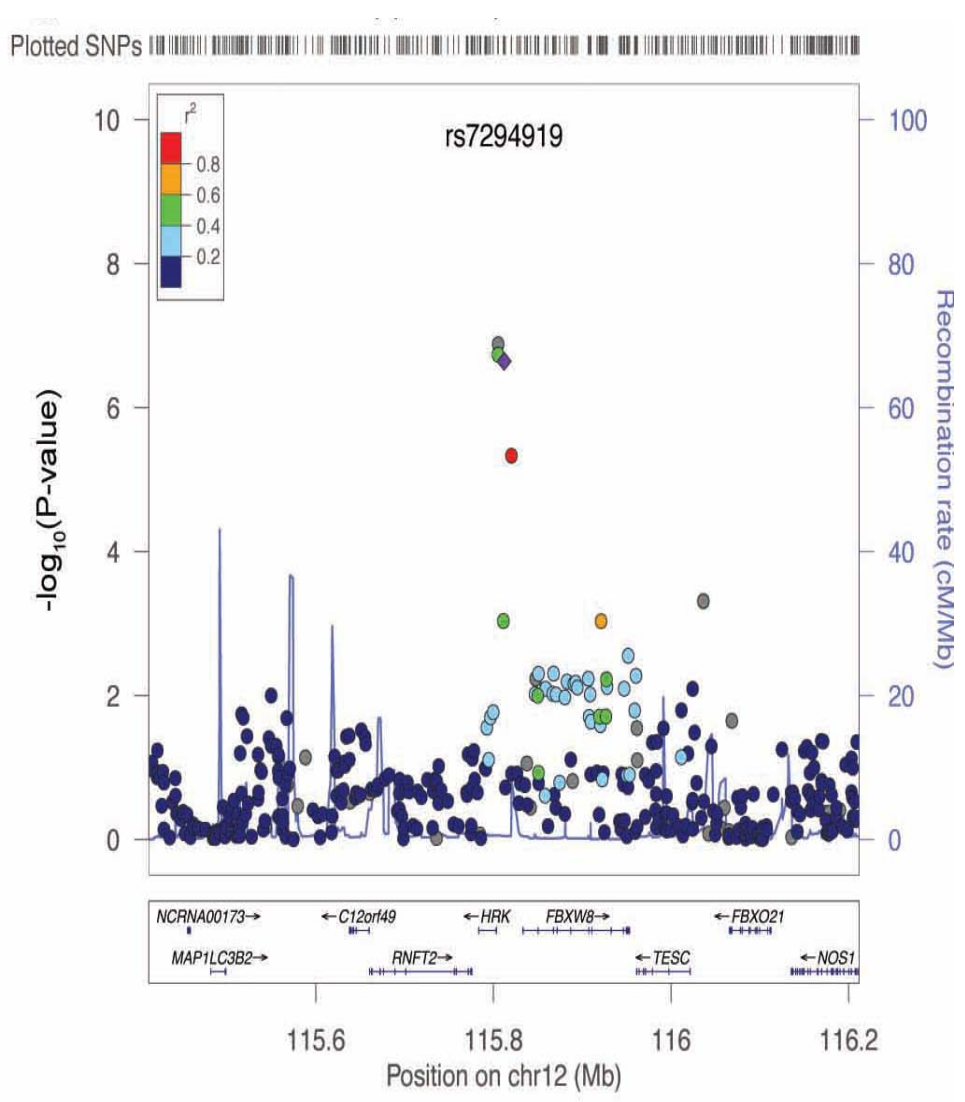


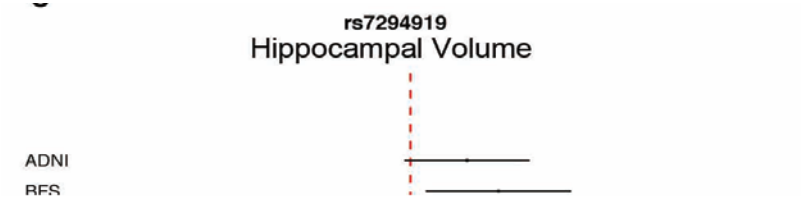
Stein et al. Neuroimage, 2010

ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis)

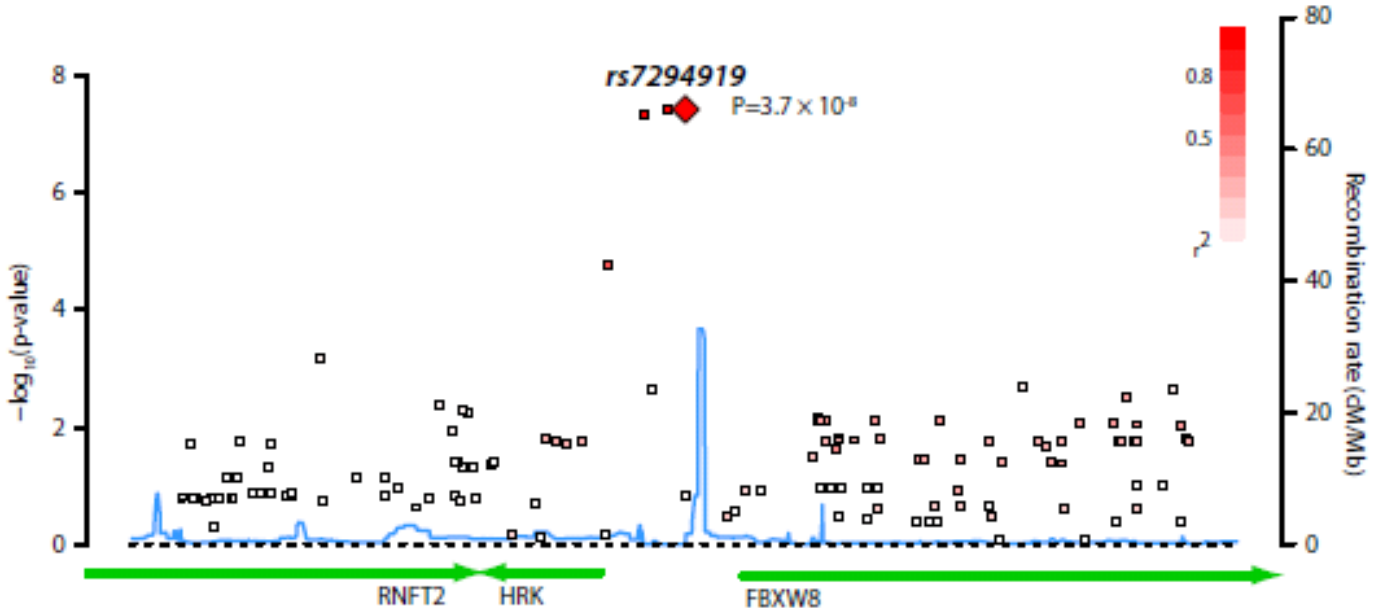
- ENIGMA consortium founded Dec 2009
- Proof-of-principle project – conduct GWAS MA of Hippocampal, Intra-cranial & Total brain volumes
- Developed imaging & genetics protocols
- 28 contributing sites
  - Including 5 research networks
- Whole life-span data
- Case/control & population

ENIGMA GWAS meta-analysis for hippocampal volume (*N*=7,795)

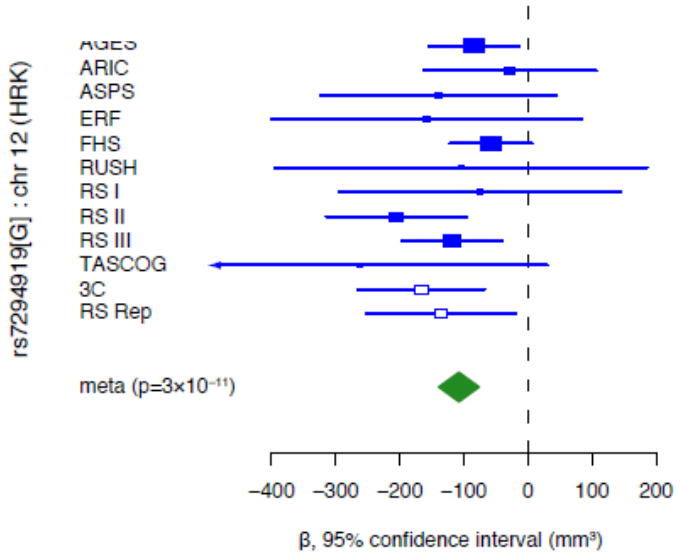




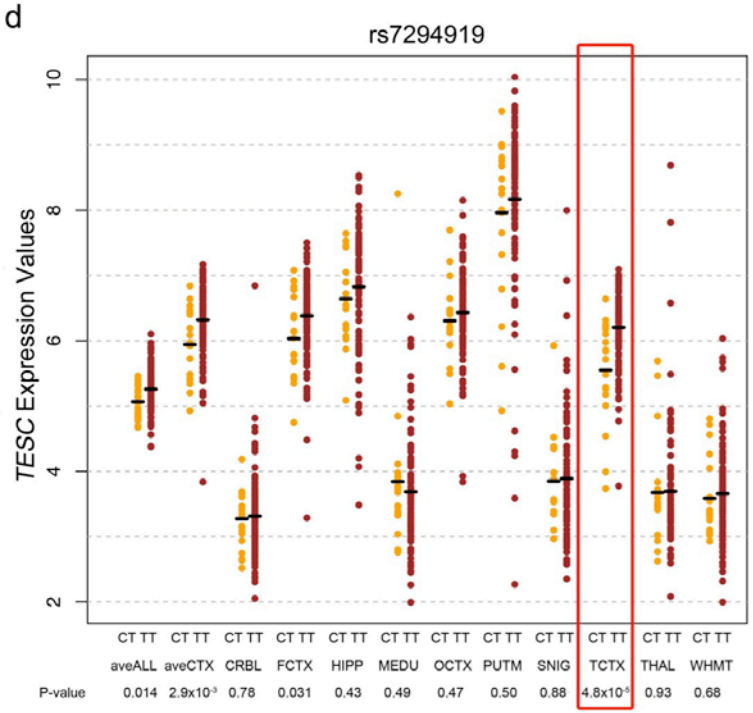
Chromosome 12 (HRK)



Top hit for hippocampal volume replicated in CHARGE

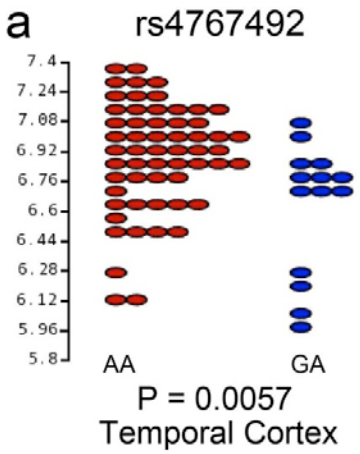


- Complementary focus on functional studies to improve our understanding of the effects being identified

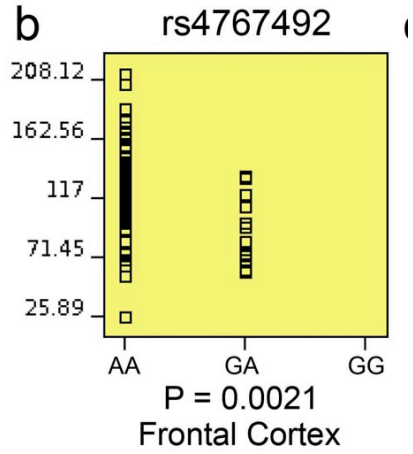


UK Brain Expression Database

Proxy SNP



UCL Epilepsy Cohort



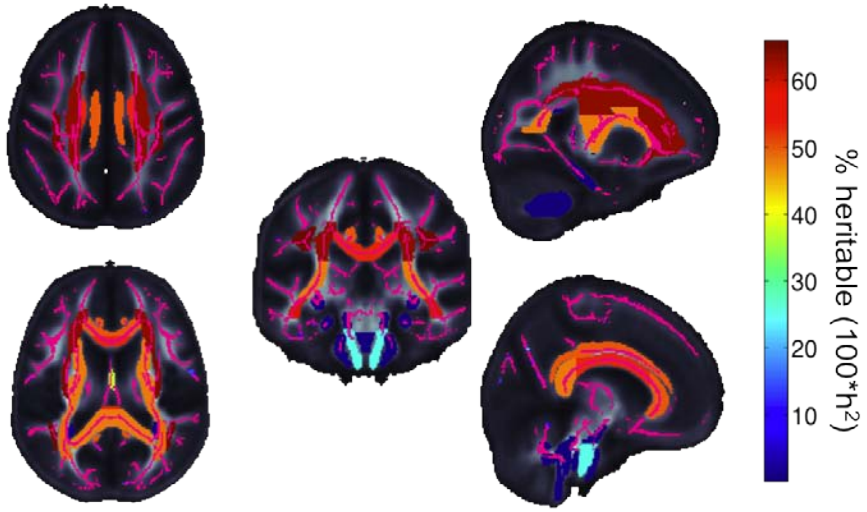
SNPExpress Database

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 – DTI working group

- Leaders: Neda Jahanshad & Peter Kochunov
- Major protocol development effort
- Proof-of-principle paper examining heritability of the extracted phenotypes



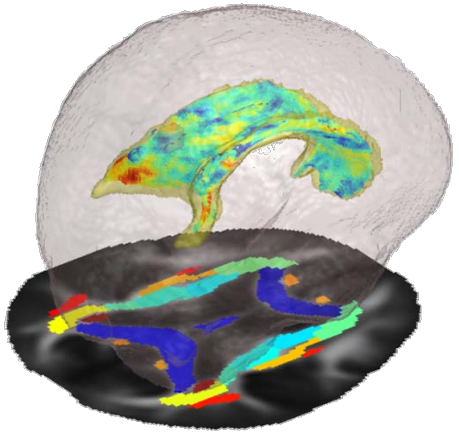
Neuroimage. 2013 Apr 28. pii: S1053-8119(13)00408-4. doi: 10.1016/j.neuroimage.2013.04.061. [Epub ahead of print]

Multi-site genetic analysis of diffusion images and voxelwise heritability analysis: A pilot project of the ENIGMA-DTI working group.

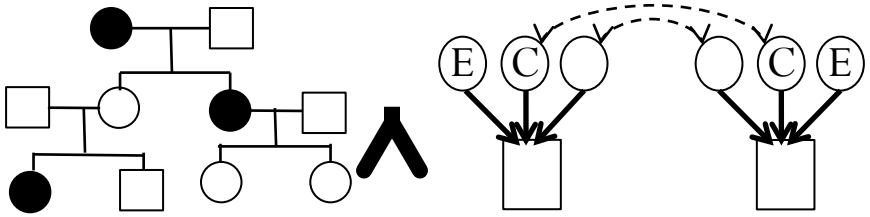
Jahanshad N, Kochunov P, Sprooten E, Mandl RC, Nichols TE, Almassy L, Blangero J, Brouwer RM, Curran JE, de Zubicaray GI, Duggirala R, Fox PT, Hong LE, Landman BA, Martin NG, McMahon KL, Medland SE, Mitchell BD, Olvera RL, Peterson CP, Starr JM, Sussmann JE, Toga AW, Wardlaw JM, Wright MJ, Hulshoff Pol HE, Bastin ME, McIntosh AM, Deary IJ, Thompson PM, Glahn DC.

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



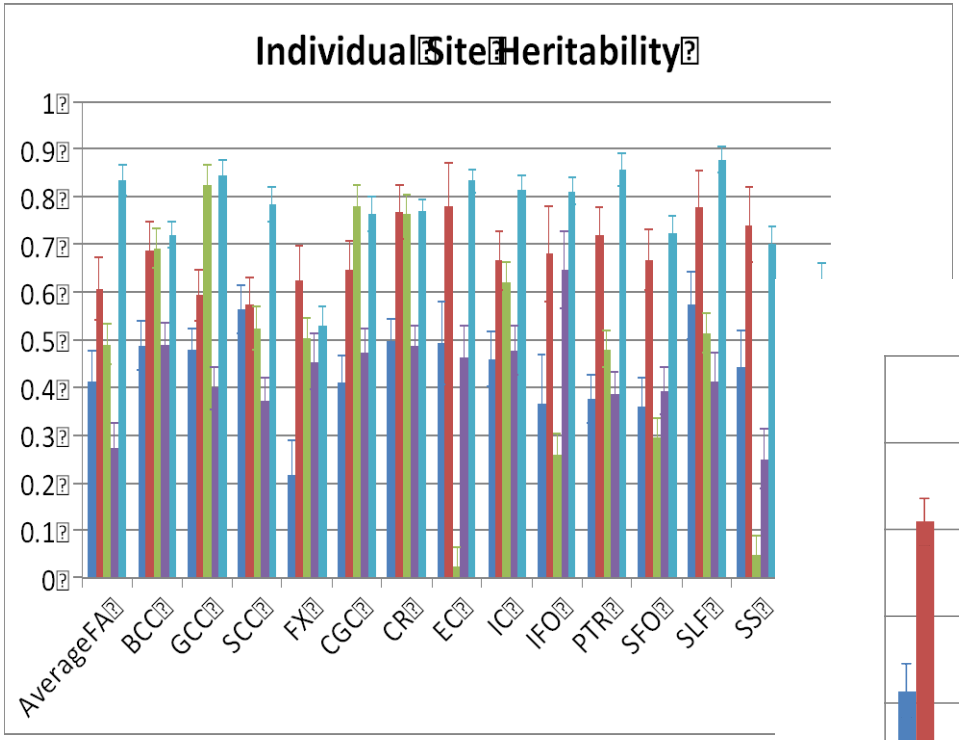
1. Multi-site heritability analysis
   - Are heritability measures stable and reliable across cohorts in regions
   - If not, then they are not good targets for multi-site GWAS-MA



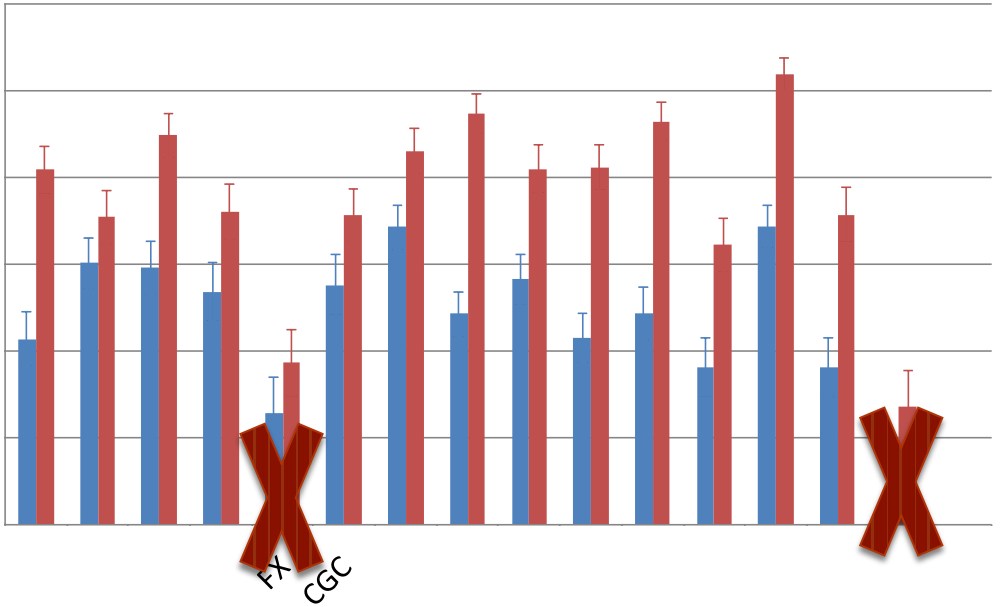
Jahanshad & Kochunov et al, NIMG 2013

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)



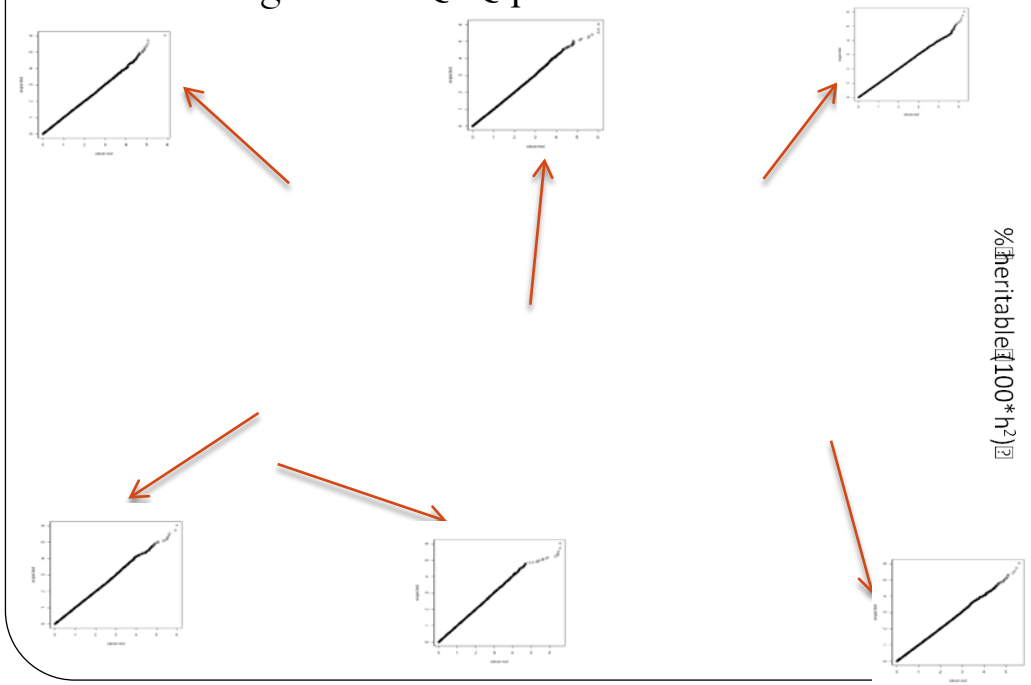
- Compare 2 meta-analysis approaches
  - Weight by N and SE
- 13/15 regions found to be highly reliable and heritable in all cohorts



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

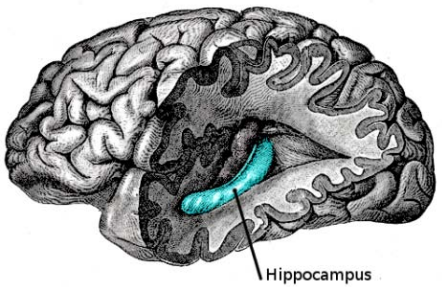
http://enigma.ini.usc.edu/ongoing/dti-working-group/

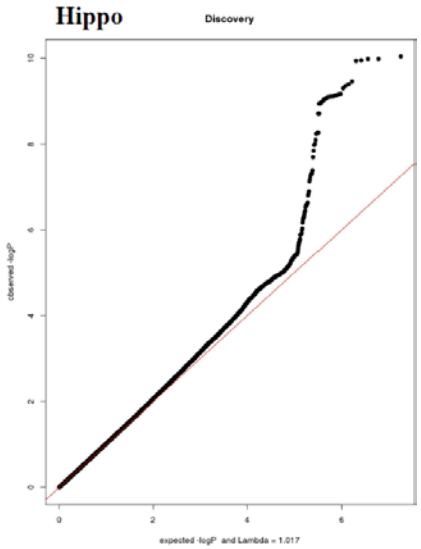
ENIGMA2 core analyses…

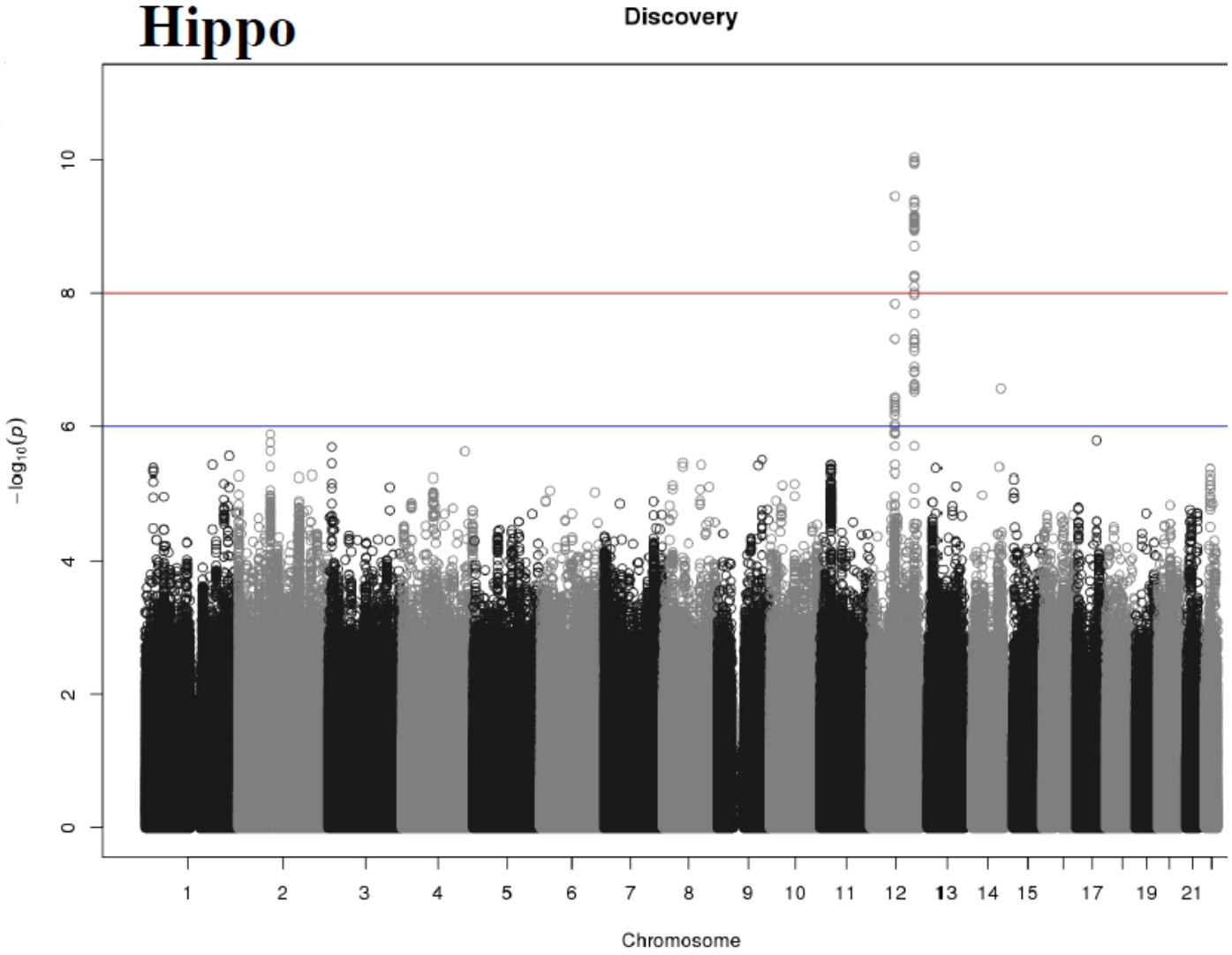
- Discovery sample
  - N= 11,740; Cohorts=22
  - Phenotypic distributions uploaded and checked
  - Cohort level QQ & Manhattans produced and examined
  - Data freeze recently established

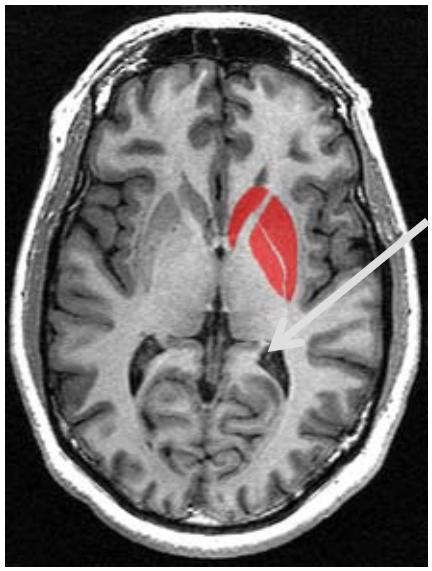
- Anticipated replication + Discovery
  - N= 16,500; Cohorts=32

ENIGMA2 preliminary results: Hippocampus

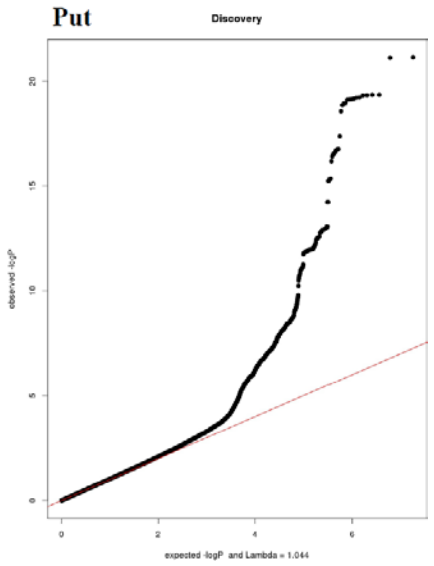


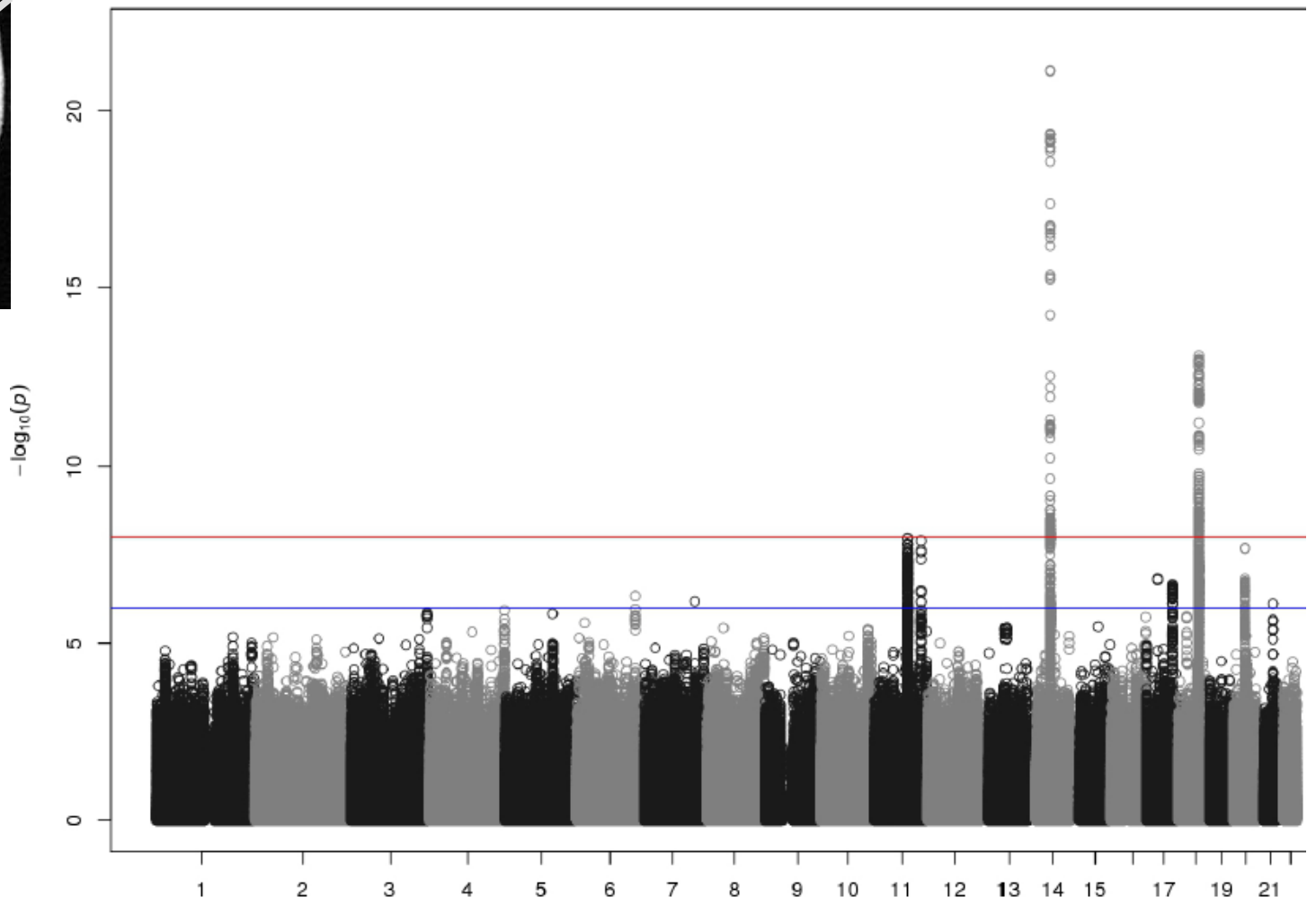






ENIGMA2 preliminary results: Putamen

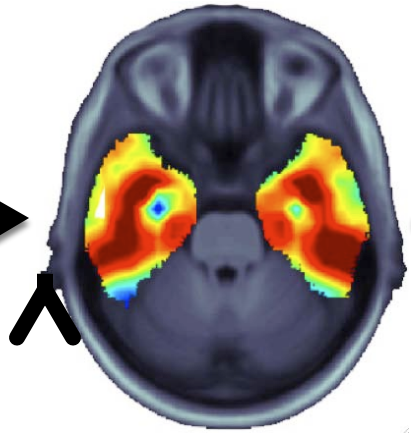


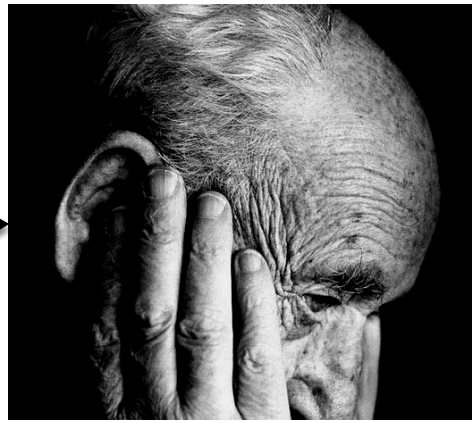


ENIGMA2-PGC2-SZ Collaboration:
Do genetic variants which create risk for changes in brain structure also create risk for schizophrenia?

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

Analysis ongoing!





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

			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					0.01		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 ?

Thanks to...

The ENIGMA Consortium: Large-scale Collaborative Analyses of Neuroimaging and Genetic Data. (ENIGMA1 and ENIGMA2 Support Groups) Paul M. Thompson1a,2a, Jason L. Stein1a,3a, Sarah E. Medland4a, Alejandro Arias Vasquez5a,6a, Derrek P. Hibar1a, Miguel Renteria4a,7a, Roberto Toro8a,9a,10a, Gunter Schumann11a, Barbara Franke5a,6a, Margaret J. Wright4a, Nicholas G. Martin4a **ENIGMA PIs and their Teams** Derrek P. Hibar1, Miguel E. Renteria2, Sarah E. Medland2,3,4, Alejandro Arias Vasquez5,6, Roberto Toro7,8,9, Jason L. Stein1, Neda Jahanshad1, Anderson M. Winkler10,11,12, Katharina Wittfeld13, Christopher R. K. Ching1, Ingrid Agartz14,15, Saud Alhusaini16, Laura Almasy17, Nancy C. Andreasen18, Ole A. Andreassen14, Liana G. Apostolova19, Katja Appel13, Nicola J. Armstrong20,21, Benjamin Aribisala22,23,24, Mark E. Bastin22,23,24,25, Ørjan Bergmann14, Elisabeth B. Binder26, John Blangero17, Jeremy Bockholt27, Dorret I. Boomsma28, Janita Bralten5,29, Rachel M. Brouwer30, Han G. 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Toga1, Diana Tordesillas-Gutierrez48,49, Daniah Trabzuni67, Jessica Turner27, Martijn Van den Heuvel30, Nic J. van der Wee99, Kristel van Eijk112, Theo G.M. van Erp82, Neeltje E.M. Van Haren30, Dennis van 't Ent28, Marie-Jose van Tol113,99, Maria C. Valdés Hernández22,23,24, Dick J. Veltman89, Henry Völzke114, Robert Walker110, Henrik Walter57,115, Joanna M. Wardlaw22,23,24, Michael E. Weale101, Michael W. Weiner116,117, Wei Wen83,102, Lars T. Westlye14,58, Christopher D. Whelan16, Tonya White118, Christiane Wolf26, Marcel P. Zwiers6,119, Manon Bernard89**, Marc Bohlken30**, Stefan Brauns55**, David G. Brohawn78, Andrew A. Brown14,120**, Aiden Corvin54**, Anders M. Dale121,122**, Norman Delanty16,123**, Wayne C. Drevets124,103**, Jesen Fagerness33, Iryna Fedko28**, Nelson B. Freimer39**, Michael Gill54**, Catharina Hartman125**, Wolfgang Hoffmann63**, Norbert Hosten68**, Deborah Janowitz13**, Mark Jenkinson126, Matthew P. Johnson17**, Ryota Kanai127**, Maria Keil65**, Jack W. 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Acknowledgements

*X*avier Castellanos (NYU)
Greig de Zubicaray (UQ)
Nick Martin (QIMR)
Katie McMahon (UQ)
Mike Milham (NYU)
Paul Thompson (UCLA)
Arthur Toga (UCLA)
Sarah Medland (QIMR – ENIGMA1/2)
Margie Wright (QIMR)

Radiographers, RAs, IT

***Thanks* to twins and sibs**

Gabriella Blokland (QIMR, UQ)
Meredith Braskie (UCLA)
Caroline Brun (UCLA)
Ming-Chan Chiang (UCLA)
Narelle Hansell (QIMR)
Neda Jahanshad (UCLA)
Kori Johnson (QIMR)
Mitzy Kennis (QIMR, UQ, Utrecht)
Baptiste Couvy-Duchesne (QIMR)
Aaron Quiggle (QIMR)
Miguel Renteria (QIMR, UQ)
Ben Sinclair (QIMR, UQ)
Jason Stein (UCLA)