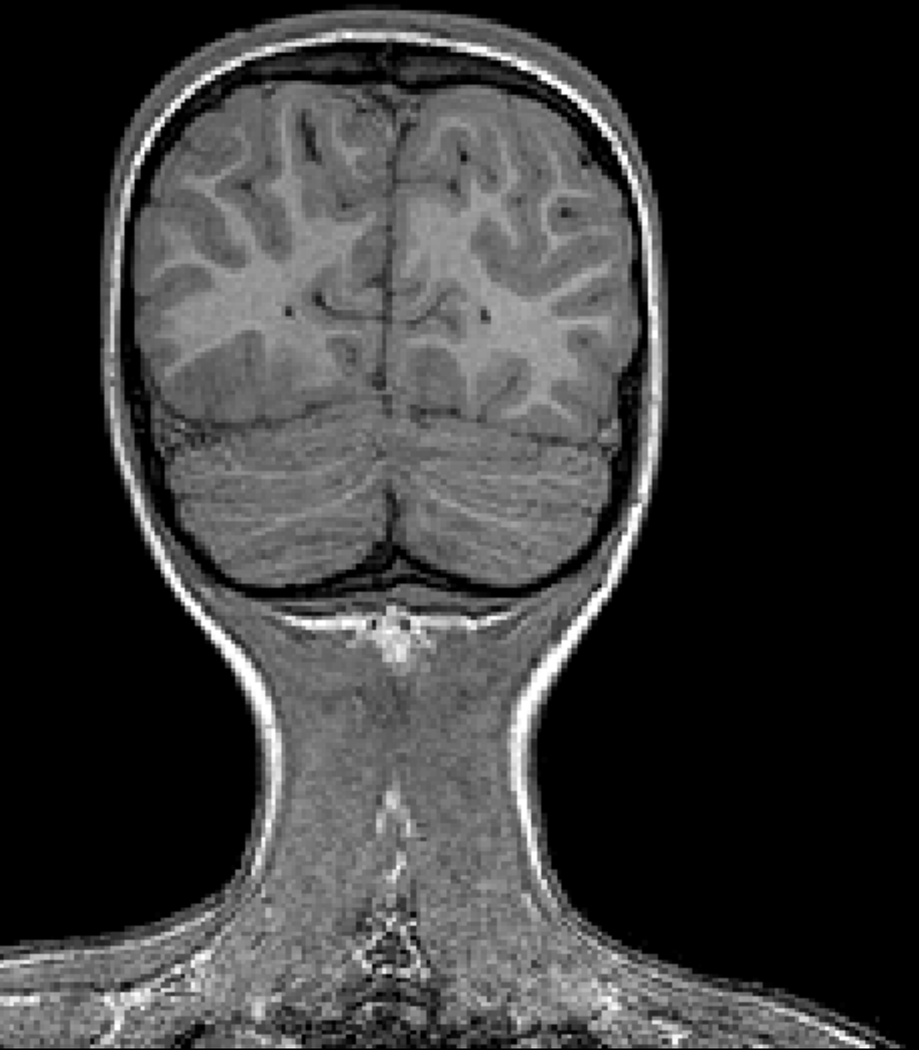

Overview of neuroimaging phenotypes

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roberto toro • rto@pasteur.fr

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 pedegree studies) suggest that inheritable factors largely determine various structural properties of the brain, supporting the use of neuroimaging endophenotypes in the research for the genetic causes of psychiatric diseases.

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

In the last 10 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 disorders.

early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

axon growth

myelination

maturation

puberty

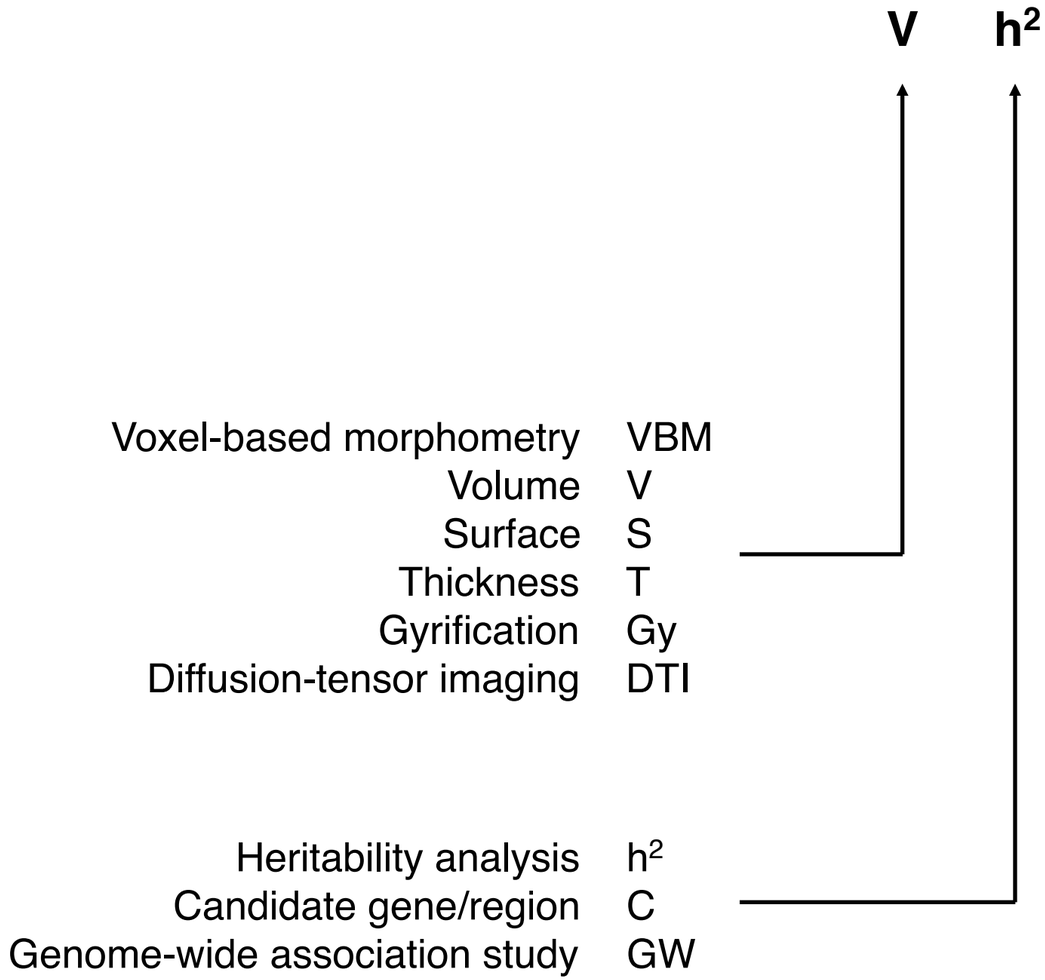
aging

plasticity

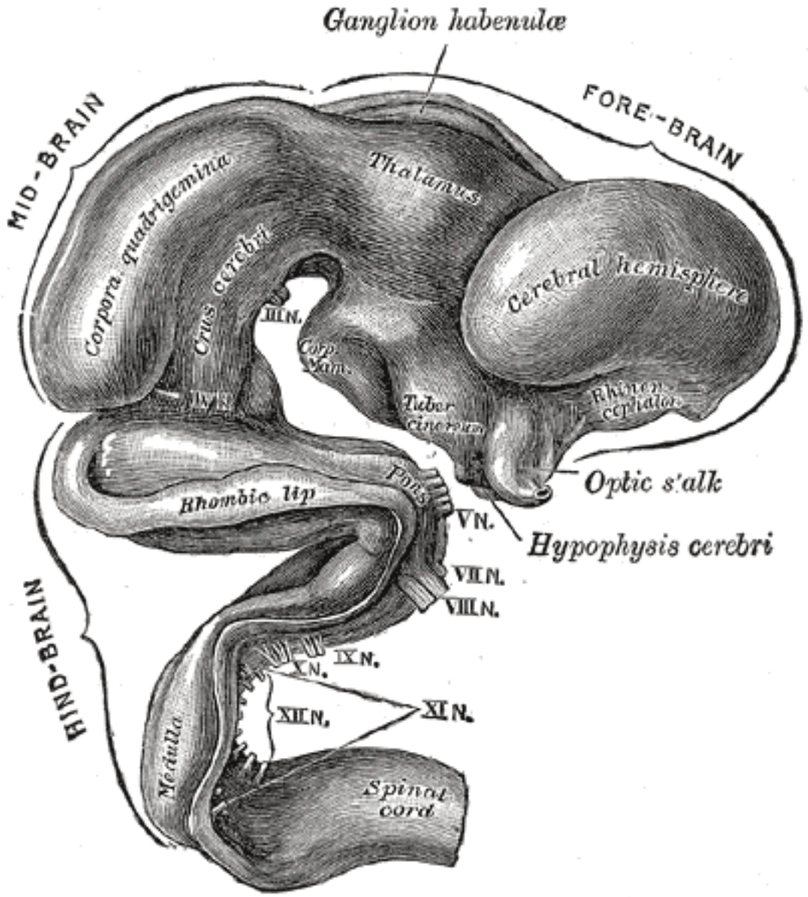
Gene:
MECP2

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



"Brain volumes and surface morphology in monozygotic twins", White et al, Cereb Cortex 2002

V **h^2**

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)

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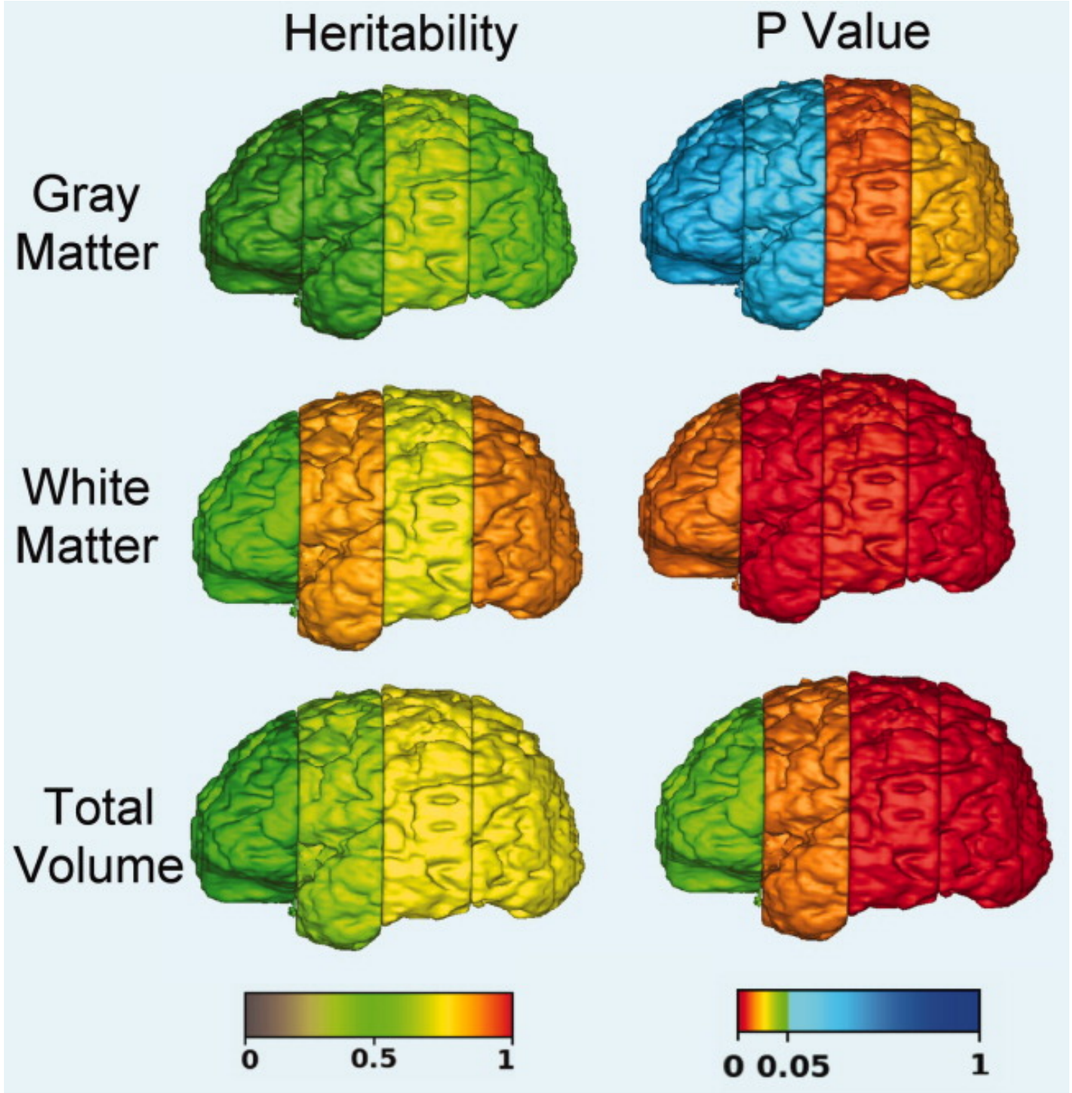
"Genetic and environmental contributions to neonatal brain structure: a twin study", Gilmore et al, Hum Brain Mapp 2010

V **h^2**



N=217 (MZ=2*21, DZ=2*50, 35 single)
h2(ICV)=73%
h2(WM)=85%
h2(GM)=56%
h2(Lateral ventricles)=71%
h2(Cerebellum)=17%

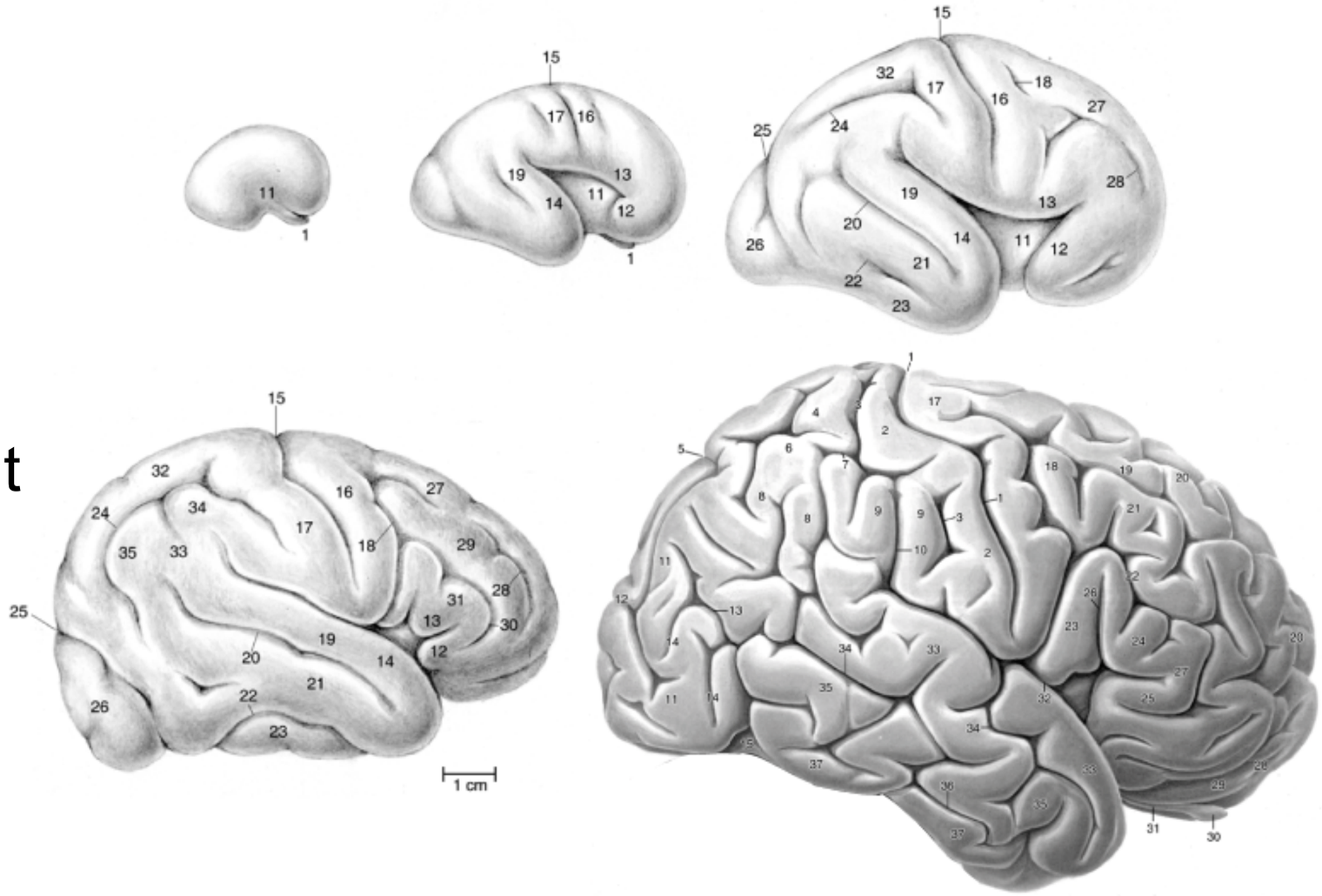
For grey matter, heritability appears higher in posterior regions compared with anterior regions.

White matter heritability appears similar throughout the brain.

Ventricles 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

Cortical development



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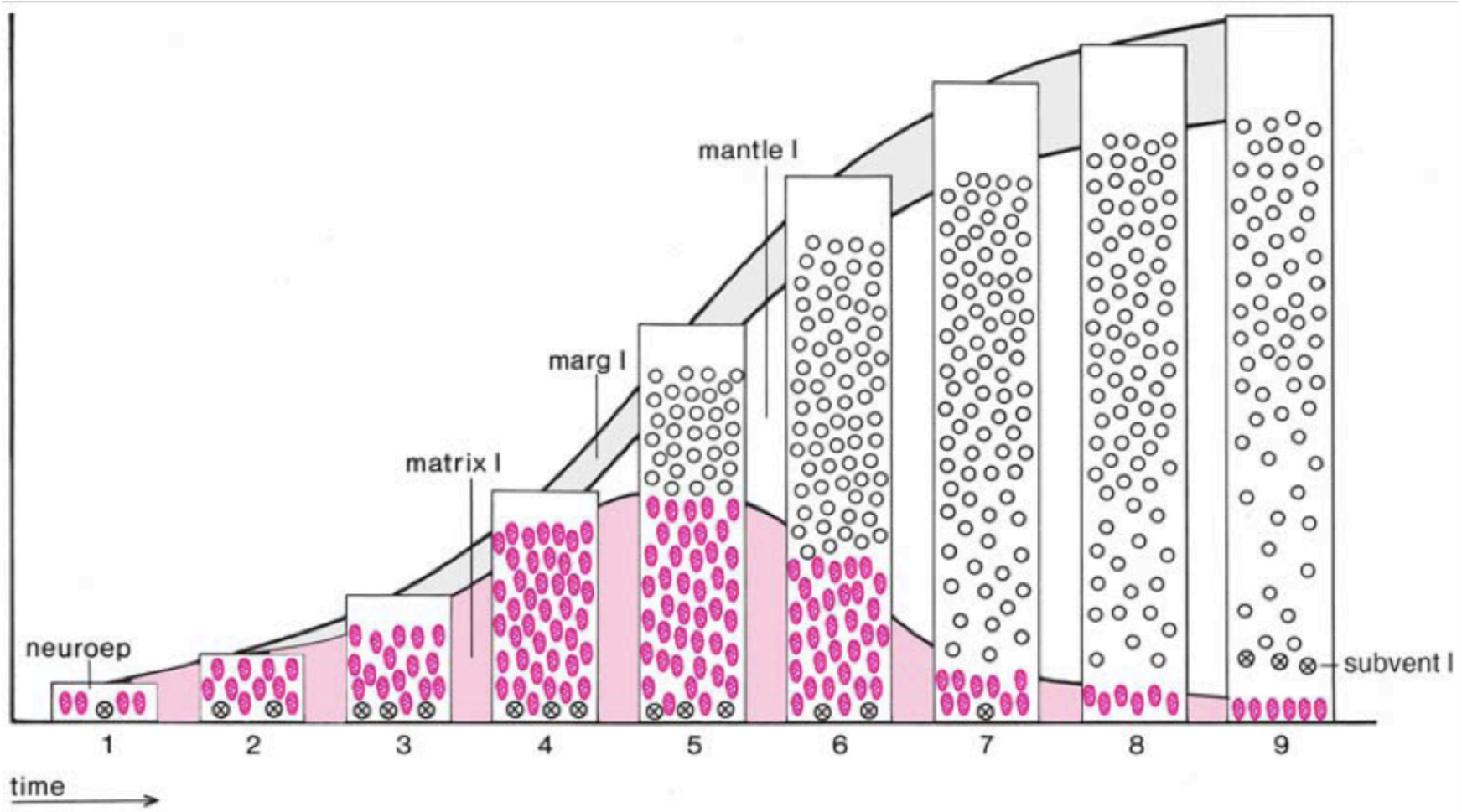
puberty

aging

plasticity



Nieuwenhuys, 2008

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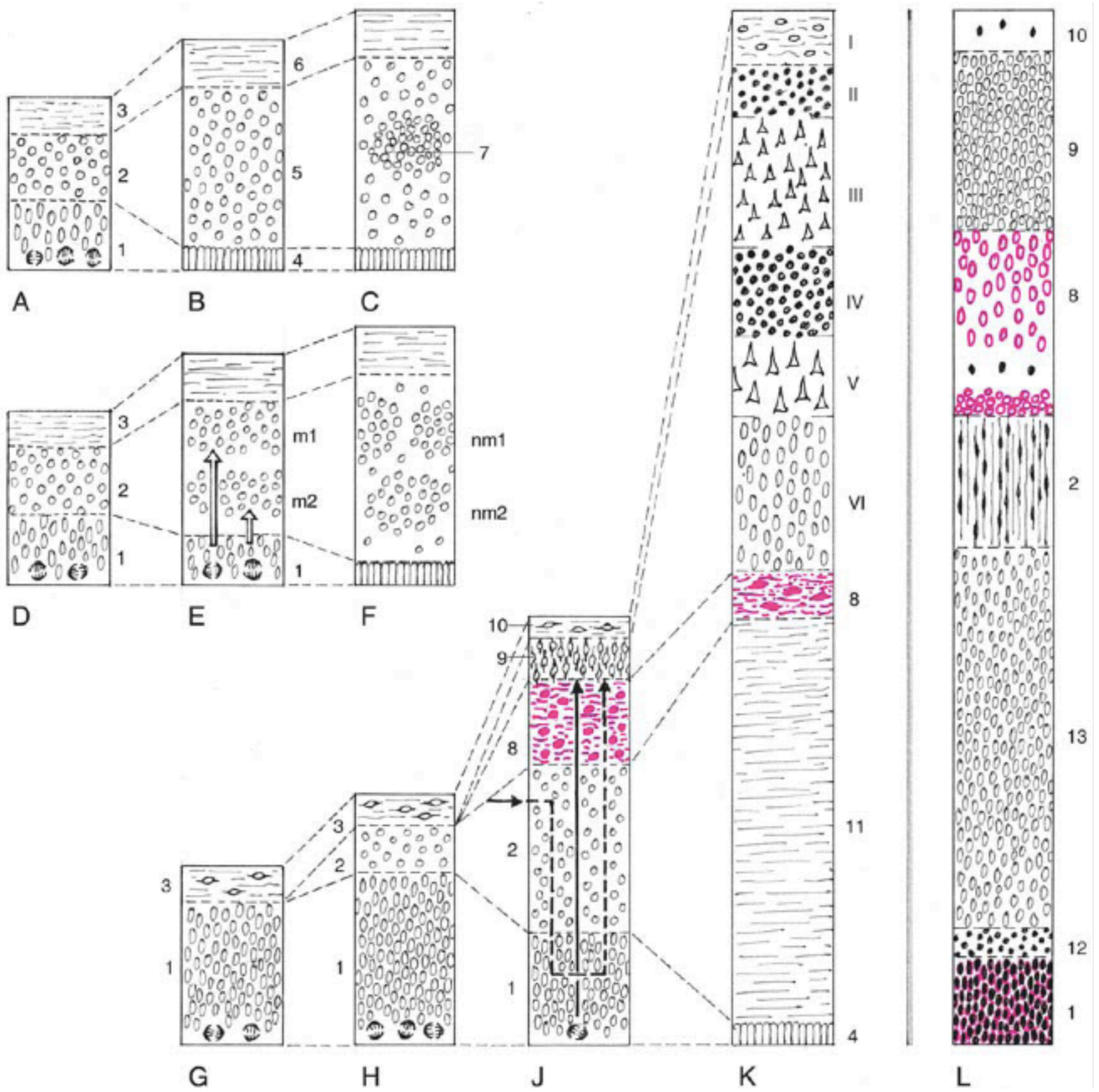
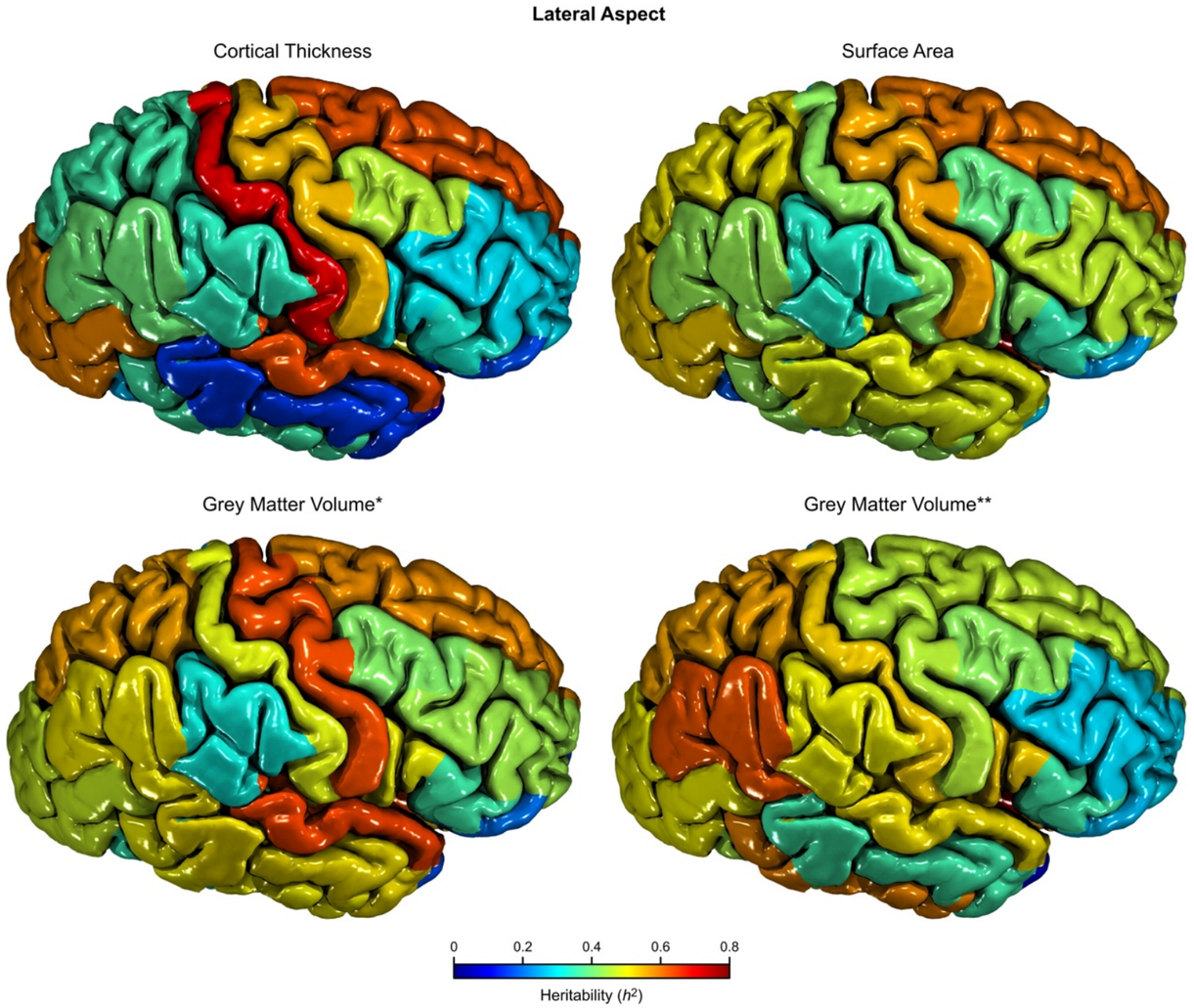


Nieuwenhuys, 2008

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

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

S T h^2



N=486 (extended pedigrees)
h2(Brain Vol)=70%
h2(Surf)=70%
h2(Thickn)=69%
h2(GM surf-based)=72%
h2(GM vox-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 (rg=-0.15) suggests that different genetic mechanisms are at play 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

early development

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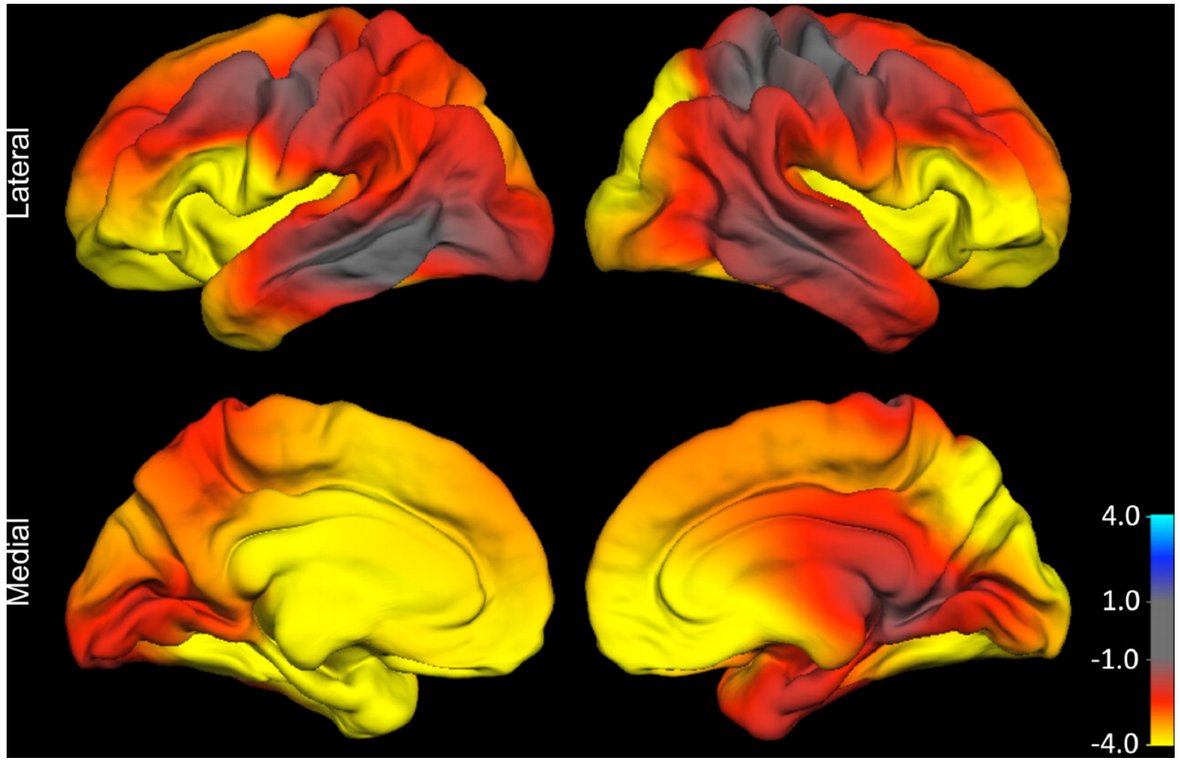
“A common MECP2 haplotype associates with reduced cortical surface area in humans in two independent populations”, Joyner et al, PNAS 2009



MECP2 (rs2266887, rs2266888, rs3027898, rs17435, **rs2239464** [TOP+ADNI)

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

N=289 (TOP) + 655 (ADNI)

Various mutations of MECP2 (located in the X chromosome) have been found in subjects with Rett syndrome (which affects only females).

Here, the association was only found in males.

Reduced surface was found in specific cortical regions (cuneus, fusiform gyrus, pars triangularis). A local effect?

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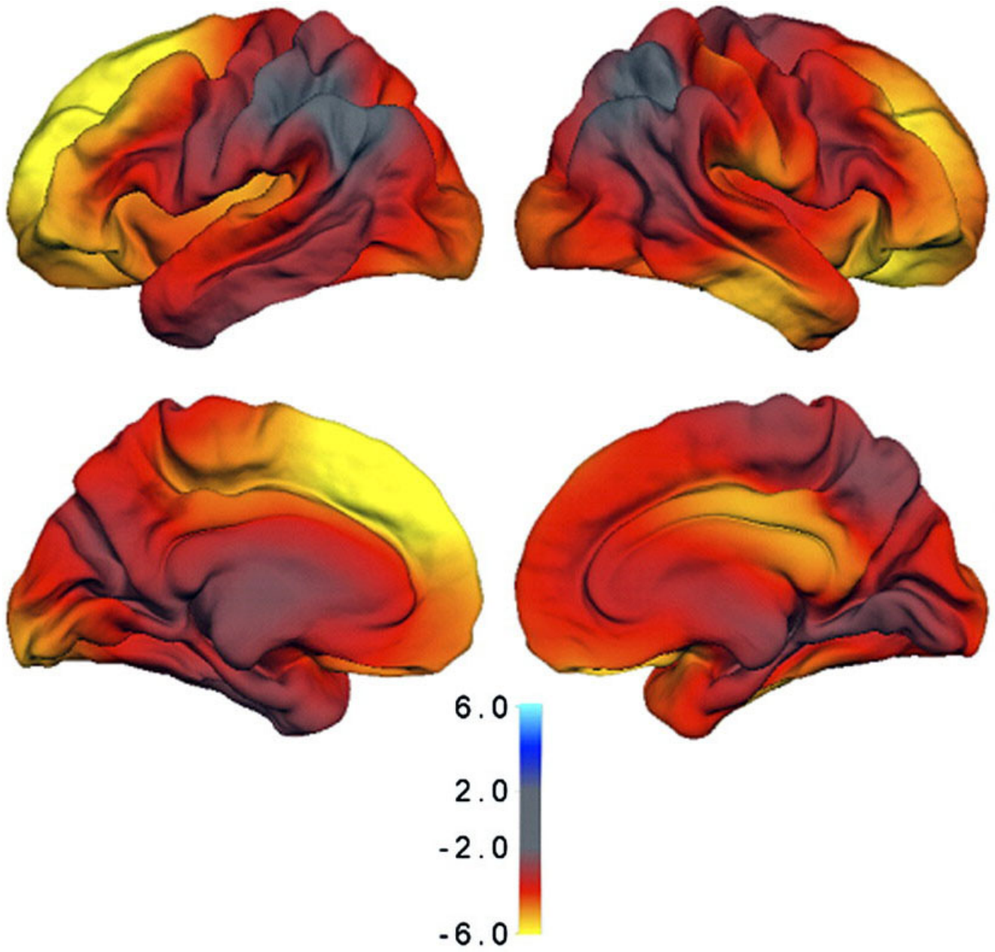
“Sex-dependent association of common microcephaly genes with brain structure” Rimol et al, PNAS 2009

S **C**



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

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

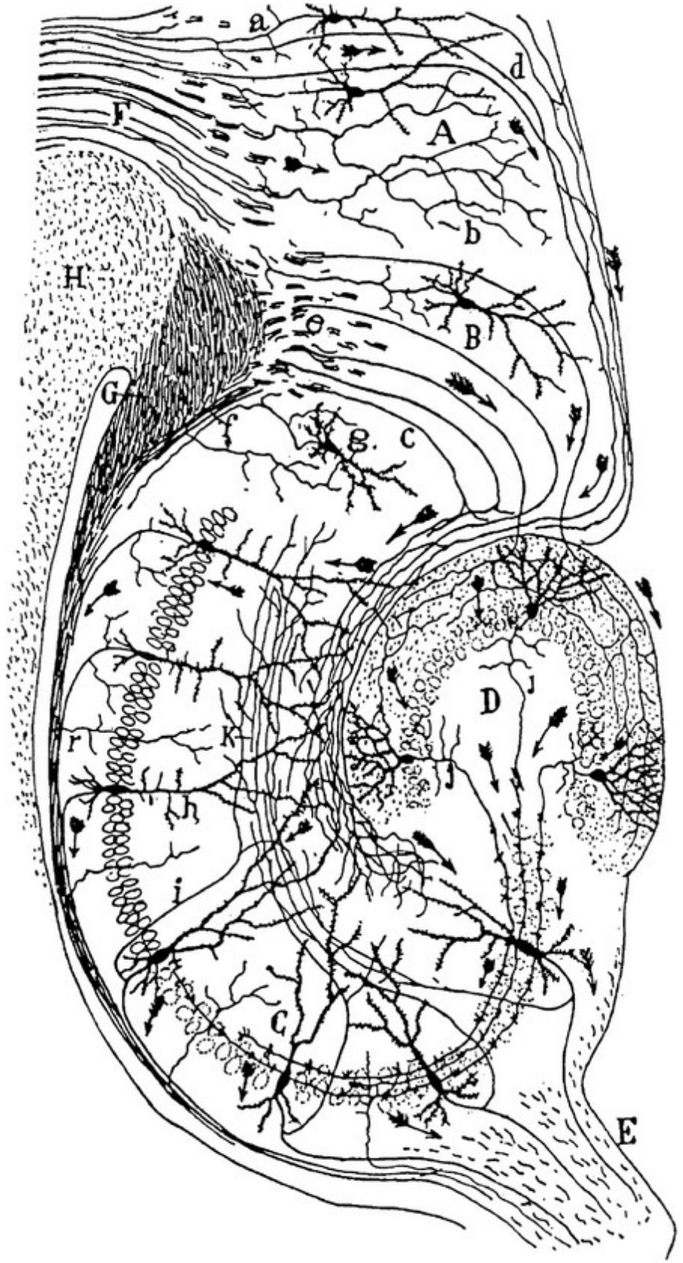
MCPH1 (rs2816514, rs2816517, rs11779303, rs11779303)

[no biol. proc. in GO]

ASPM (rs10922168)

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

Connectivity



early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

axon growth

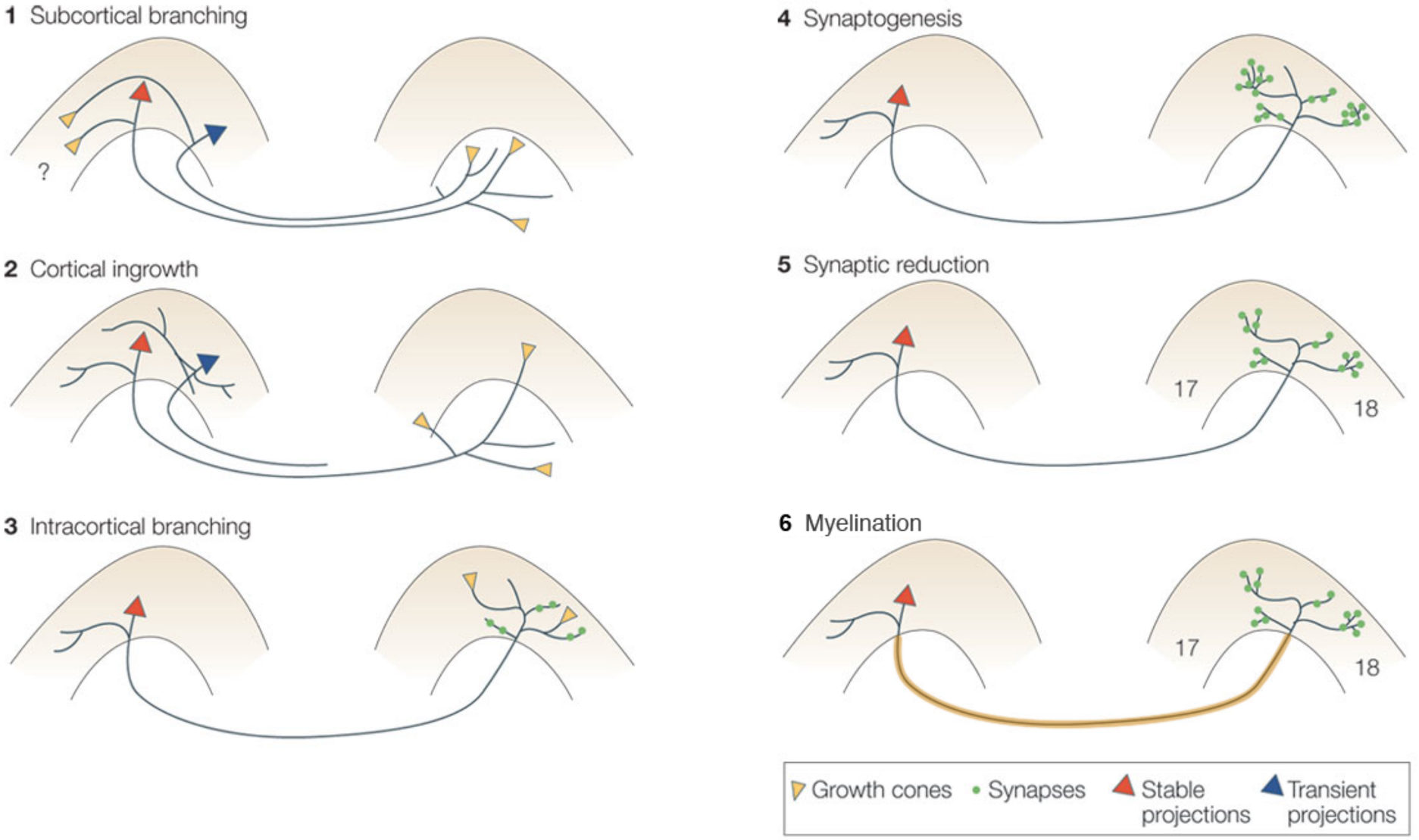
myelination

maturation

puberty

aging

plasticity



Innocenti and Price, 2005

early development

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mitosis

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neuropil develop.

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axon growth

myelination

maturation

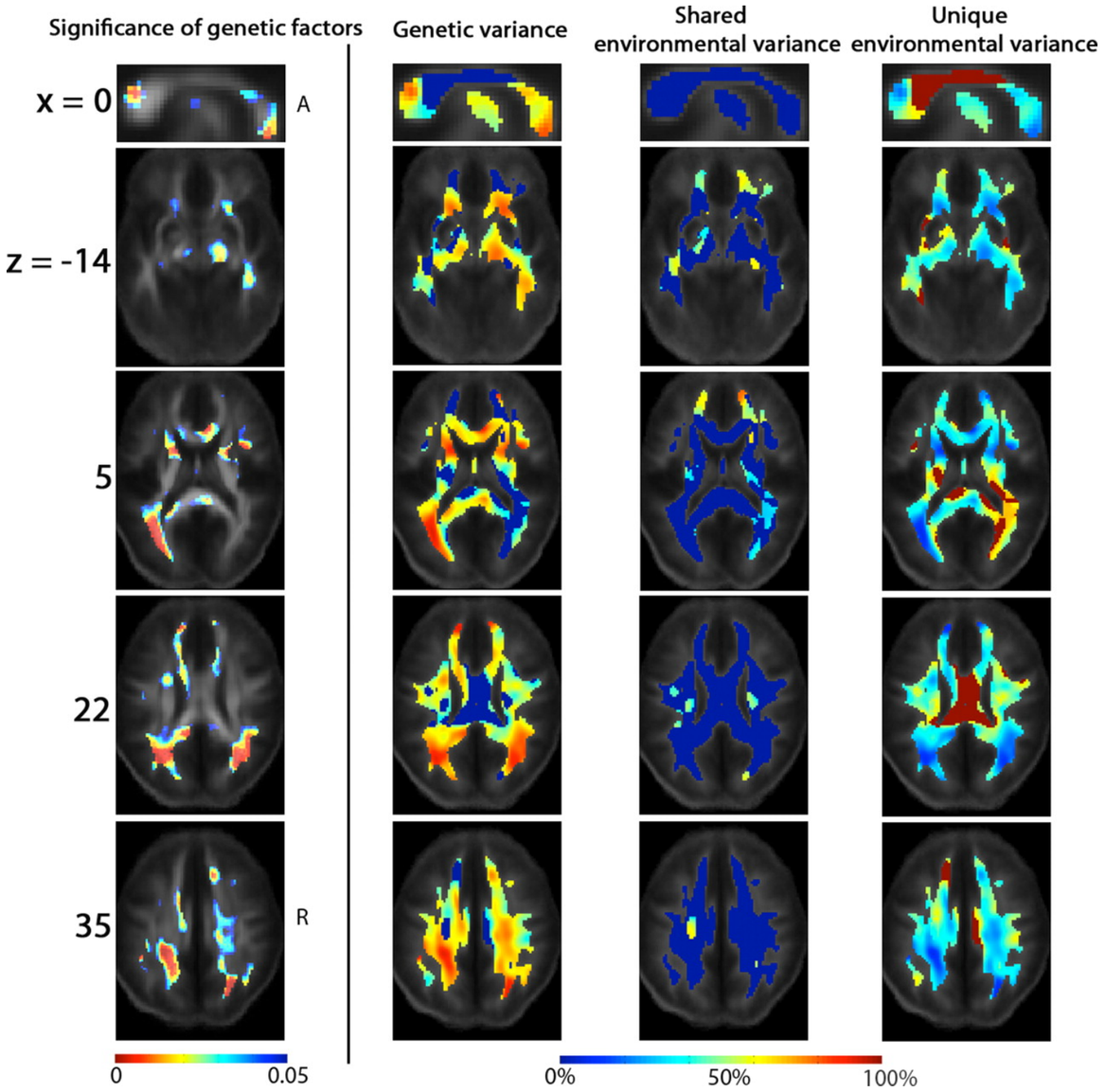
puberty

aging

plasticity

“Genetics of brain fibre architecture and intellectual performance”, Chiang et al, J Neurosci 2009

DTI **h^2**



N= 92 (MZ=2*23, DZ=2*23)
h2(FA) values between 55% (Frontal left) to 85% (Parietal left)

Common genetic factors mediated the correlation between IQ and white matter integrity.

early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

axon growth

myelination

maturation

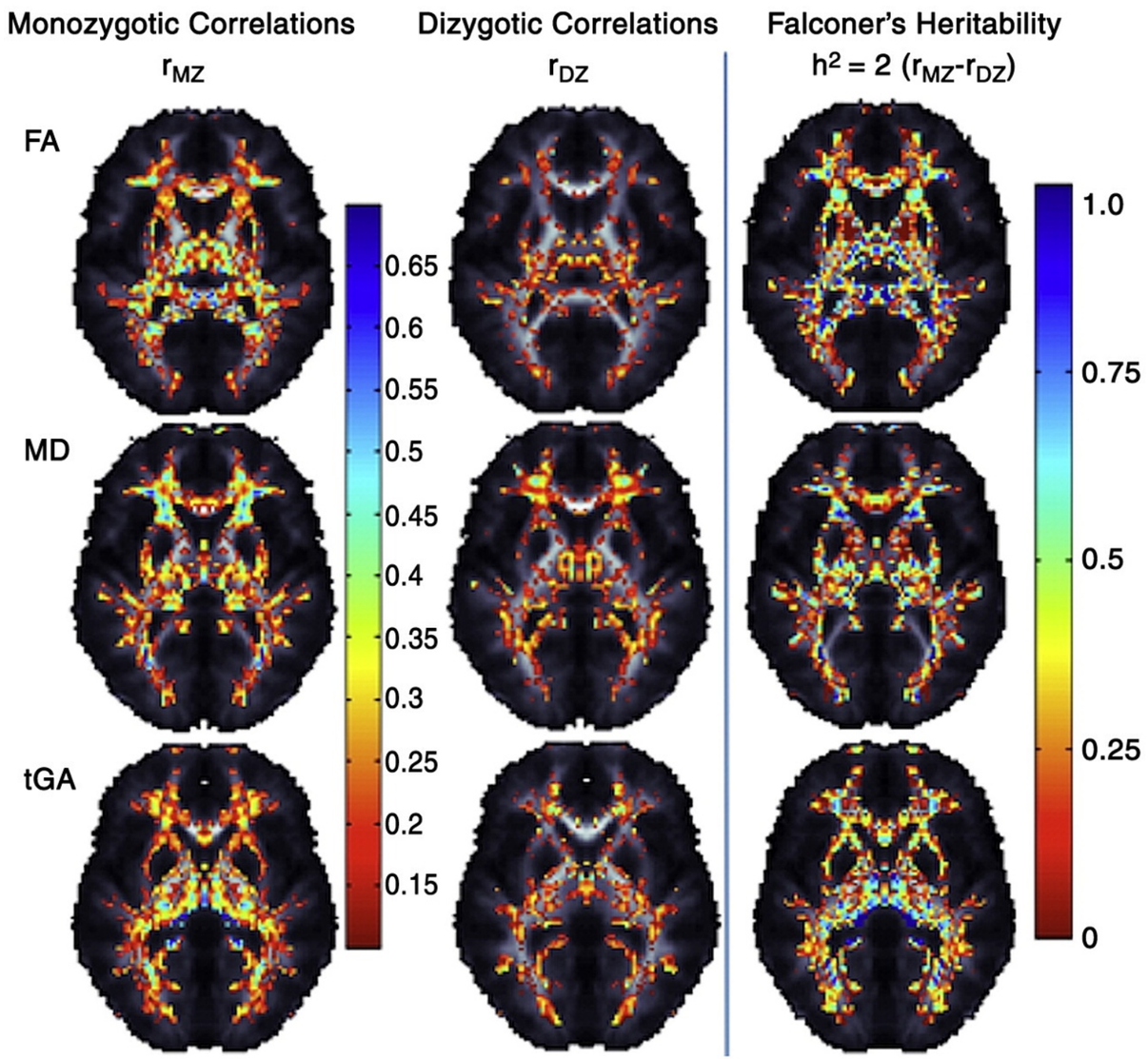
puberty

aging

plasticity

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

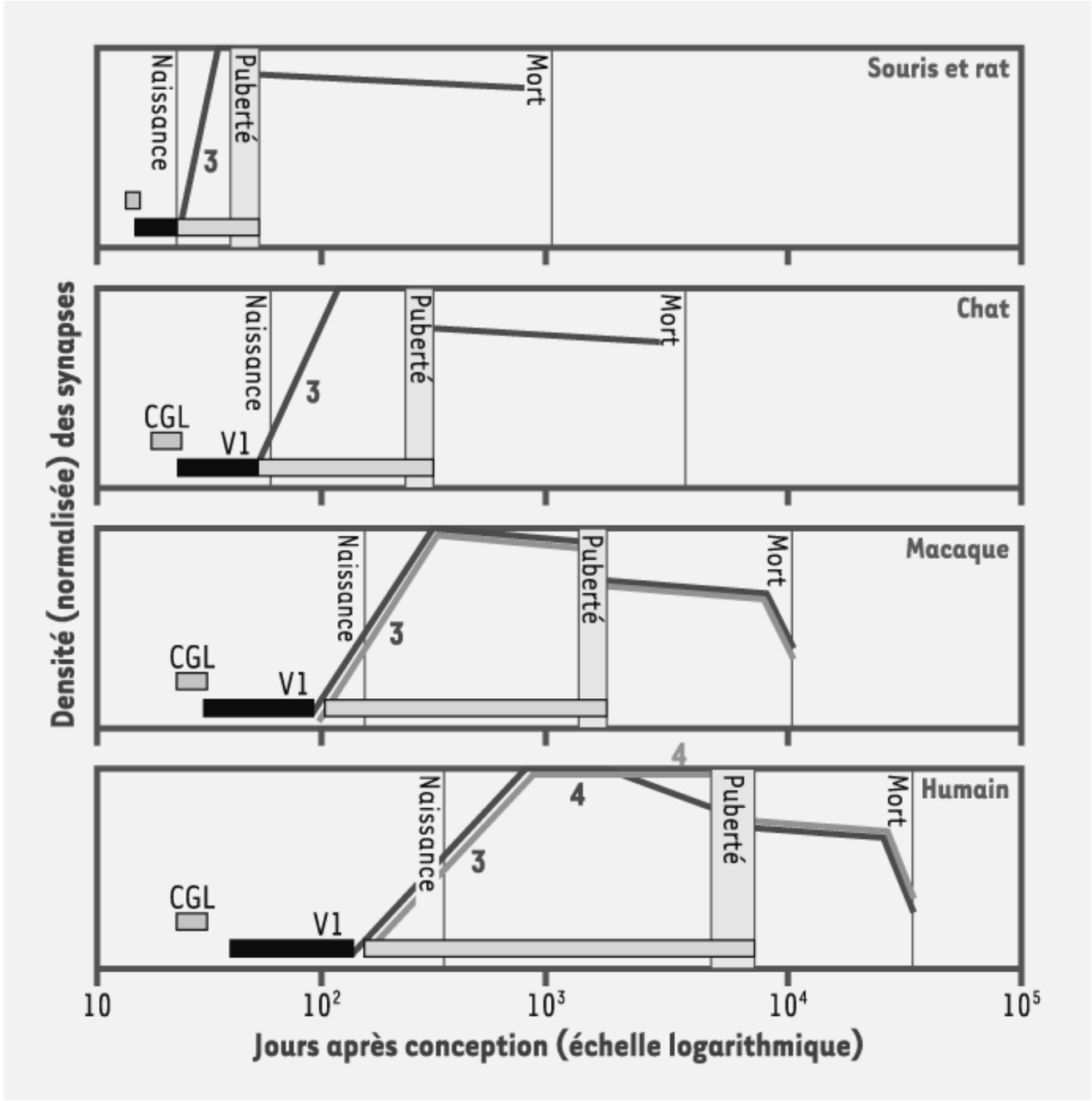
DTI **h^2**



N=374 (MZ=2*60, DZ=2*119, 16 sibs)
h2(Asymmetry) values between 10% (forceps minor) and 37% (anterior thalamic radiation).

There were significant difference in the heritability of DTI asymmetry between males and females, suggesting a sex-dependent mechanism.

Maturation


Souris et rat
Chat
Macaque
Humain
Naissance
Puberté
Mort
CGL
V1
3
4
Densité (normalisée) des synapses
10
10^2
10^3
10^4
10^5
Jours après conception (échelle logarithmique)

early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

axon growth

myelination

maturation

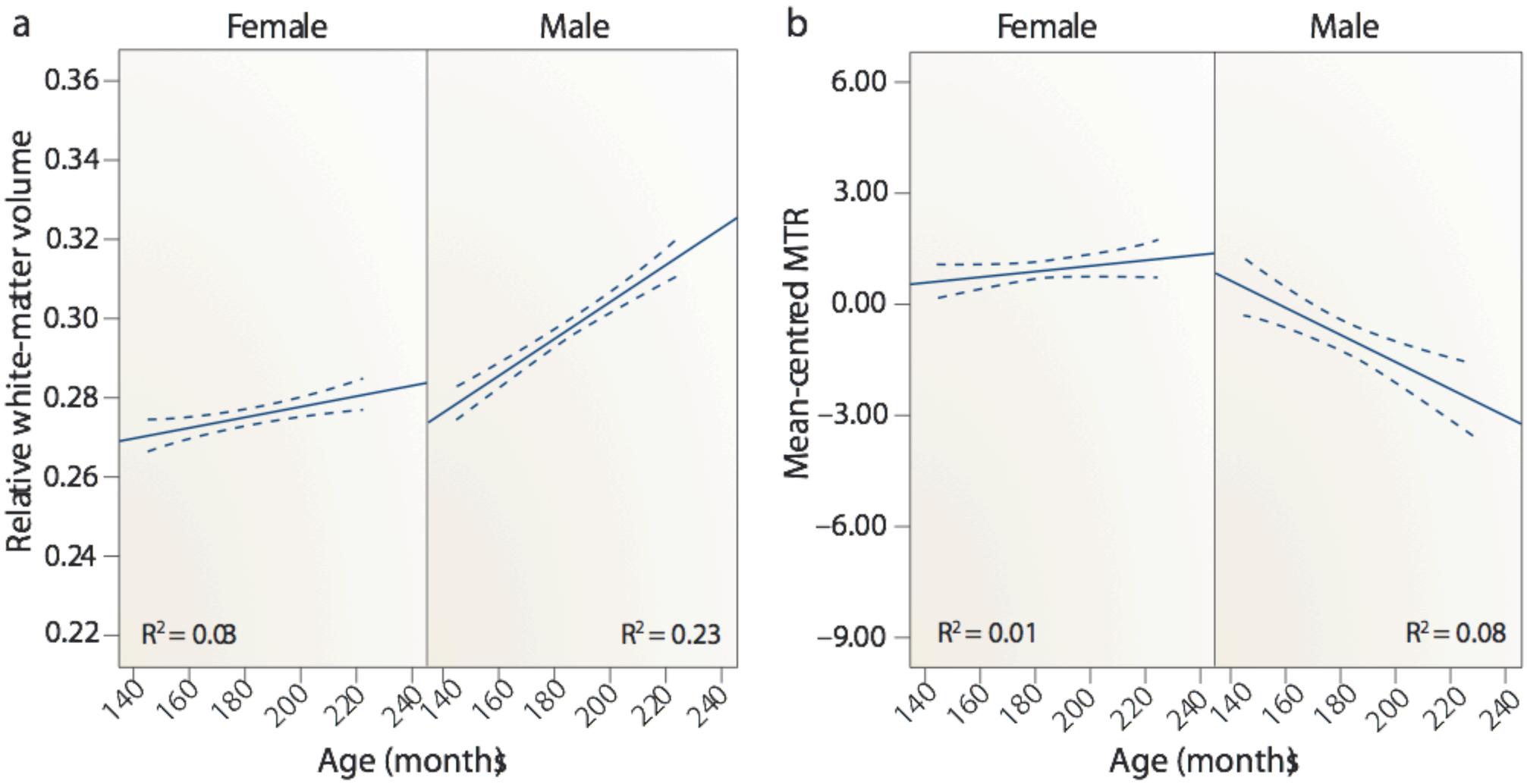
puberty

aging

plasticity

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

V **C**



early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

axon growth

myelination

maturation

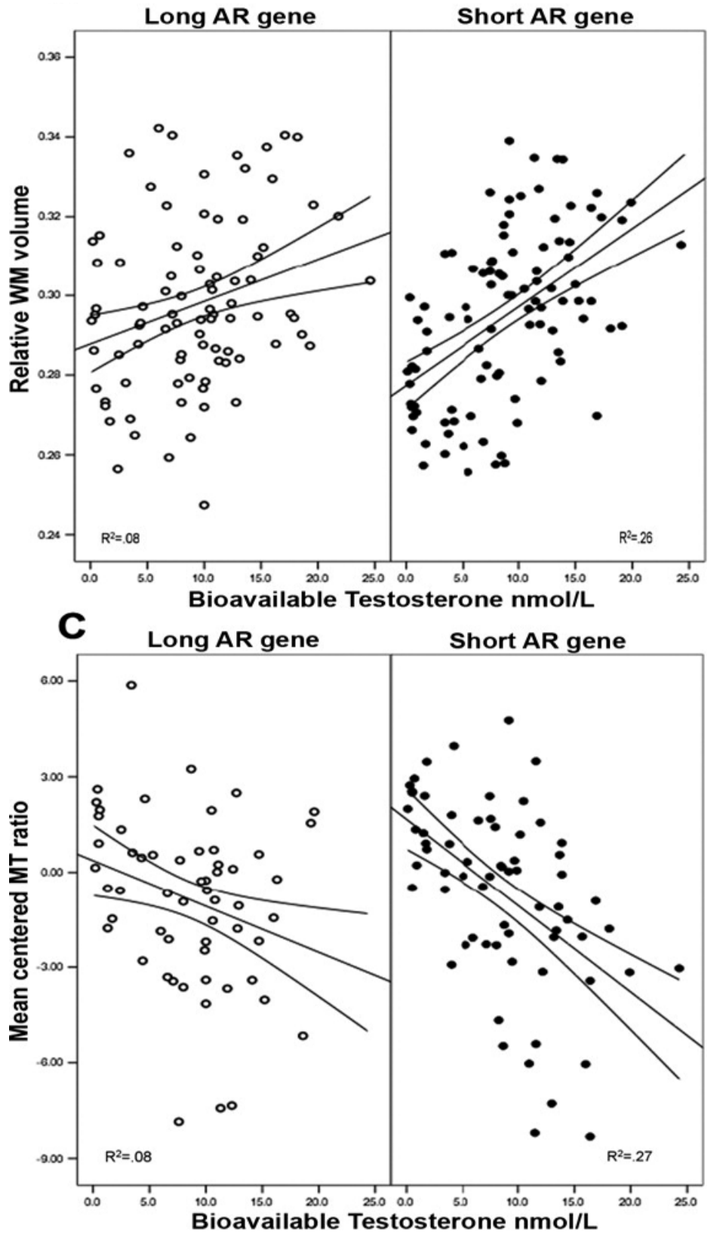
puberty

aging

plasticity

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

V C



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 (R2 of 26% vs 8%)

WM growth does not seem to be due to myelination.

early development

rostrocaudal axis

cortical development

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neuropil develop.

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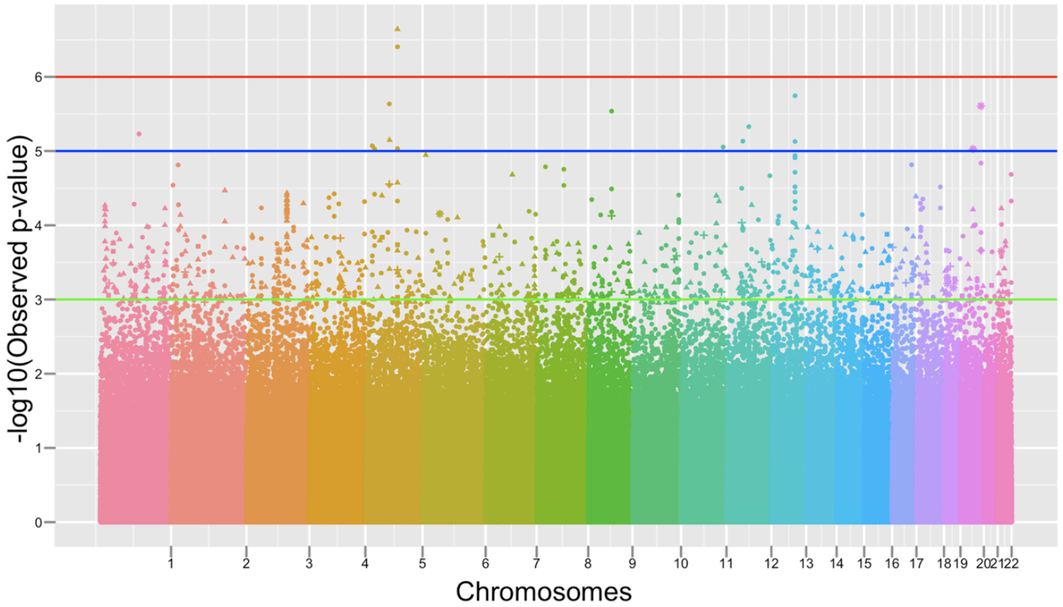
aging

plasticity

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

V GW



← TOMM40

← Including APOE, CAND1, MAGI2, ARSB, PRUNE2

N=381 (ADNI)
Chip Illumina Human610

Found genes involved in regulation of protein degradation, apoptosis, neuronal loss and neurodevelopment.

APOE (rs429358, rs7412)
0001937 negative regulation of endothelial cell proliferation
0006916 anti-apoptosis
0010468 regulation of gene expression
0045471 response to ethanol
0007271 synaptic transmission, cholinergic
0007010 cytoskeleton organization
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:
Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort , Kim et al, 2011, Neurology

early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

axon growth

myelination

maturation

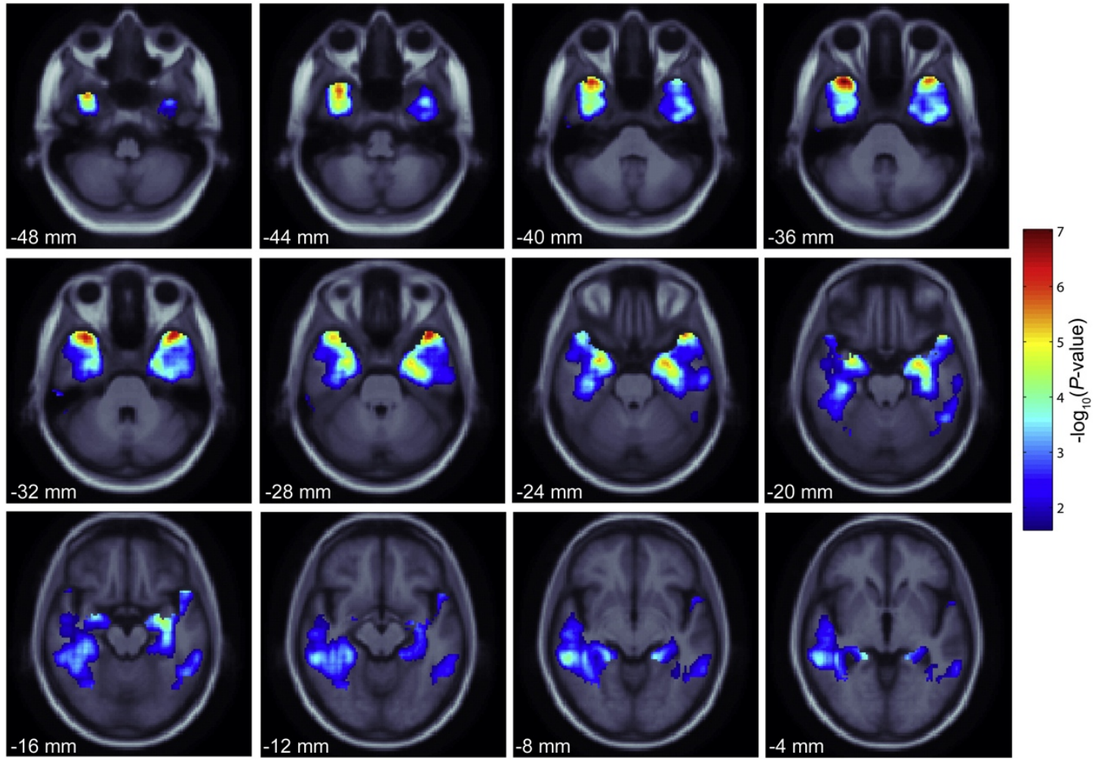
puberty

aging

plasticity

“Genome-wide analysis reveals novel genes influencing temporal lobe structure with relevance to neurodegeneration in Alzheimer's disease”, Stein et al, 2010, NeuroImage

VBM GW



GRIN2B (rs10845840)

0007612 learning
0007613 memory
0009790 embryonic development
0060079 regulation of excitatory postsynaptic membrane potential
0007215 glutamate signaling pathway
0014049 positive regulation of glutamate secretion
0045471 response to ethanol
0001701 in utero embryonic development
0043408 regulation of MAPKKK cascade
0048167 regulation of synaptic plasticity
+ 0001662, 0001967, 0006812, 0006816, 0050966, 0048266, 0001964, 0007423

N=742 (ADNI)
Chip Illumina Human610

Association was stronger with temporal lobe volume than with hippocampal volume (which has been observed to be less heritable)

early development

rostrocaudal axis

cortical development

mitosis

apoptosis

neuropil develop.

connectivity

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maturation

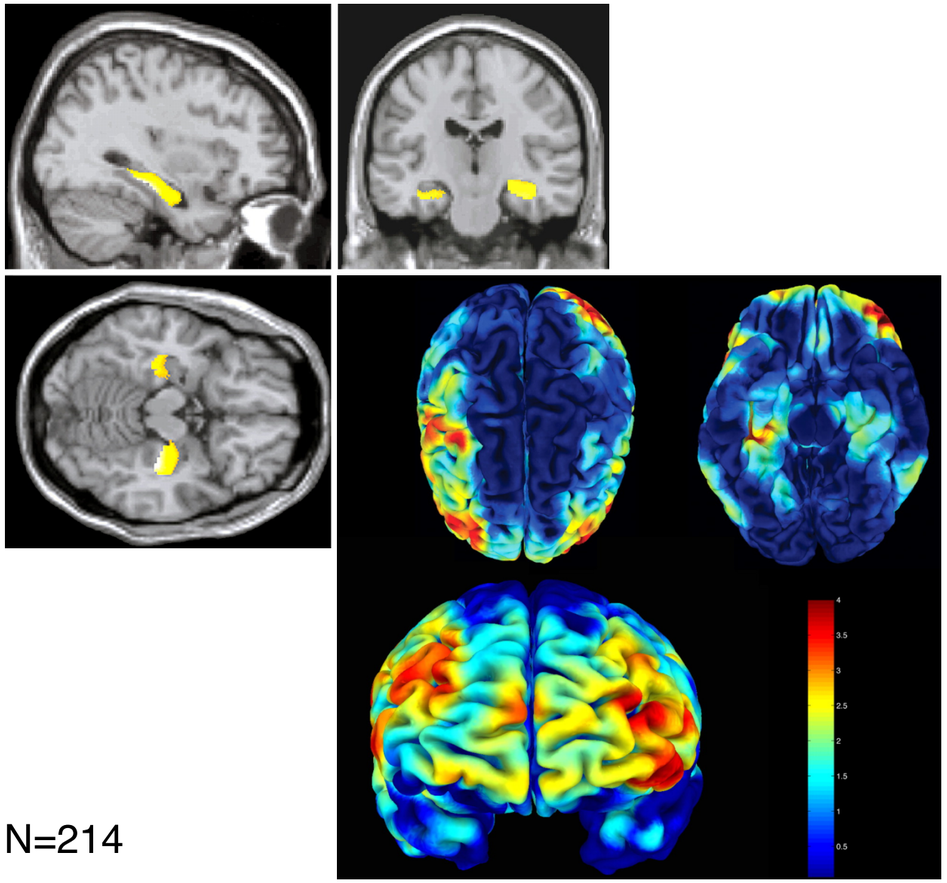
puberty

aging

plasticity

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

VBM C



N=214

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

early development

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neuropil develop.

connectivity

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puberty

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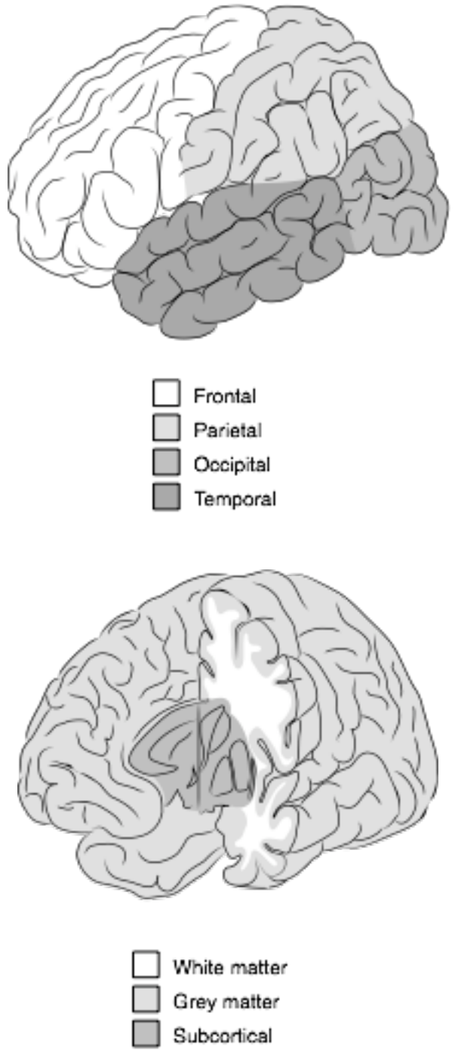
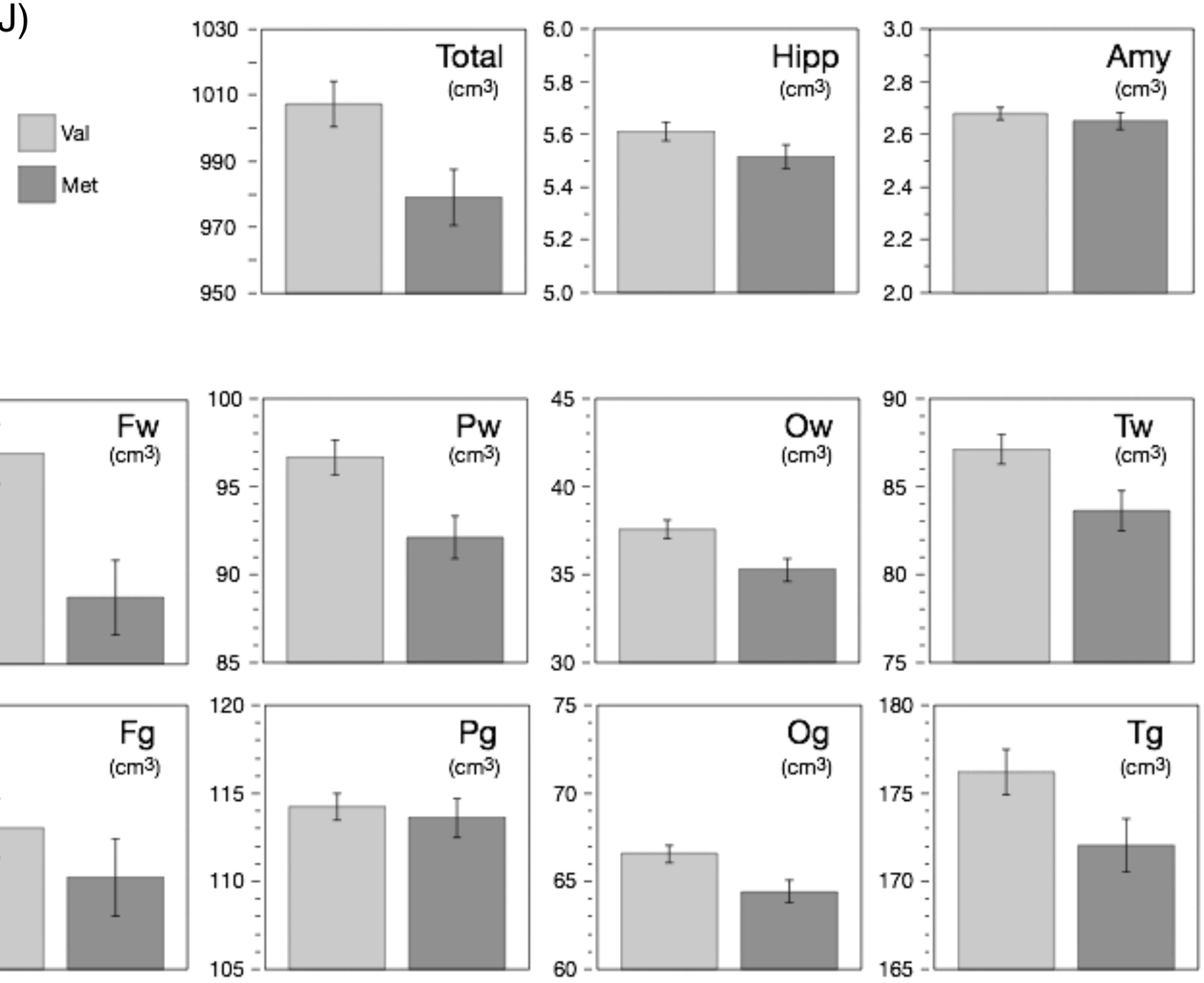
plasticity

“Brain volumes and Val66Met polymorphism of the BDNF gene: local or global effects?”, Toro et al, Brain Struct Func 2009

V **C**



N=314 (SLSJ)



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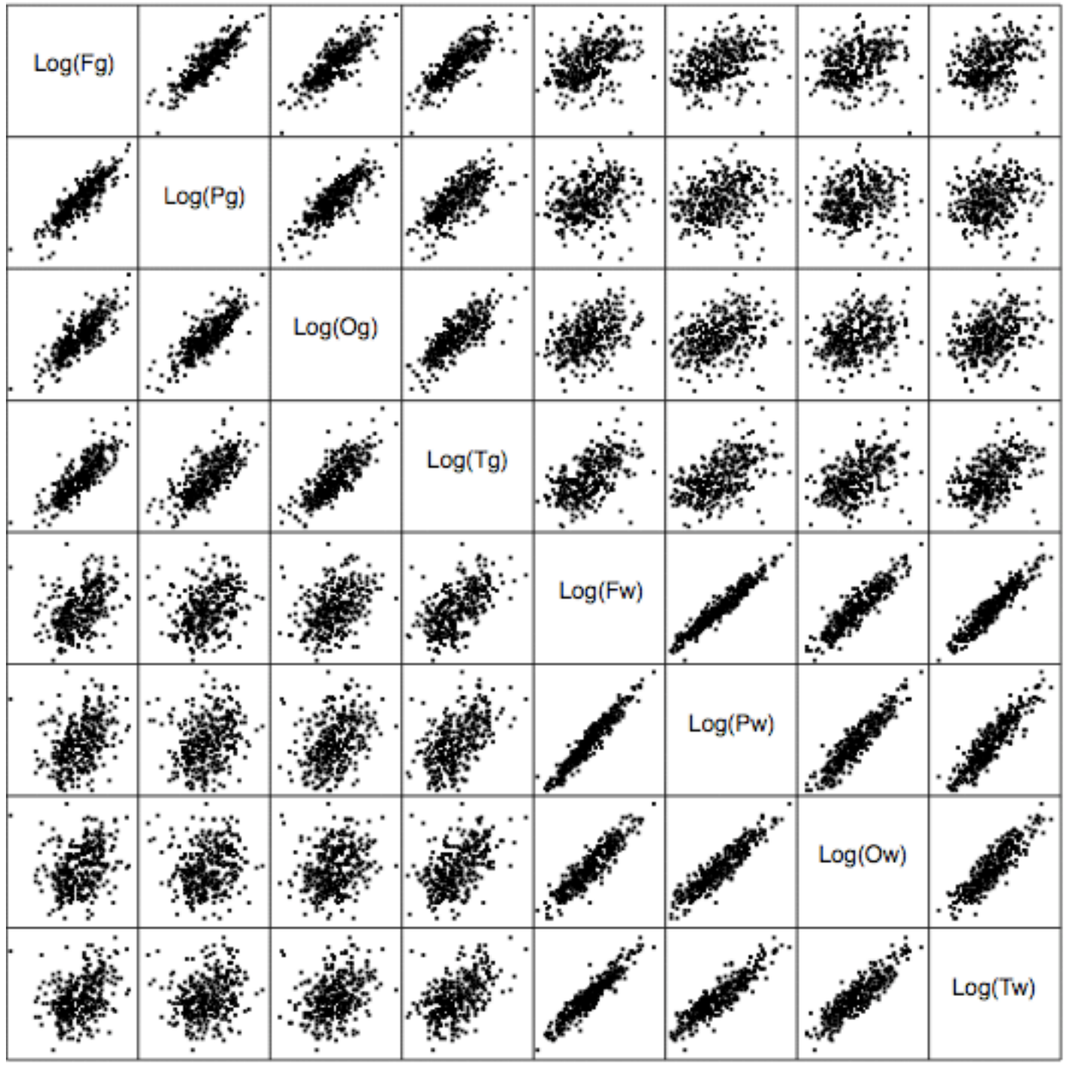

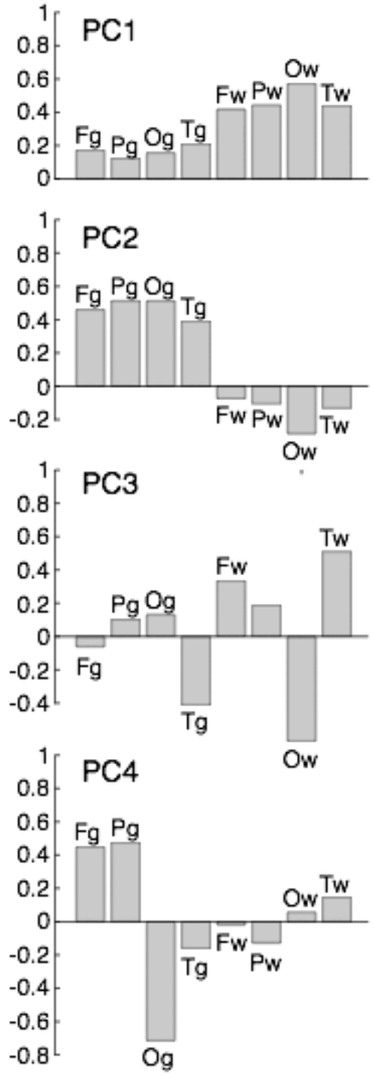

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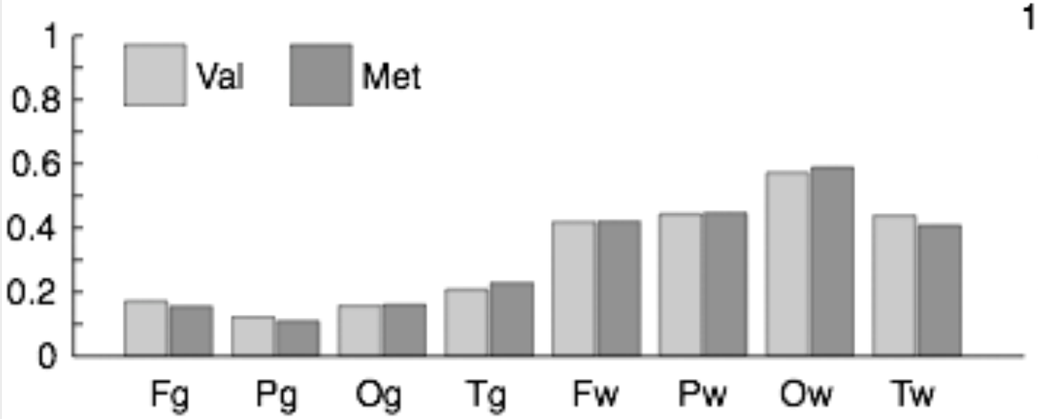

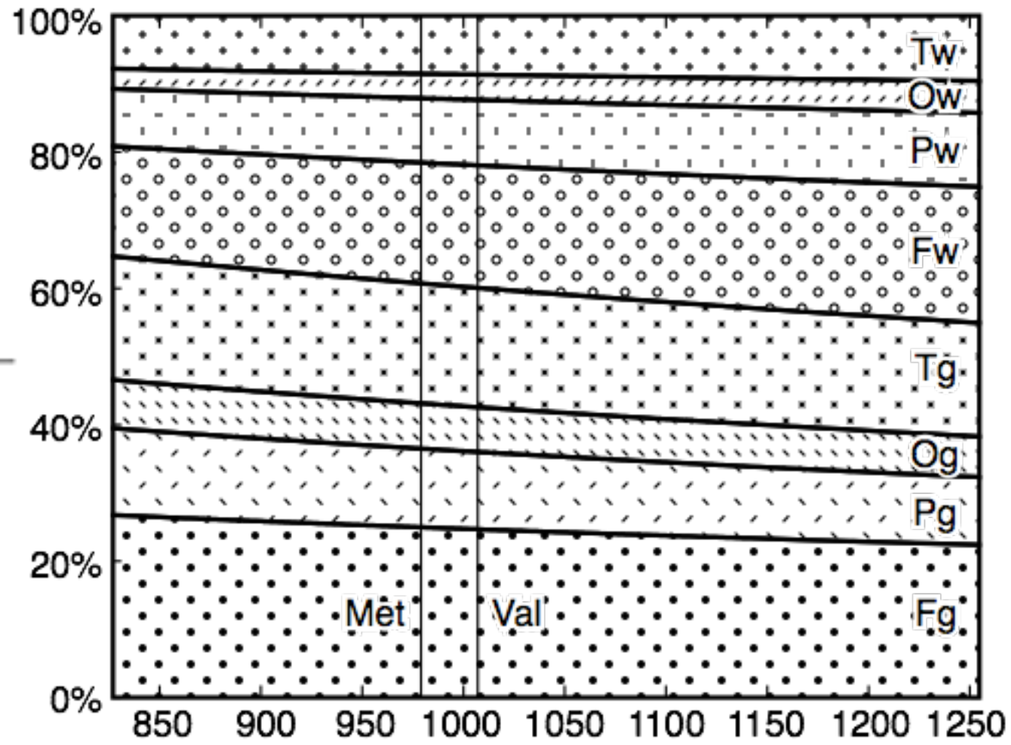

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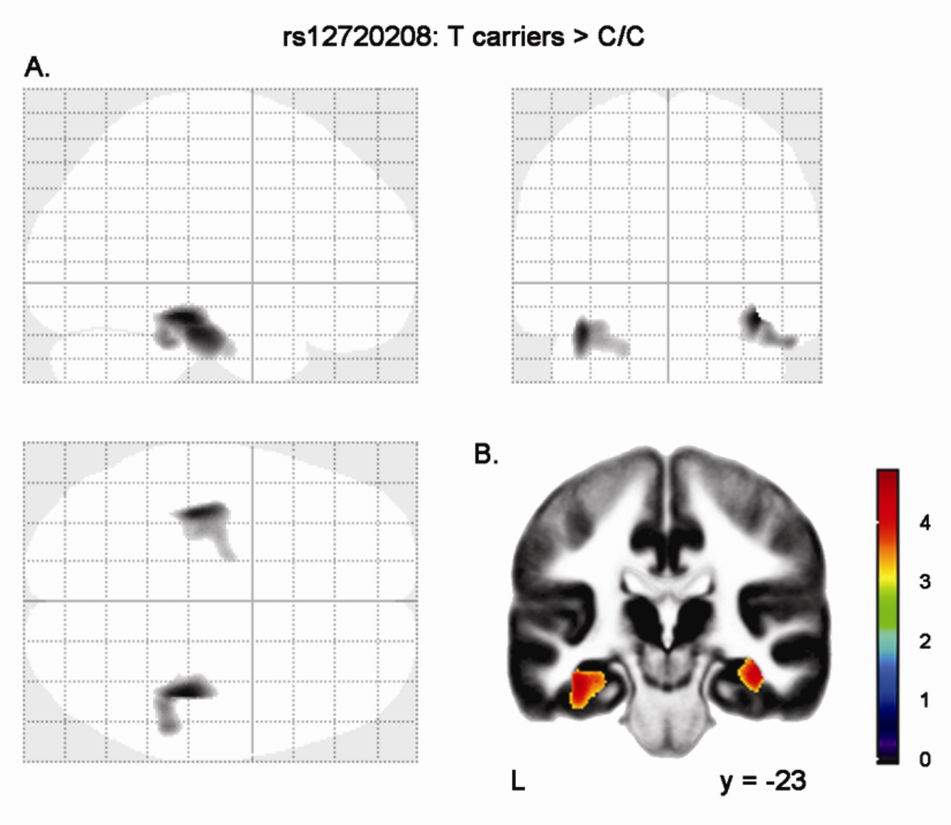
“Genetic Variation in FGF20 Modulates Hippocampal Biology”, Lemaitre et al, Journal of neuroscience 2010

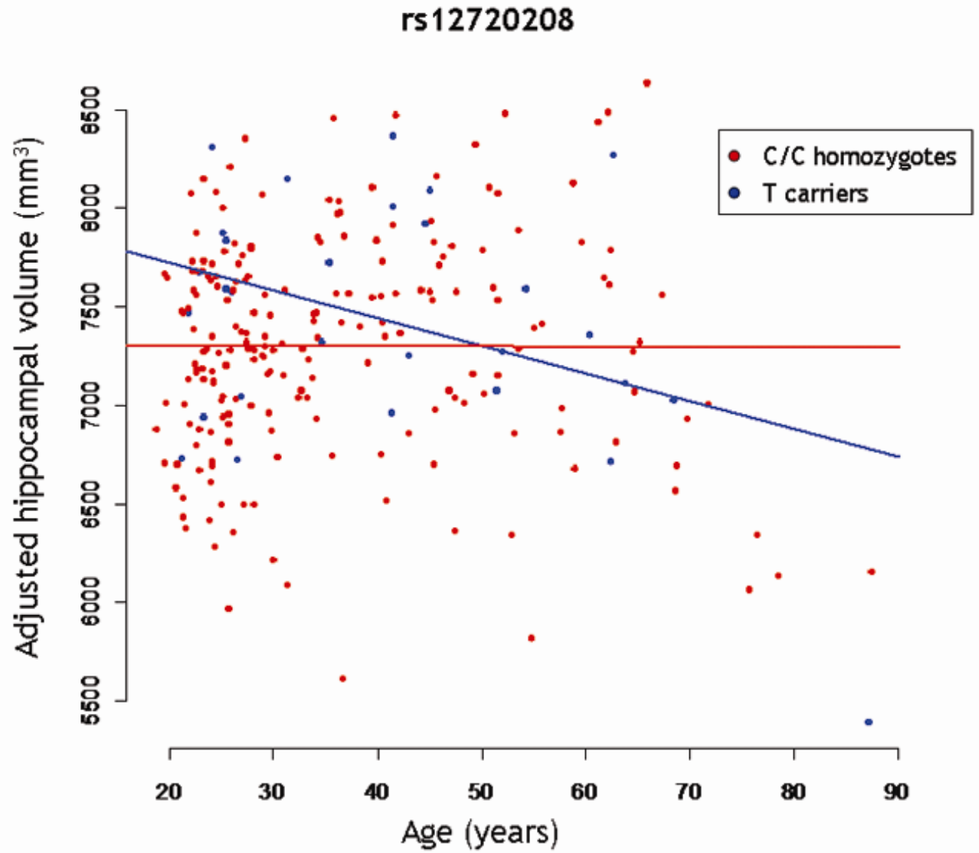
VBM C

FGF20

rs12720208

0030154 cell differentiation (486)
0007267 cell-cell signaling (239)
0008284 positive regulation of cell proliferation (329)





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 of the neuroimaging endophenotypes used.

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

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

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