

Introduction to Imaging Genetics

## Overview of neuroimaging phenotypes

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génétique humaine et fonctions cognitives



# 1

Researchers have used various neuroimaging measurements as quantitative **endophenotypes** in genetic analyses to look for the **biological processes** that underlie functional and structural brain variability.

Neuroimaging endophenotypes are **intermediate steps** between the molecular and behavioural levels, and should be **more easy to relate to biological processes** than behavioural phenotypes.

**Which endophenotypes are available** through neuroimaging and **which biological processes** shape them?

# 2

Two different timescales can be distinguished: The common aspects of brain development, shaped by our **evolutionary history**, and the individual plastic changes, reflecting our **life-long experiences**.

**Heritability** analyses (in twin or extended pedigree studies) suggest that inheritable factors determine a substantial proportion of structural (and maybe also functional) brain variability, supporting the use of neuroimaging endophenotypes in the research for the genetic causes of psychiatric conditions.

# 3

The precise genetic causes of this high heritability remain, however,  
**largely unknown.**

In the last 15 years, the research for these genetic causes has been tackled through the study of **candidate genes** and biological pathways. More recently, agnostic **genome-wide** association has been successfully used to discover new candidates for brain variability and psychiatric conditions.

$V$     $h^2$



Voxel-based morphometry   VBM  
Volume   V  
Surface   S  
Thickness   T  
Gyration   Gy  
Diffusion-tensor imaging   DTI  
Functional MRI   fMRI

Heritability analysis    $h^2$   
Candidate gene/region   C  
Genome-wide association study   GW

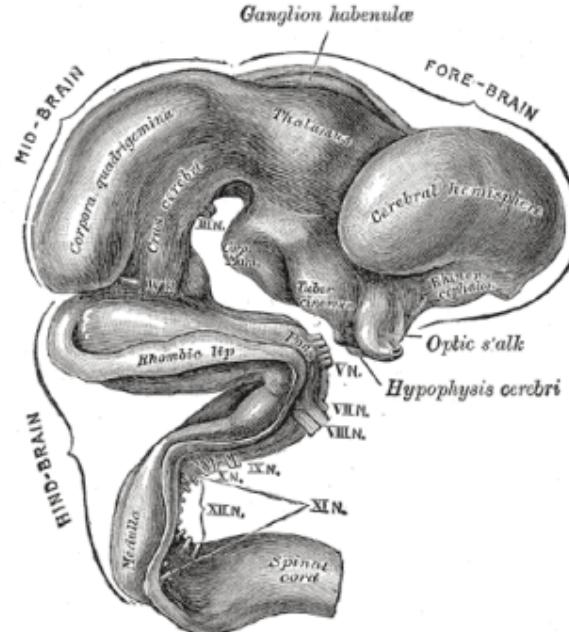
Gene:  
***MECP2***

dbSNP:  
rs2266887, rs2266888, rs3027898,  
rs17435, rs2239464

Gene ontology:  
0000122 negative regulation of  
transcription from RNA polymerase II  
promoter (214 genes in the category)  
0045449 regulation of  
transcription (978)

early development  
rostrocaudal axis  
cortical development  
mitosis  
apoptosis  
neuropil develop.  
connectivity  
axon growth  
myelination  
maturation  
puberty  
ageing  
plasticity

*early development*



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puberty

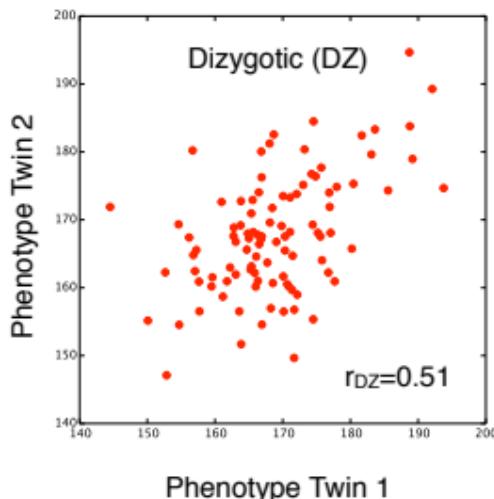
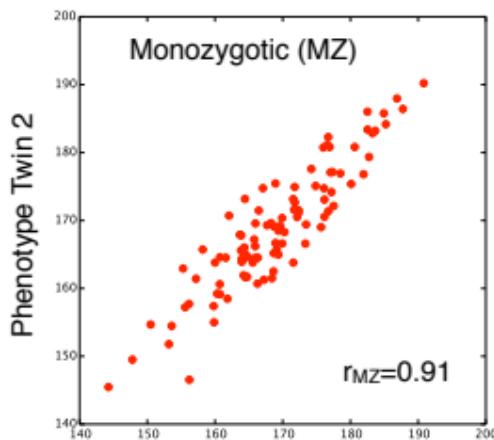
ageing

plasticity

	Brain region	r Twins	r Controls
	Total brain tissue	0.99	-0.03
	Cerebrum	0.99	-0.02
	Cerebral GM	0.98	-0.15
	Cerebral WM	0.98	0.40
	Cortical GM	0.99	-0.14
	Ventricles	0.85	0.52
	Caudate Nucleus	0.84	-0.17
	Putamen	0.75	0.29
	Thalamus	0.75	0.0
	Cerebellum	0.99	0.20

N=20 (10 MZ, 10 Controls)

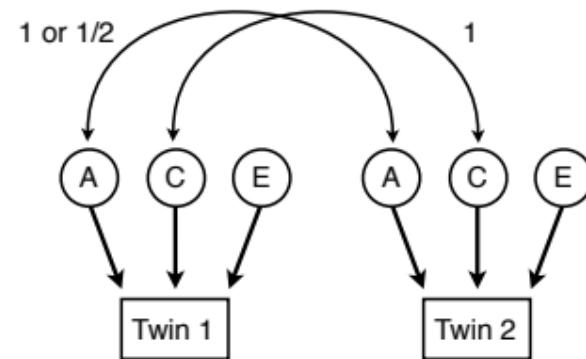
$h^2$



$$r_{MZ} = A + C$$

$$r_{DZ} = (1/2)A + C$$

$$\rightarrow h^2 = A = 2(r_{MZ} - r_{DZ})$$



*"Genetic and environmental contributions to neonatal brain structure: a twin study", Gilmore et al, Hum Brain Mapp 2010*

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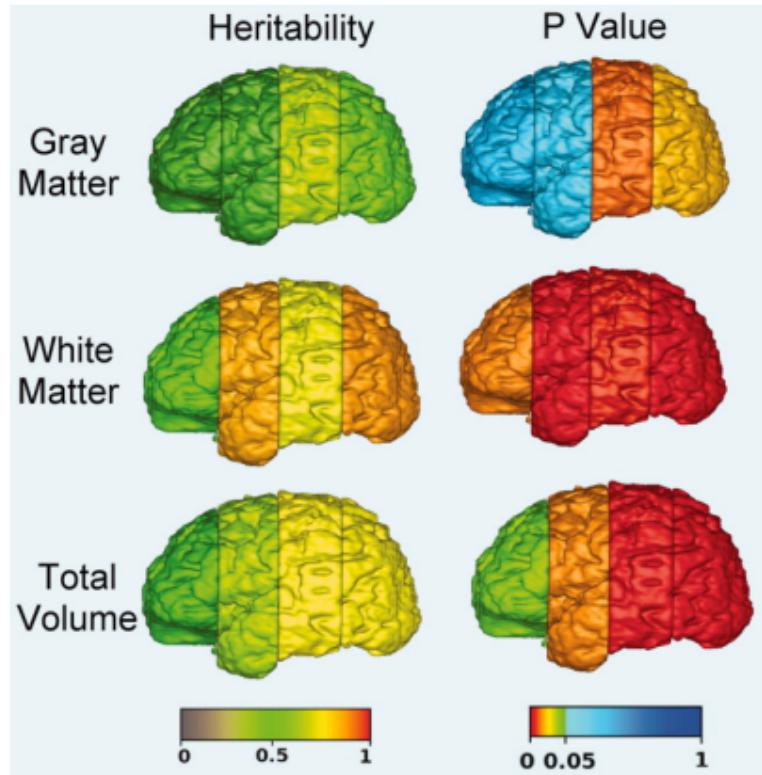
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N: 217 (MZ=2\*21, DZ=2\*50, 35 single)

$h^2$ (ICV) = 73%

$h^2$ (WM) = 85%

$h^2$ (GM) = 56%

$h^2$ (Vent.) = 71%

$h^2$ (Cb) = 17%

- For grey matter, heritability appears higher in posterior regions compared with anterior regions.
- White matter heritability appears similar throughout the brain.
- Ventricle appear more heritable in neonates than adults

Also:

"A pediatric twin study of brain morphology", Wallace et al, J Child Psychol Psyc 2006

"The changing impact of genes and environment on brain development during childhood and adolescence: initial findings from a neuroimaging study of pediatric twins", Lenroot and Giedd, Dev Psychopathol 2008

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

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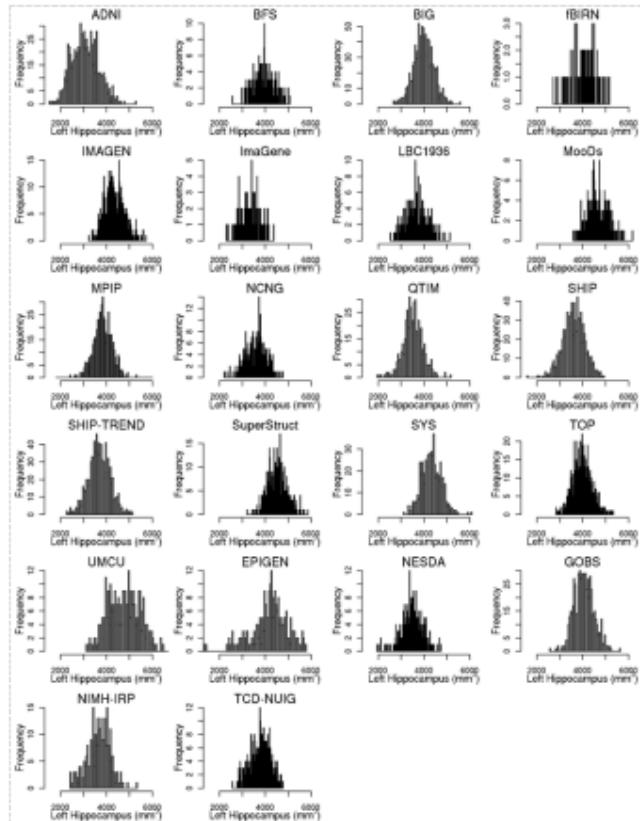
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### Hippocampal volume

**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

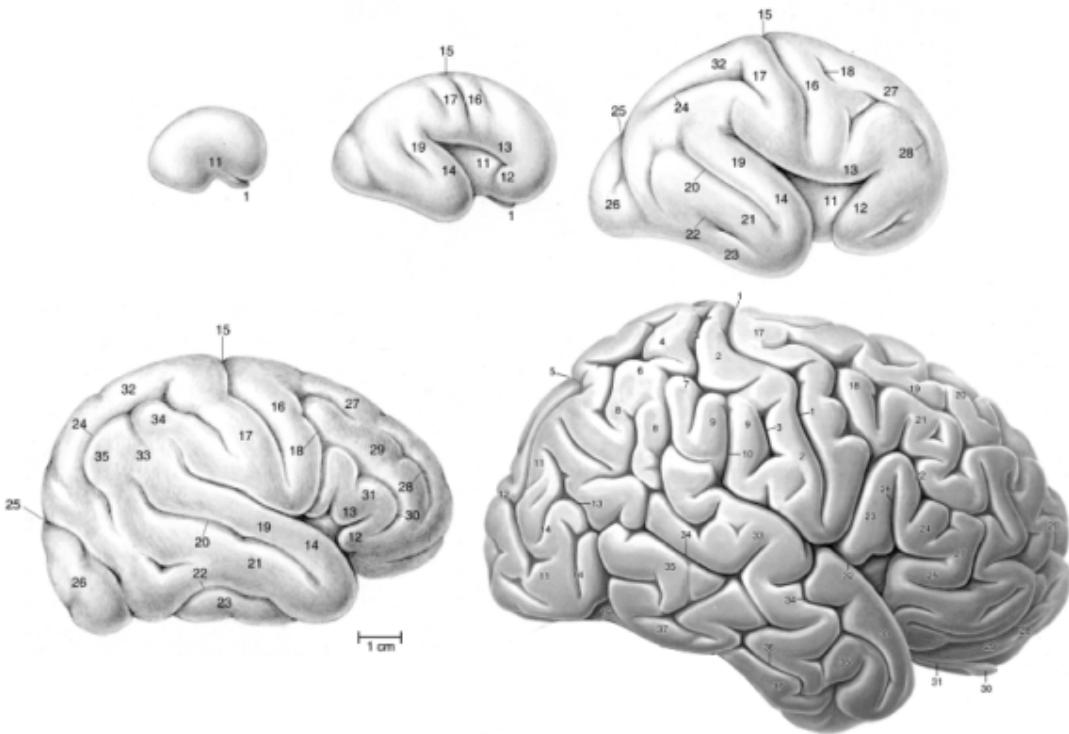
0040008 regulation of growth

N: 7795

(authors N: 209, +consortia N~1200, i.e., 8 subj/auth)

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

*cortical development*



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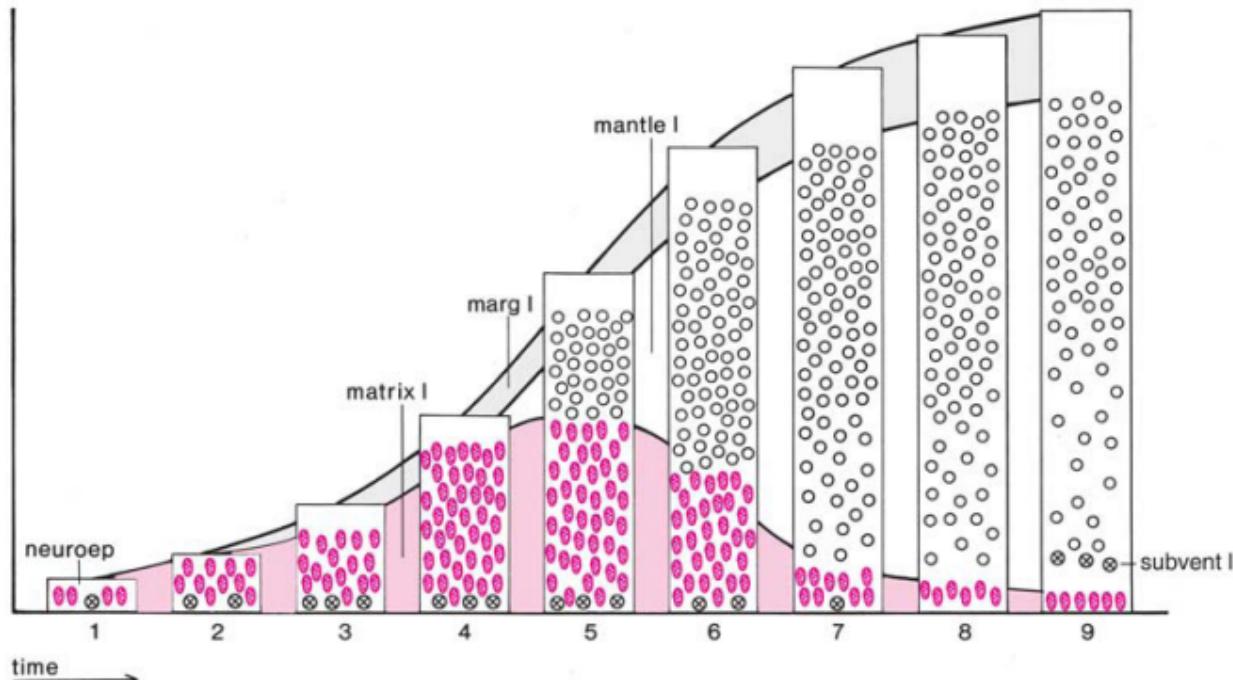
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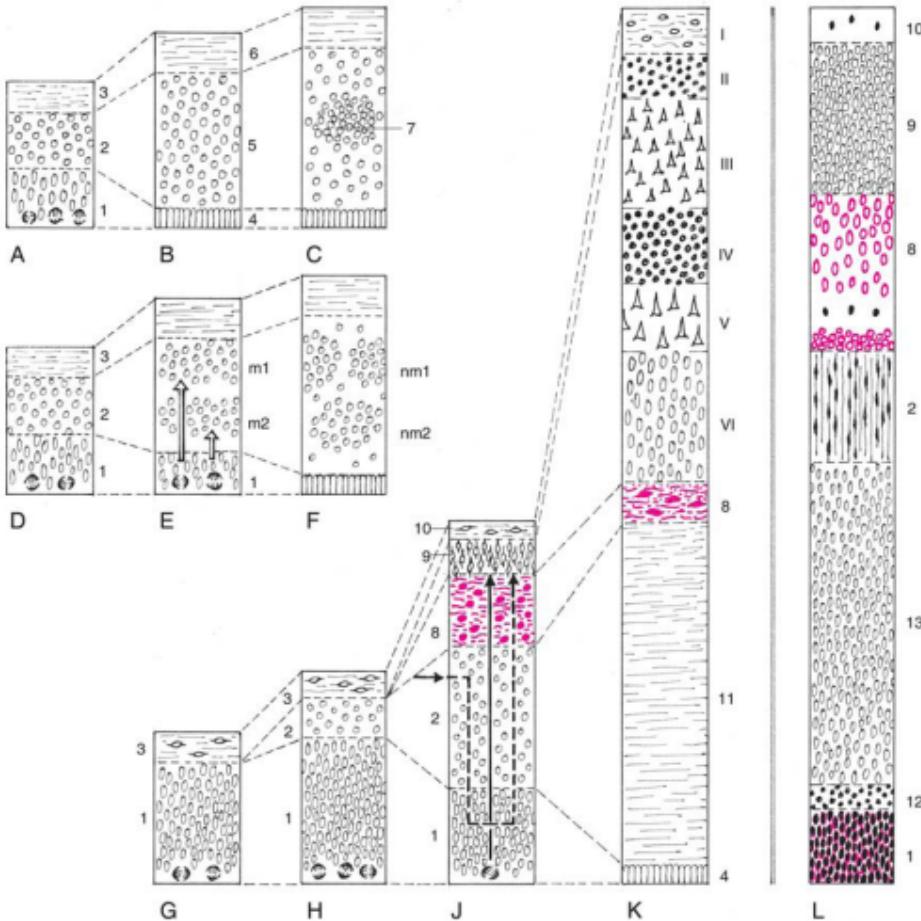
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*"Cortical thickness or gray matter volume? The importance of selecting the phenotype for imaging genetic studies", Winkler et al, NeuroImage 2009*

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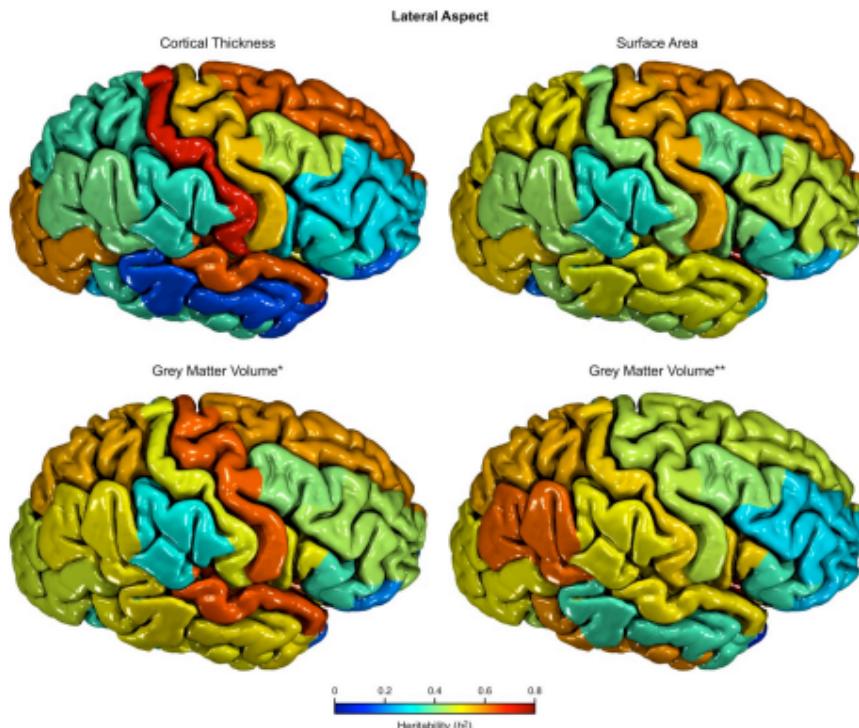
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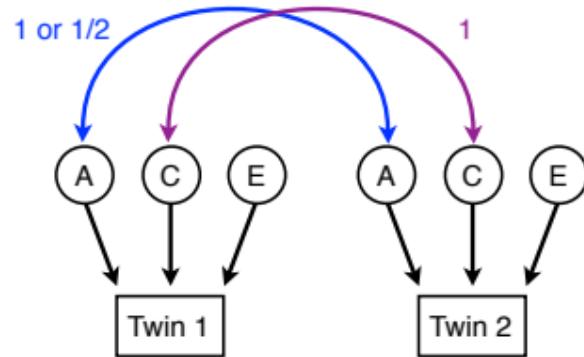
- N: 486 (extended pedigree)
- $h^2(\text{Brain Volume}) = 70\%$
- $h^2(\text{Surface}) = 70\%$
- $h^2(\text{Thickness}) = 69\%$
- $h^2(\text{GM surface-based}) = 72\%$
- $h^2(\text{GM voxel-based}) = 67\%$

- 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 their development.

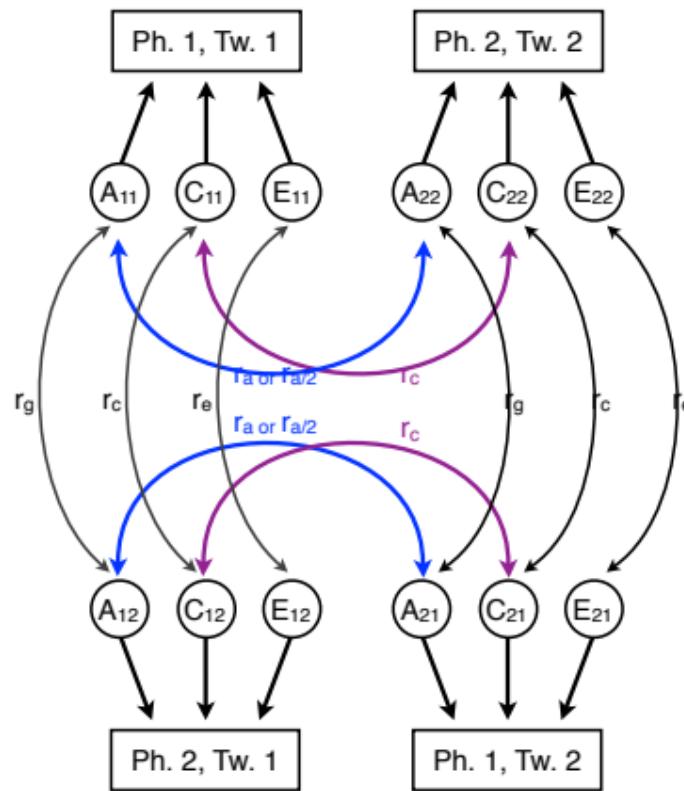
Also:

*"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*



Single phenotype



Two phenotypes: Ph. 1 and Ph. 2

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

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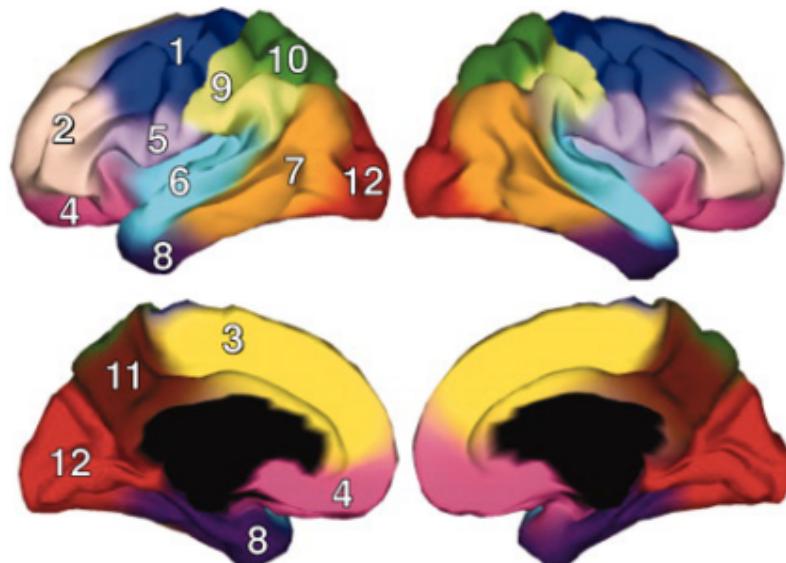
myelination

maturity

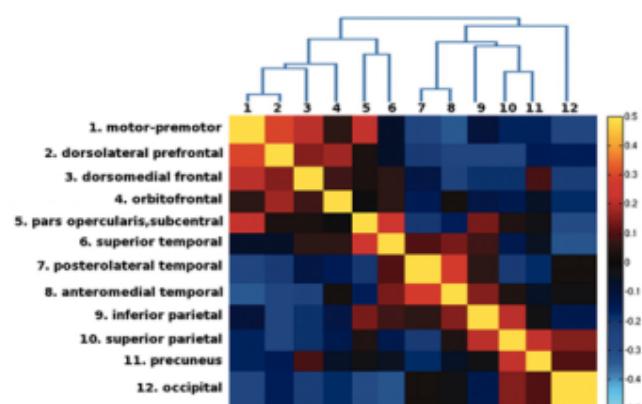
puberty

ageing

plasticity



- N: 406 (110 MZ, 93 DZ)
- Genetic-correlation-based parcellation
- The genetic organization 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

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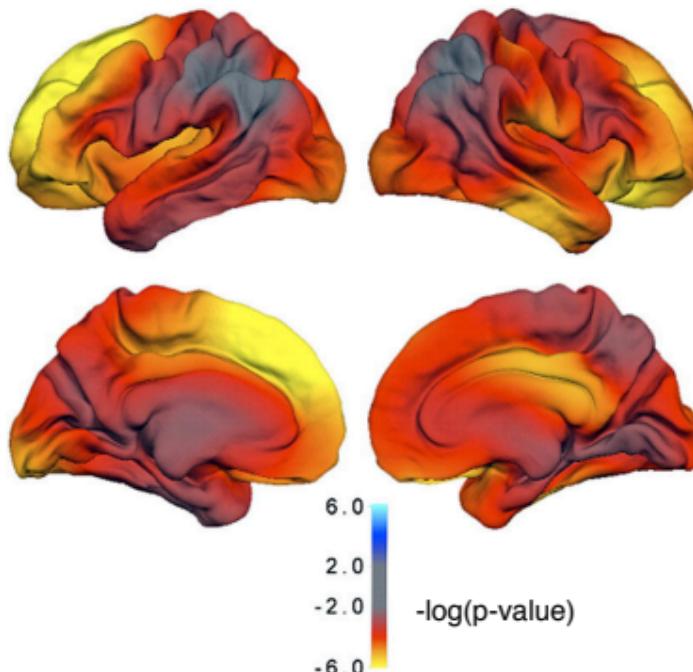
myelination

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**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)

- MCPH1, ASPM: Significant in females
- MCPH3: Significant in males

Also:

"A common MECP2 haplotype associates with reduced cortical surface area in humans in two independent populations", Joyner et al, PNAS 2009

*"Association of common genetic variants in GPCPD1 with scaling of visual cortical surface area in humans"*, Bakken et al, PNAS 2012

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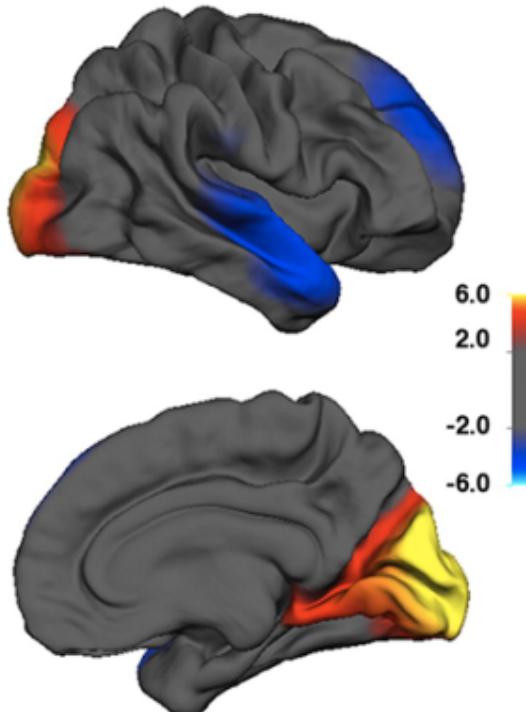
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**GPCPD1 (rs6116869, rs238295)**

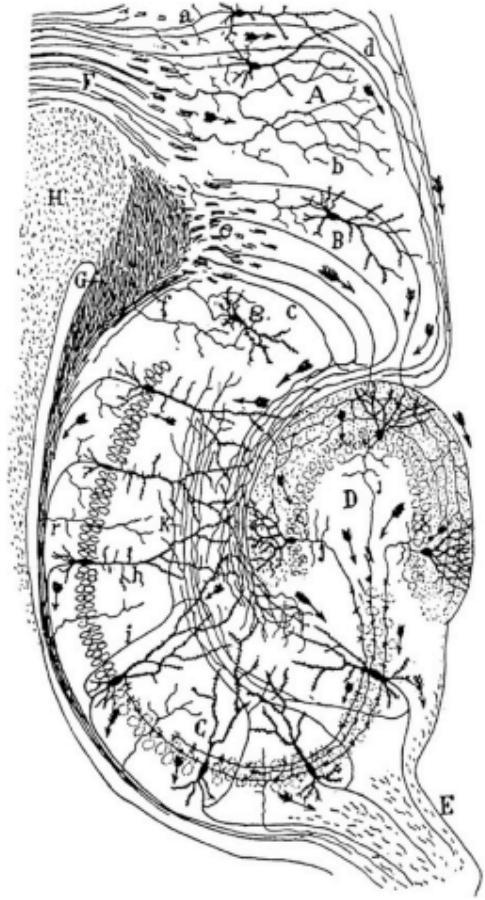
0005975 carbohydrate metabolic process (295 genes)  
0006629 lipid metabolic process (219 genes)  
0006071 glycerol metabolic process (18 genes)

- N: 421, TOP cohort
- Replication:
  - N=482, 1-tailed P=0.0083, ADNI cohort
  - N=278, 1-tailed P=0.018, PING cohort
- GPCPD1 was associated with changes in the proportion occupied by occipital cortical surface
- GPCPD1 is highly expressed in occipital cortex compared with the remainder of cortex

Also:

*"KCTD8 Gene and Brain Growth in Adverse Intrauterine Environment: A Genome-wide Association Study"*,  
Paus et al, Cereb Cortex 2011

*connectivity*



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1 Subcortical branching



2 Cortical ingrowth



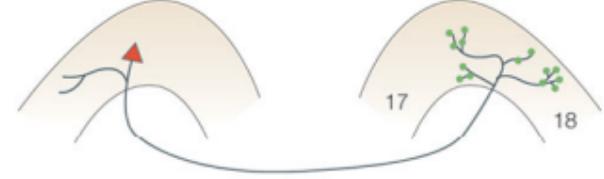
3 Intracortical branching



4 Synaptogenesis



5 Synaptic reduction



6 Myelination



Yellow triangle = Growth cones   Green dot = Synapses   Red triangle = Stable projections   Blue triangle = Transient projections

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

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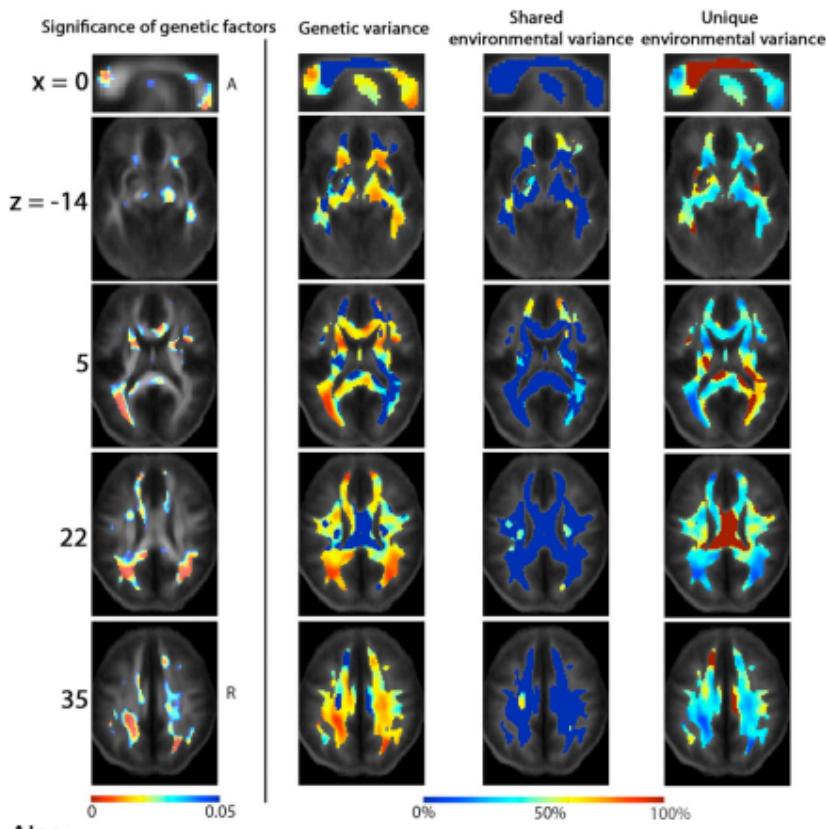
myelination

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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

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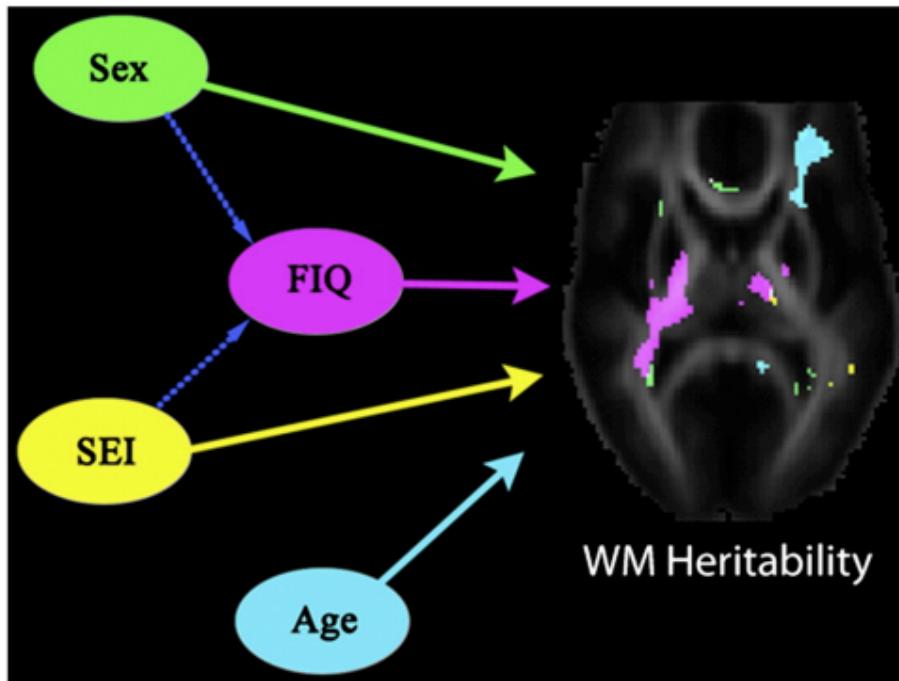
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N: 705 (119 MZ, 152 DZ, 5 TZ, + sibs)

- In adolescents:  $h^2(FA)=70\text{--}80\%$ , in adults:  $h^2(FA)=30\text{--}40\%$
- $h^2(FA)$  larger in males than in females
- $h^2(FA)$  is modulated by socioeconomic status (larger in some regions, smaller in others)

Also:

*"A Multimodal Assessment of the Genetic Control over Working Memory"*, Karlsgodt et al, J Neurosci 2010

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

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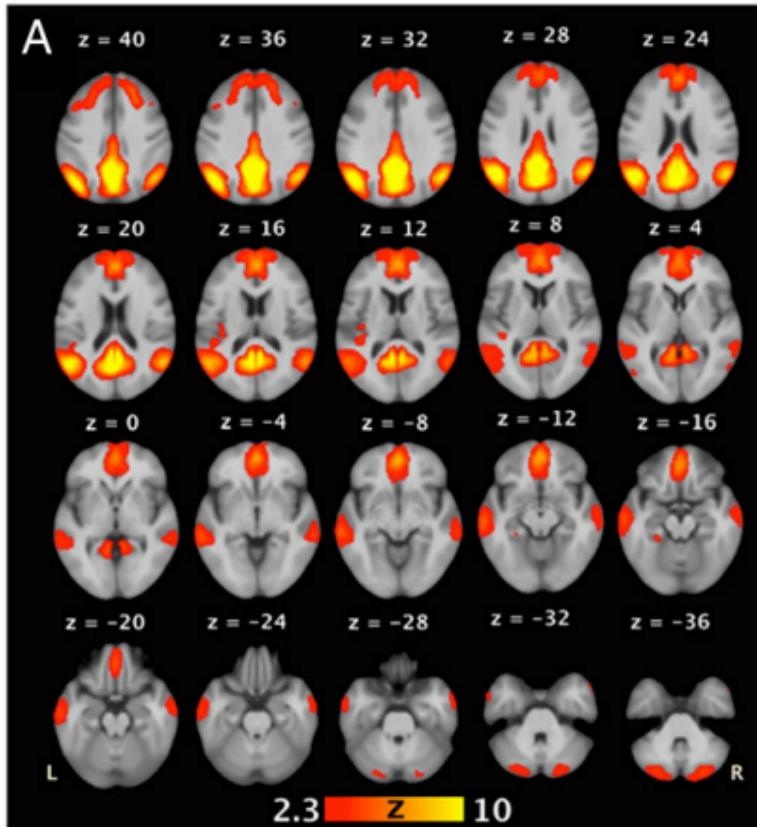
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- N: 333 (extended pedigree)

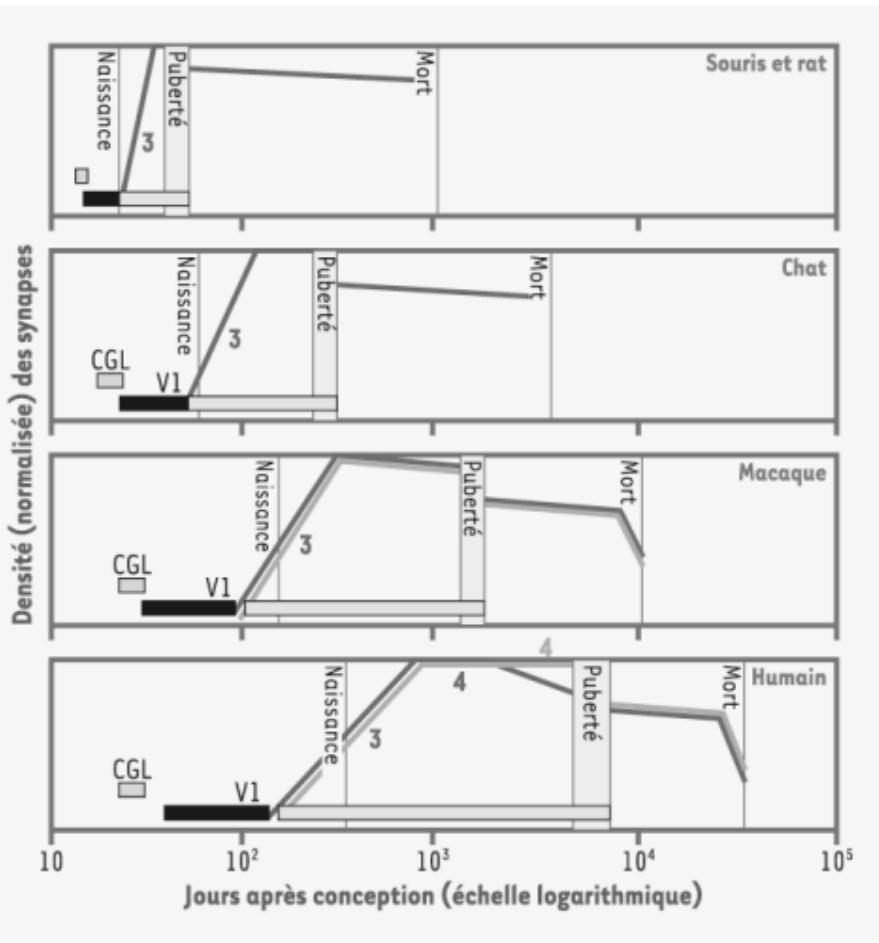
$h^2$ (Funct. Conn) = 42%

$h^2$ (GM density) = 32%

$r_g$  = 0.07

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

*maturation*



*"Why do many psychiatric disorders emerge during adolescence?", Paus et al, Nat Rev Neurosci 2008*

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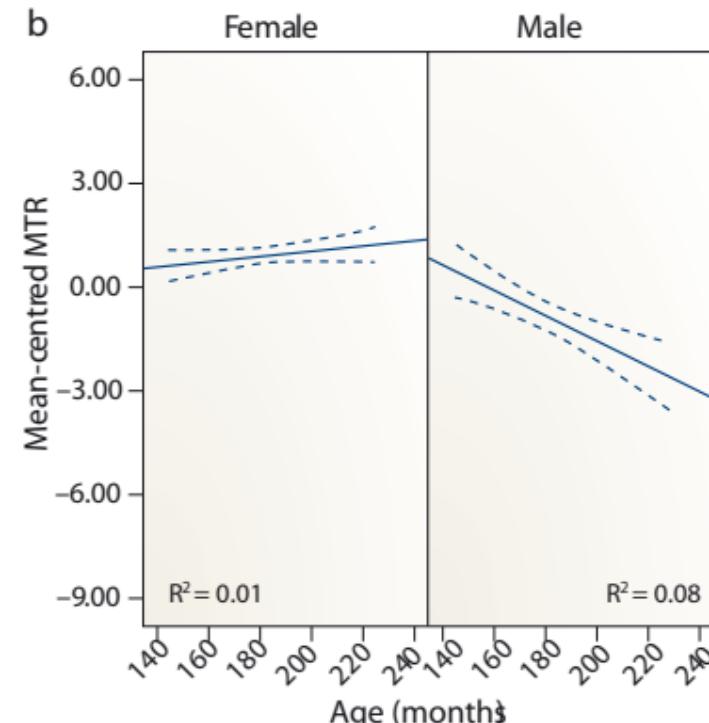
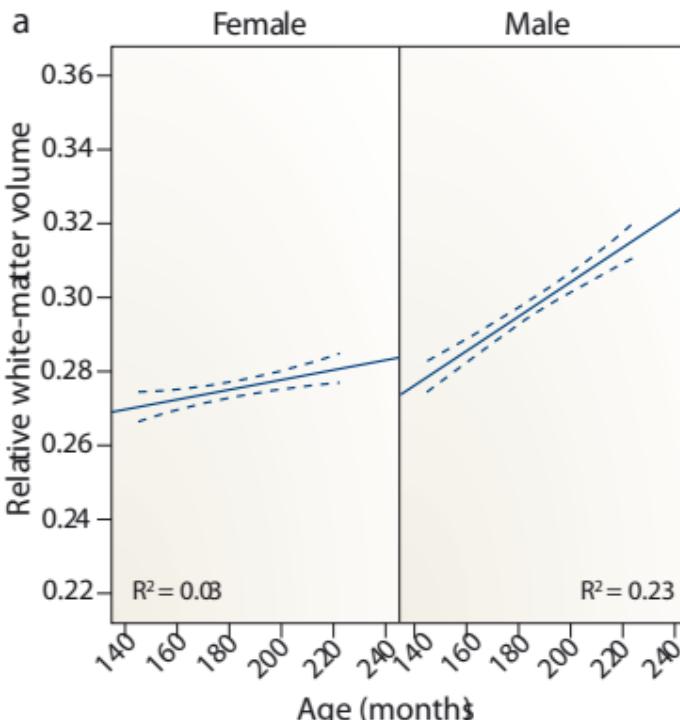
myelination

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*"Growth of white matter in the adolescent brain: role of testosterone and androgen receptor",  
Perrin et al, J Neurosci 2008*

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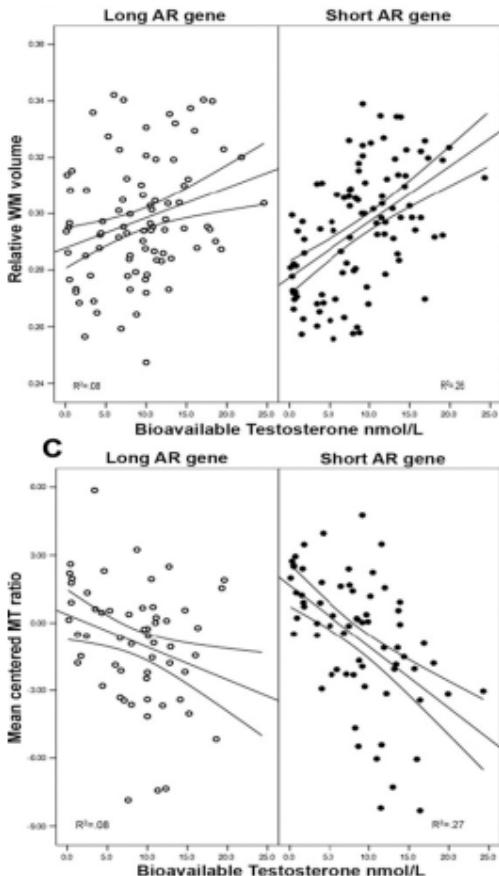
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**AR** (number of CAG repeats in exon 1)  
 0008584 male gonad development (30)  
 0050790 regulation of catalytic activity (8)  
 0001701 in utero embryonic development (103)  
 0030521 androgen receptor signaling pathway (37)  
 0019102 male somatic sex determination (1)  
 0007267 cell-cell signaling (239)  
 0008219 cell death (100)  
 0007548 sex differentiation (18)  
 0008283 cell proliferation (265)  
 0030850 prostate gland development (10)  
 0016049 cell growth (46)  
 + 0045944, 0006810, 0007165

- N: 408

- The number of CAG repeats in Exon 1 believed to be inversely proportional to the AR transcriptional activity.
- Testosterone-related increase of WM was stronger in males with the lower number of CAG repeats ( $R^2$  of 26% vs 8%)
- WM growth does not seem to be due to myelination.

*"The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology"*, Pezawas et al, J Neurosci, 2004

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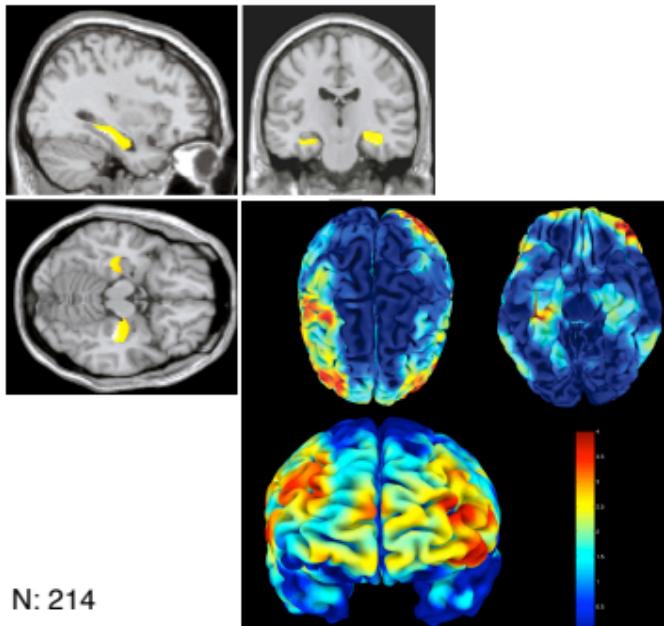
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- BDNF Val66Met has been associated with variation in human memory and the susceptibility to various psychiatric disorders.

- Carriers of the Met allele were observed to have smaller hippocampal volume and prefrontal GM volume compared with Val carriers. A local effect of BDNF?

### ***BDNF (rs6265)***

- 0014047 glutamate secretion (4)
- 0007611 learning or memory (22)
- 0048167 regulation of synaptic plasticity (14)
- 0007406 negative regulation of neuroblast proliferation (7)
- 0007411 axon guidance (66)
- 0007412 axon target recognition (3)
- 0021675 nerve development (6)
- 0043524 negative regulation of neuron apoptosis (39)
- 0045666 positive regulation of neuron differentiation (16)
- 0046668 regulation of retinal cell programmed cell death (2)
- 0006916 anti-apoptosis (180)
- 0016358 dendrite development (19)
- + 0001657, 0007631, 0048839, 0042596, 0042490, 0042493, 0008038, 0019222

*"Genetic Contribution to Variation in Cognitive Function: An fMRI Study in Twins"*,  
Koten et al, Science 2009

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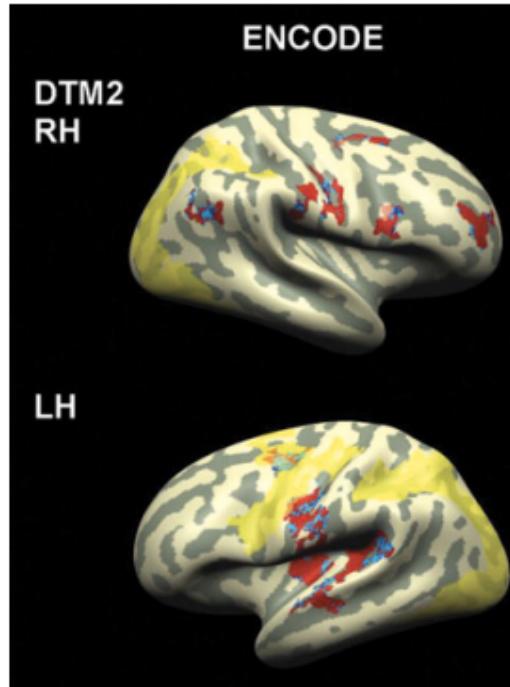
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N: 30 ( =10\*2 MZ + 10 Sib)

Age:  $28.6 \pm 9.8$  years

Netherlands Twin Registry

- Digit memory task (2 or 4 digits) with distraction
- Significant genetic influence on brain activation in neural networks supporting digit working memory tasks
- Genetically influenced differences in brain activation cause qualitative differences in neurocognitive processing
- DTM2: 2 digit memorisation task with arithmetic distractor

Red:  $h^2(\text{BOLD}) > 80\%$ ,

Light blue:  $h^2(\text{BOLD})$  in 60-80%

Blue:  $h^2(\text{BOLD}) < 60\%$

Also:

*"Quantifying the heritability of task-related brain activation and performance during the N-back working memory task: A twin fMRI study"*, Blokland et al, Biological Psychology 2008

*"Heritability of Working Memory Brain Activation"*, Blokland et al, J Neurosci 2011

*"Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease"*, Potkin et al, PLoS One 2009

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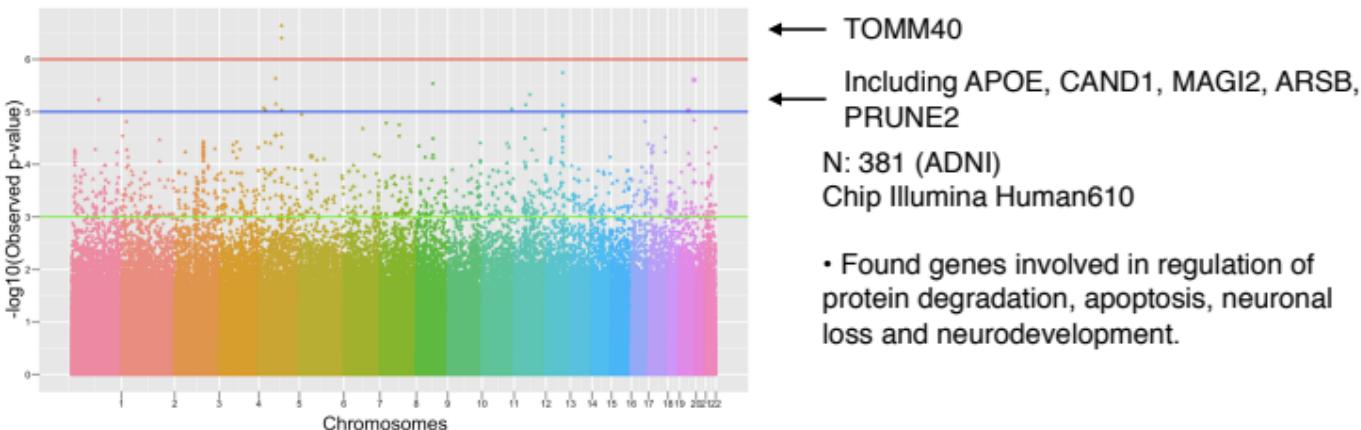
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**APOE (rs429358, rs7412)**

0006916 anti-apoptosis  
0010468 regulation of gene expression  
0045471 response to ethanol  
0006917 induction of apoptosis  
0048168 regulation of neuronal synaptic plasticity  
0030516 regulation of axon extension  
+ many more (82 categories in total!)

**TOMM40 (rs2075650, rs11556505, rs157580)**

0006820 anion transport  
0015031 protein transport  
0006626 protein targeting to mitochondrion

Also: "Common variants at 12q14 and 12q24 are associated with hippocampal volume", Bis et al, Nature Genetics 2012 -> N=9232, 67.1 years (56-84), New genes: DPP4, HRK/FBXW8, MSRB3/WIF1, Replicate: APOE (P=0.005), BIN1 (P=0.02), MS4A4E (P=0.001) and TOMM40 (P=0.01)

*summary & discussion*

Neuroimaging provides **interesting** and **relevant** endophenotypes to study brain development and psychiatric disorders.

Heritability studies show that brain anatomy has a **strong genetic component**. The little variance explained by the current candidate genes suggests the presence of **many genes of small effect**. It is then fundamental to ensure the biological pertinence and the accuracy in the neuroimaging endophenotypes used.

Brain morphogenesis is subject to strong **developmental constraints**, understanding this process is essential to understand brain variability

Genetic polymorphisms reflect the **diversity of human populations**, but do they encode **neuroanatomical diversity** or the susceptibility to common psychiatric diseases?

## *Acknowledgments*

### **Institut Pasteur, Université Paris 7, CNRS**

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