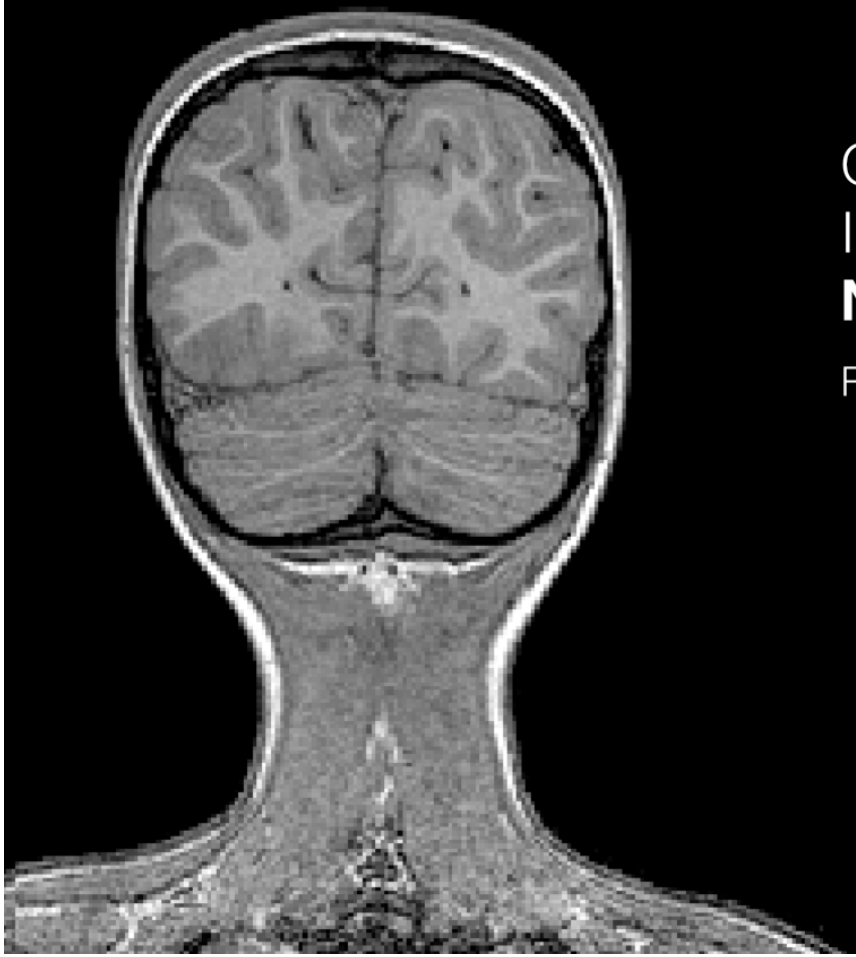
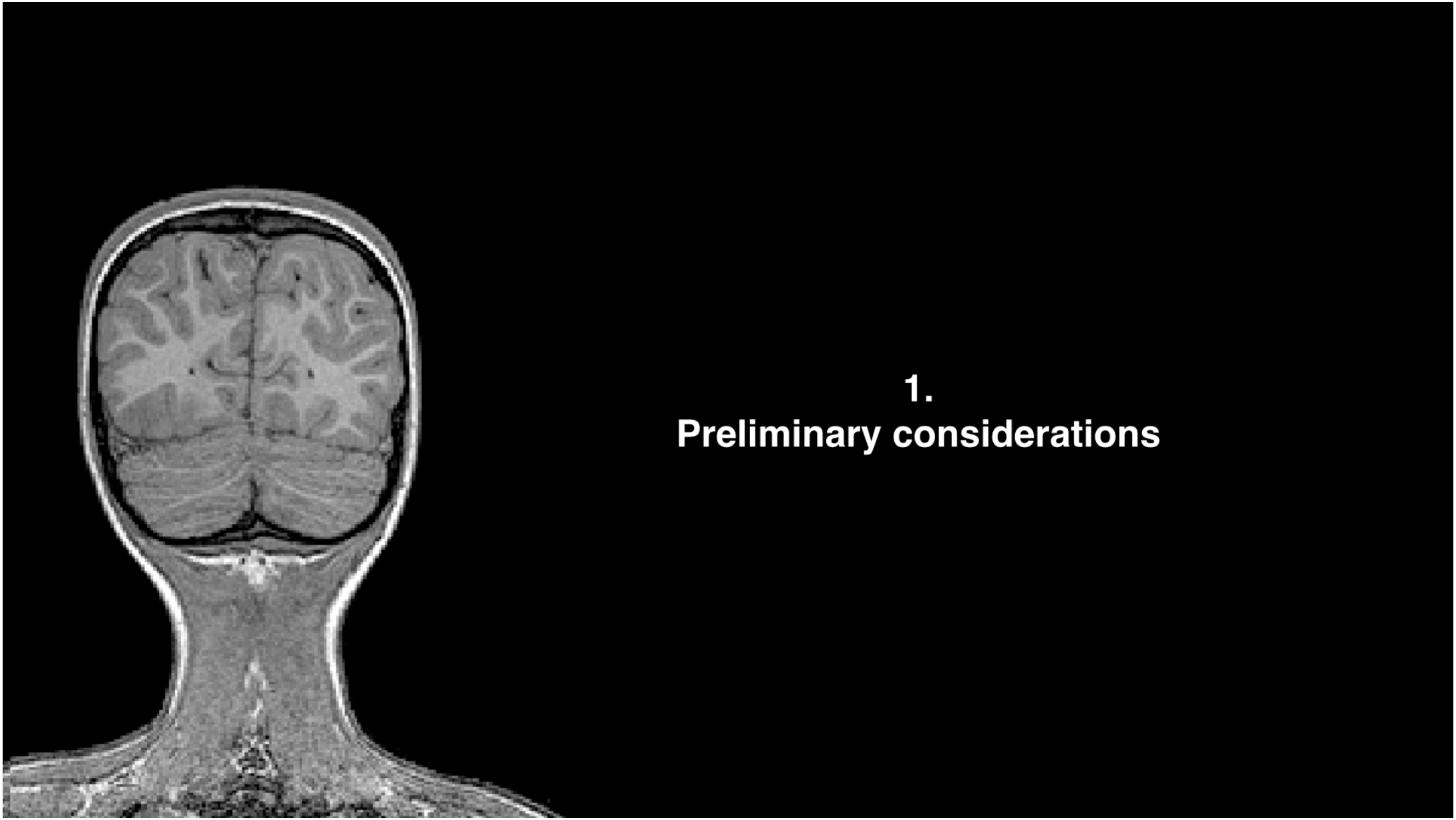


OHBM 2014

Imaging Genetics Course

Neuroimaging phenotypes for Imaging Genetics

ROBERTO TORO • INSTITUT PASTEUR • rto@pasteur.fr



1.
Preliminary considerations

Phenotype and Genotype

A ***phenotype*** is any observable characteristics of an individual (biochemical, physiological, morphological,etc.) resulting from the interaction of the environment and its ***genotype*** (the genetic constitution of the individual)

Endophenotypes

In psychiatry, an endophenotype is an ***internal*** characteristic that can be ***objectively measured***, ideally in a robust and reliable fashion. An endophenotype should be ***closer to the causative biological process*** than an external phenotype (Flint&Munafò, 2007)

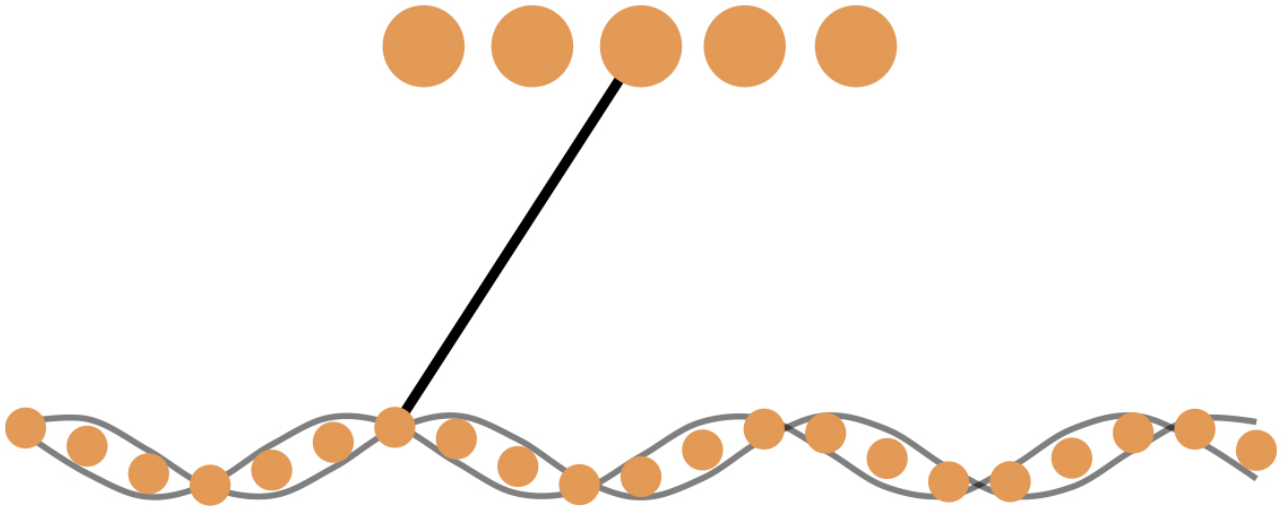
Glahn et al defined the ***endophenotype ranking value*** (ERV) based on the heritability of the disorder (h_I^2), the heritability (h_e^2) of the endophenotype, and their genetic correlation (ρ_g):

$$ERV=|\sqrt{h_I^2}\ \sqrt{h_e^2}\ \rho_g|$$

Genetic architecture of a phenotype (inheritance and heritability)

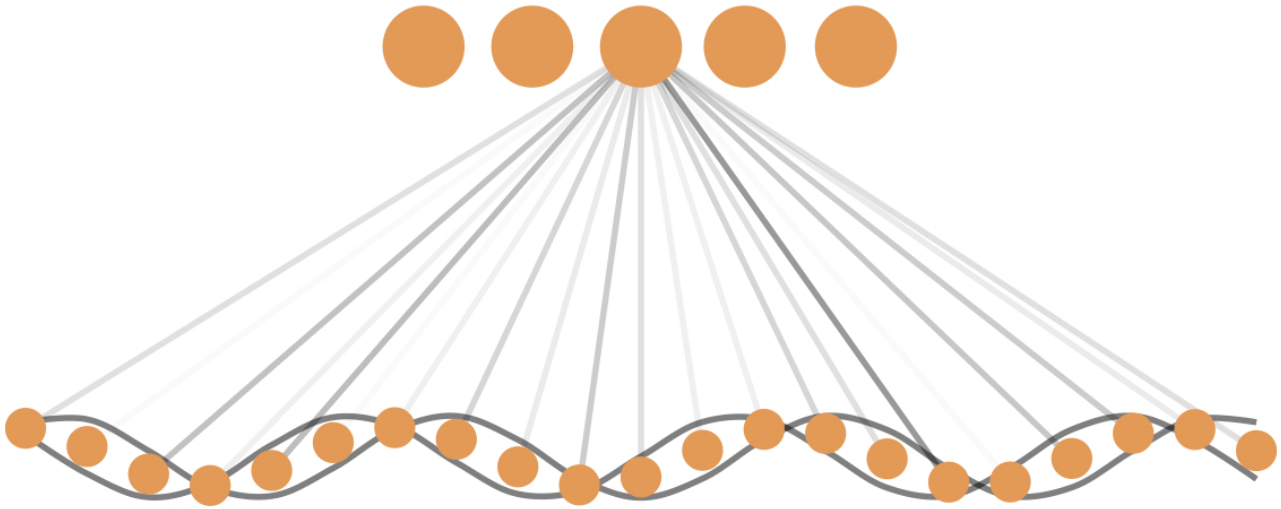
Genetic architecture of a phenotype
(inheritance and heritability)

Mendelian

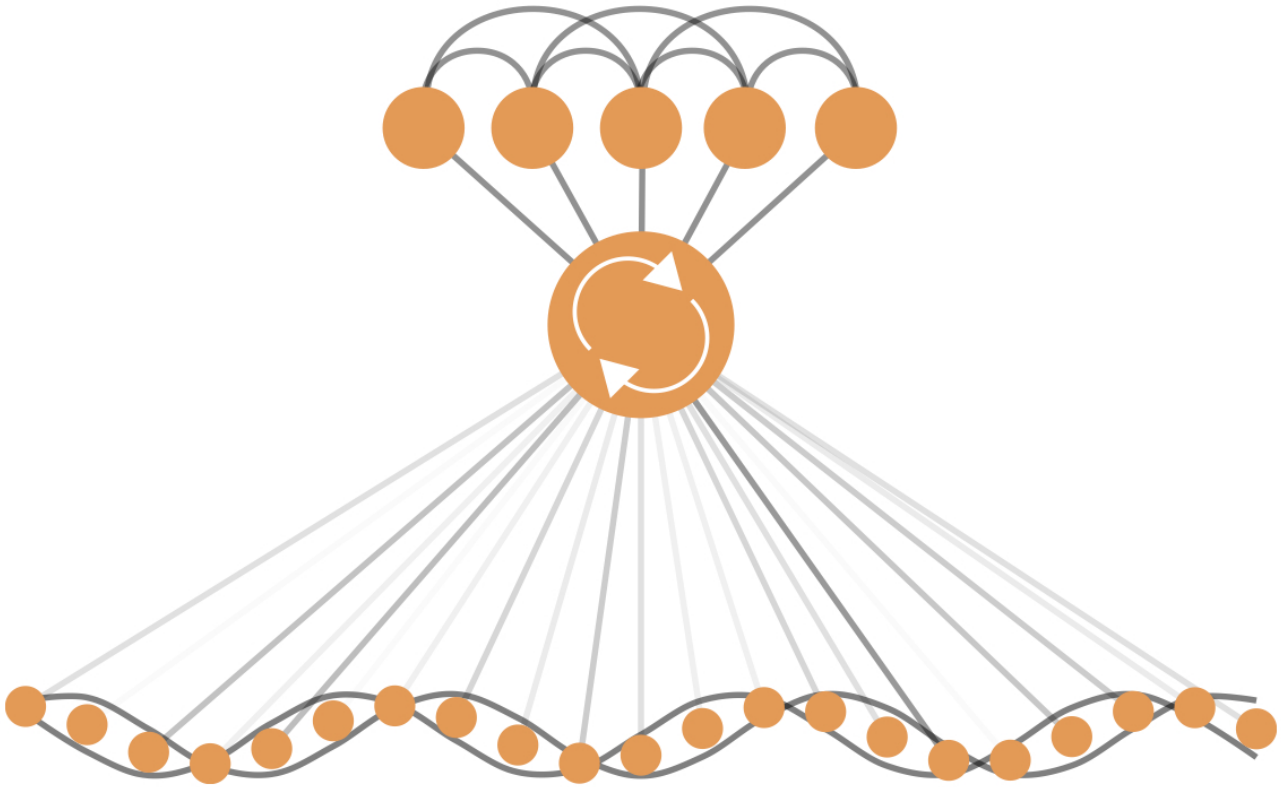


Genetic architecture of a phenotype
(inheritance and heritability)

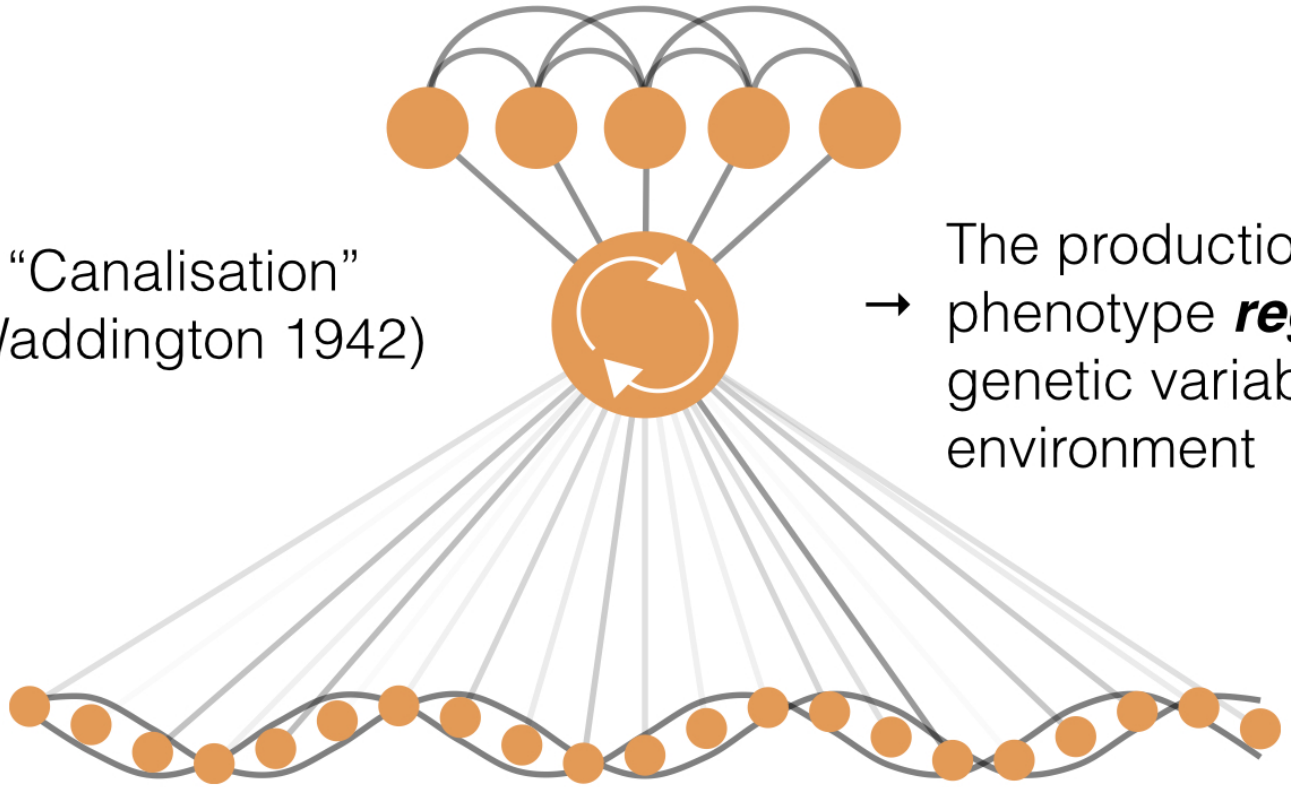
Infinitesimal
(Fischer)



Genetic architecture of a phenotype
(inheritance and heritability)



Genetic architecture of a phenotype
(inheritance and heritability)



"Canalisation"
(Waddington 1942)

→ The production of the same phenotype ***regardless*** genetic variability or environment

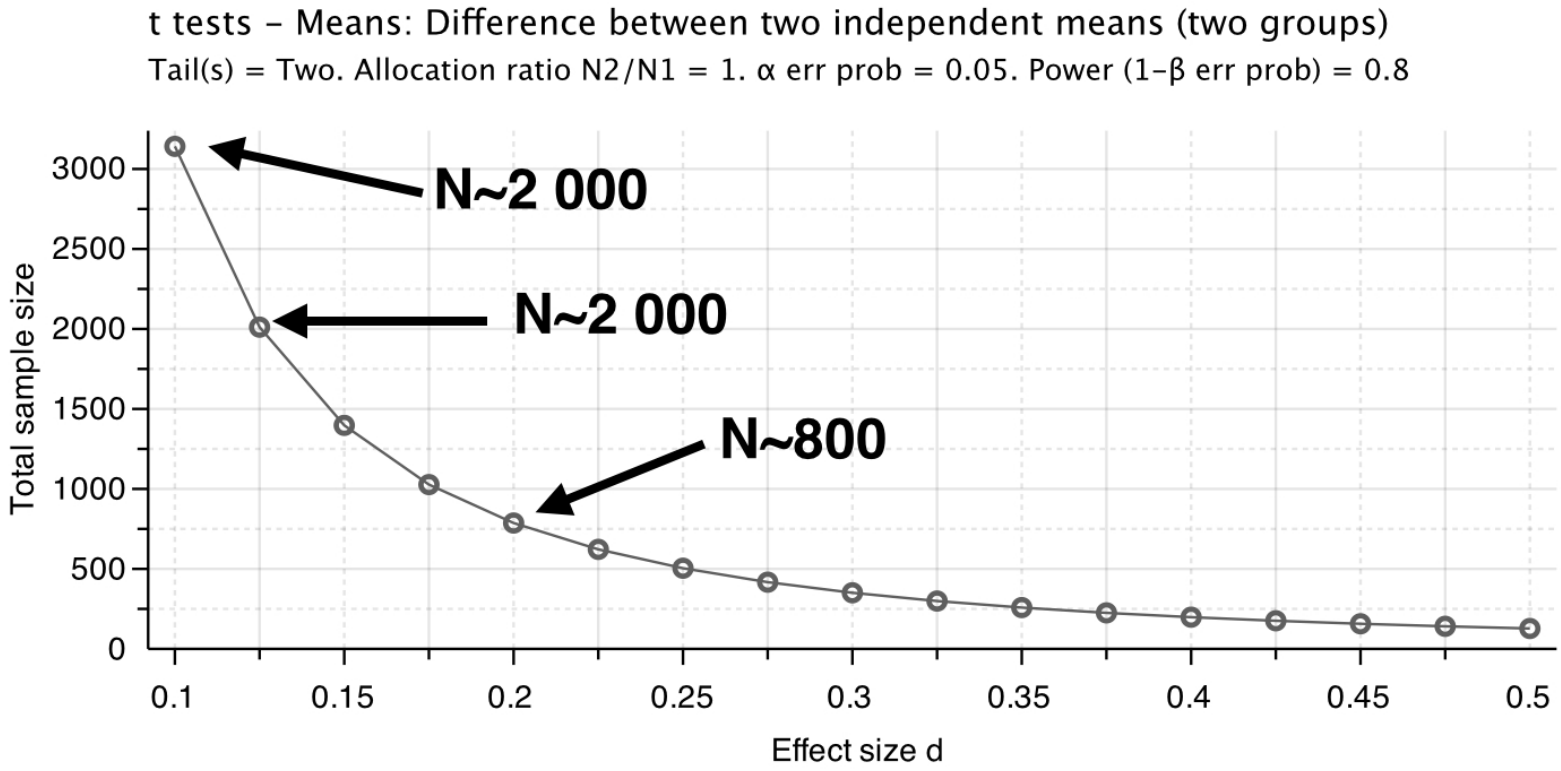
Statistical Power

Mendelian hypothesis, candidate gene

Statistical Power

Mendelian hypothesis, candidate gene

→G*Power (http://www.gpower.hhu.de)



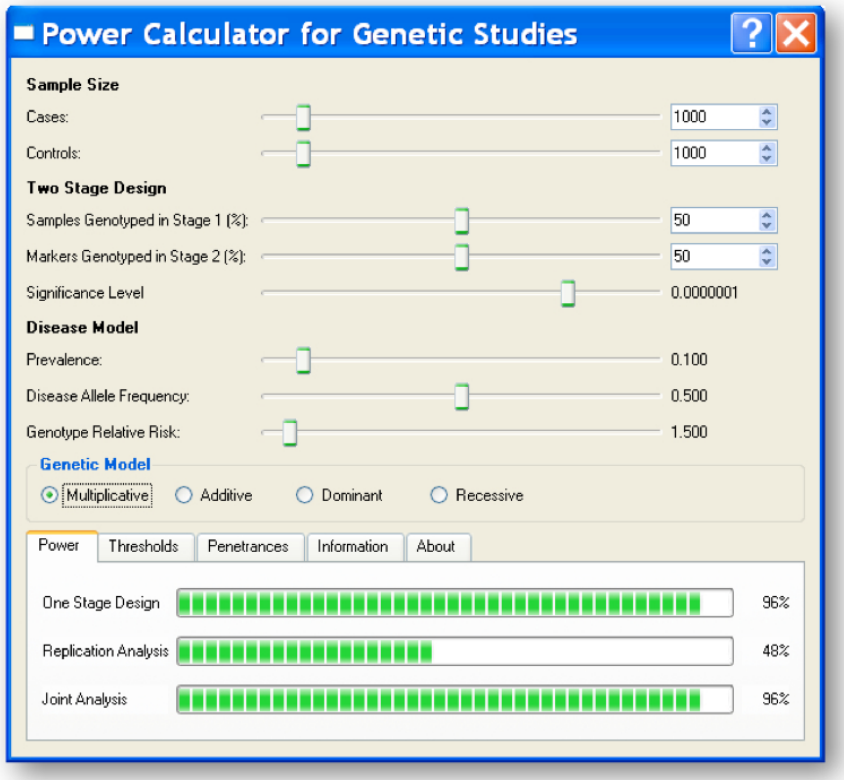
Statistical Power

Mendelian hypothesis, GWAS

Statistical Power

Mendelian hypothesis, GWAS

→ CaTS (http://www.sph.umich.edu/csg/abecasis/cats/)



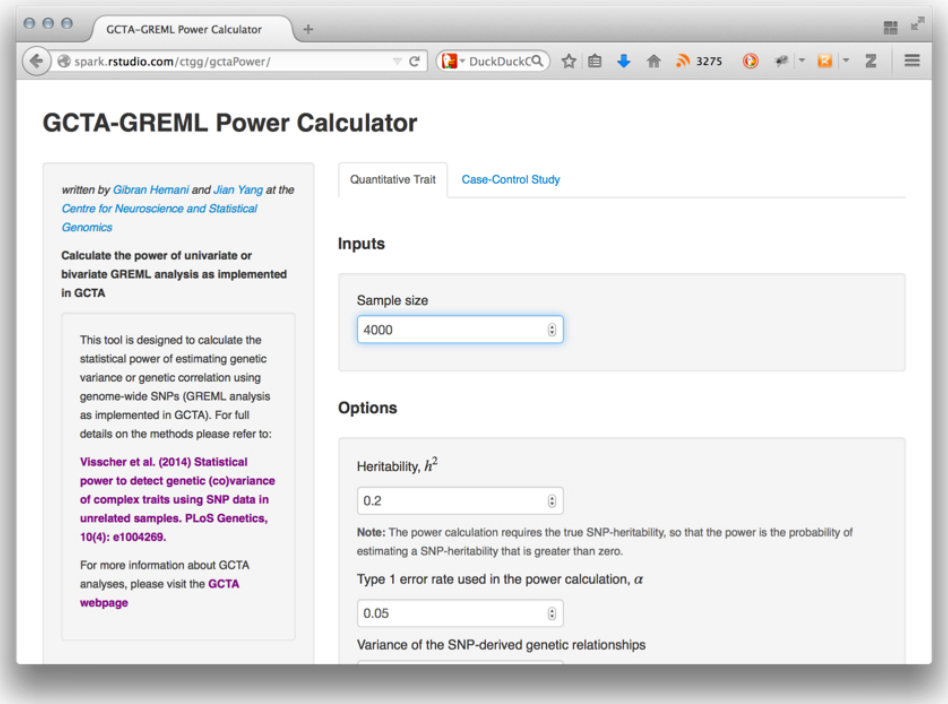
additive model,
freq=0.5, OR=1.5,
N~2 100

Statistical Power

Infinitesimal hypothesis

Statistical Power

Infinitesimal hypothesis
→ GCTA power calculator
(http://spark.rstudio.com/ctgg/gctaPower)



h^2=0.5, **N~1 770**
h^2=0.2, **N~4 450**

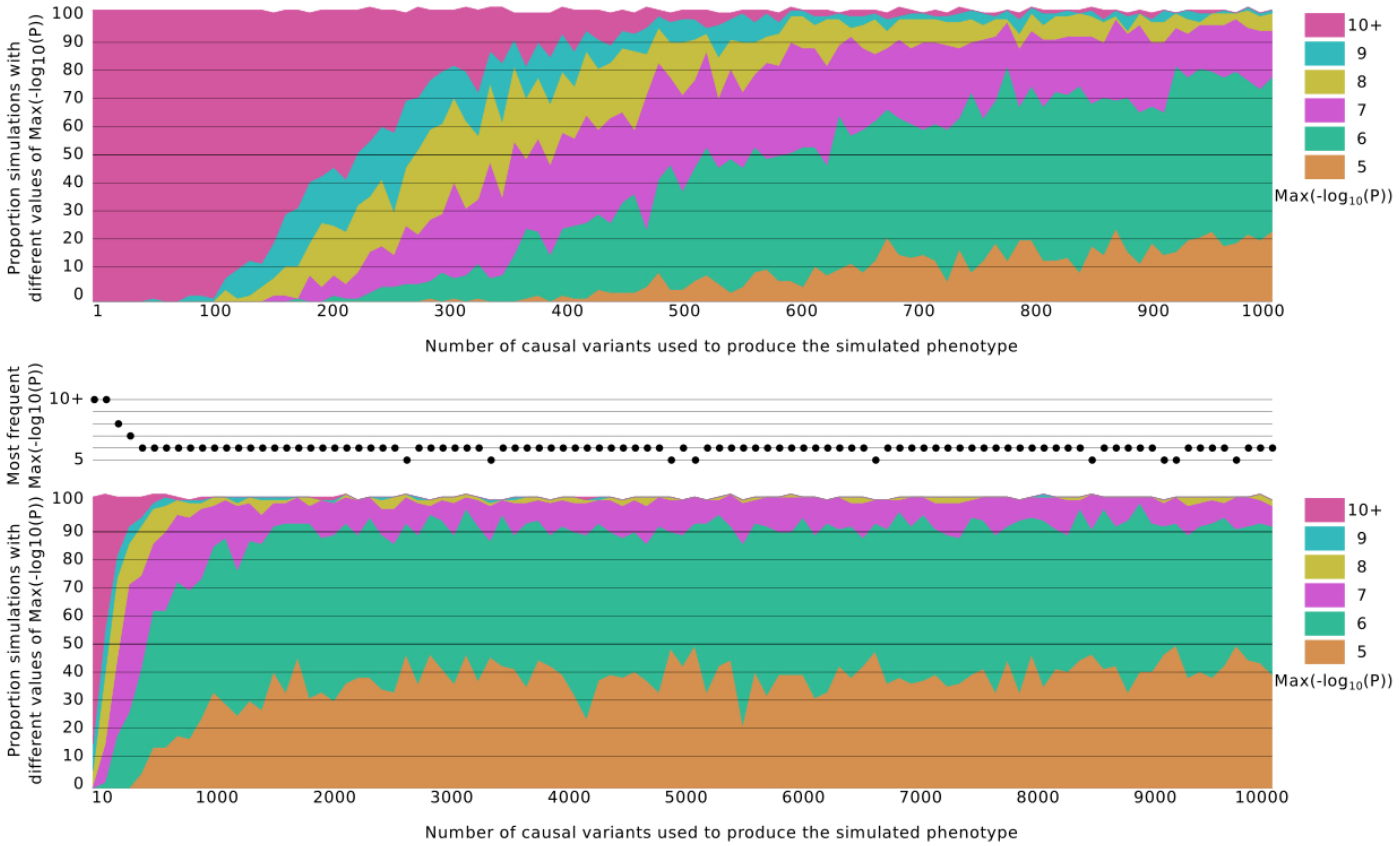
Statistical Power

Infinitesimal hypothesis, GWAS

Poster 3392
Wednesday

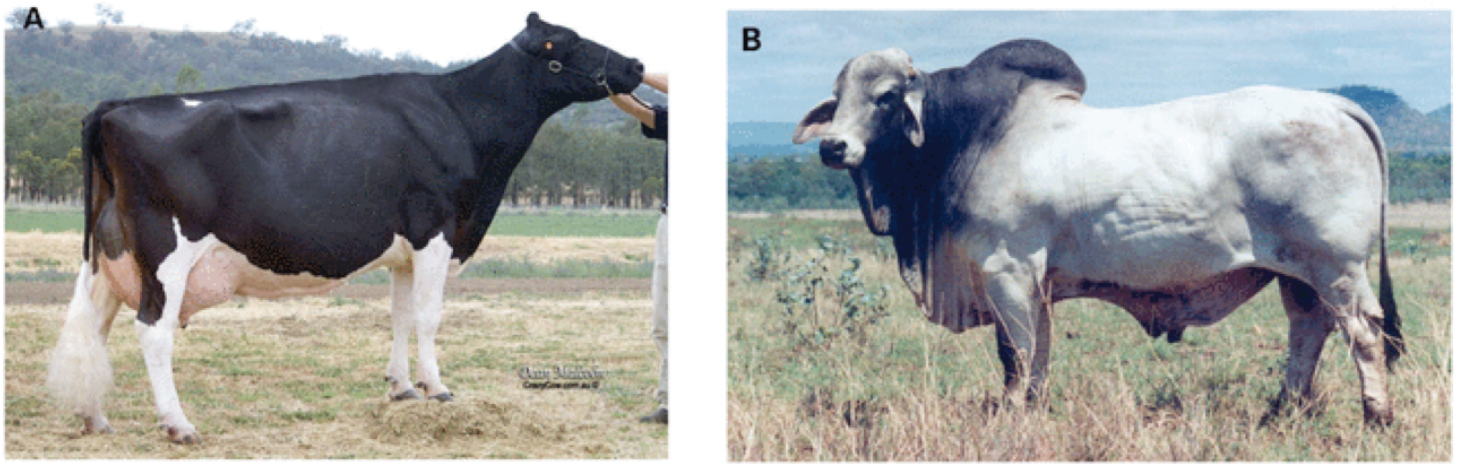
Statistical Power

Infinitesimal hypothesis, GWAS



Statistical Power

Infinitesimal hypothesis, GWAS



Statistical Power

Infinitesimal hypothesis, GWAS

Effective population size (Wright, 1938): “minimum number of individuals that would be required to show the same amount of dispersion of allele frequencies as the population under consideration”

For cattle, the effective population is $N_e \sim 100$
⇒ **N~2 500** animals required to predict *genetic value* accurately.

For humans, the effective population is $N_e \sim 10\,000–15\,000$
⇒ more than **N~145 000** subjects required to reach a similar accuracy.

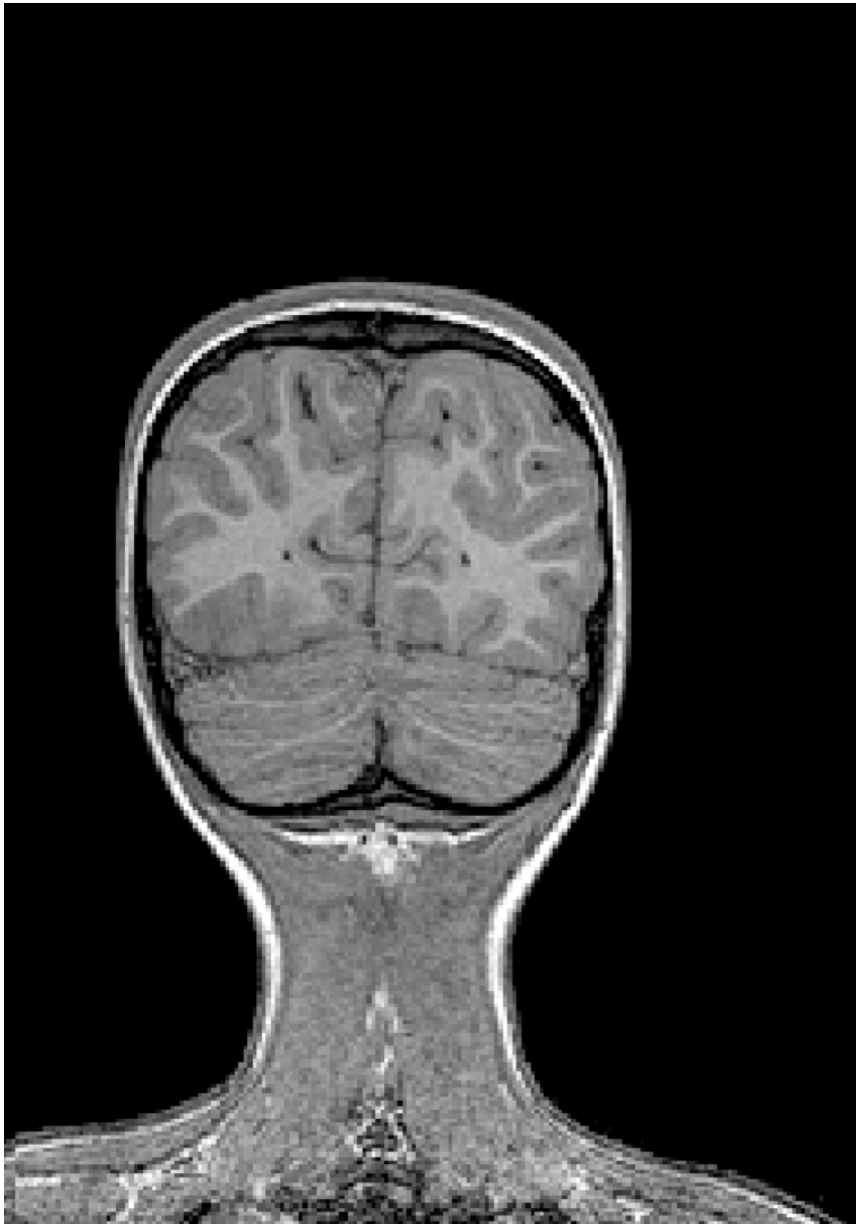
Further references

Flint and Munafò (2007) *The endophenotype concept in psychiatric genetics, Psychological Medicine, doi:10.1017/S0033291706008750*

Sham and Purcell (2014) *Statistical power and significance testing in large-scale genetic studies, Nat Rev Genet, doi:10.1038/nrg3706*

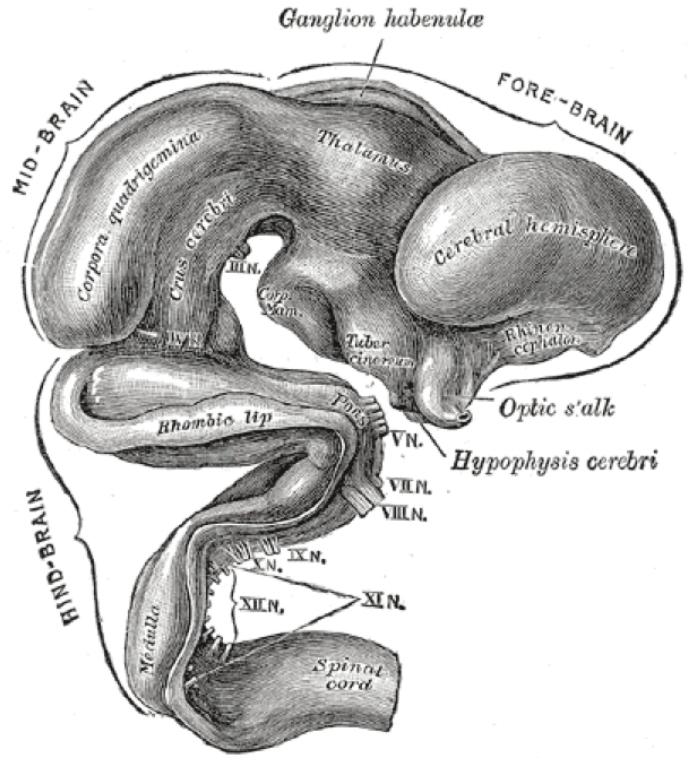
Visscher et al (2014) *Statistical Power to Detect Genetic (Co)Variance of Complex Traits Using SNP Data in Unrelated Samples, PLoS Genet, doi:10.1371/journal.pgen.1004269*

Kemper and Goddard (2012) *Understanding and predicting complex traits: knowledge from cattle, Hum Mol Genet, doi:10.1093/hmg/dds332*



2.
Overview of neuroimaging phenotypes

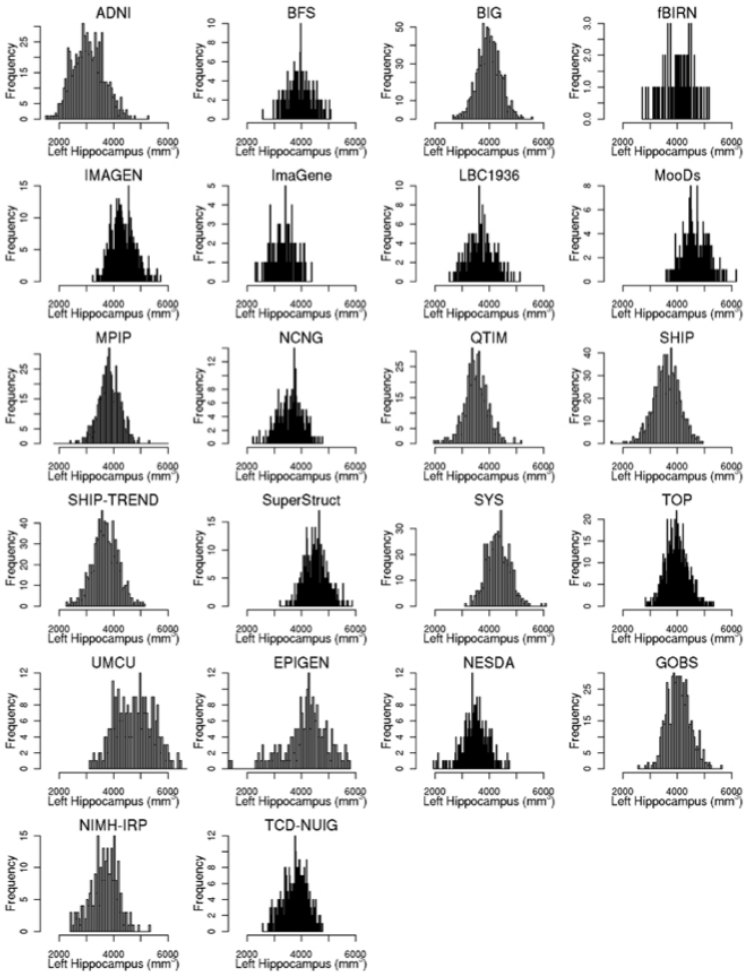
early development



Brain region	h^2 (95% CI)	Reference
ICV	79% (52-87)	Kremen et al (2010)
BV	70% (34-81)	Yoon et al (2011)
Hippocampus	76% (66-83)	den Braber et al (2013)
Thalamus	81% (74-85)	den Braber et al (2013)
Caudate nucleus	87% (82-91)	den Braber et al (2013)
Pallidum	70% (56-80)	den Braber et al (2013)
Putamen	85% (56-90)	den Braber et al (2013)
Amygdala	67% (57-76)	den Braber et al (2013)
Accumbens	67% (56-75)	den Braber et al (2013)

Kremen et al: N=474 (202 twin pairs, 70 unpaired)
Yoon et al: N=184 (57 MZ, 35 DZ, infants)
den Braber et al: N=528 (176 MZ pairs, 88 DZ pairs)

***"Identification of common variants associated with human hippocampal and intracranial volumes"*, Stein et al, Nat Genet 2012**



Hippocampal volume

TESC (rs7294919) (regulation of intracellular pH, cell volume and cytoskeletal organization)

0008285 negative regulation of cell proliferation
0010628 positive regulation of gene expression
0033628 regulation of cell adhesion mediated by integrin
0045654 positive regulation of megakaryocyte differentiation
0043193 positive regulation of gene-specific transcription

Intracranial volume

HMGA2 (rs10784502) (already associated with height)

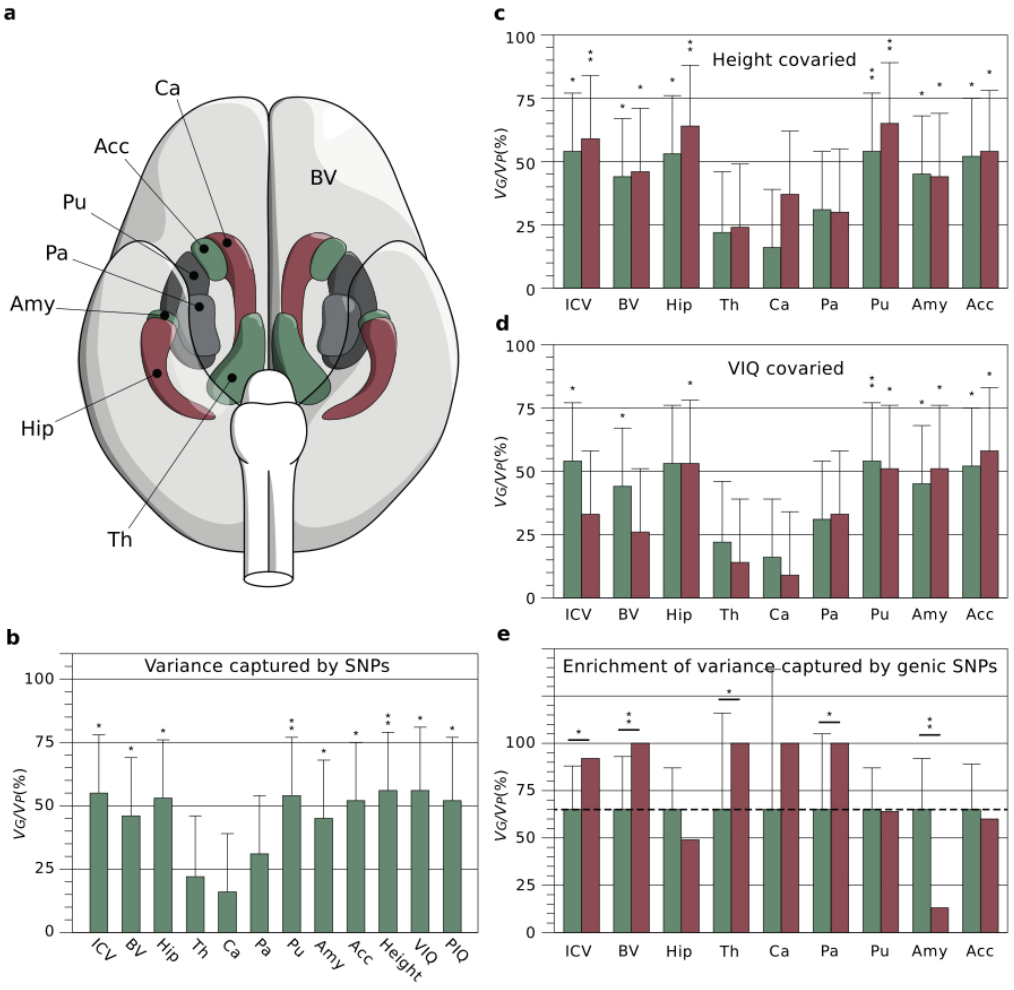
0051301 cell division
0007049 cell cycle
0006325 chromatin organization
0007275 multicellular organismal development
0007067 mitosis
0006355 regulation of transcription, DNA-dependent
0040008 regulation of growth

N: 7 795
(authors N: 209, +consortia N~1 200, i.e., 8 subj/auth)

Also: Ikram et al, Nature Genetics 2012, Taal et al, Nature Genetics 2012

"*Genomic architecture of human neuroanatomical diversity*" Poster 3392; biorxiv, doi:10.1101/001198

Poster 3392 Wednesday

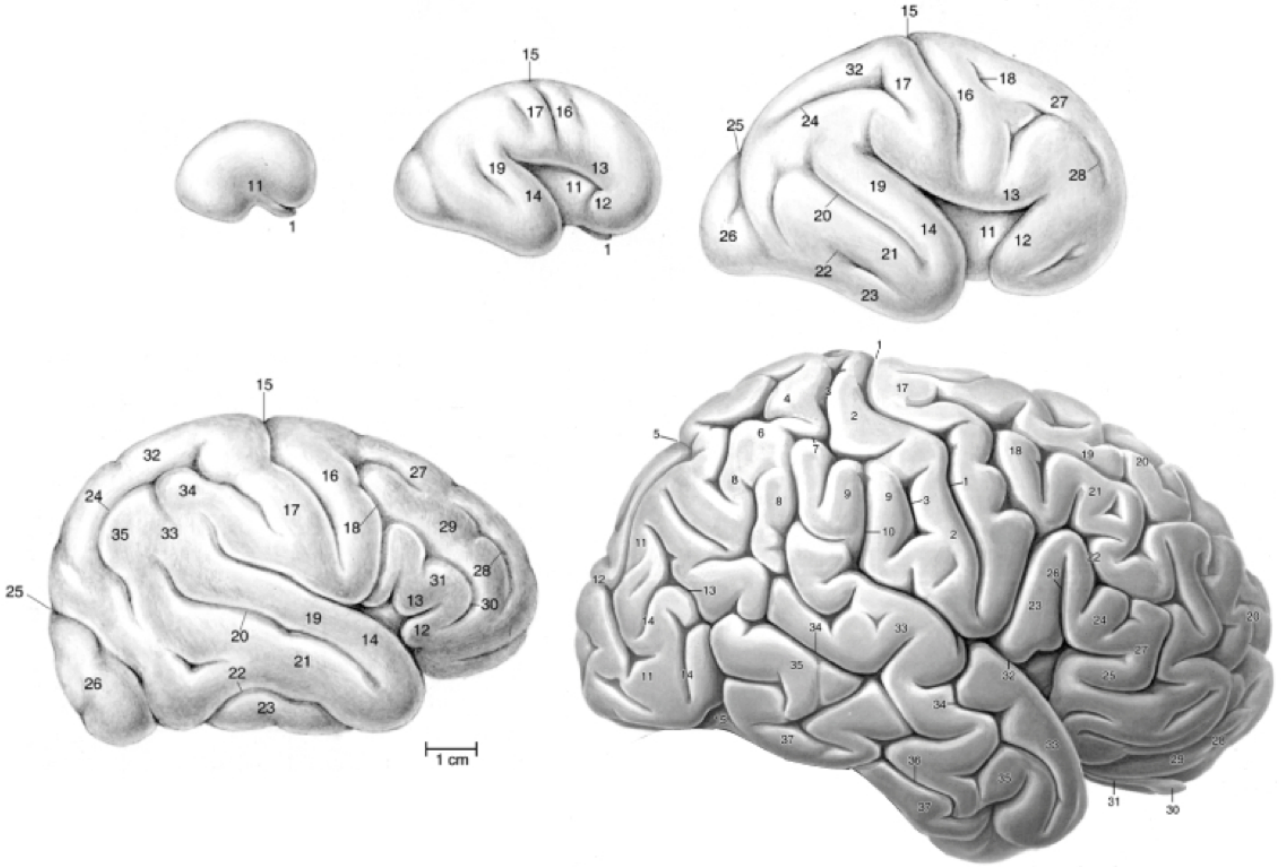


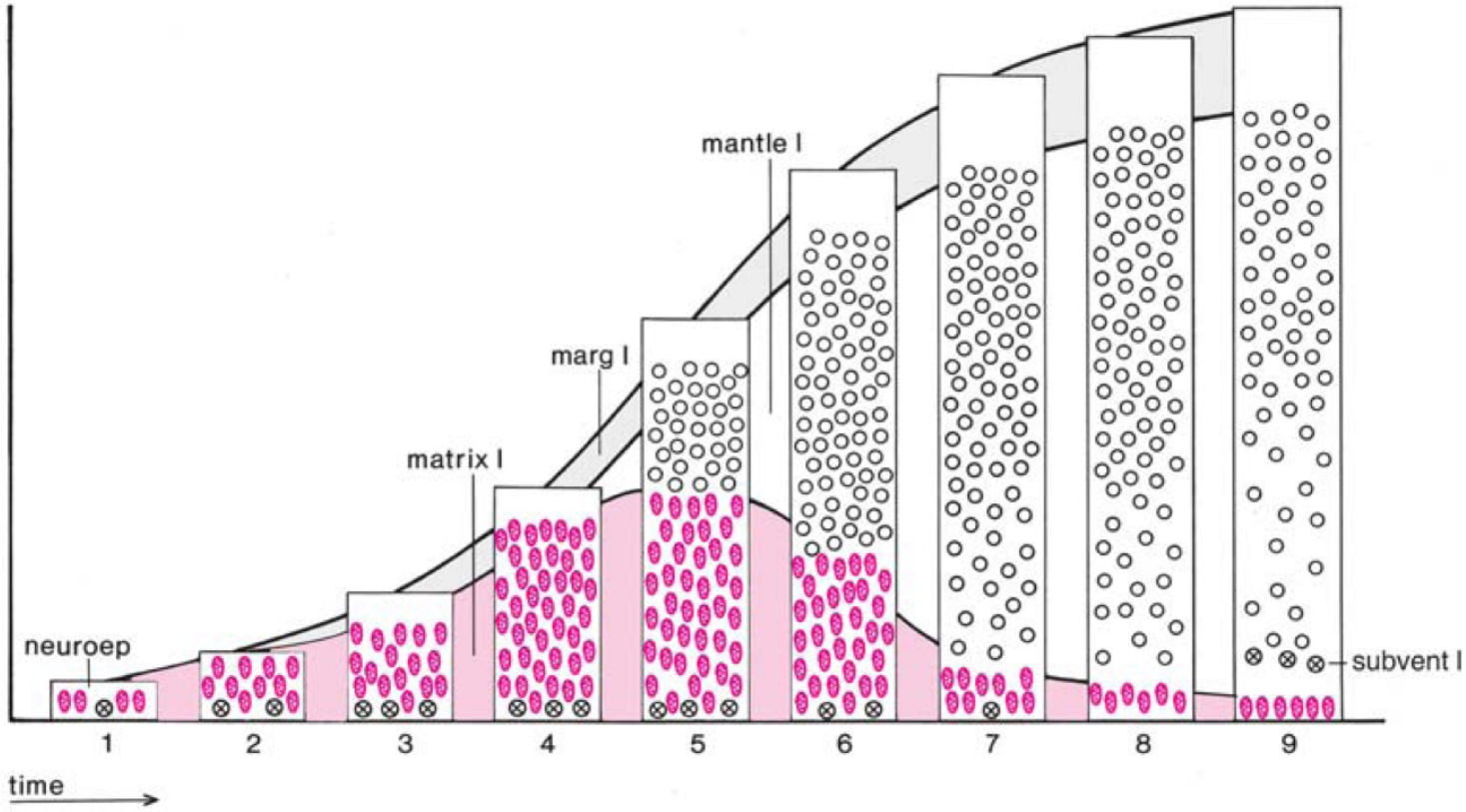
N: 1 765
VG/VP(ICV) = 54%
VG/VP(BV) = 44%
VG/VP(Hip) = 53%
r(BV,VIQ)=0.89
r(BV,Height) = 0.23 (N.S.)

Genome-wide SNPs capture a substantial proportion of phenotypic variance.
Up to 90% of this variance could be captured by SNPs within genes and close regulatory regions.

Protocols for processing and quality control of volumetric data: http://enigma.ini.usc.edu/protocols/

cortical development

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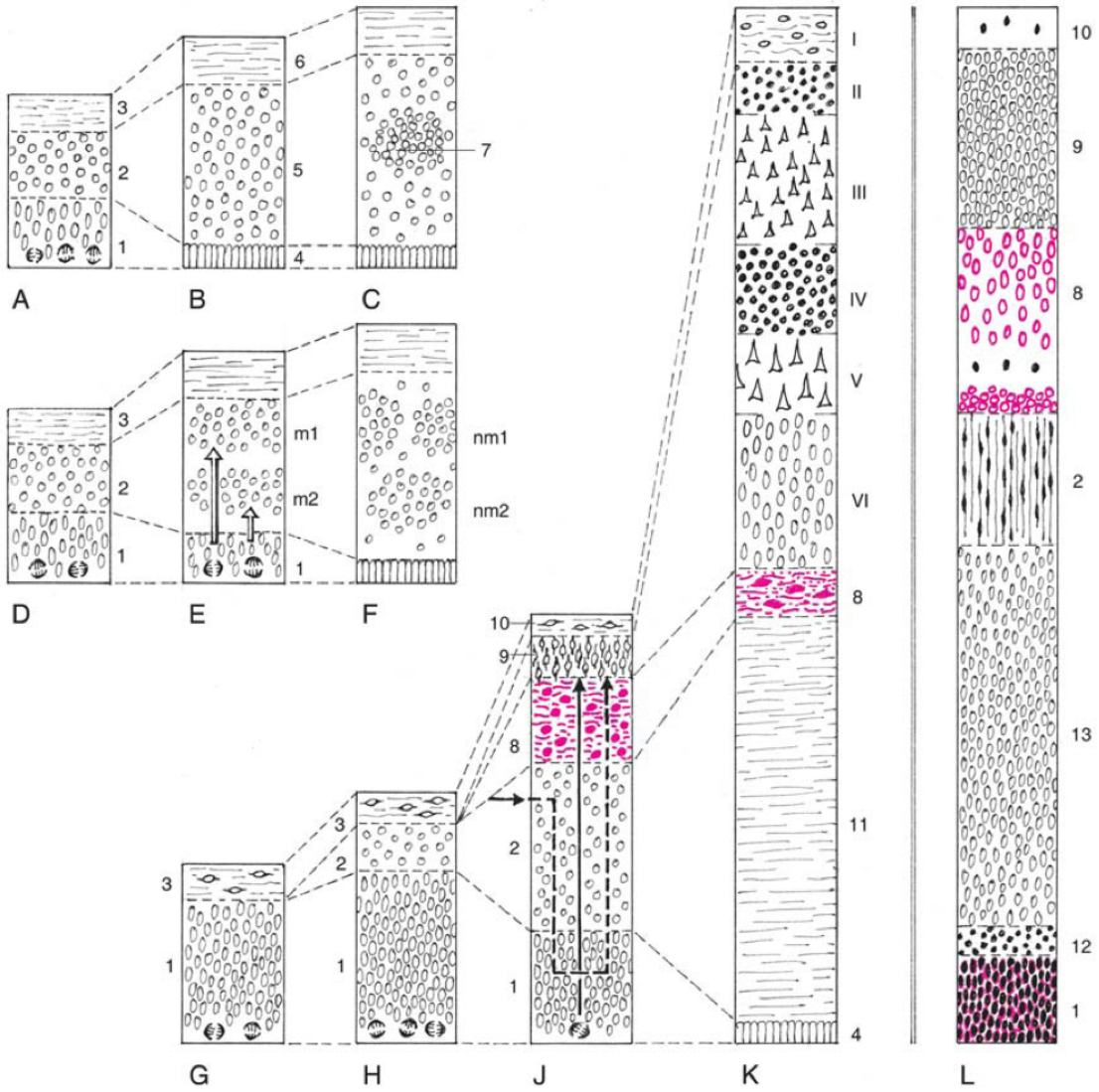
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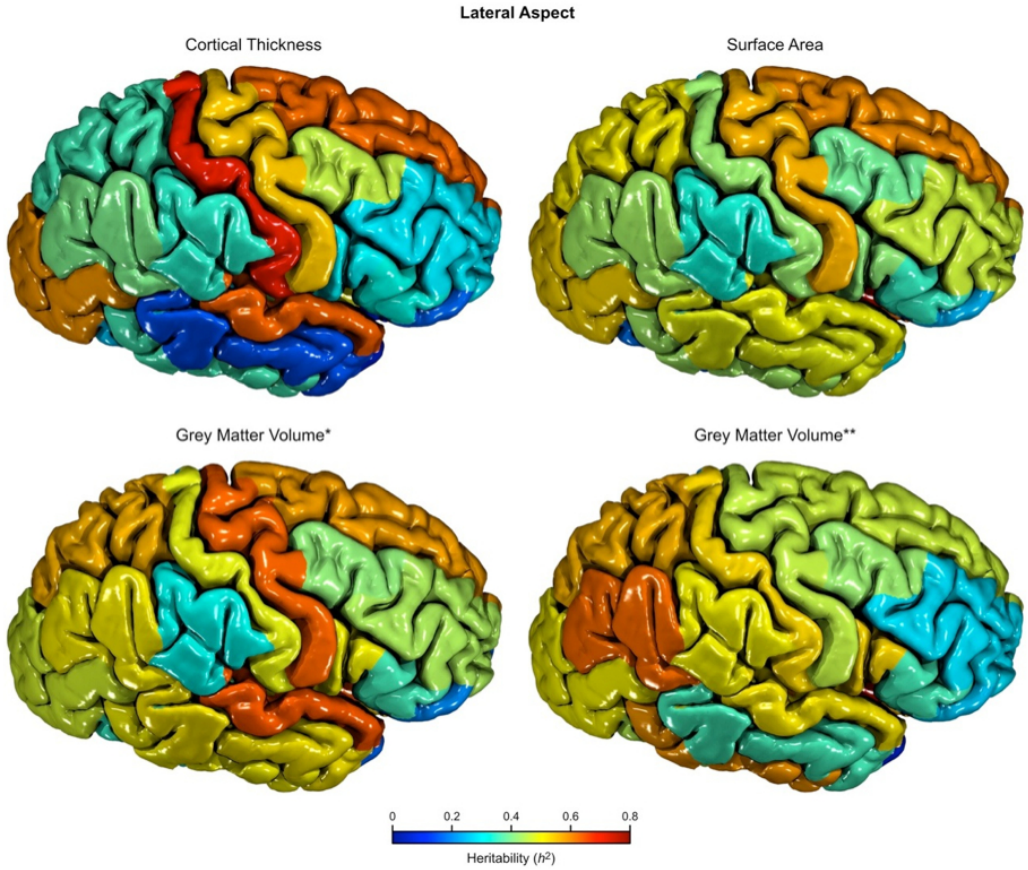
VI

***"Cortical thickness or gray matter volume? The importance of selecting the phenotype for imaging genetic studies"*, Winkler et al, NeuroImage 2009**



- N: 486 (extended pedigree)

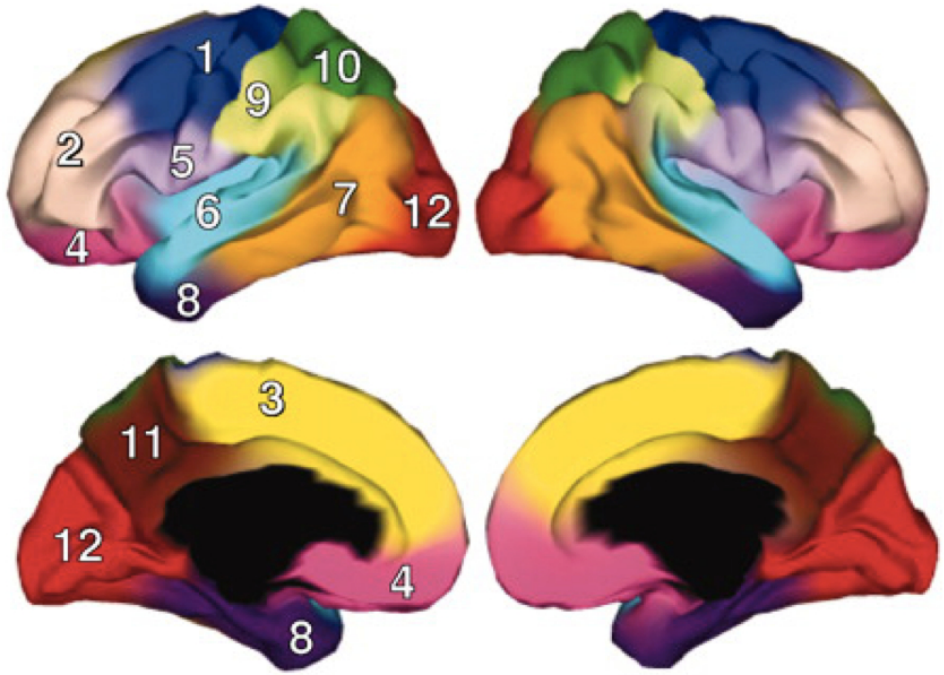
h^2(Brain Volume) = 70%
h^2(Surface) = 70%
h^2(Thickness) = 69%
h^2(GM surface-based) = 72%
h^2(GM voxel-based) = 67%

- The heritability of surface, thickness and grey matter volume were high.

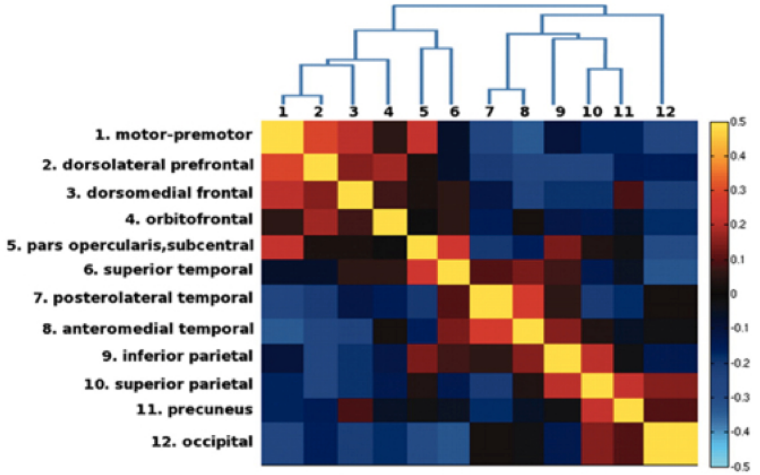
- The low genetic correlation between the additive genetic factors of surface and thickness (r_g=-0.15) suggests that different genetic factors are involved in the their development.

Also:
"Distinct genetic influences on cortical surface and cortical thickness", Panizzoni et al, Cereb Cortex 2009
"Cortical thickness is influenced by regionally specific genetic factors", Rimol et al, Biol Psychiatry 2010
"Heritable changes in regional cortical thickness with age", Chouinard-Decorte et al, Brain Imaging Behav 2014

***"Hierarchical genetic organization of human cortical surface area",* Chen et al, Science 2012**

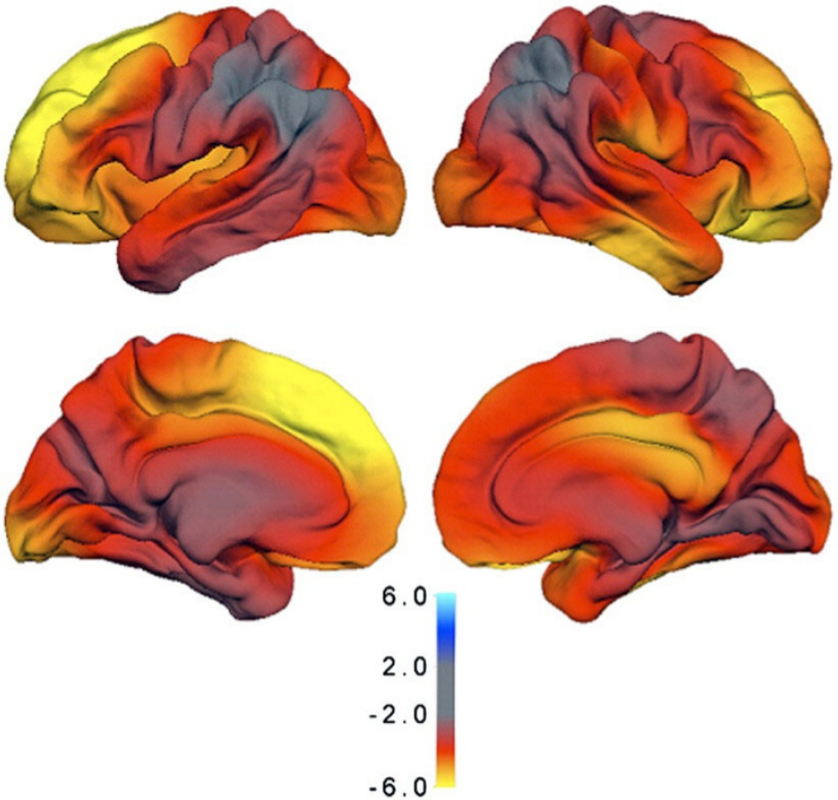


- N: 406 (110 MZ, 93 DZ)
- Phenotype: local cortical area expansion
- Genetic-correlation-based parcellation
- The genetic organisation of cortical area was hierarchical, modular, and predominantly bilaterally symmetric



Also:
"Genetic Influences on Cortical Regionalization in the Human Brain", Chen et al, Neuron 2011

***"Sex-dependent association of common microcephaly genes with brain structure",* Rimol et al, PNAS 2010**



CDK5RAP2/MCPH3 (rs4836817, rs10818453, rs4836819, rs4836820, rs7859743, rs2297453, rs2282168, rs1888893, rs914592, rs914593)

0045664 regulation of neurone differentiation (11 genes)
0007420 brain development (91 genes)

MCPH1 (rs2816514, rs2816517, rs11779303, rs11779303)

[no biol. proc. in GO

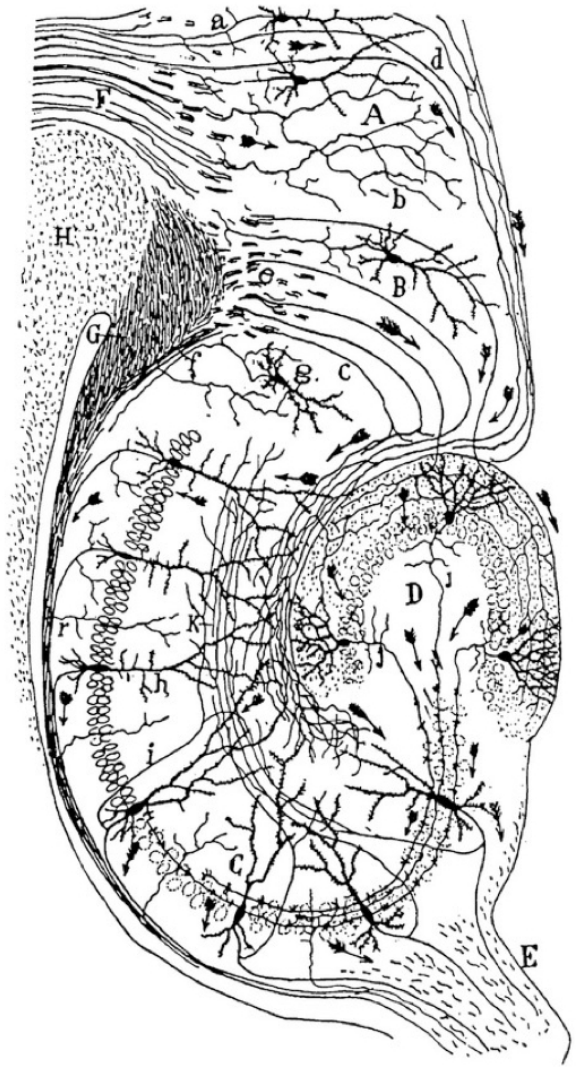
ASPM (rs10922168)

0007049 cell cycle (443 genes)
0007067 mitosis (171 genes)
0051301 cell division (221)

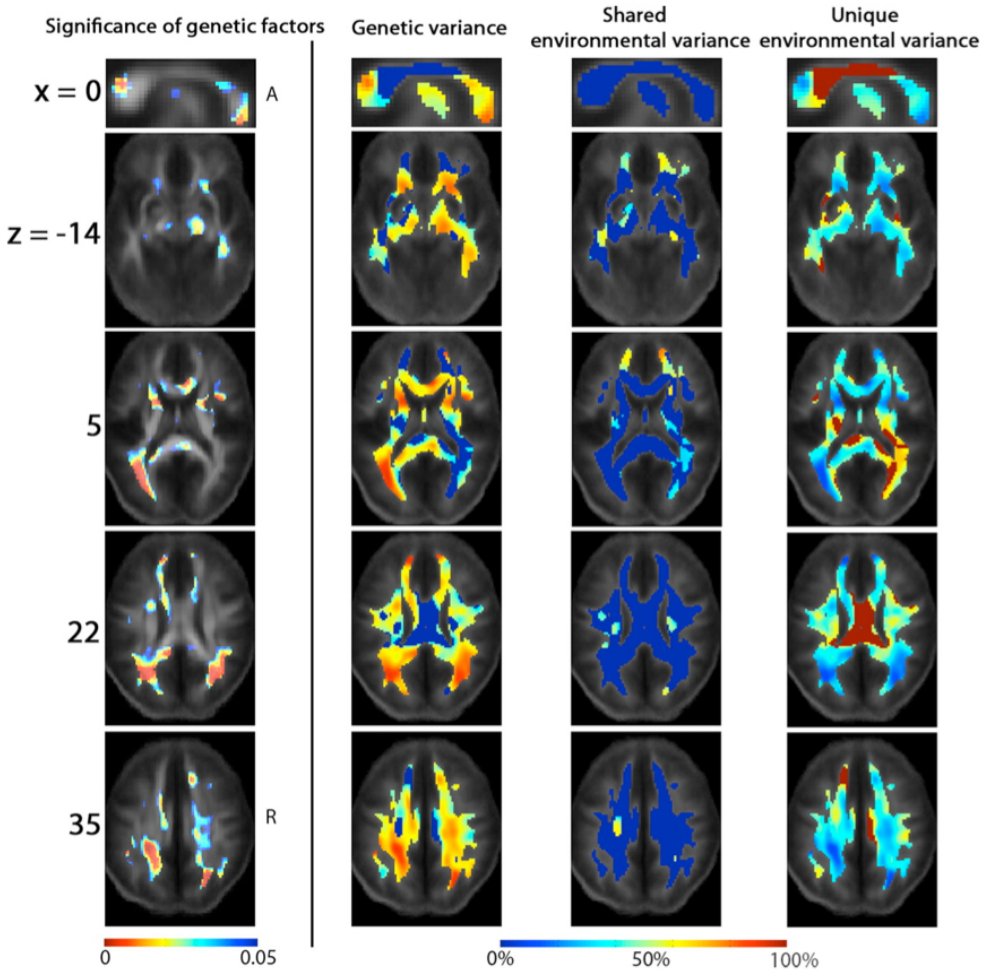
- Phenotype: local cortical area expansion
- N=287, replication N=656
- MCPH1, ASPM: Significant in females
- MCPH3: Significant in males

Accurate cortical reconstructions can be obtained automatically using Freesurfer (http://www.freesurfer.net). Several measurements of cortical geometry can be obtained using Mindboggle (http://www.mindboggle.org).

connectivity



***"Genetics of brain fiber architecture and intellectual performance"*, Chiang et al, J Neurosci 2009**

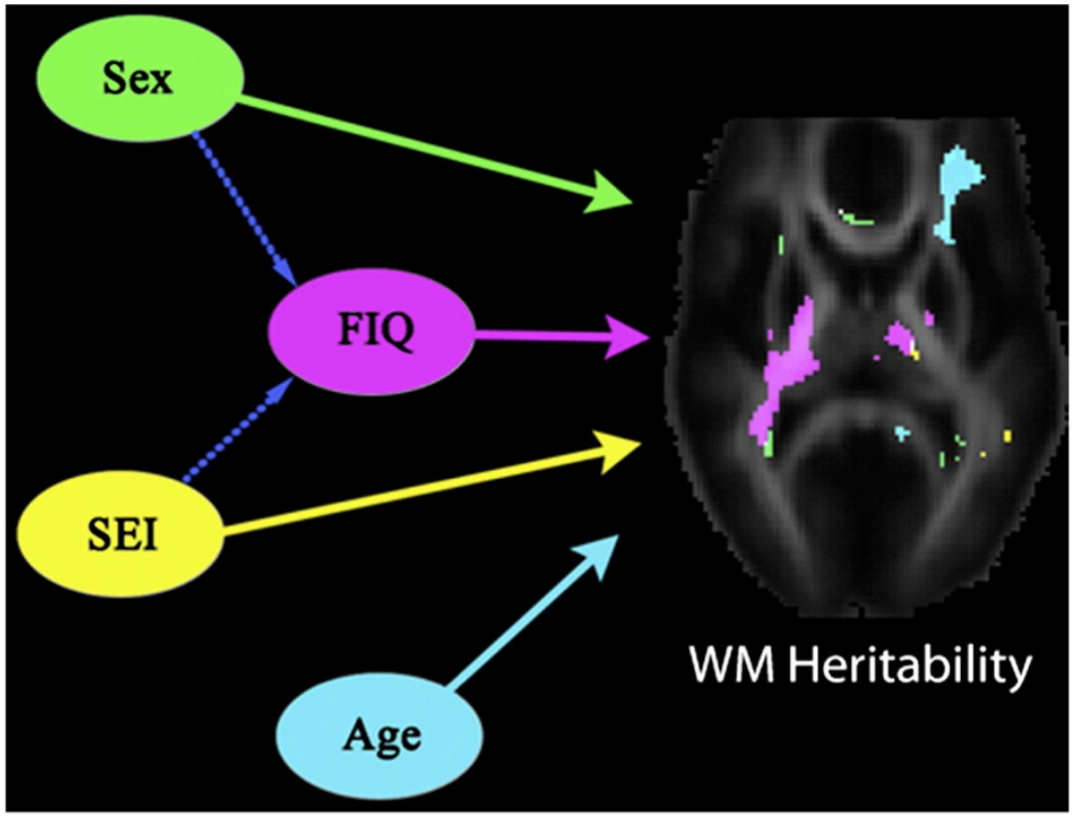


N: 92 (MZ=2*23, DZ=2*23)
h^2(FA) values from 55% (Frontal left) to 85% (Parietal left)

• The genetic determinants of FA seem to be shared with those of IQ.

Also:
"Genetic influences on brain asymmetry: a DTI study of 374 twins and siblings", Janhashad et al, NeuroImage 2010

***"Genetics of white matter development: A DTI study of 705 twins and their siblings aged 12 to 29"*, Chiang et al, Neuroimage 2011**

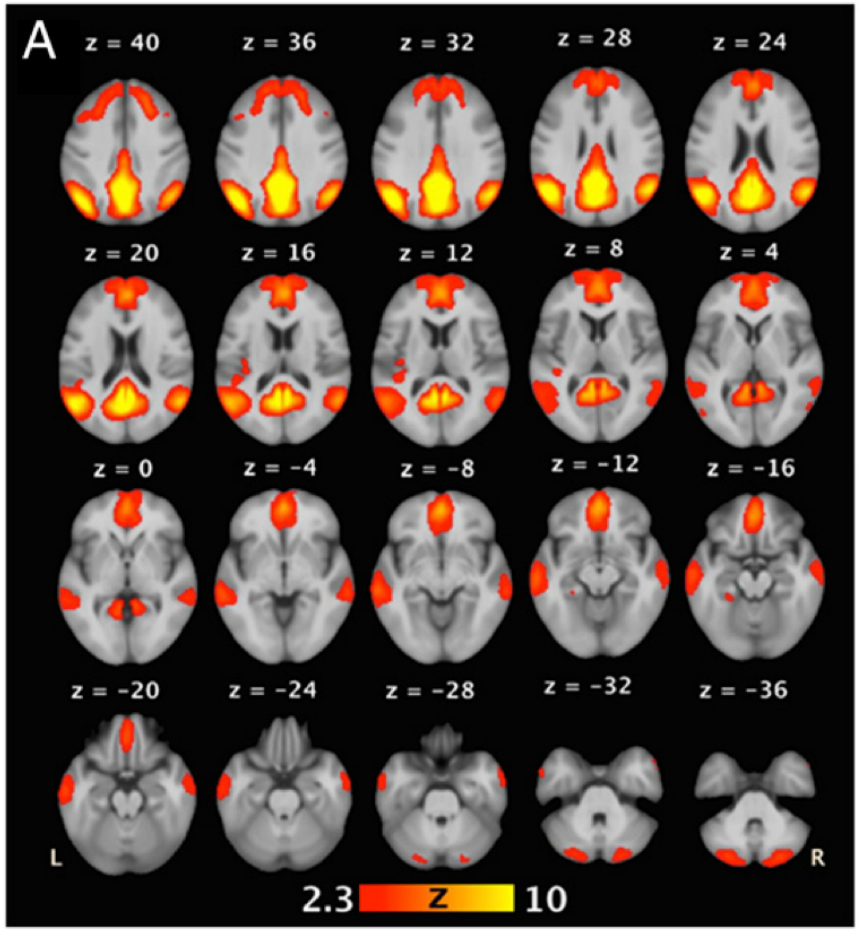


- N: 705 (119 MZ, 152 DZ, 5 TZ, + sibs)
- In adolescents: h^2(FA)=70–80%, in adults: h^2(FA)=30–40%
- h^2(FA) larger in males than in females
- h^2(FA) is modulated by socioeconomic status (larger in some regions, smaller in others)

Also: Jahanshad, N. et al. Multi-site genetic analysis of diffusion images and voxelwise heritability analysis: a pilot project of the ENIGMA-DTI working group. Neuroimage 81, 455–469 (2013).

Enigma is working to develop reliable methods for DTI genetics analyses: http://enigma.ini.usc.edu/protocols/dti-protocols/

***"Genetic control over the resting brain"*, Glahn et al, PNAS 2010**



- N: 333 (extended pedigree)
- h^2(Funct. Conn) = 42%
- h^2(GM density) = 32%
- r_g = 0.07

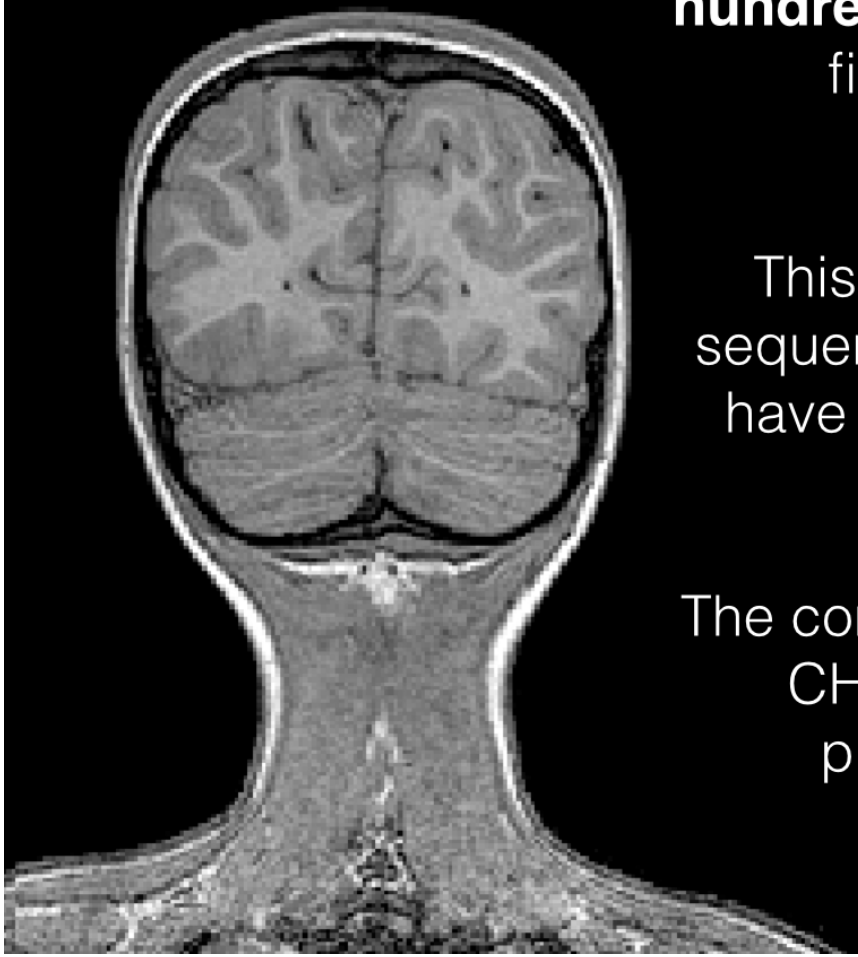
- Genes involved in functional connectivity are different from those involved in brain anatomy

Scripts for multi-centric analyses of functional connectivity have are available from the 1000 functional connectomes project: http://www.nitrc.org/projects/fcon_1000/

Further references

Thompson et al (2013) *The ENIGMA Consortium: Large-scale Collaborative Analyses of Neuroimaging and Genetic Data, Brain Imaging and Behav, doi: 10.1007/s11682-013-9269-5*

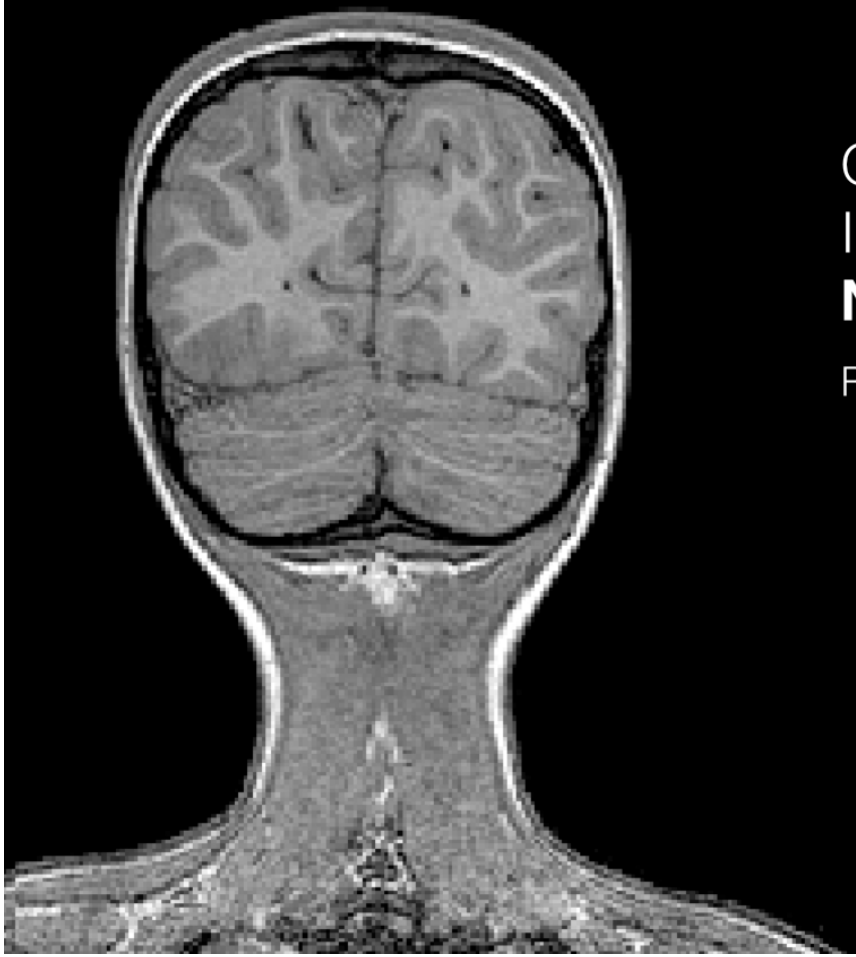
Medland et al (2014) *Whole-genome analyses of whole-brain data: working within an expanded search space, Nat Neurosci, doi:10.1038/nn.3718*



Depending on the approach, **thousands** or even **hundreds of thousands** of subjects may be required to find causal genetic variants associated with neuroimaging phenotypes.

This puts strong limitations on the type of imaging sequence and the type of analyses we can use, which have to be **accurate**, **reproducible** and as much as possible **automatic**.

The constitution of **large consortia** such as ENIGMA or CHARGE, and the development of methods for processing **multi-centric data** are essential.



OHBM 2014

Imaging Genetics Course

Neuroimaging phenotypes for Imaging Genetics

ROBERTO TORO • INSTITUT PASTEUR • rto@pasteur.fr