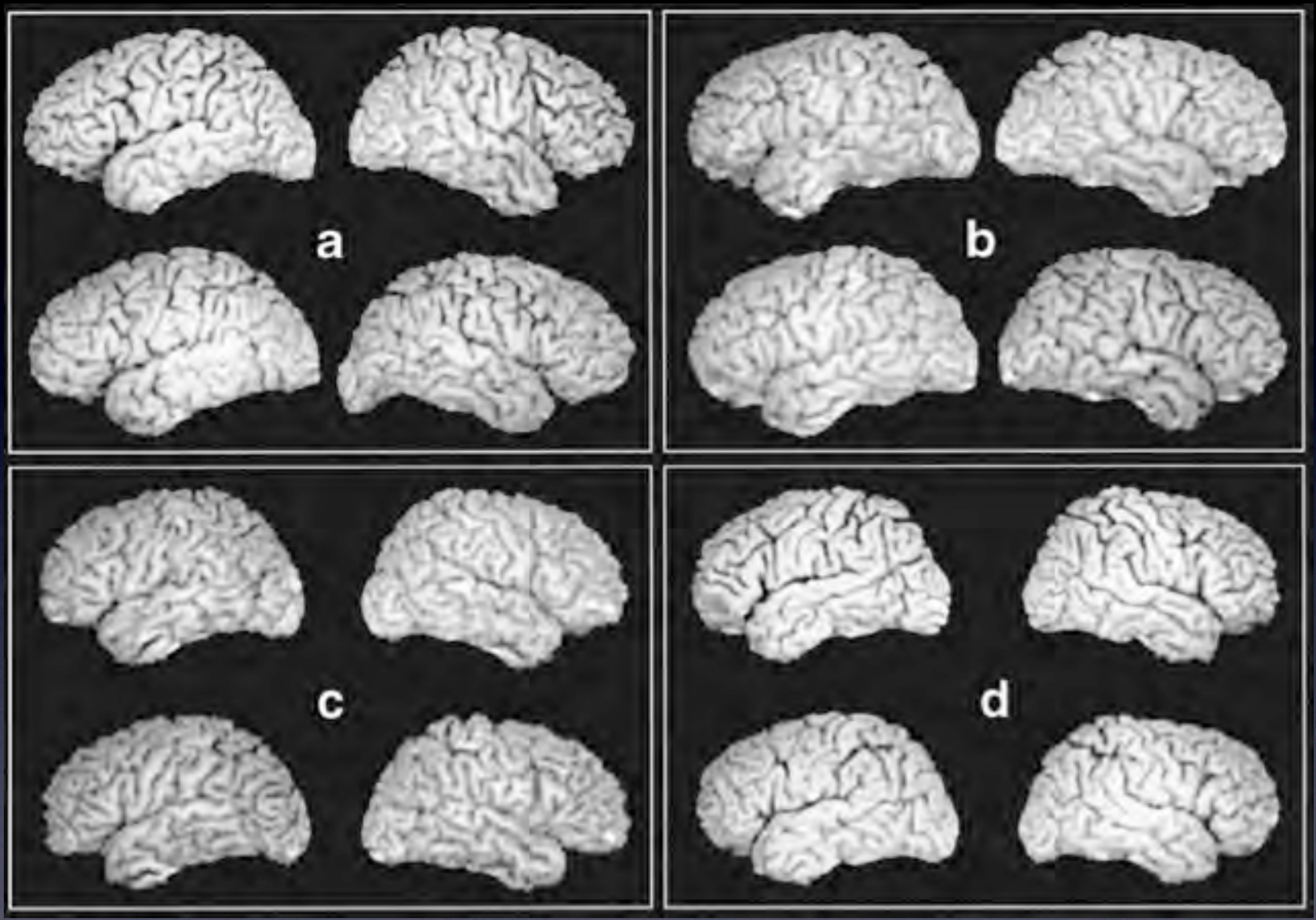
Quantitative Analysis of Brain Structure

Roger P. Woods, M.D.

Learning Objectives

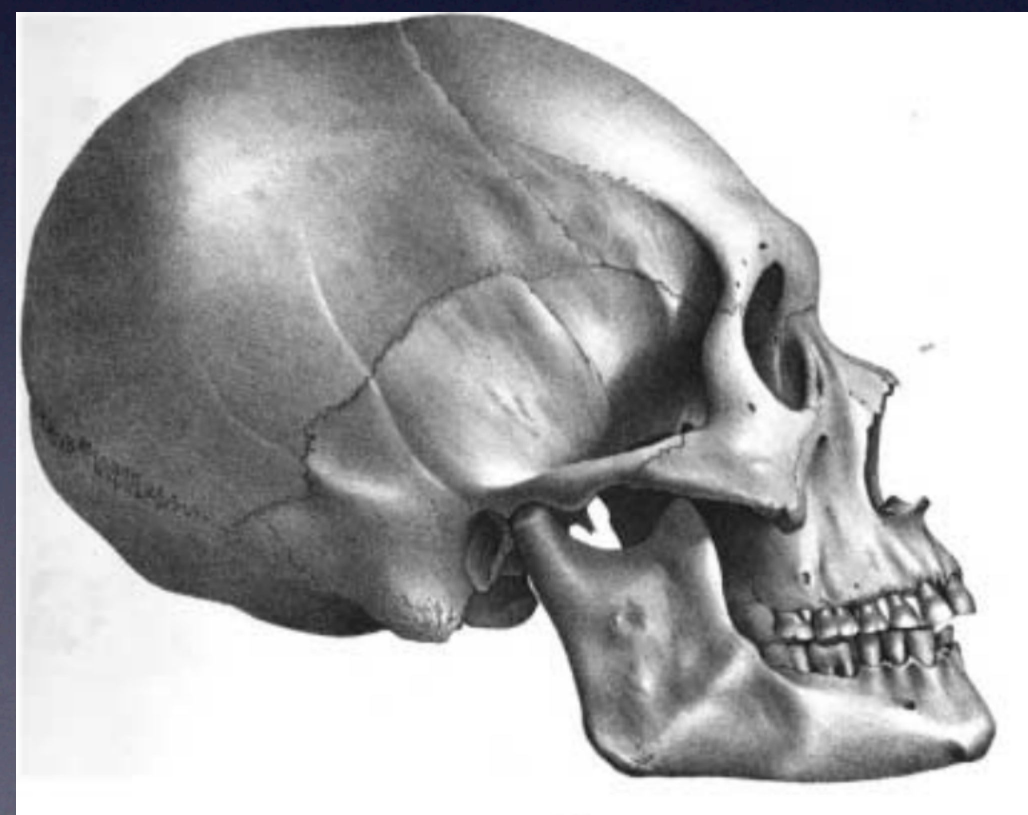
- Limitations and biases of MRI based quantification
- Managing human biases while utilizing their anatomic expertise
- Anatomic models and their assumptions
- The non-Euclidean nature of shape

What causes brain size variation in normal subjects?



Bartley AJ, Jones DW, Weinberger DR. *Brain* 1997;120:257-269


804 - 821
87
804



tIn order to measure the capacity of a cranium, the foramina were first stopped with cotton, and the cavity was then filled with white pepper seed* poured into the foramen magnum until it reached the surface, and pressed down with the finger until the skull would receive no more.

*White pepper seed was selected on account of its spherical form, its hardness, and the size of the grains. It was also sifted to render the equality still greater

The material used for filling the skull, as there directed, was white pepper seed, which was chosen on acount of its spheroidal form, and general uniformity of size. Finding, however, that considerable variation occurred in successive measurements of the skull, I substituted leaden shot one tenth of an inch in diameter, in place of the seeds. The skull must be completely filled by skaking it while the shot is poured in at the foramen magnum, into which the figure must be frequently pressed for the same purpose, until the sinuosities will receive no more.

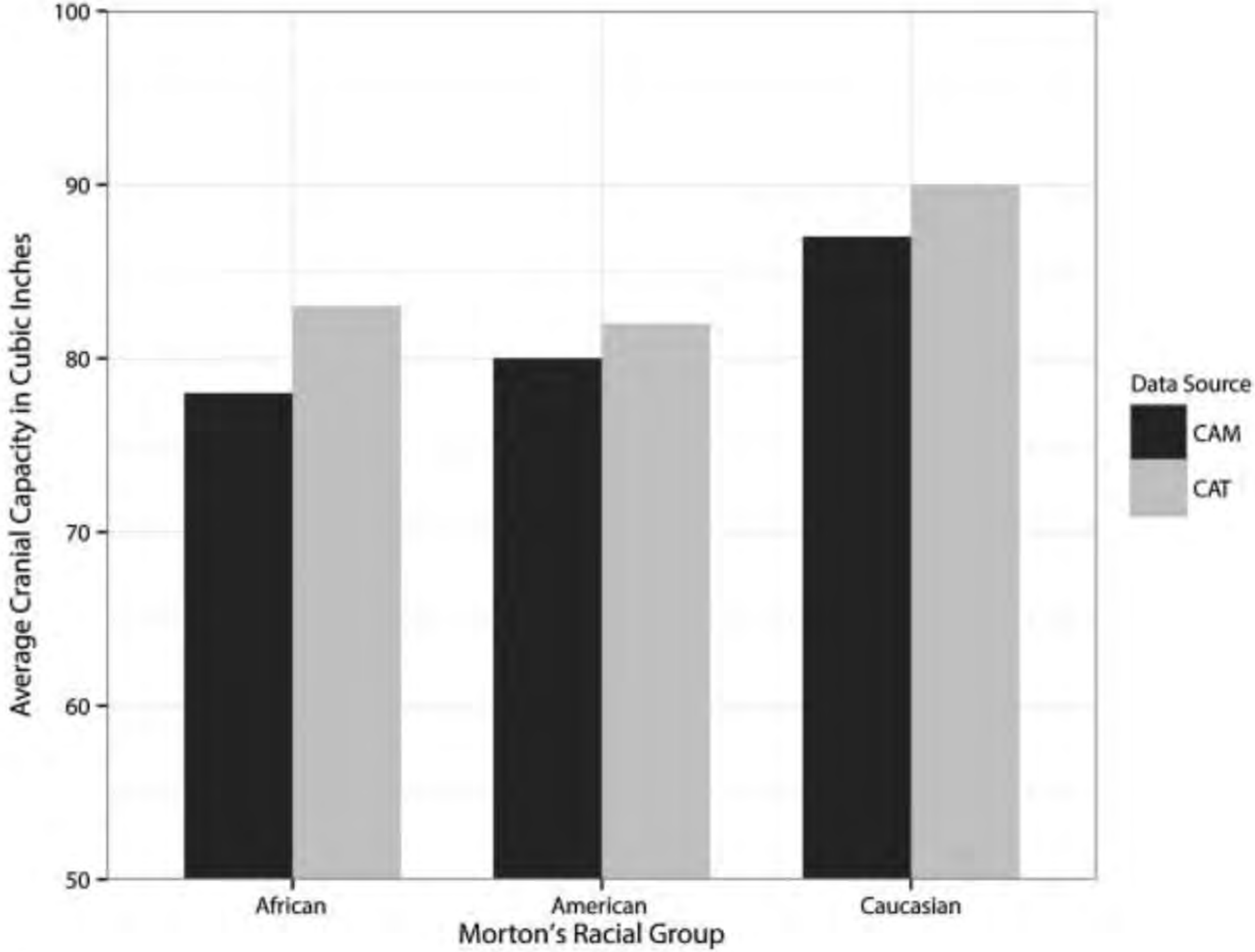
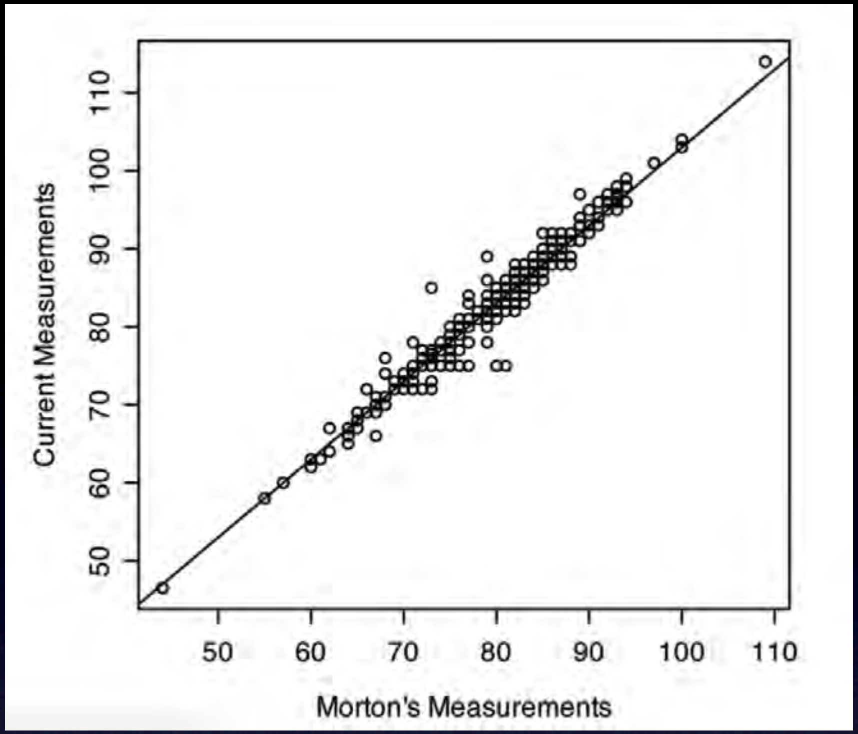
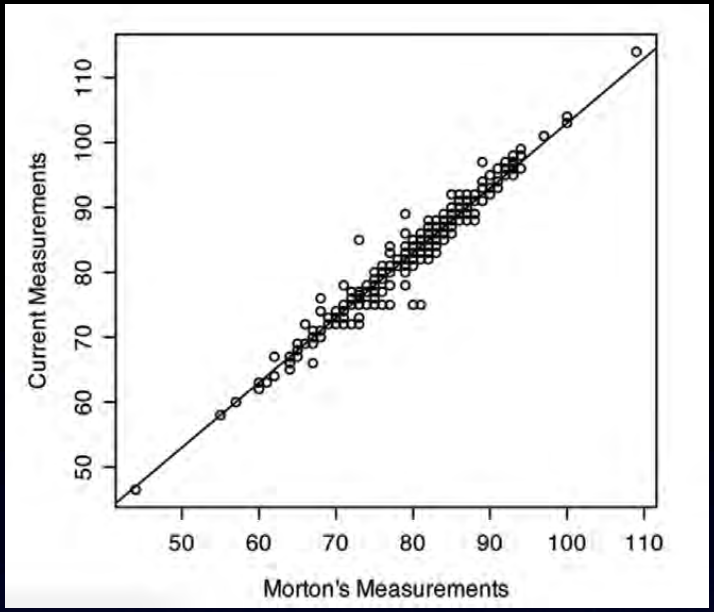


Fig. 4. Change in mean cranial capacity from *Crania Americana* (1839) to *Catalogue of Skulls of Man and the Inferior Animals* (1849).



Six-millimeter diameter (0.1 cm3) solid precision molded non-compressible acrylic balls were poured into the foramen magnum until the balls would no longer flow freely into the cranium … To avoid unconscious packing of the acrylic balls, the measurer would not place their fingers into the neurocranium to pack or push on the balls, but only shake intermittently.

Lewis *et al. PLoS Biol 2011;9(6): e1001071*



"In general, then, our measurement method yields cranial capacities that are circa 50 cm3 less than, or are on average 96% of, those produced by Morton's."

"Biased Scientists Are Inevitable, Biased Results Are Not"

Lewis *et al. PLoS Biol 2011:9(6): e1001071*

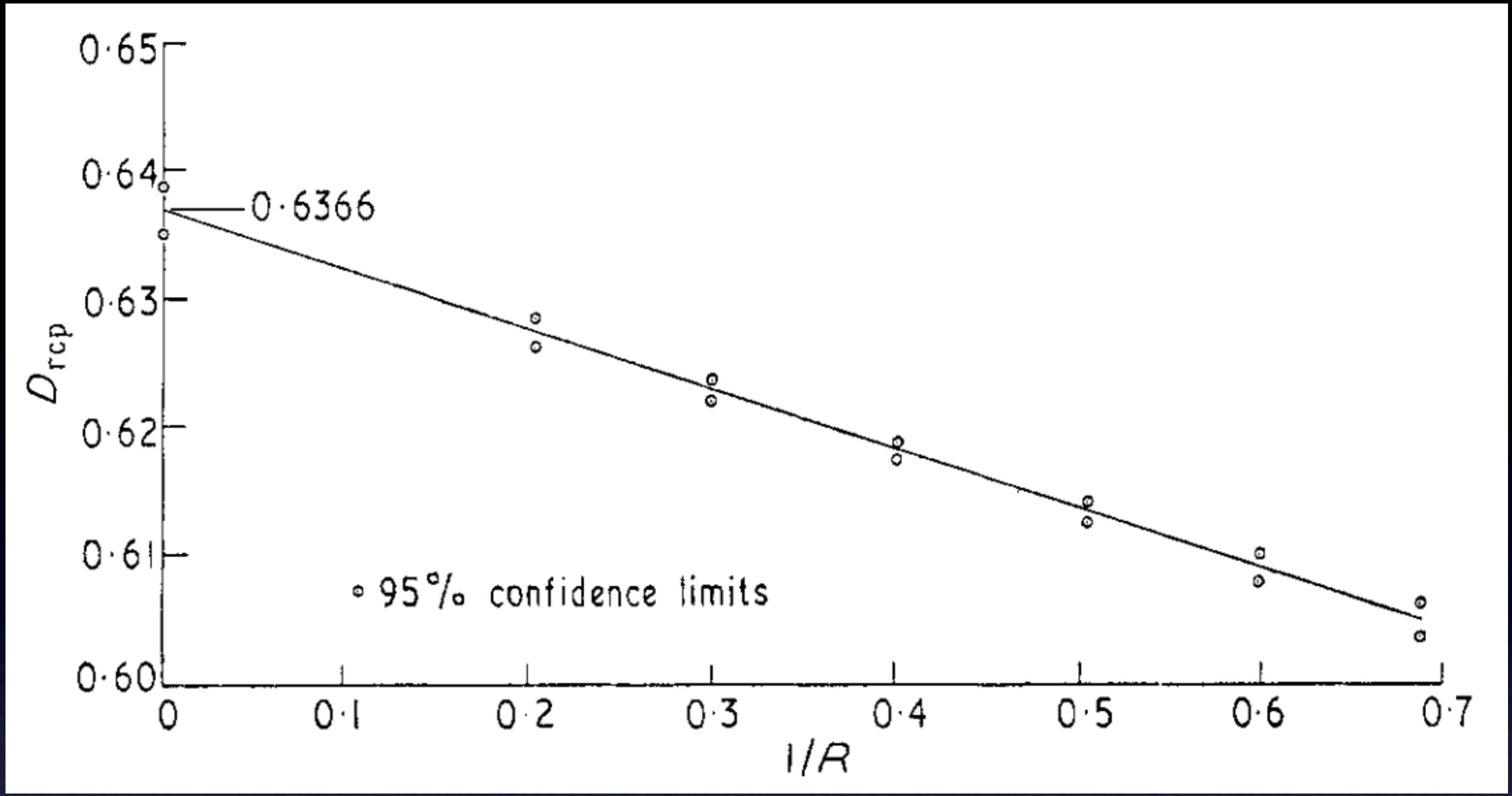
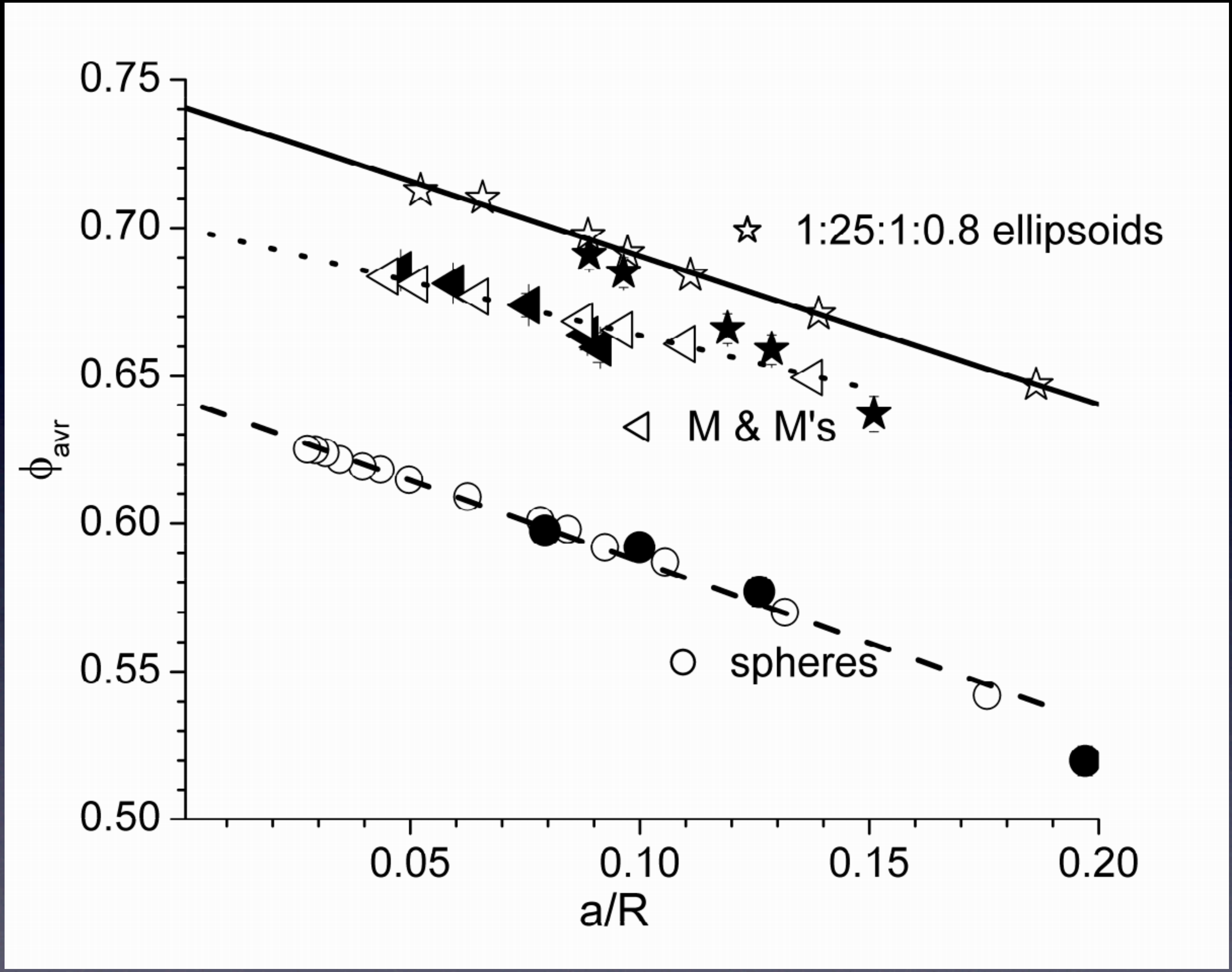


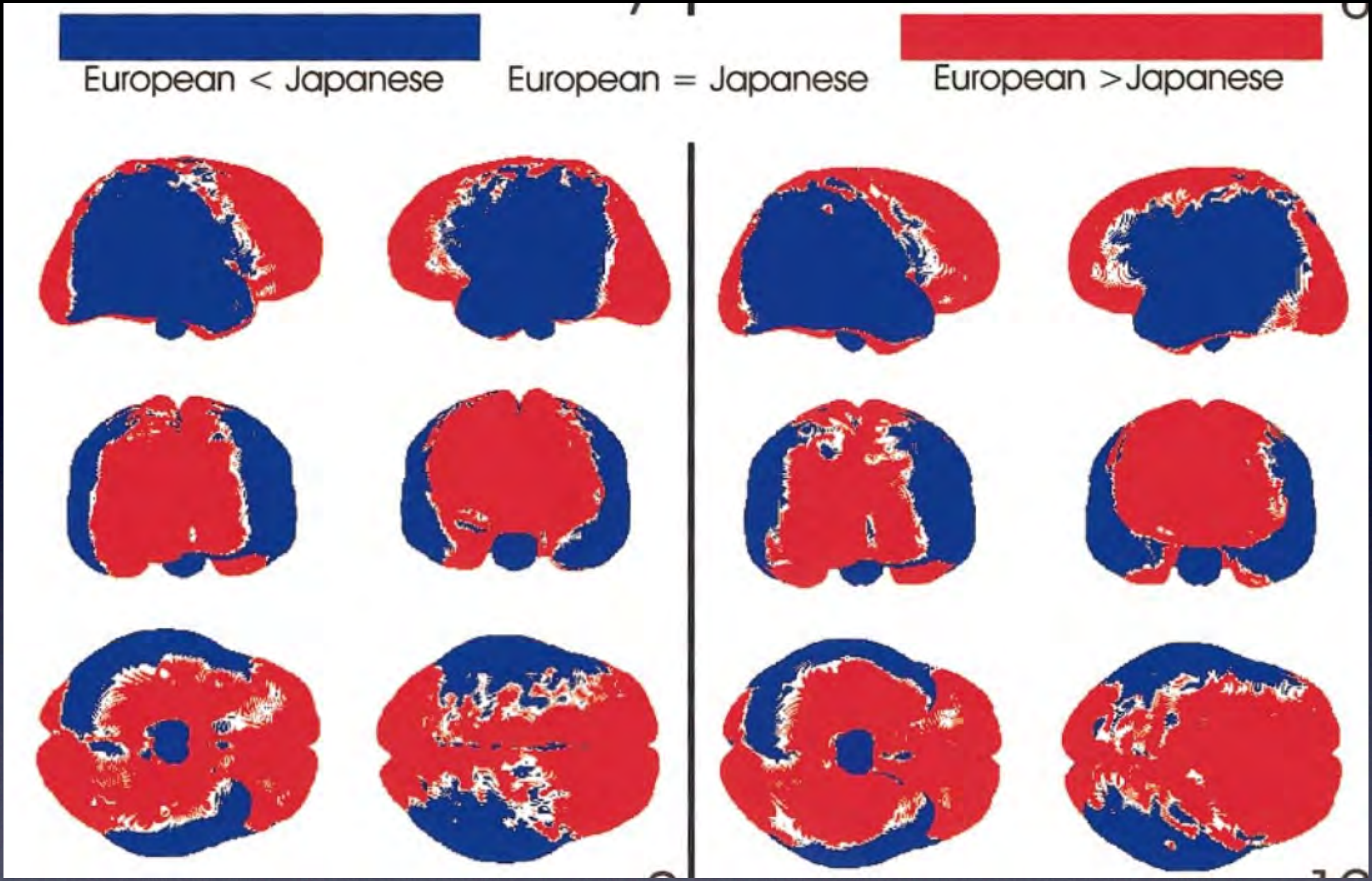
Table 1. Densities of randomly packed spheres

	Friction†		Loose	Close packed
	μ_s	μ_k		
Steel balls	$0{\cdot}2_4$	$0{\cdot}1_7$	$0{\cdot}60_8$	$0{\cdot}63_8$
Steel (in oil)	$0{\cdot}2_4$	$0{\cdot}1_7$	$0{\cdot}61_1$	$0{\cdot}63_6$
Plexiglass (polished)	$0{\cdot}4_4$	$0{\cdot}2_3$	$0{\cdot}60_5$	$0{\cdot}63_6$
Nylon (ground)	$0{\cdot}6_3$	$0{\cdot}2_5$	$0{\cdot}57_5$	$0{\cdot}62_9$

Scott GD, Kilgour DM. *Brit J Appl Phys* 1969;2:863-866

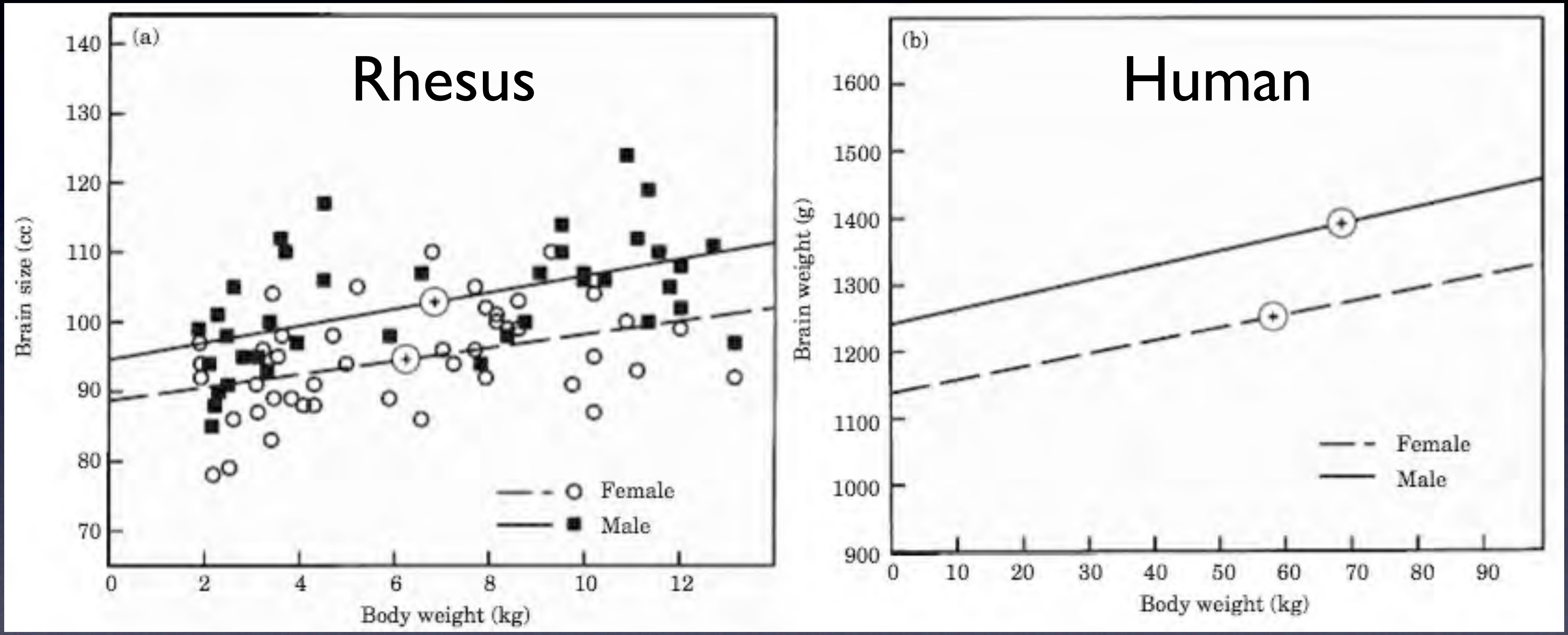


Mann *et al. Physical Review Letters* 2005:19801



Zilles *et al. Neuroimage* 2001;13:262-271

Brain Size and Sex



Falk D, *et al. Journal of Human Evolution* 1999;36:233-238

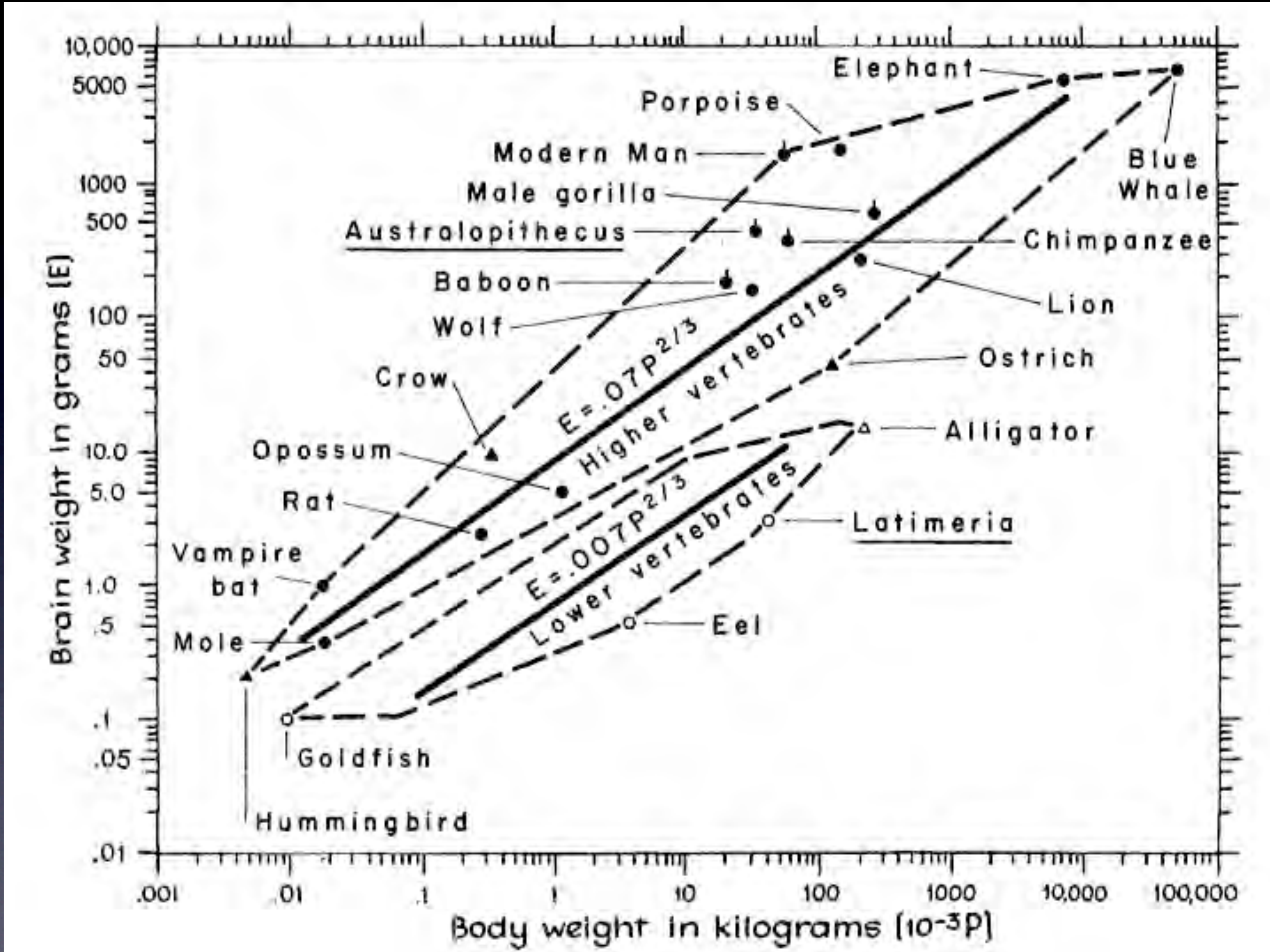
Ho K, *et al. Arch Pathol Lab Med* 1980;104:640-645.

Will Rogers Phenomenon

- "When the Okies left Oklahoma and went to California, the average intelligence of both states went up."

Feinstein, *et al. NEJM* 1985;312:1604-1608

Tower DB. *Journal of Comparative Neurology* 1954;101:19-46



Jerison, HJ. *The American Naturalist* 1969;103:575-588.

Brain Size and Height: Single Population

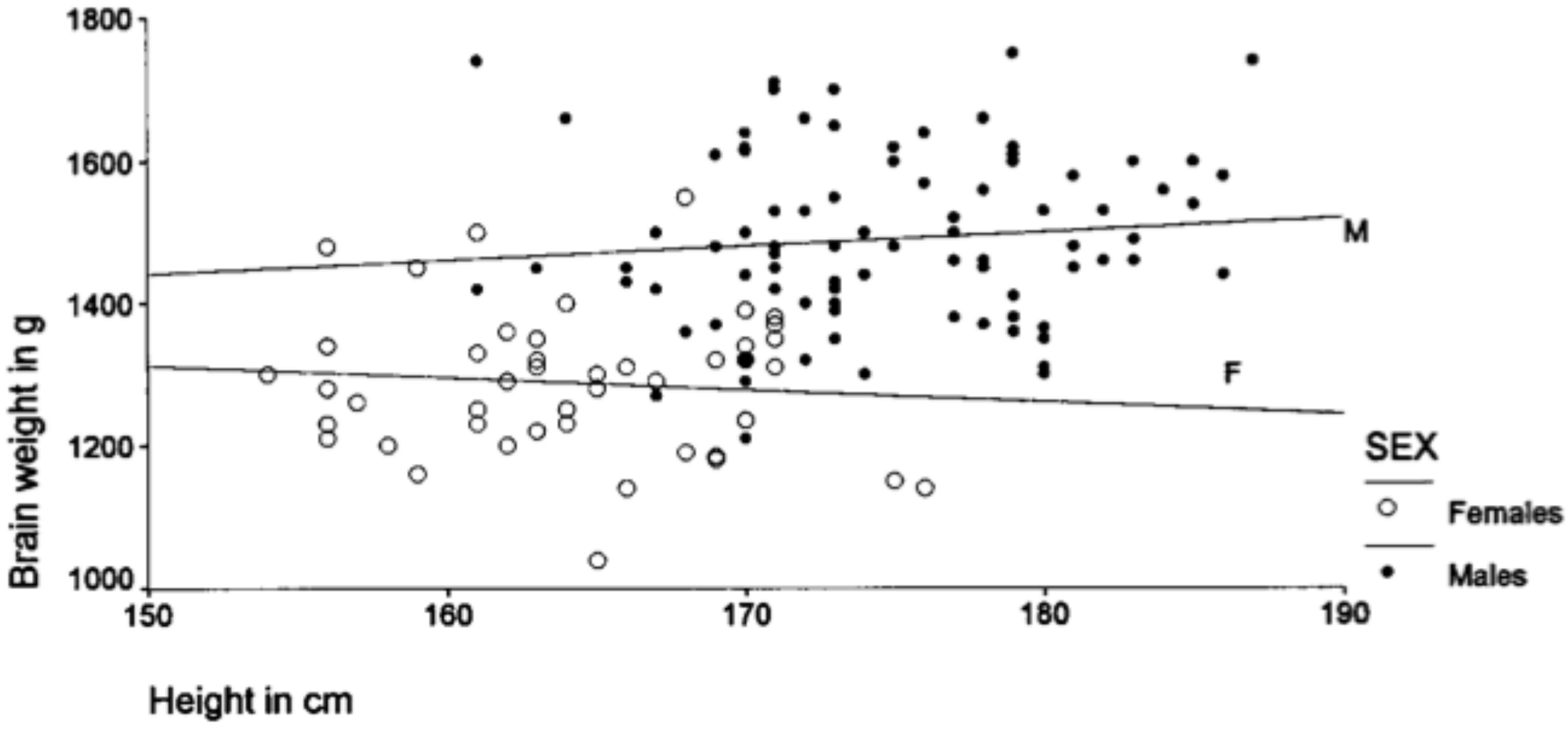
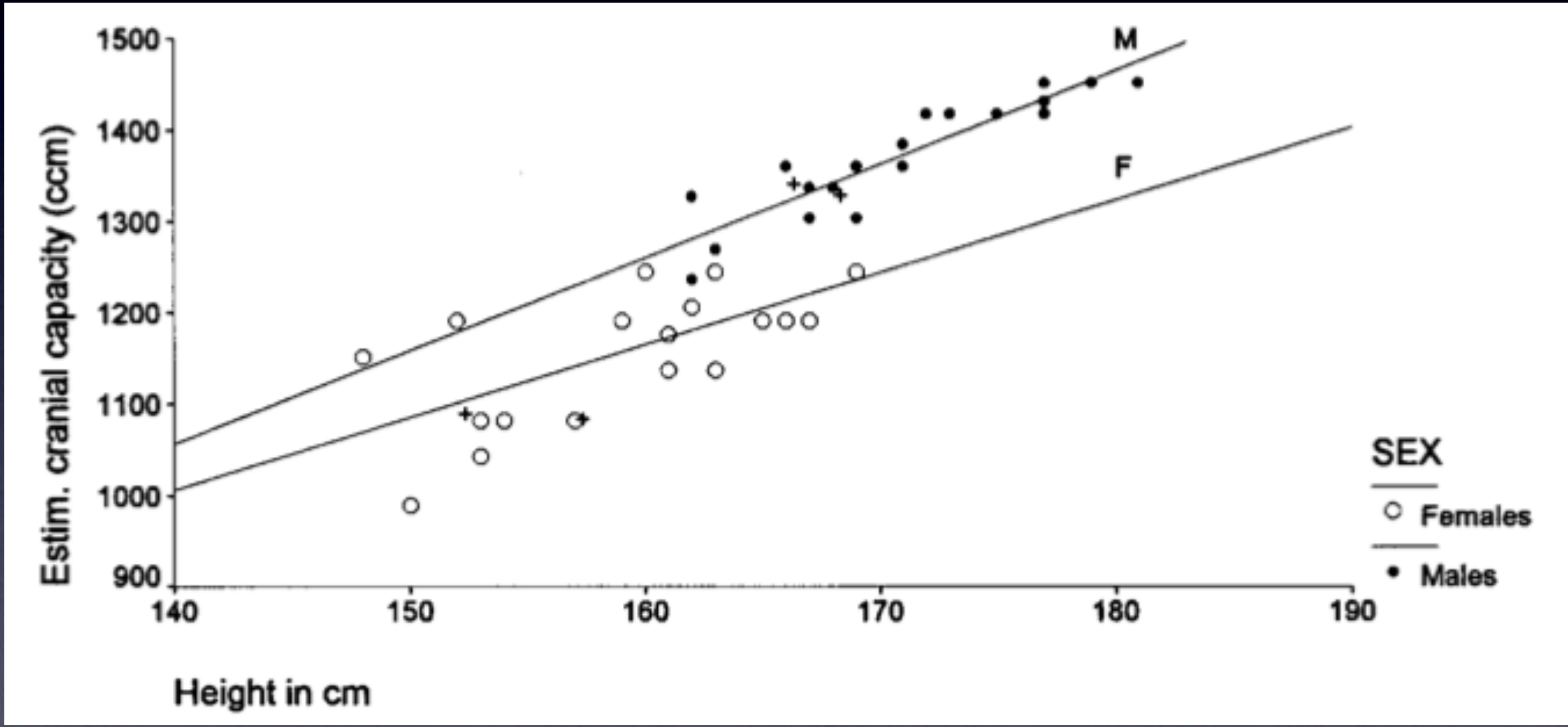


FIG. 4. Brain weight as function of height, ages 28–41, Pakkenberg and Voigt (1964) study. Females, $r = -.1$ (ns); males, $r = .1$ (ns).

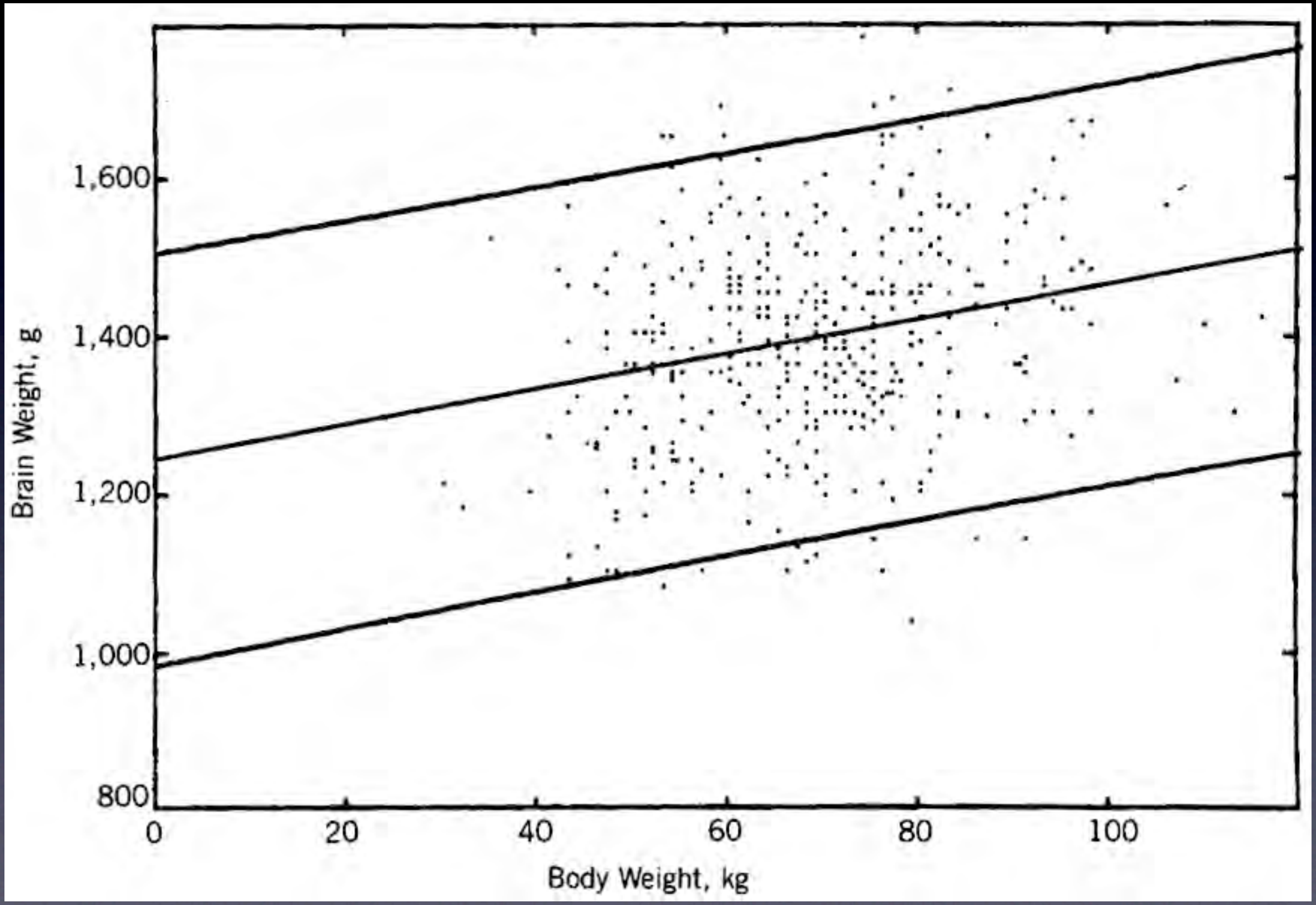
Peters M *et al. Brain Cogn* 1998;37(2):254-85.

Brain Size and Height Across Populations



Peters M *et al. Brain Cogn* 1998;37(2):254-85.

Brain/body in humans (WM)



Ho K, *et al. Arch Pathol Lab Med* 1980;104:640-645.

Leroi AM. *The Daily Telegraph, London* August 1, 2006

http://www.telegraph.co.uk/connected/main.jhtml?xml=/connected/2006/08/01/echuman01.xml

Clinical Microcephaly

- Head circumference more than 3 standard deviations below the mean for age and sex (other cutoffs used in some instances)
- Causes divided into genetic (primary) and non-genetic (secondary)
- Typically, but not always, associated with mental retardation

Potential Cellular Mechanisms

- Too few cells generated
- Too many cells lost
- Smaller cells
- Reduced extracellular volume

Genetic Microcephaly

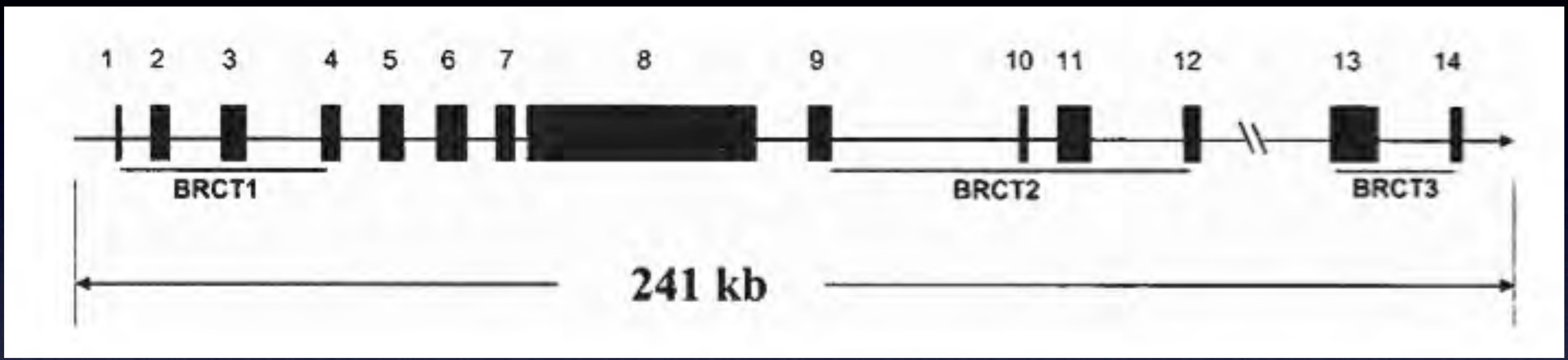
- Autosomal dominant
- Autosomal recessive (most common)
- X-linked
- Chromosomal syndromes
  - e.g., trisomy 21, trisomy 18, 5p- deletion
- Other genetic or chromosomal syndromes
  - e.g., Cornelia de Lange, Rubinstein-Taybi, Smith-Lemli-Opitz (>500 entries in OMIM)

Welker W. In: Jones EG & Peters A. Cerebral Cortex
Volume 8B 1990, Plenum Press, New York

Hypothesis: Variations in Primary Microcephaly Genes Cause Normal Brain size Variation

- No data regarding DNA content of large versus small normal brains
- No reports of brain size in parents of patients with recessive microcephaly

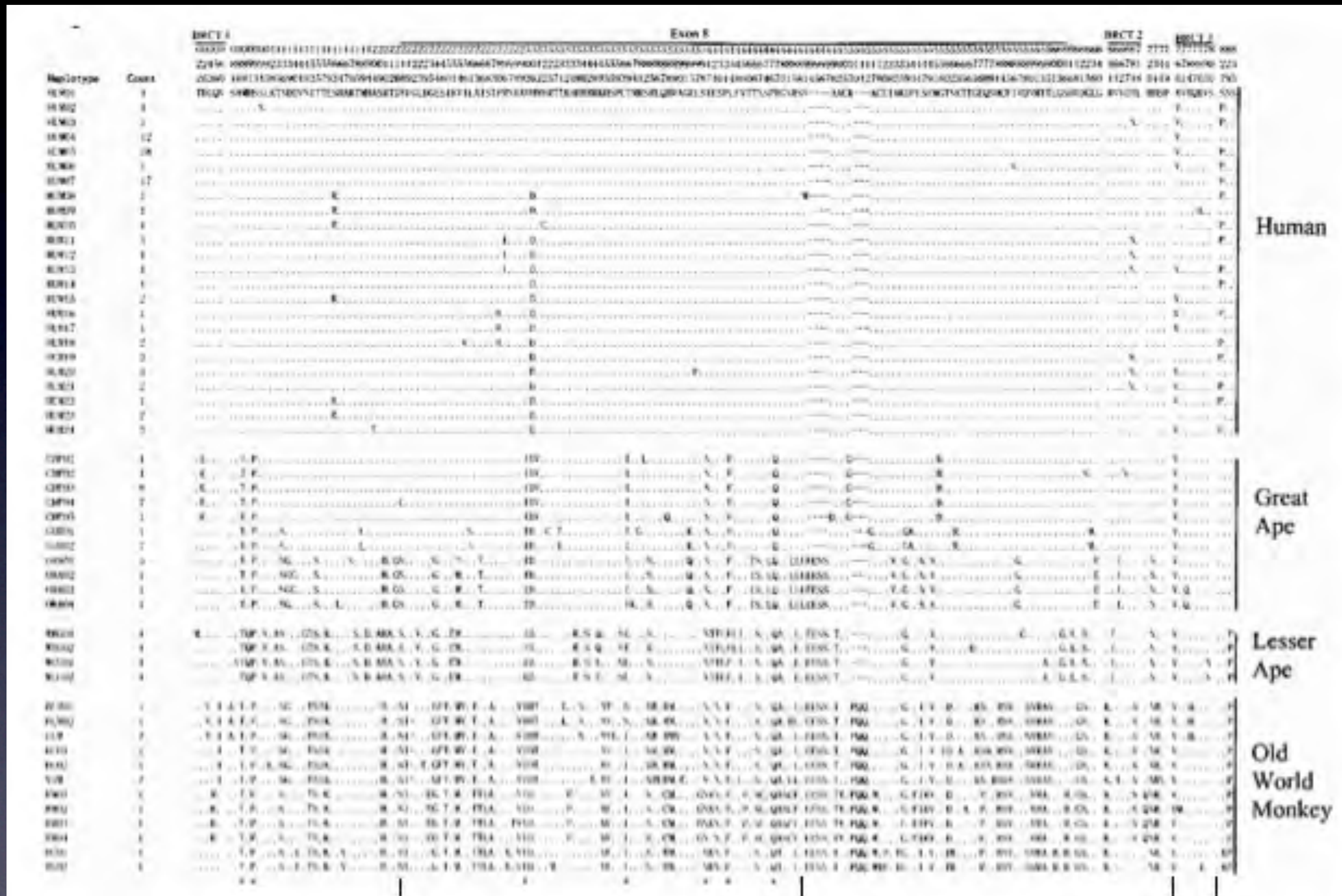
Microcephalin (MCPH1)



BRCT1, BRCT2 and BRCT3 are BRCA1 C-terminal domains involved in DNA-protein and protein-protein interactions

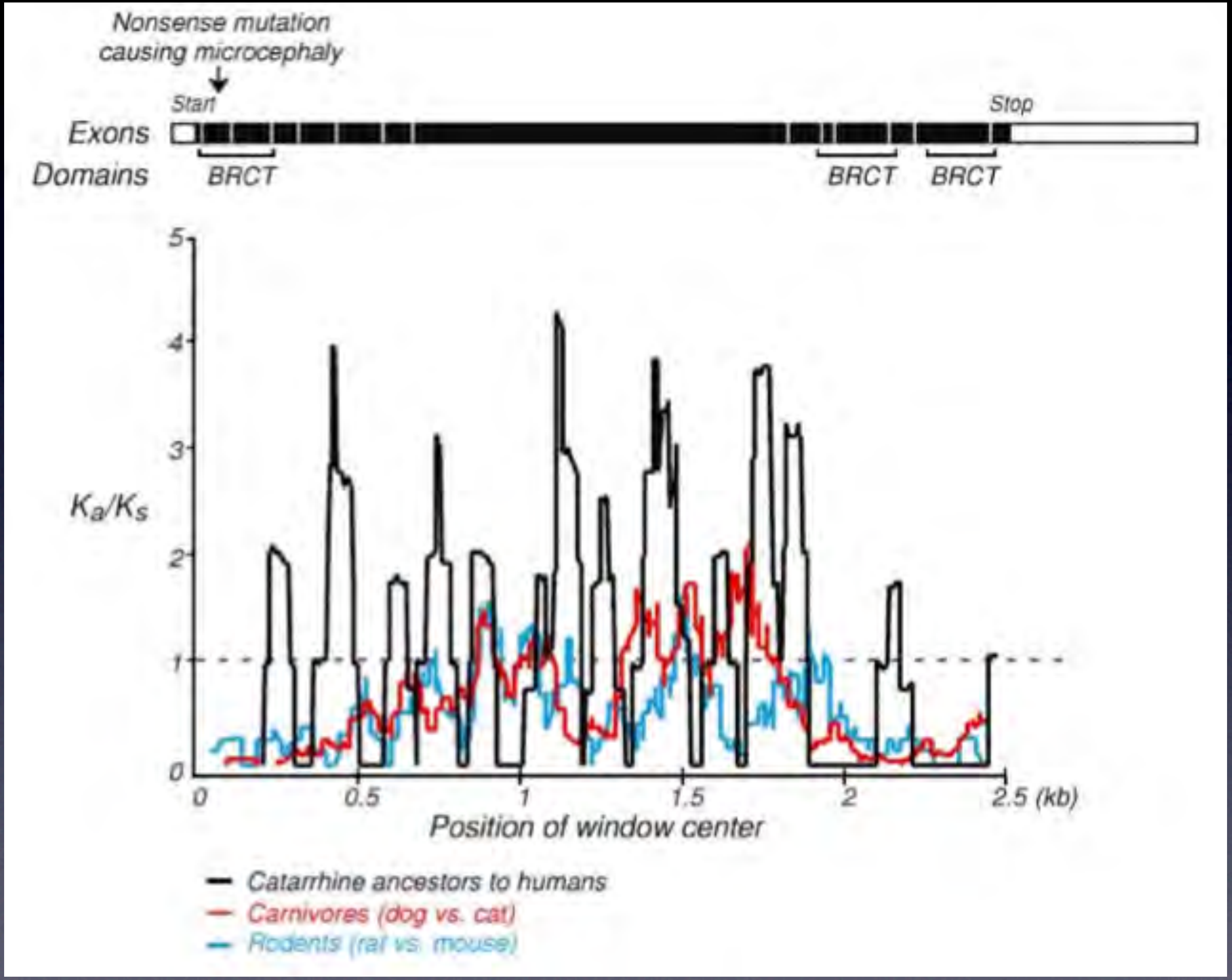
Wang Y, Su B. *Human Molecular Genetics* 2004;13:1131-1137

MCPH1



Wang Y, Su B. *Human Molecular Genetics 2004;13:1131-1137*

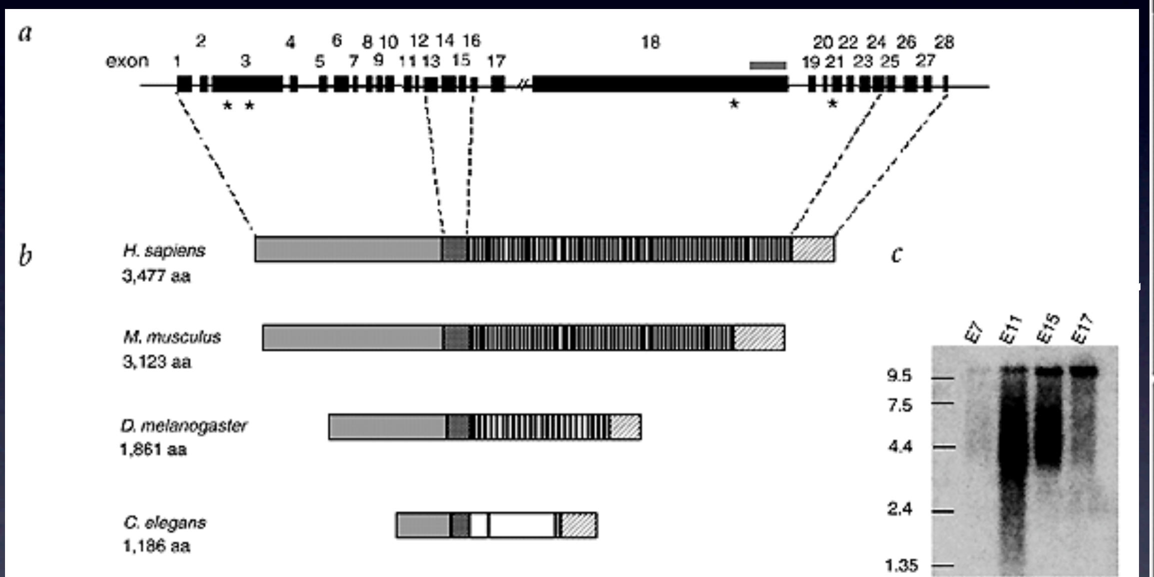
MCPH1 Selection

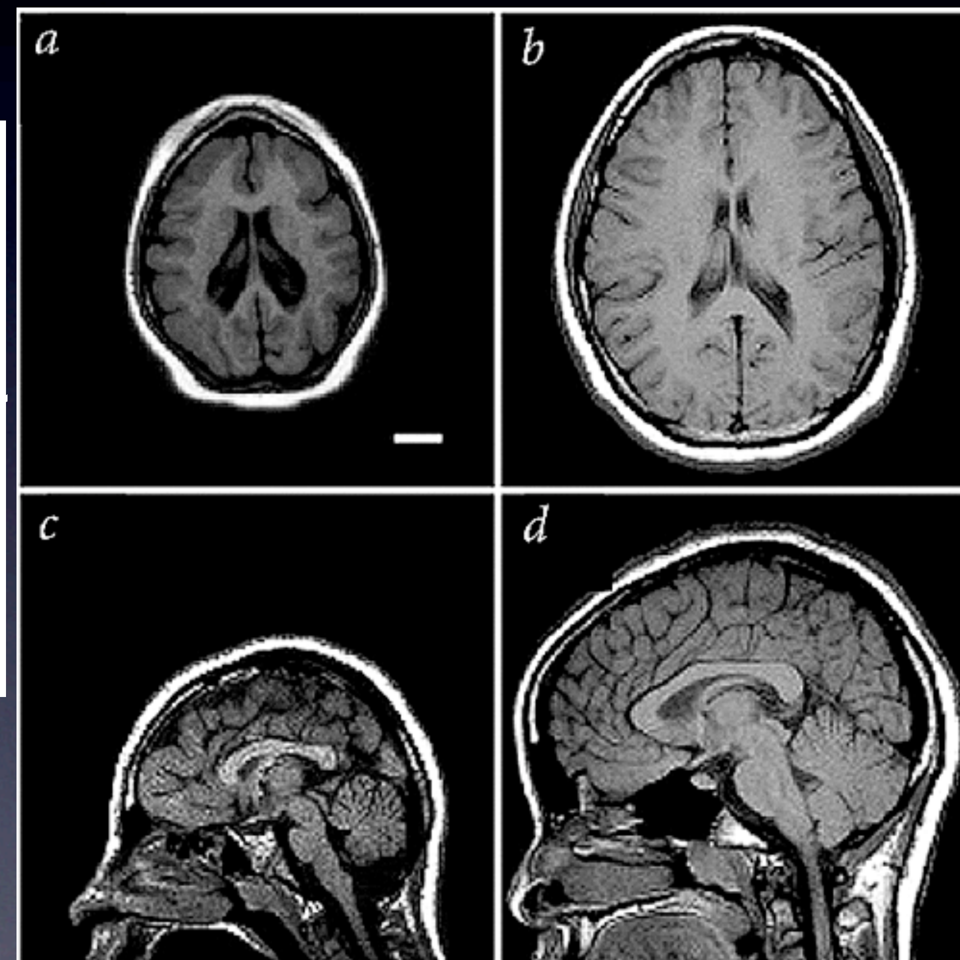


Evans PD, *et al. Human Molecular Genetics 2004;13:1139-1145*

ASPM

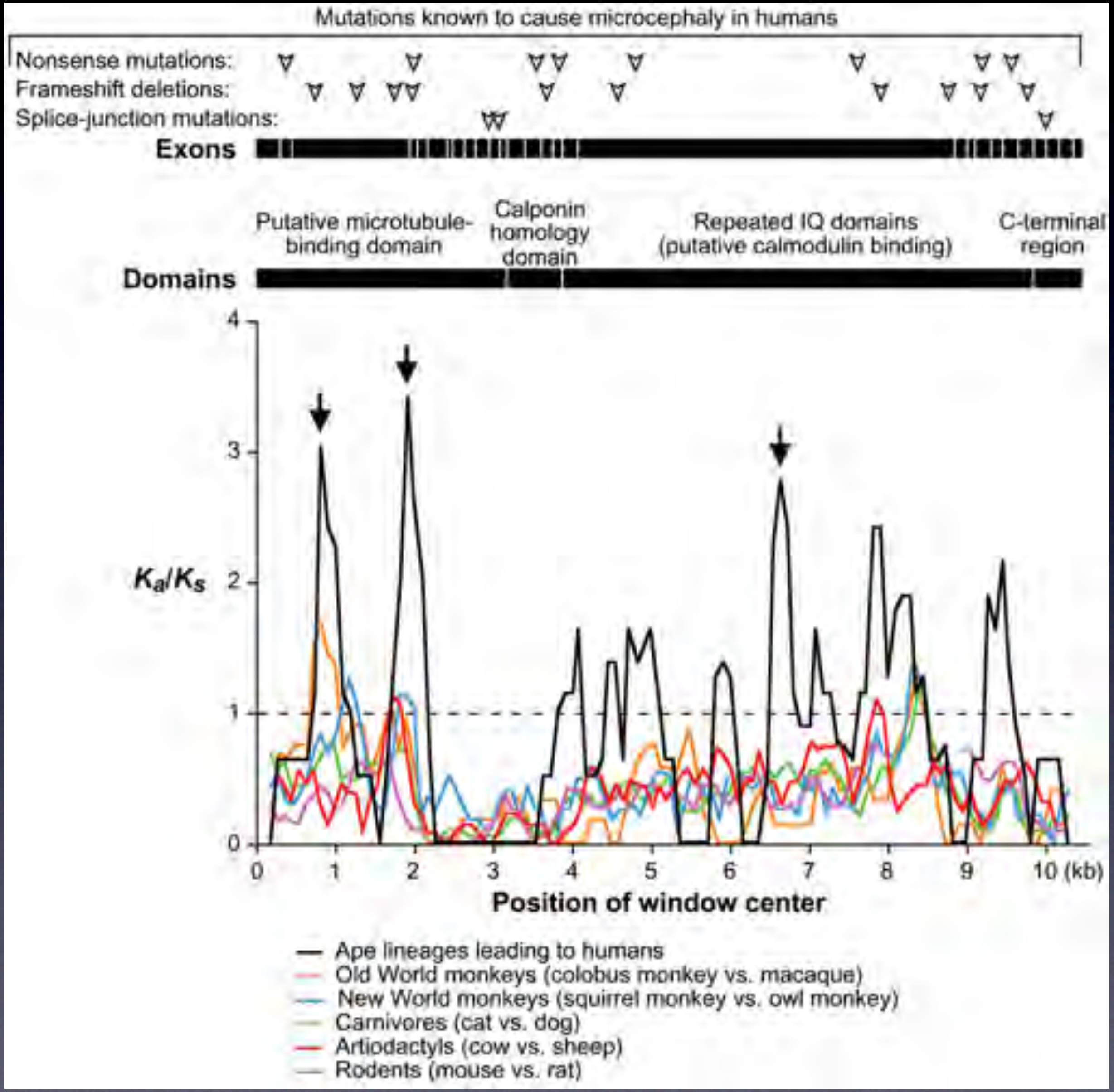
abnormal spindle−like microcephaly associated





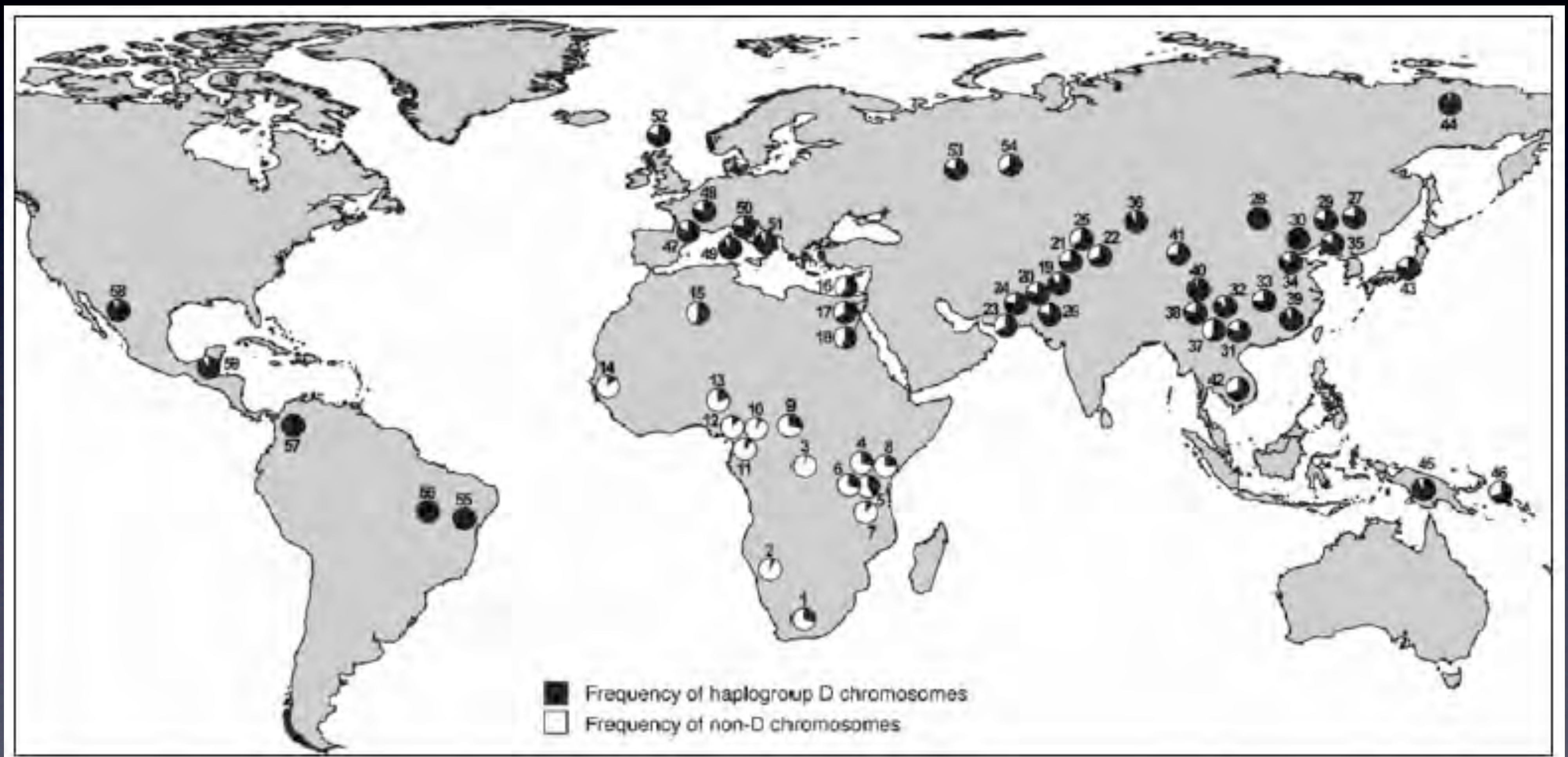
Bond J, *et al. Nature Genetics* 2002;32:316-320

ASPM Selection



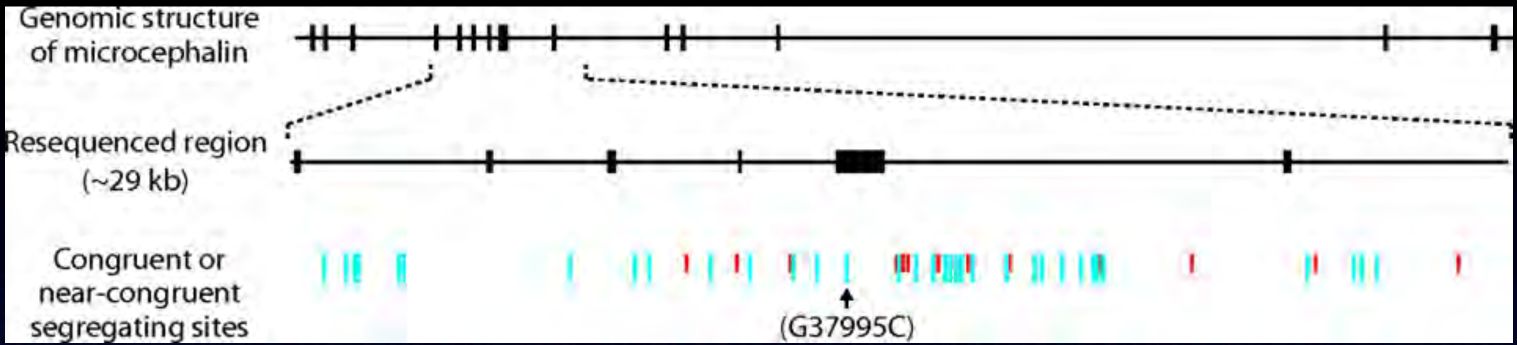
Evans PD, *et al. Human Molecular Genetics* 2004:13:489-494

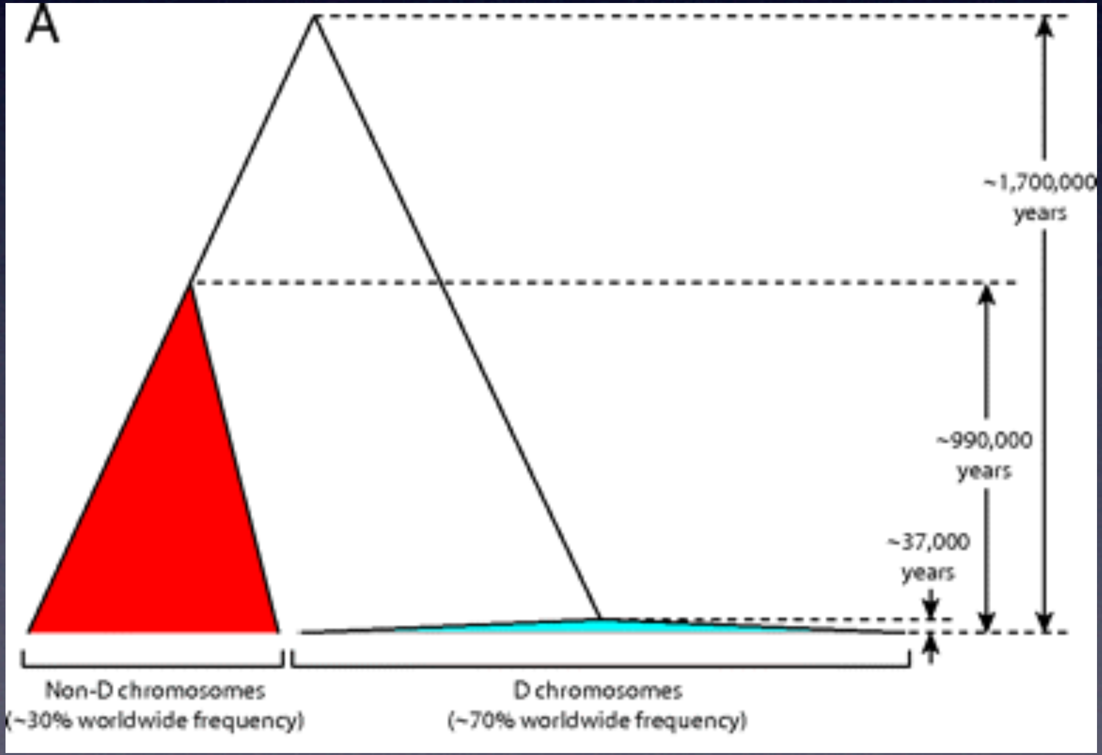
MCPH1 D Distribution

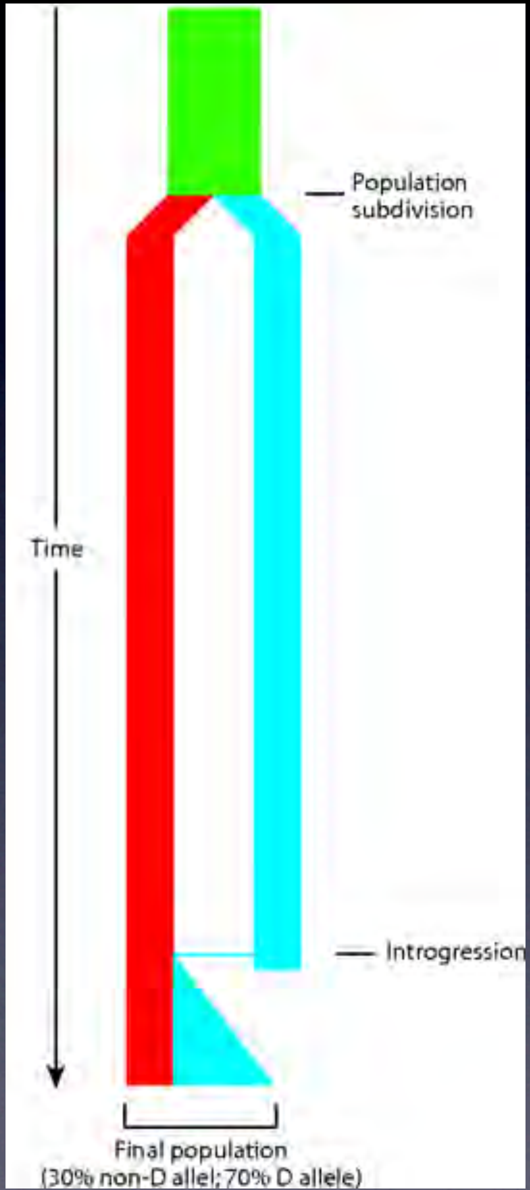


Evans PD, *et al*. *Science* 2005;309:1717-1720.

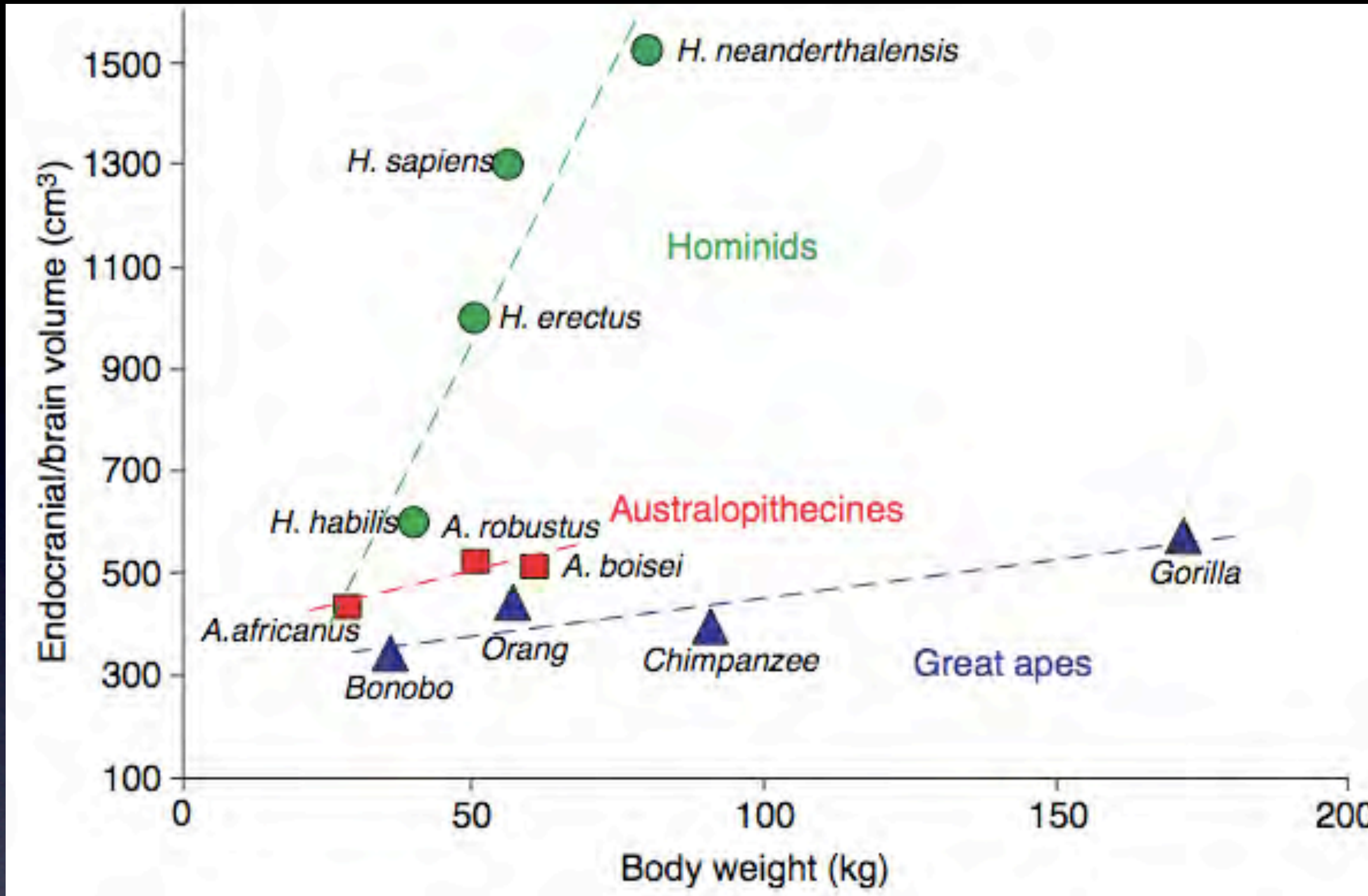
MCPH1 Introgression



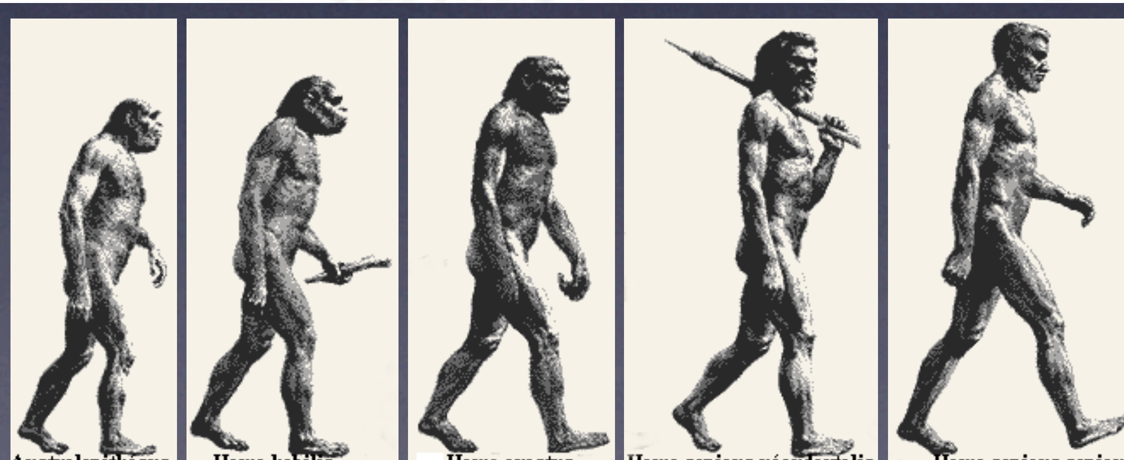




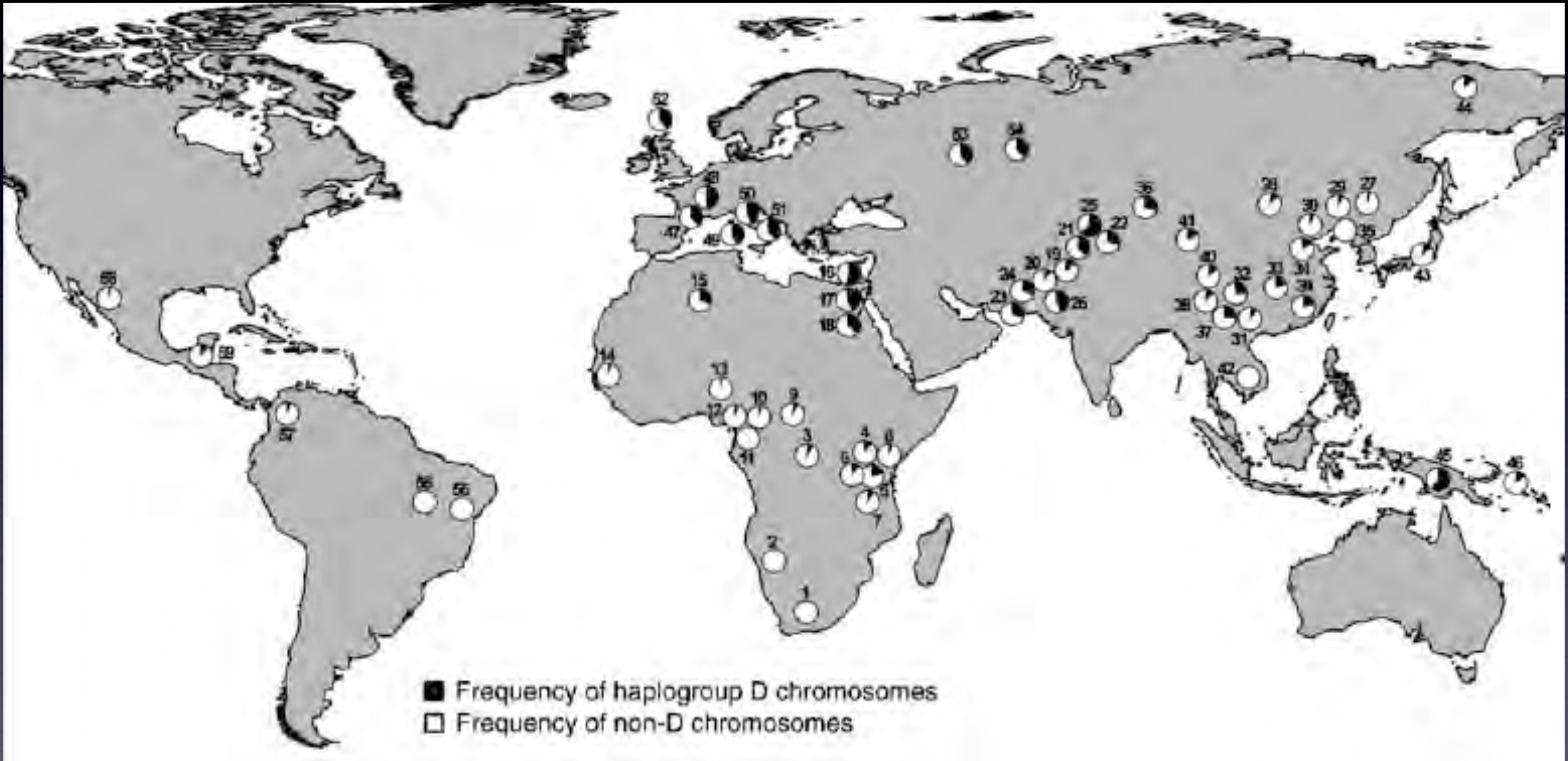
Evans PD, *et al.*, *PNAS* 2006;103:18178-83



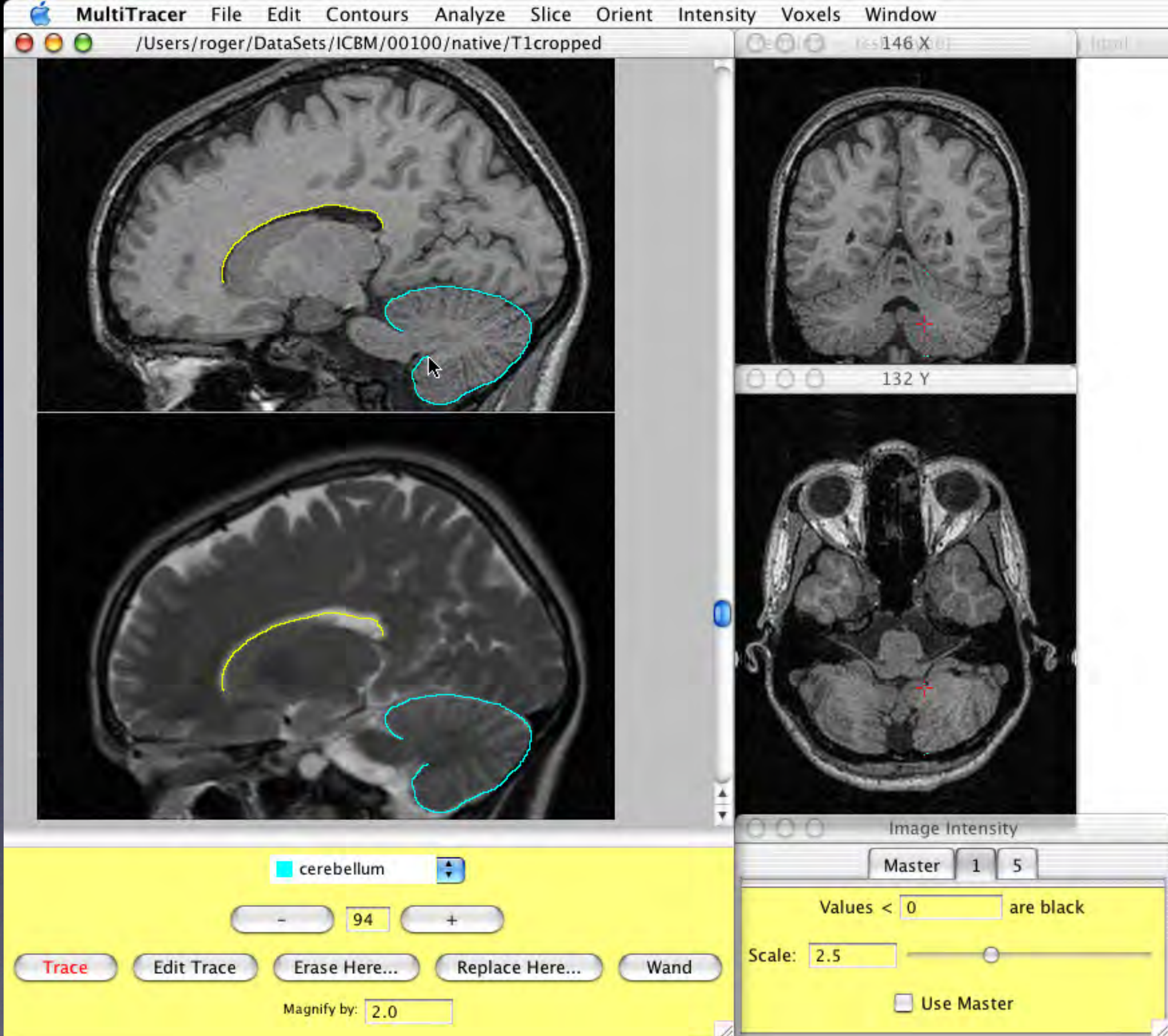
Roth G, Dicke U. *Trends in Cognitive Sciences* 2005;9:250-257



ASPM



Mekel-Bobrov N, *et al*. *Science* 2005:309:1720-1722.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cerebellum
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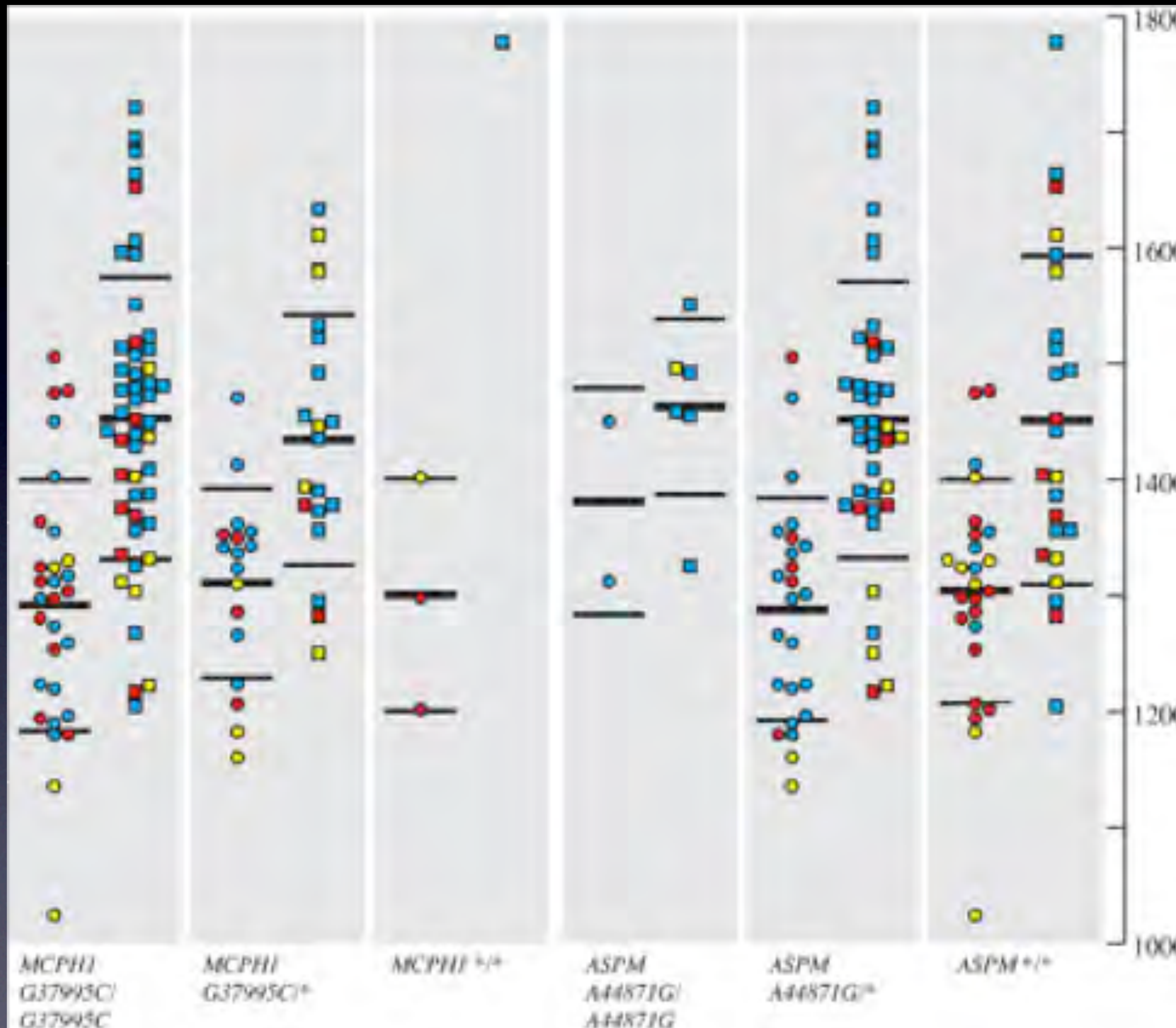
Brain Volume (cc)

Caucasian
Asian
Hispanic

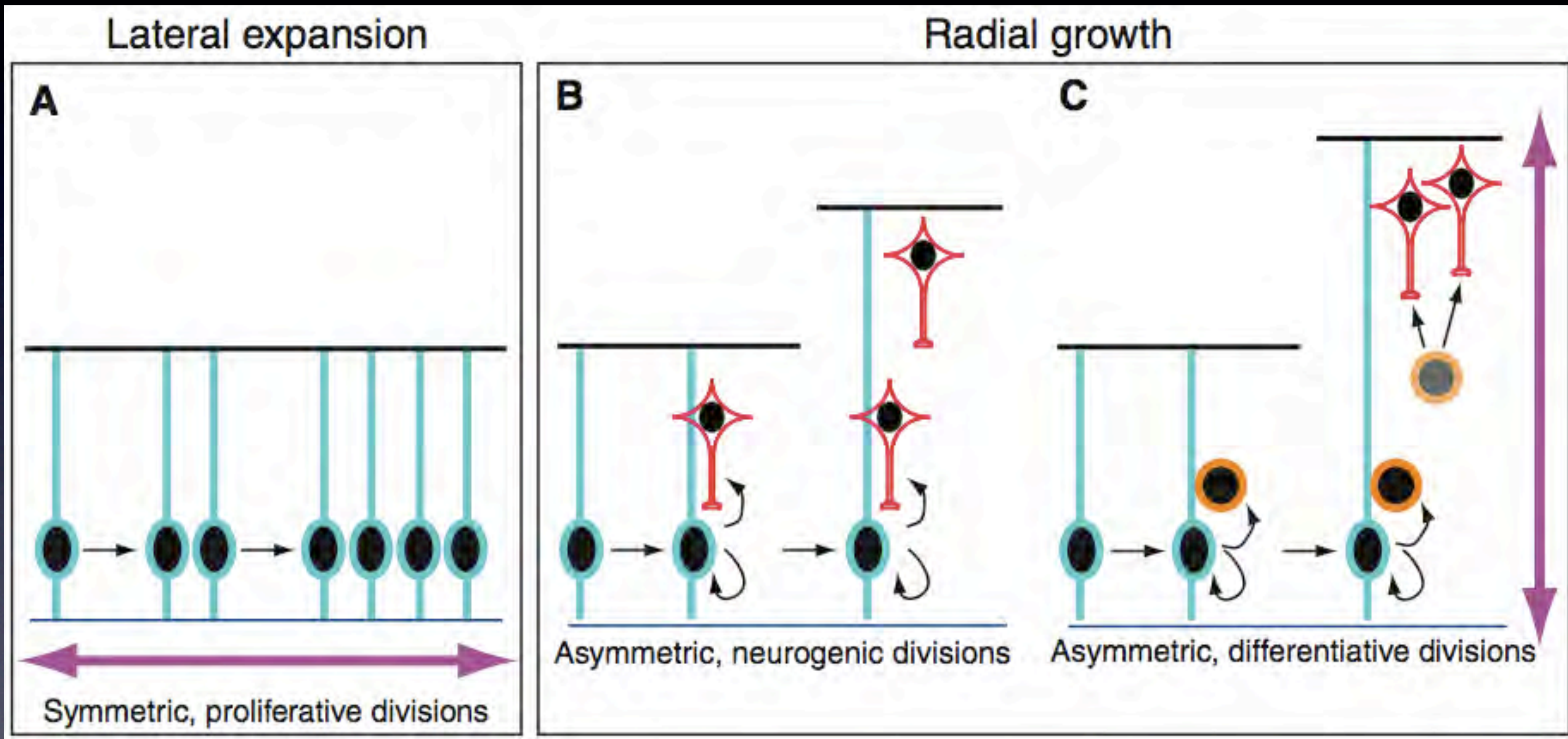


Woods RP, *et al. Hum Mol Genet* 2006:15:2025-2029.

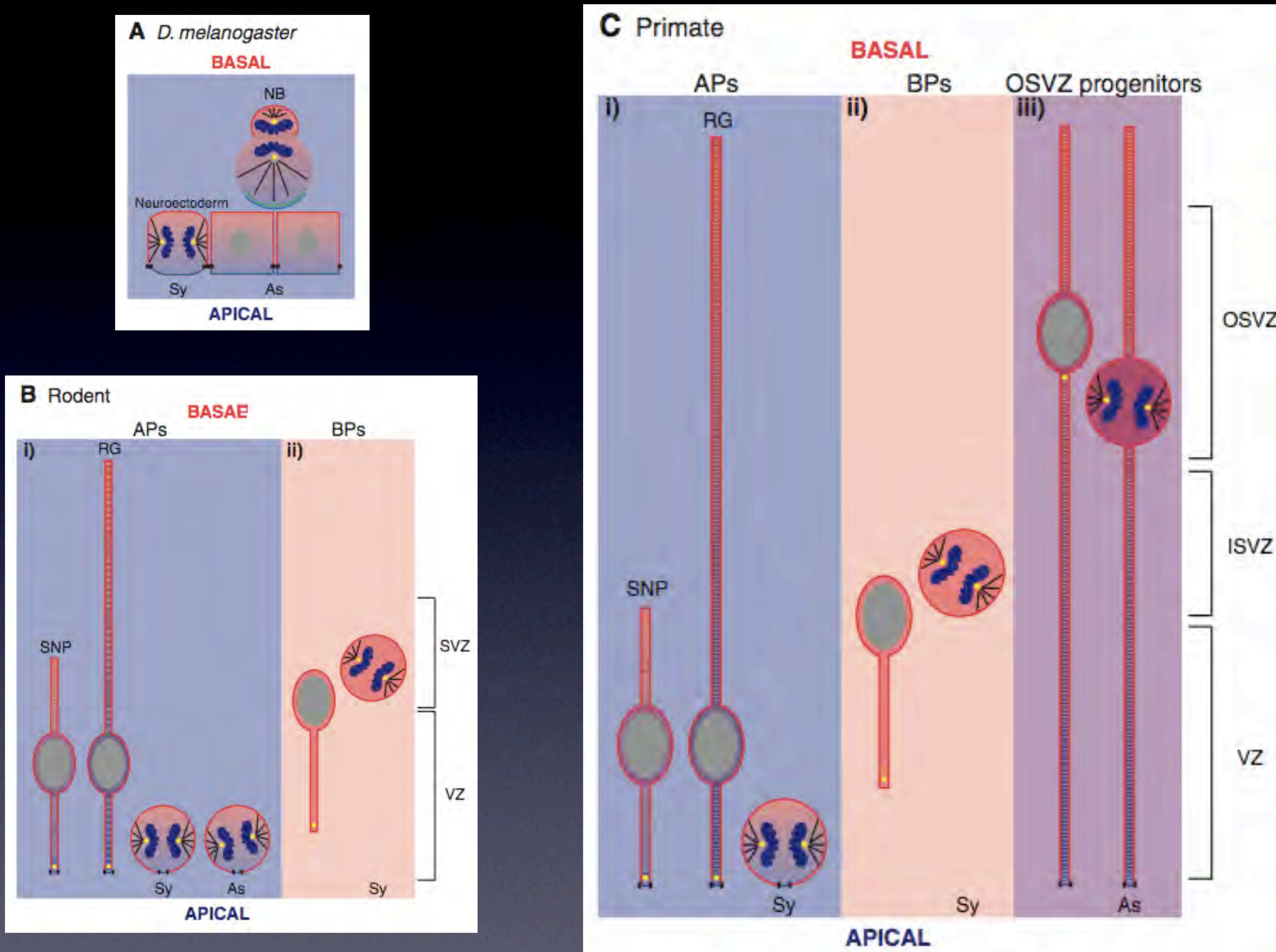
Recessive Microcephaly

- MCPH1 (microcephalin 8p23) chromosomal condensation and DNA repair
- MCPH2 (19q13.1-q13.2)
- MCPH3 (CDK5RAP2 9q33.3) centrosome
- MCPH4 (15q15-q21)
- MCPH5 (ASPM 1q31) centrosome (most common)
- MCPH6 (CENPJ 13q12.2) centrosome
- Primordial dwarfism (PCNT 21q22.3) centrosome

Embryonic Neurogenesis

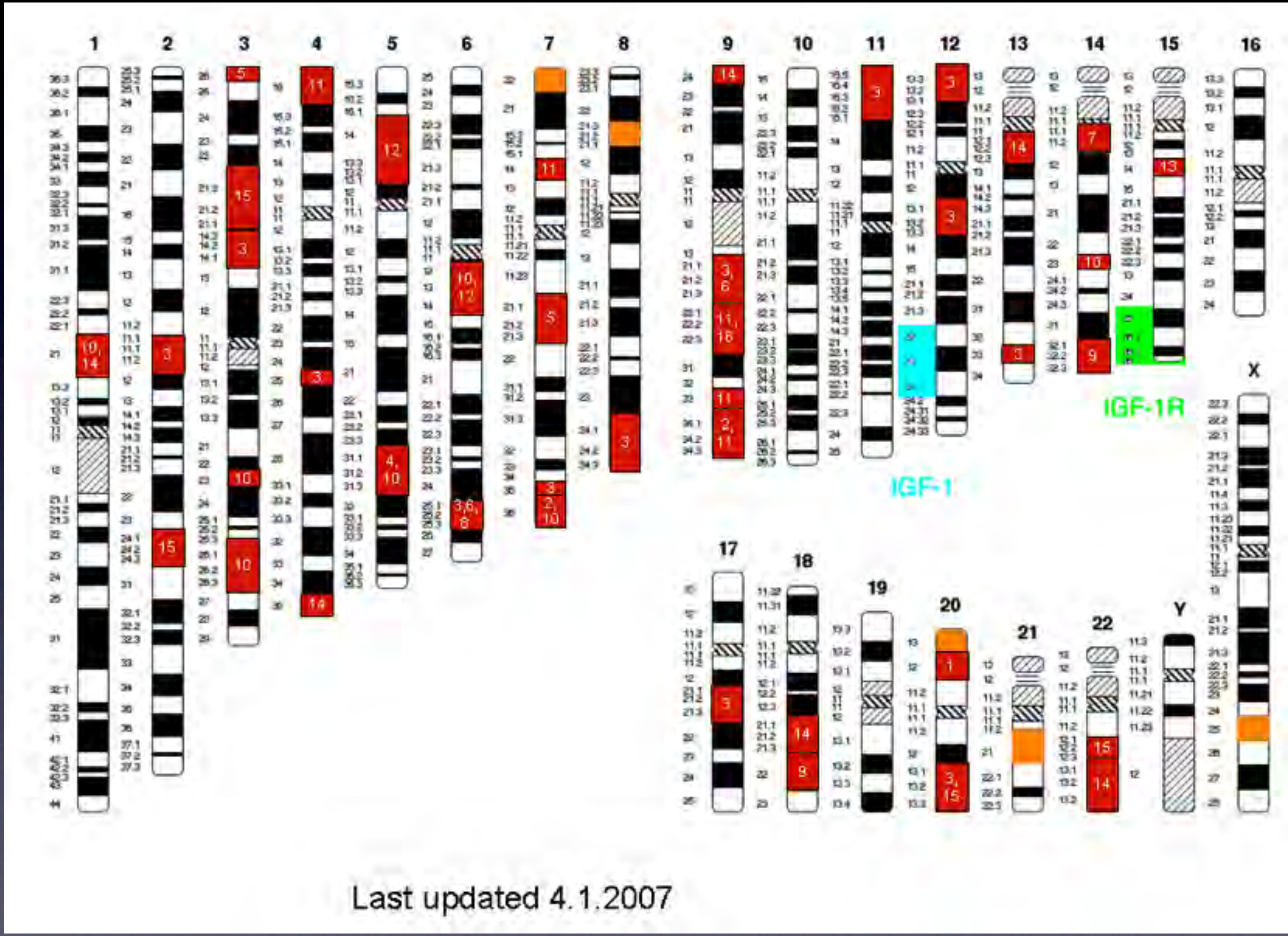


Fish JL *et al. Journal of Cell Science* 2008;121:2783-2793



Fish JL *et al. Journal of Cell Science* 2008;121:2783-2793

Human Height QTL (LOD>2)

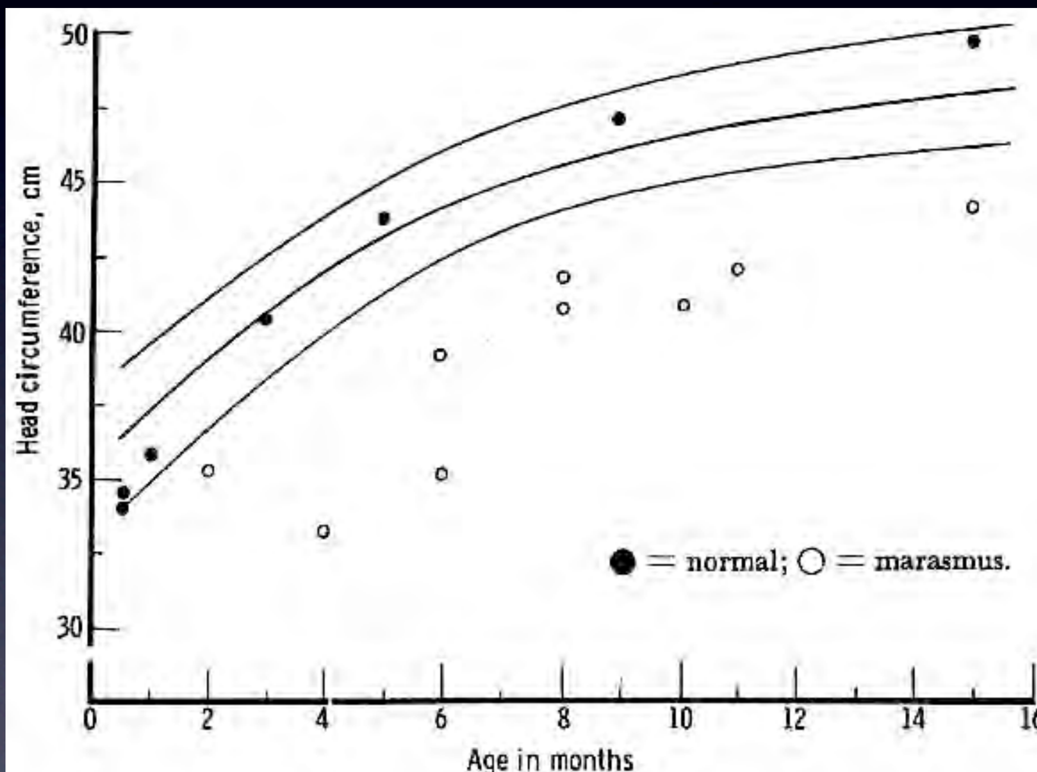


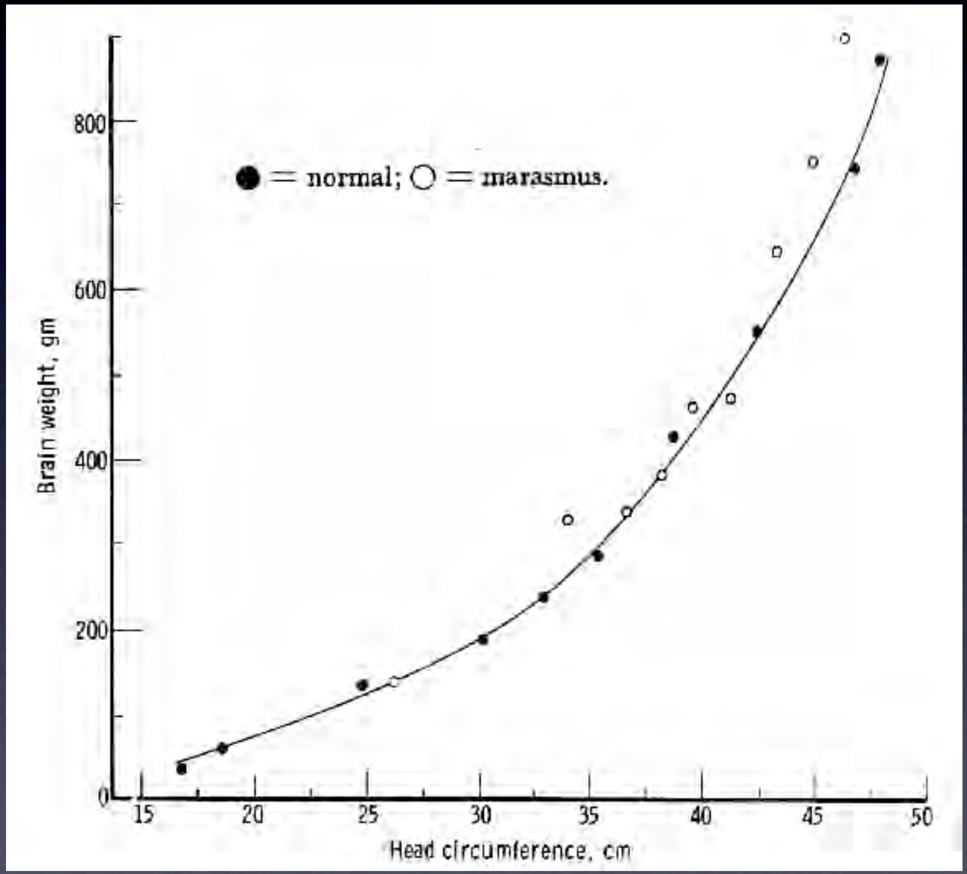
Perola M, *et al. PLoS Genetics* 2007;3(6):e97

Non-genetic microcephaly

- Ionizing radiation exposure (8-15 weeks)
- Drugs: fetal alcohol, fetal anticonvulsants
- Malnutrition
- Metabolic: maternal diabetes or PKU
- Intrauterine infections: CMV, rubella, toxoplasmosis
- Hyperthermia during early infancy
- Meningitis/encephalitis
- Hypoxic/ischemic encephalopathy

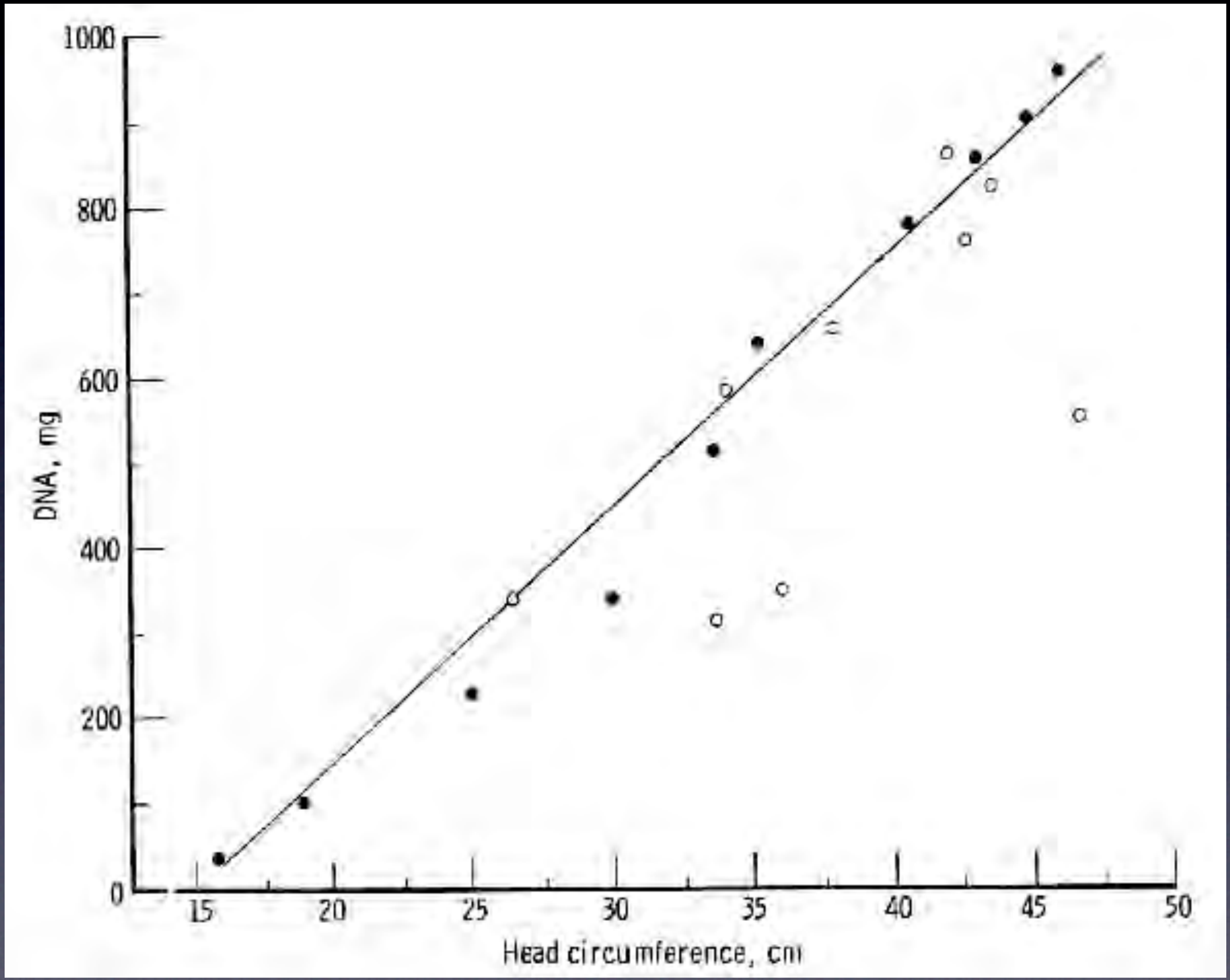
Environment and Brain Size: Nutrition





Winick M, *et al. J Pediatr* 1969;74(4):774-8.

Nutrition and Brain Size



Winick M, *et al. J Pediatr* 1969;74(4):774-8.

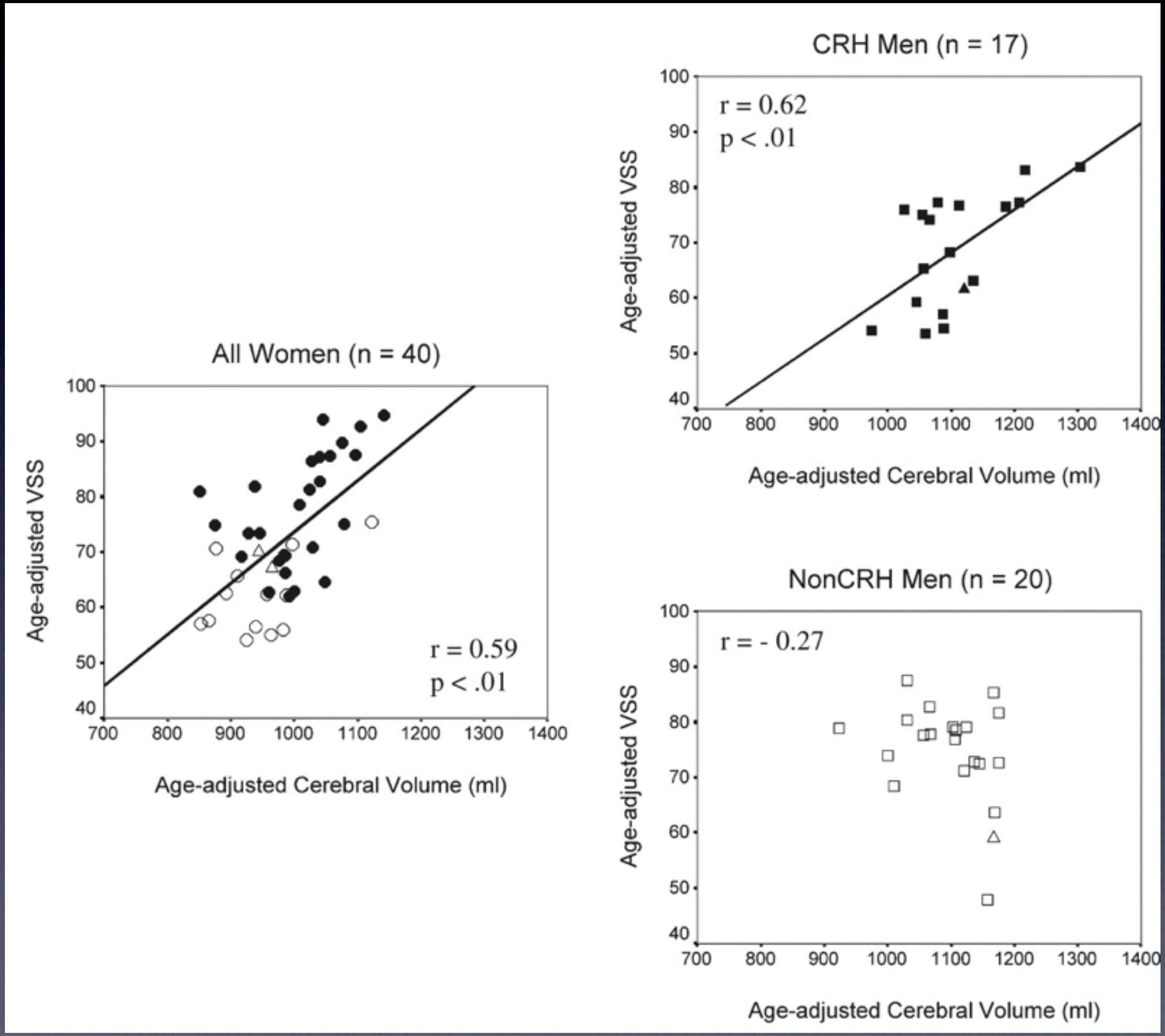
Brain Size-IQ

Meta-analytic results for in vivo brain volume and intelligence

Distribution	Number of studies	Sample size	Observed mean correlation	Mean correlation corrected for range restriction
All correlations	37	1530	0.29	0.33
Analyses by whether the degree of range restriction was interpolated				
Interpolation	21	963	0.29	0.32
No interpolation	16	567	0.30	0.34
Analyses by sex				
Females	12	438	0.36	0.40
Males	17	651	0.30	0.34
Mixed sex	8	441	0.21	0.25
Analyses by age				
Adults	24	1120	0.30	0.33
Children	13	410	0.28	0.33
Analyses by age and sex				
Female adults	8	327	0.38	0.41
Female children	4	111	0.30	0.37
Male adults	11	470	0.34	0.38
Male children	6	181	0.21	0.22

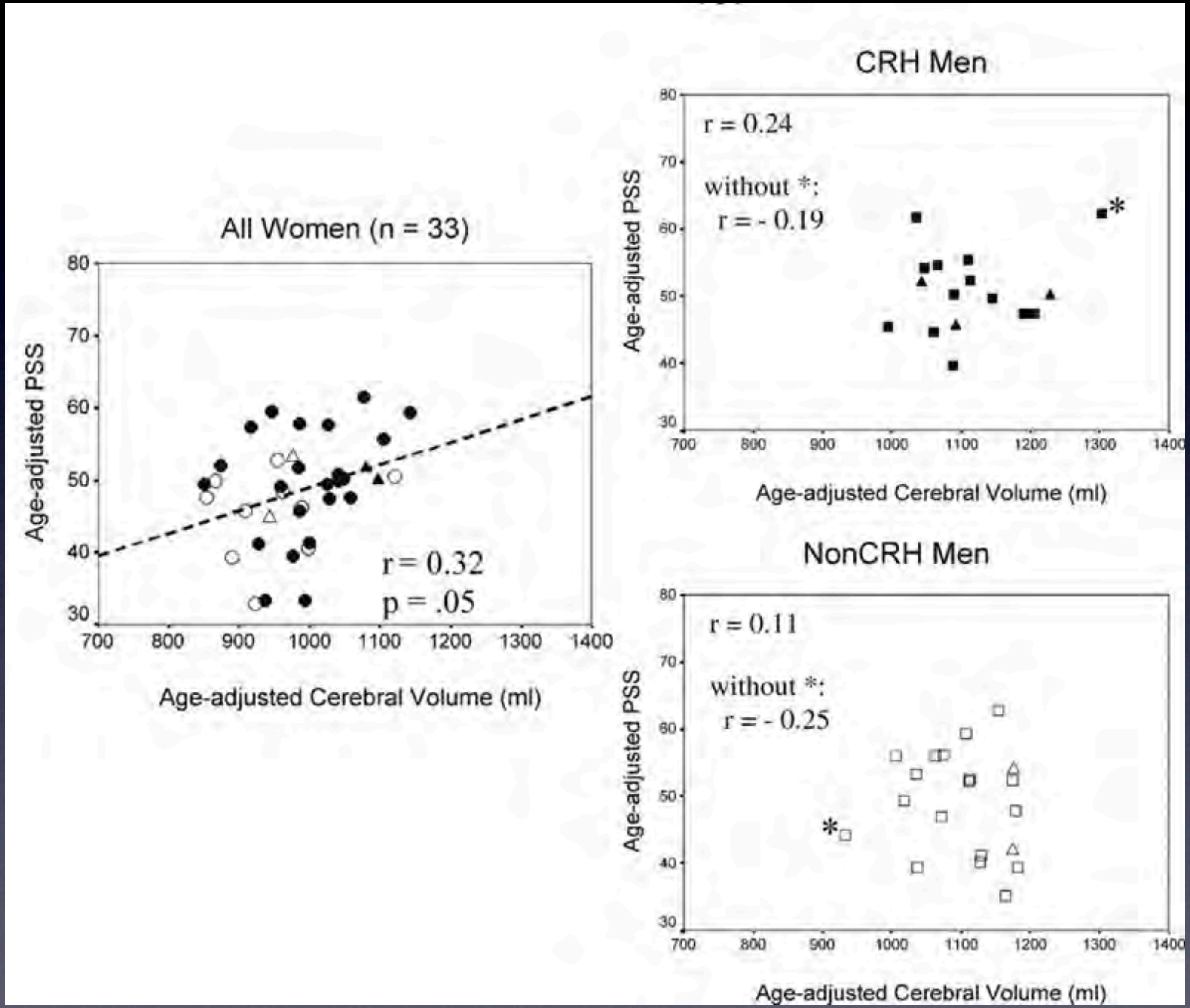
McDaniel MA. *Intelligence* 2005;33:337-346.

Brain Size-Verbal IQ



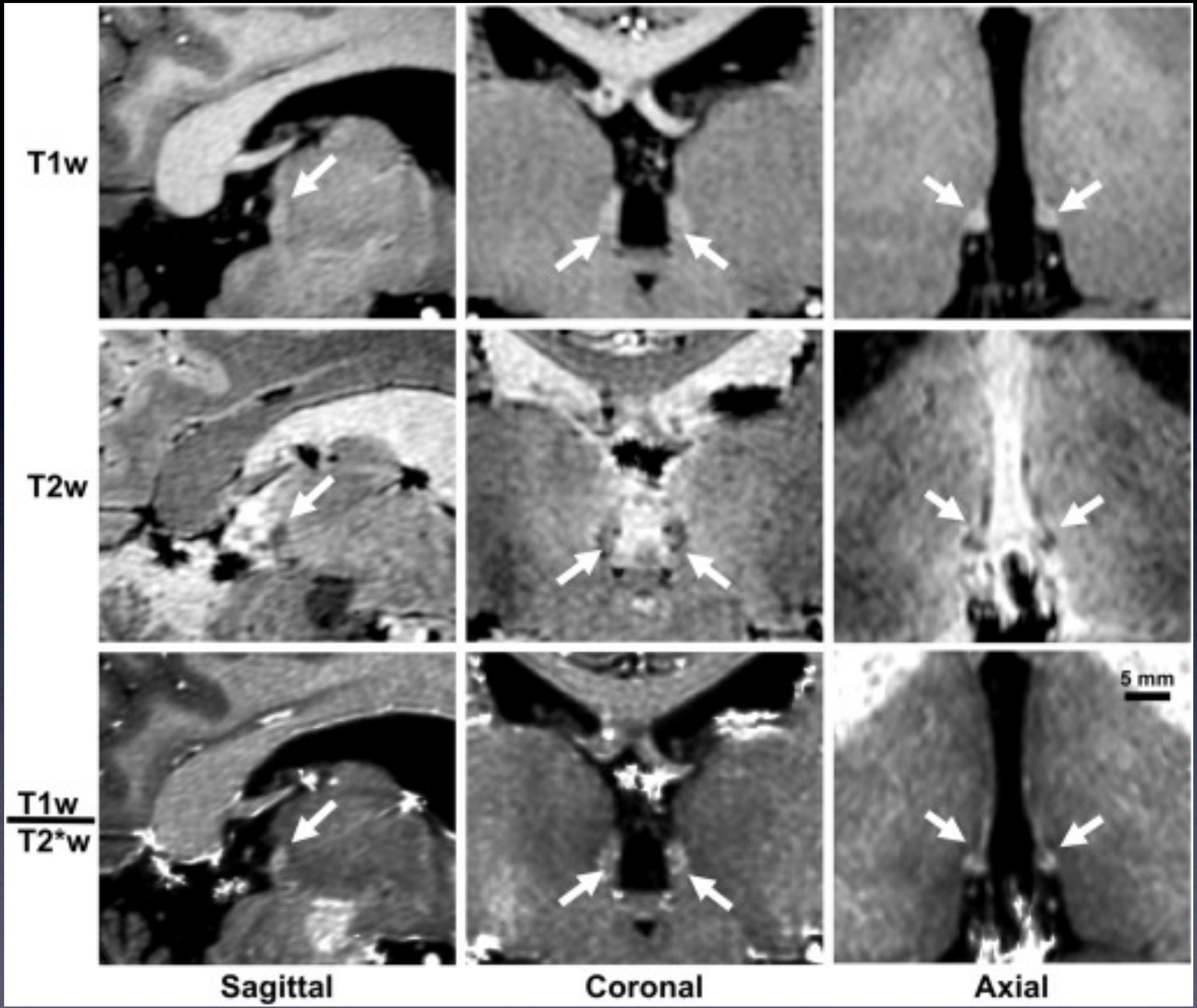
Witelson SF. *Brain* 2006;129:386-398.

Brain Size-Performance IQ



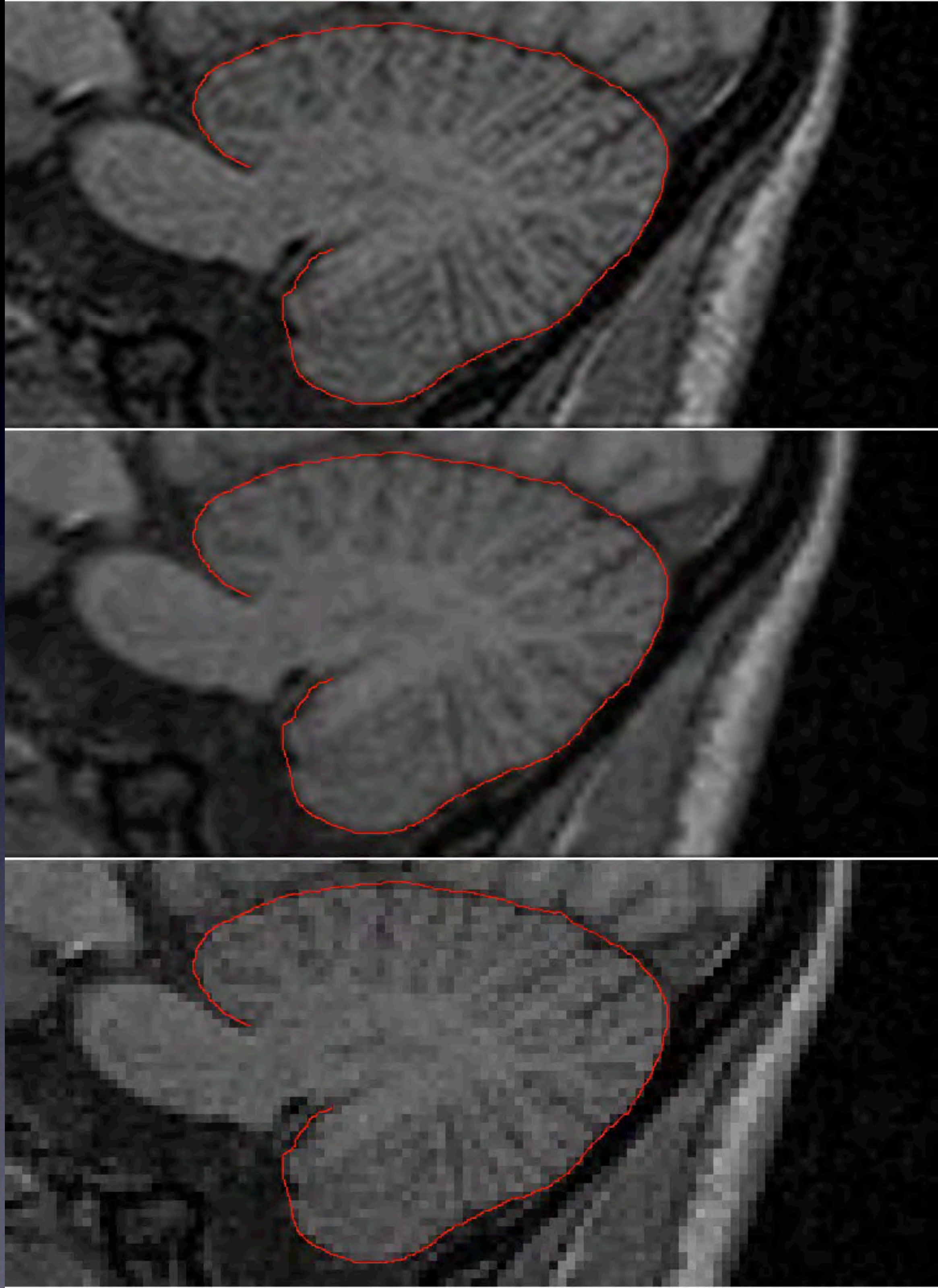
Witelson SF. *Brain* 2006;129:386-398.

Human Habenular Nuclei at 7 Tesla

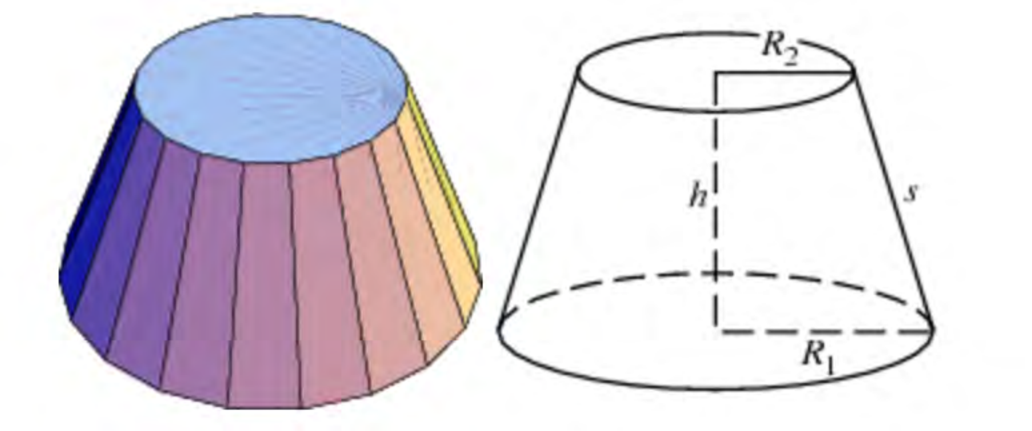


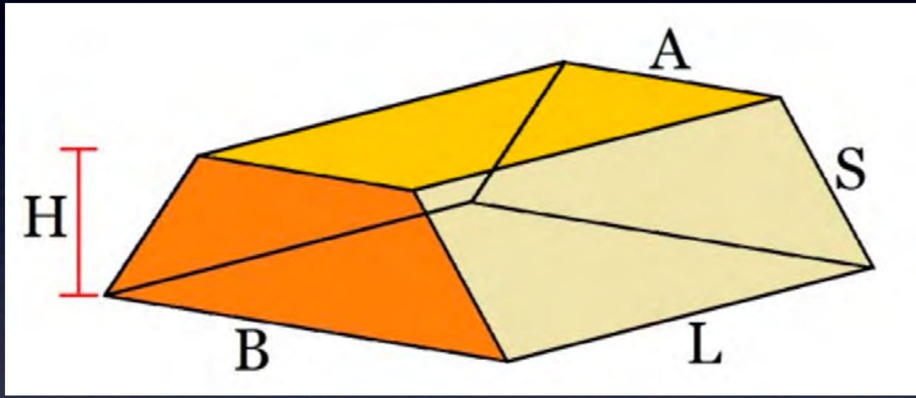
Kim *et al.* *Neuroimage* 2016, in press

Sub-voxel in-plane anatomy



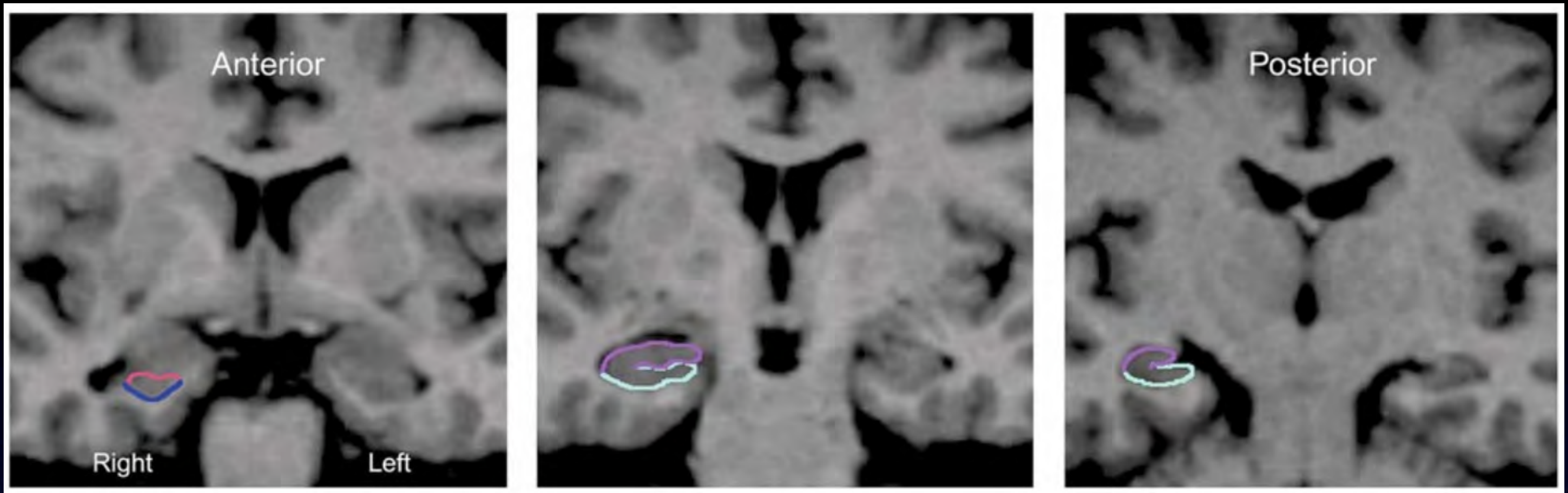
Alternatives to summing areas



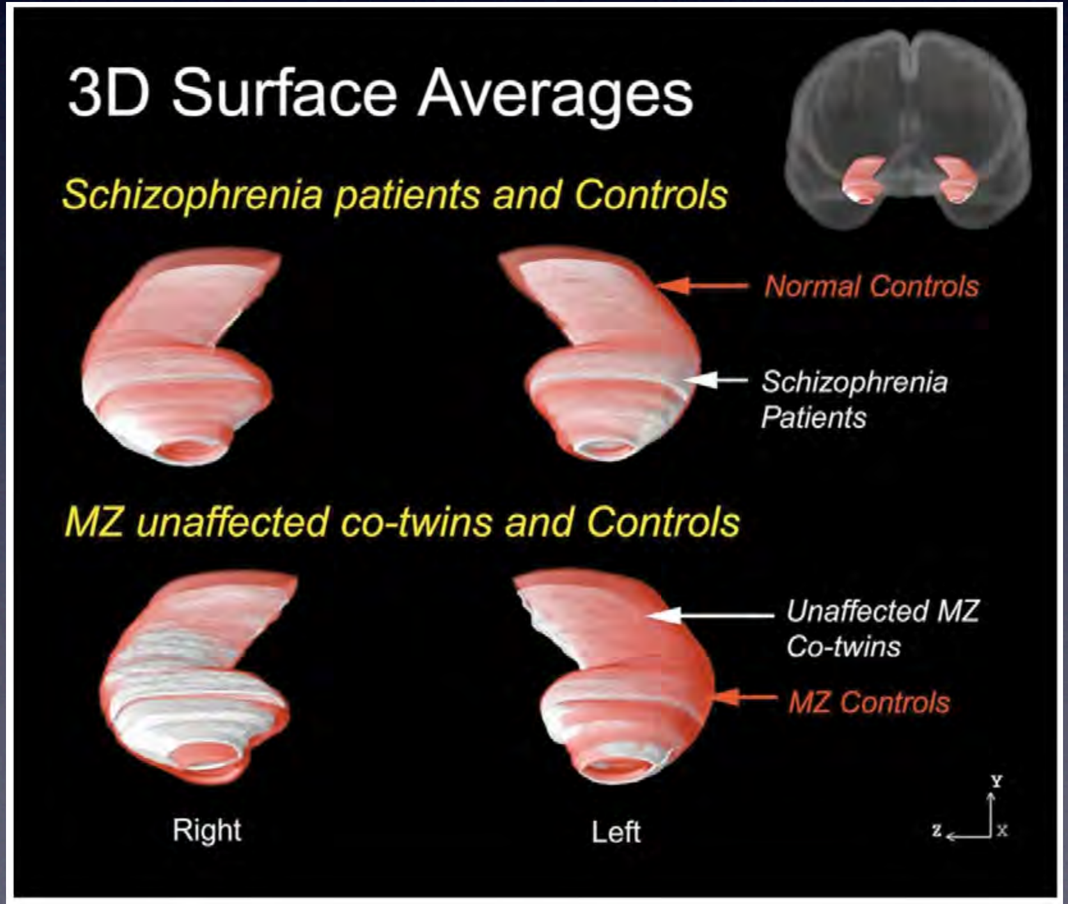


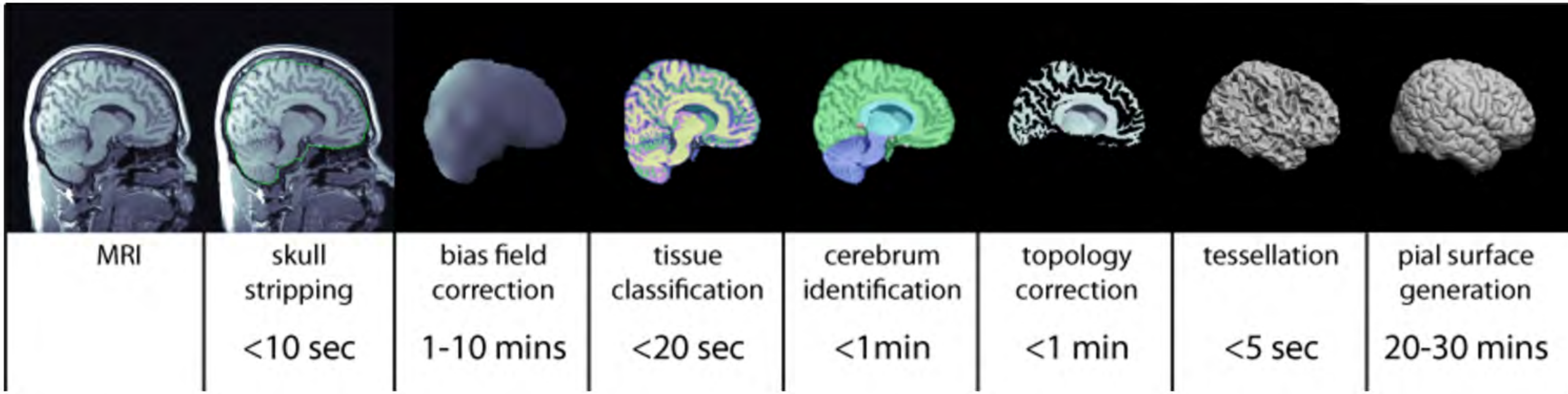
$$V = \frac{1}{3} h \left(A_1 + A_2 + \sqrt{A_1 A_2} \right).$$

$$V(L, B, A, H) = LH(A + B)/2.$$



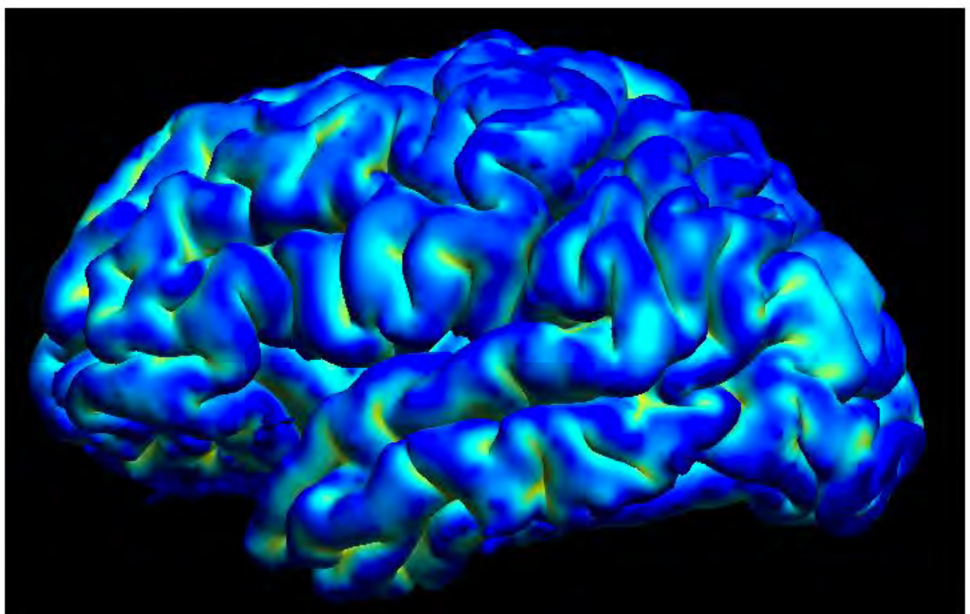
Narr *et al.*
Neurobiology of Disease
2002;11:83-95





The BrainSuite workflow

you
hello



Automatically generated cortical surface mesh

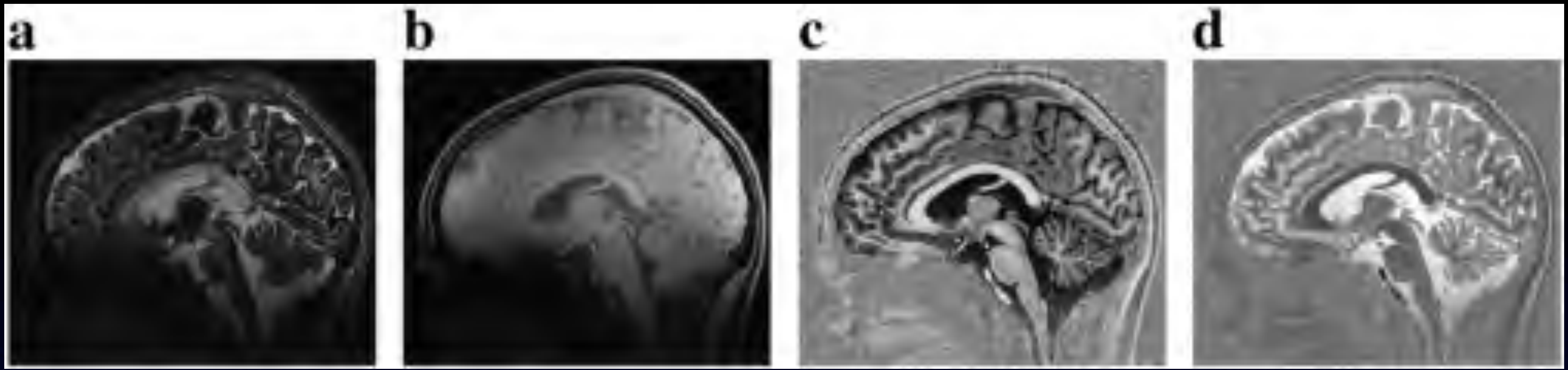


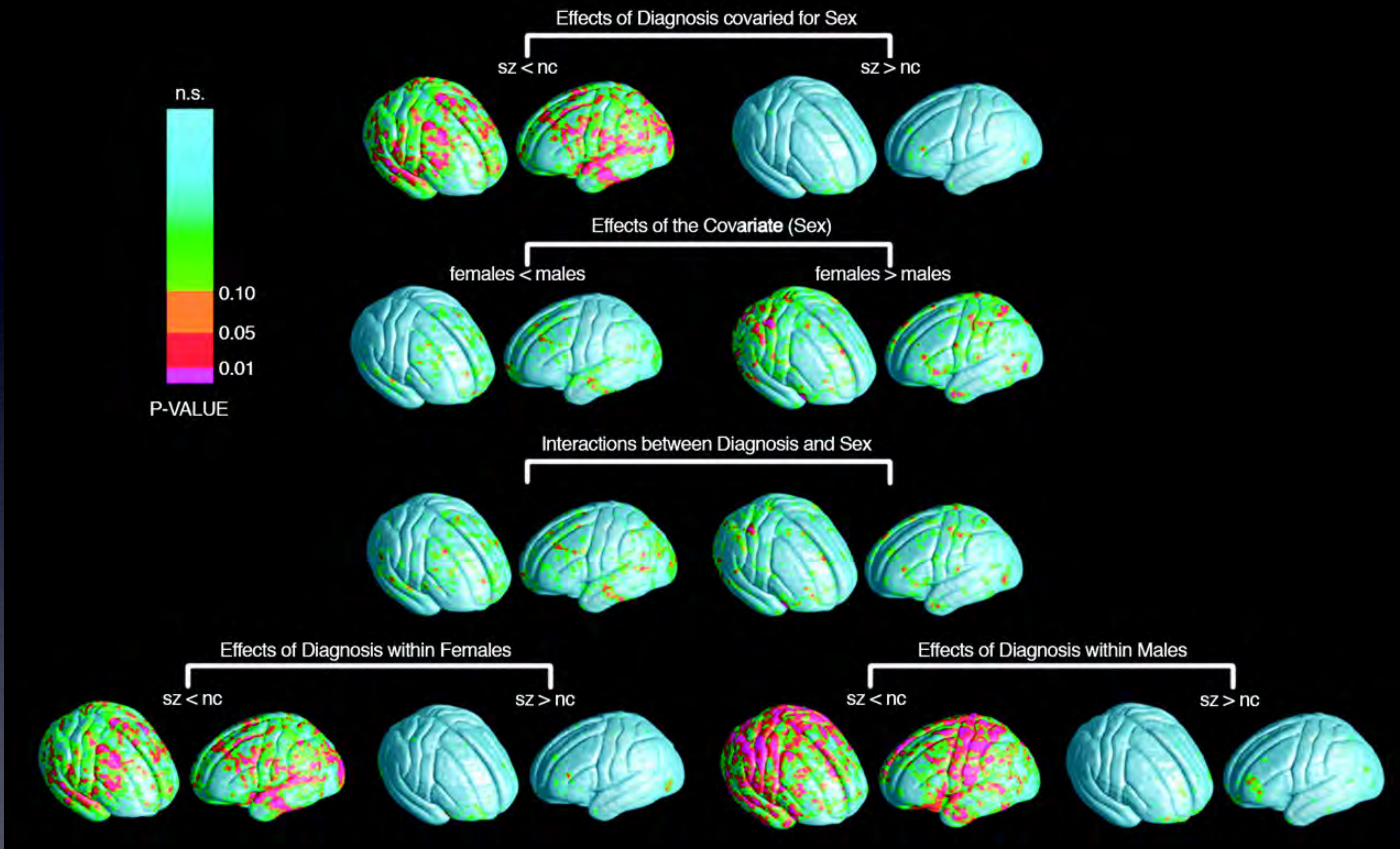
Fig. 1. MP2RAGE image: a) first inversion D1, b) second inversion D2, c) T1-weighted image DW and d) estimated T1 map DT.

Pierre-Louis Bazin, Marcel Weiss, Juliane Dinse, Andreas Schäfer, Robert Trampel, Robert Turner

A computational framework for ultra-high resolution cortical segmentation at 7 Tesla

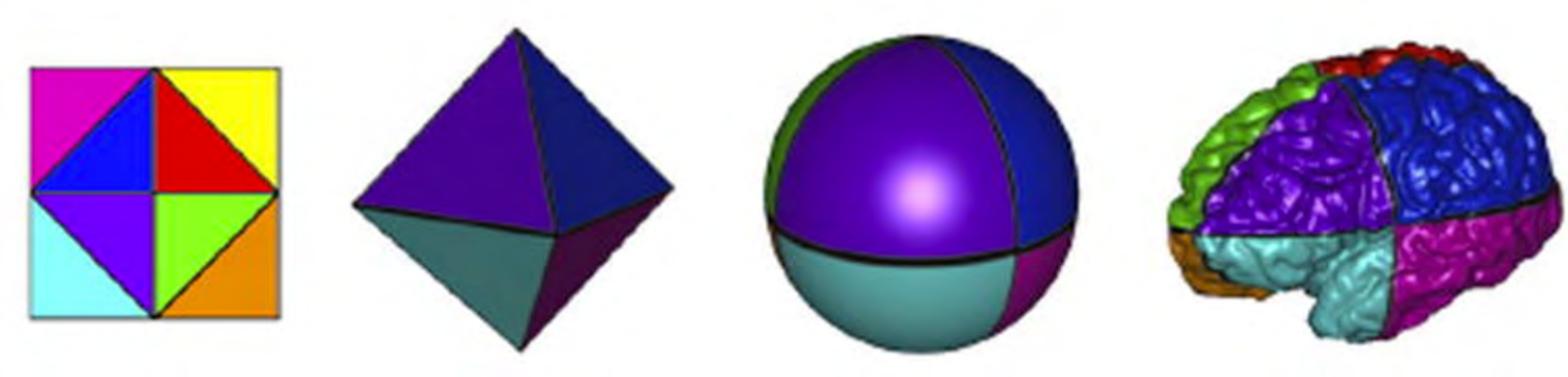
NeuroImage, Volume 93, Part 2, 2014, 201–209

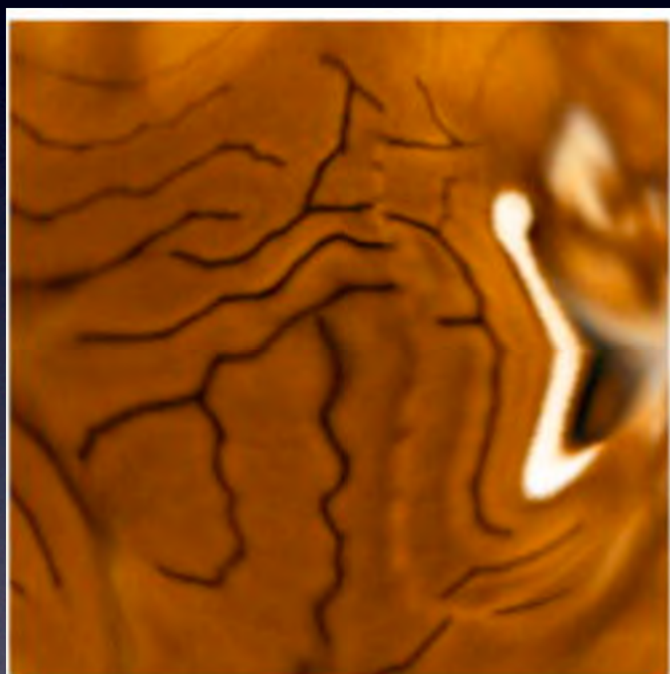
http://dx.doi.org/10.1016/j.neuroimage.2013.03.077

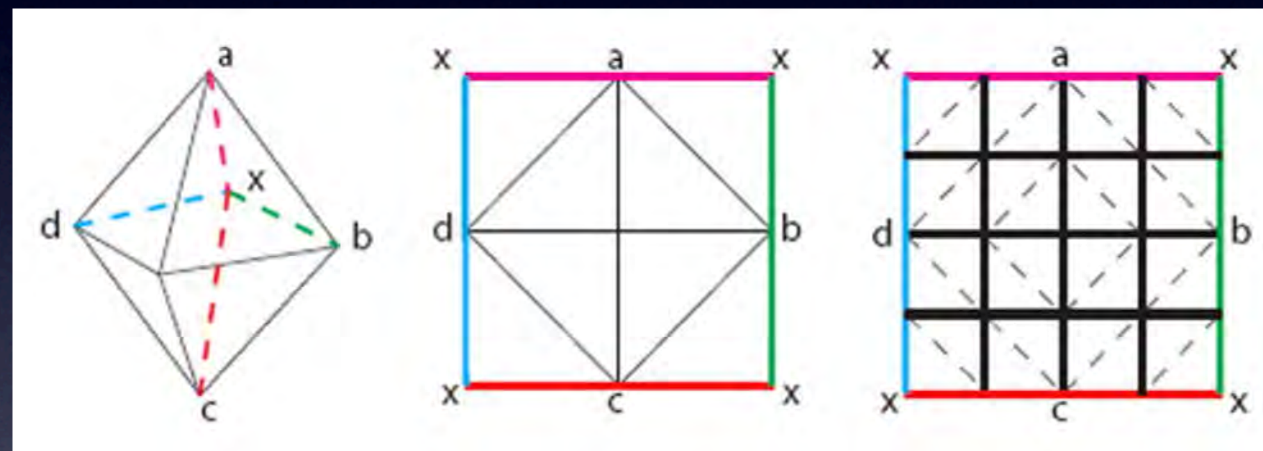


Katherine L. Narr et al. Cereb. Cortex 2005;15:708-719

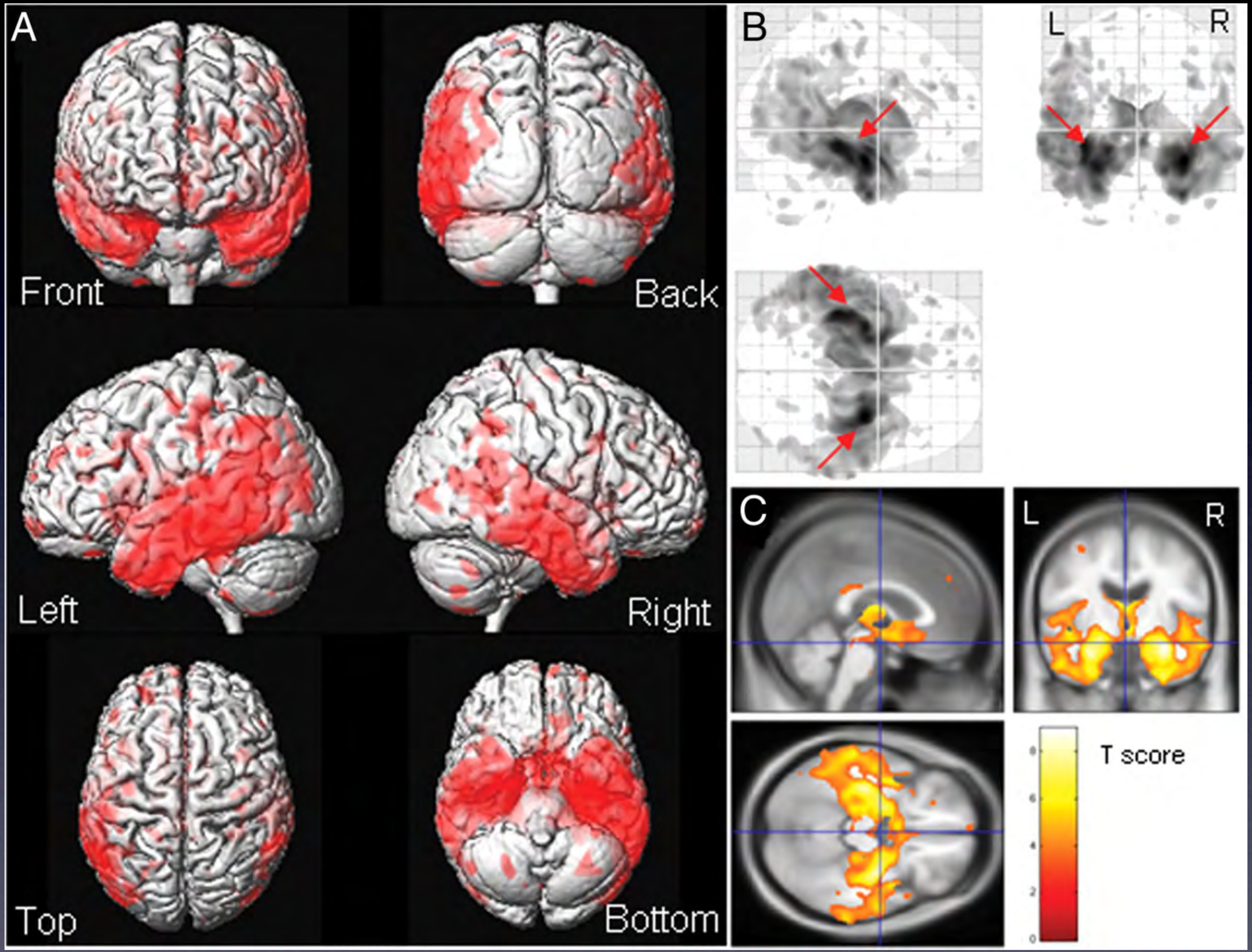
Cerebral CORTEX





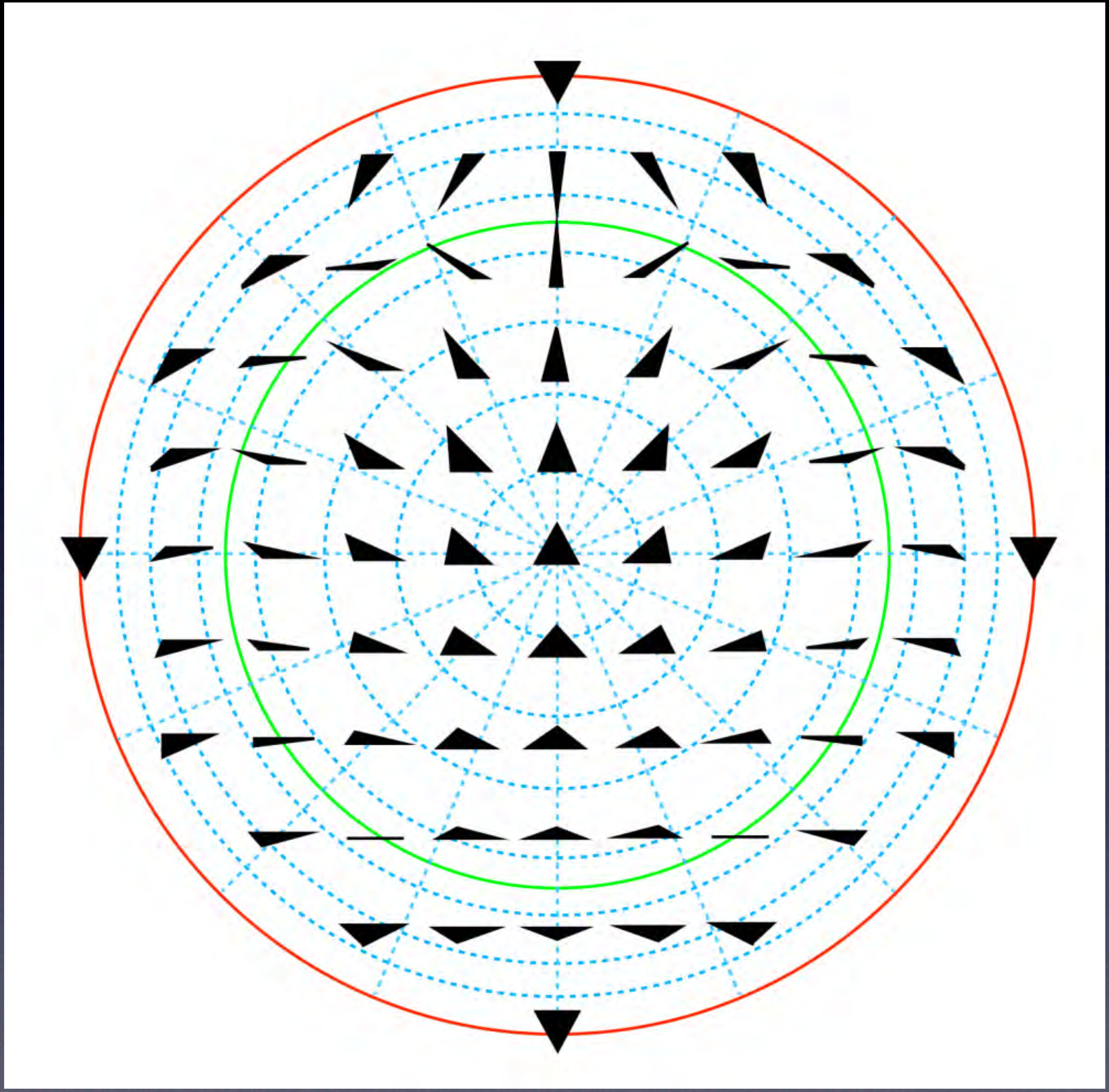


Joshi *et al*. Proc IEEE Comput Soc Conf Comput Vis Pattern Recognit 2010 Jun 1; 13-18 June: 475–482.

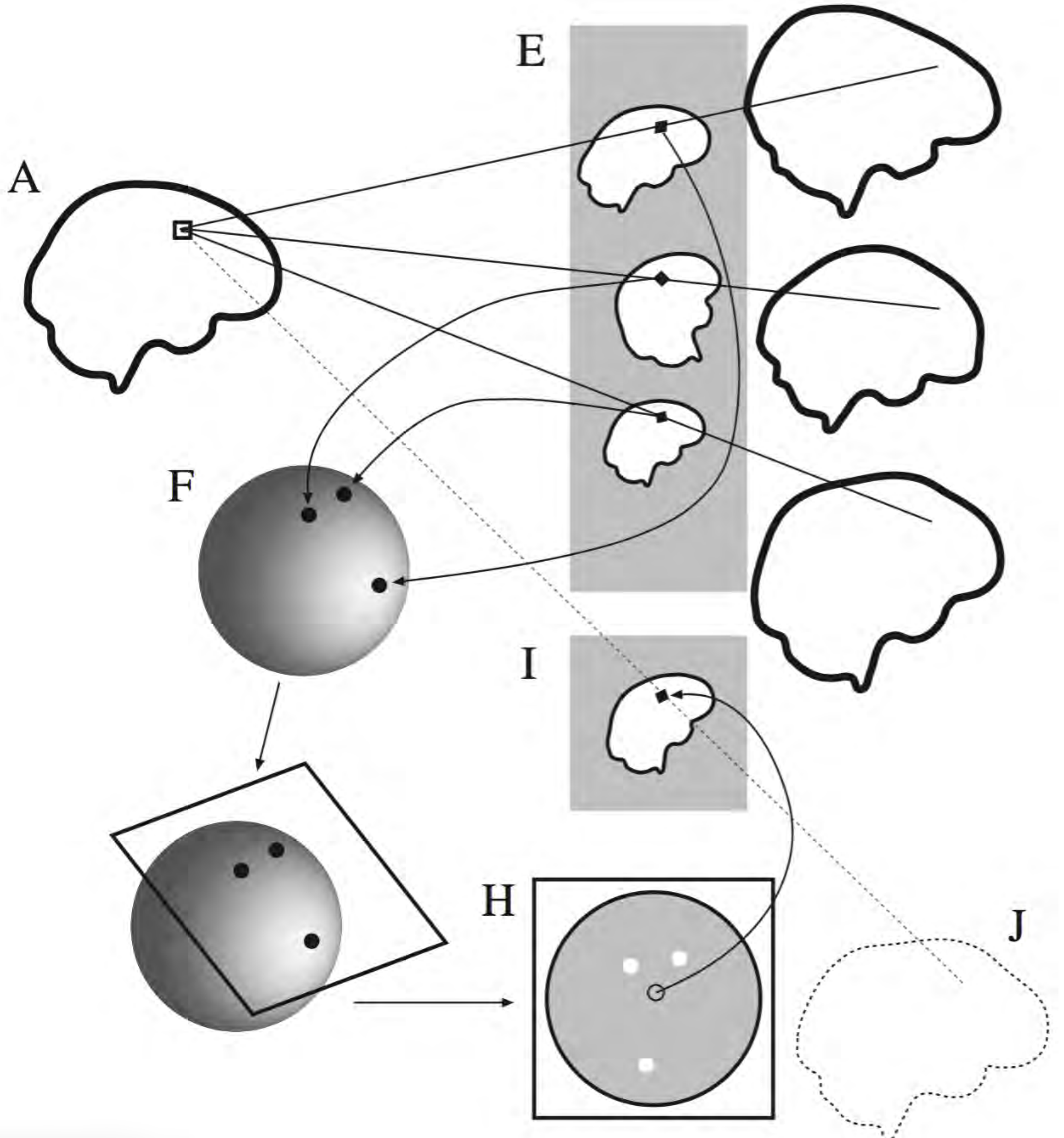


Jennifer L. Whitwell J. Neurosci. 2009;29:9661-9664

The Journal of Neuroscience



Woods. Neuroimage 2003;18: 769-88

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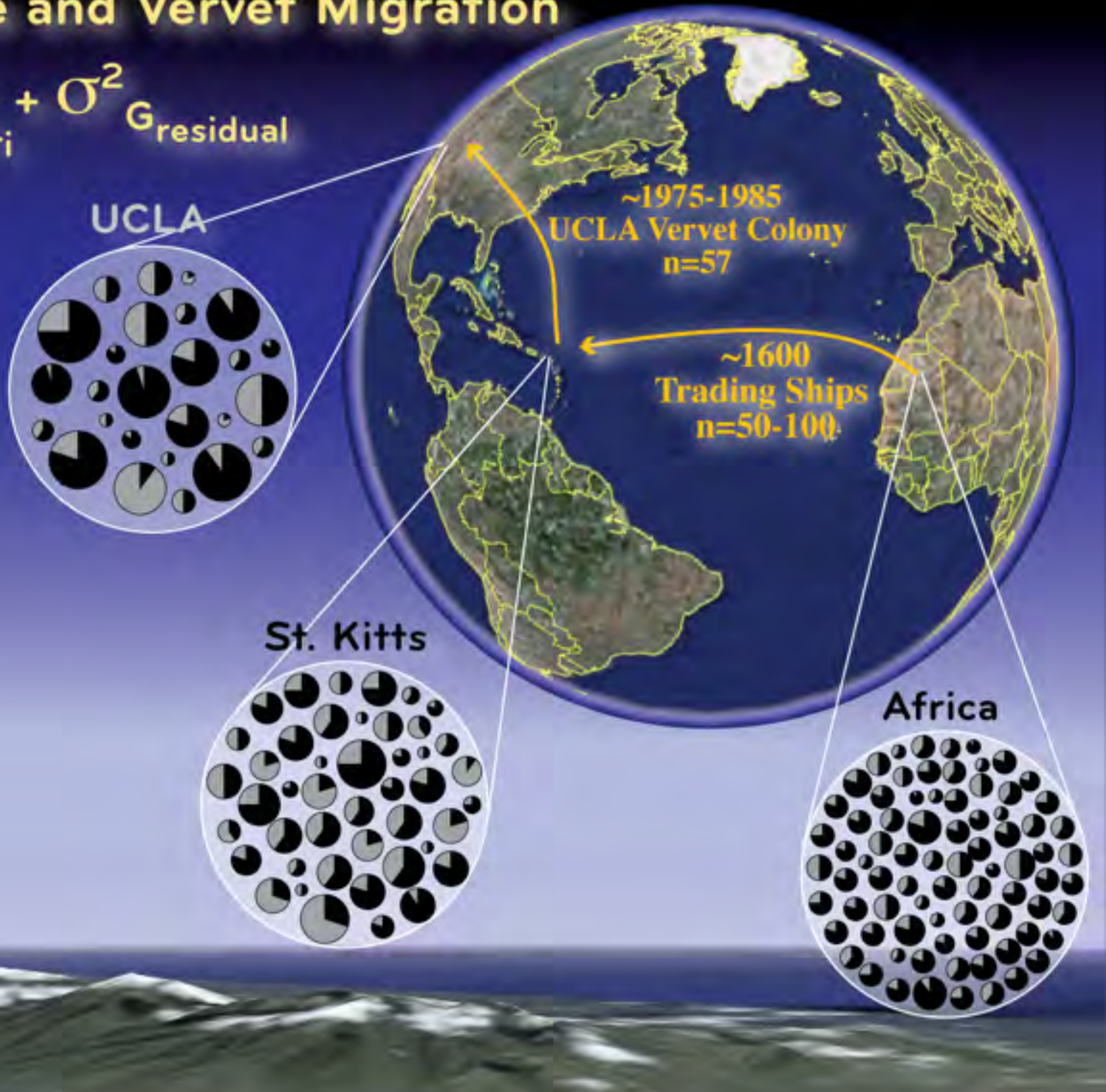
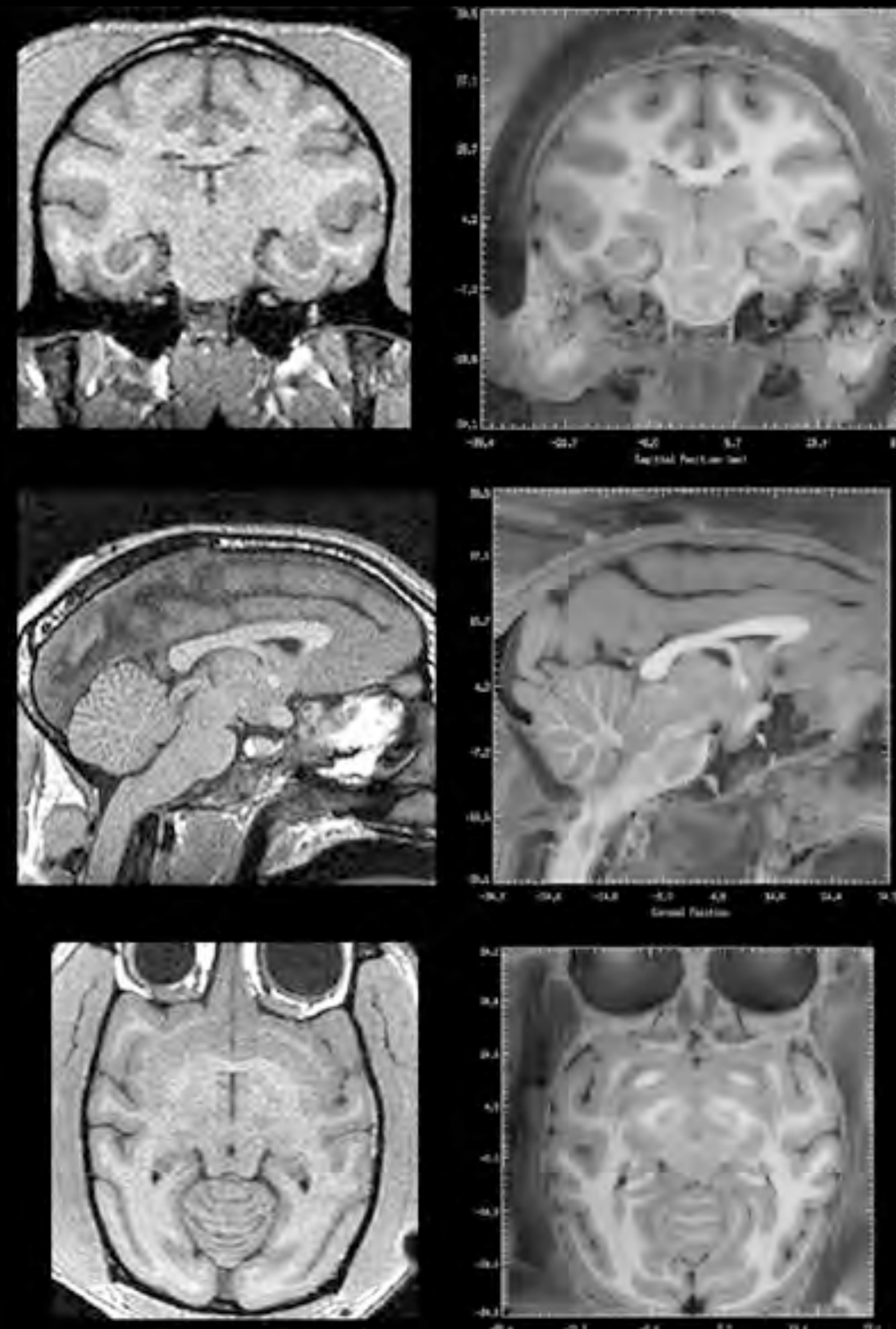
Photograph © South African Tourism

Genetic Variance and Vervet Migration

$$\sigma^2_{G_{QTL_i}} + \sigma^2_{G_{residual}}$$

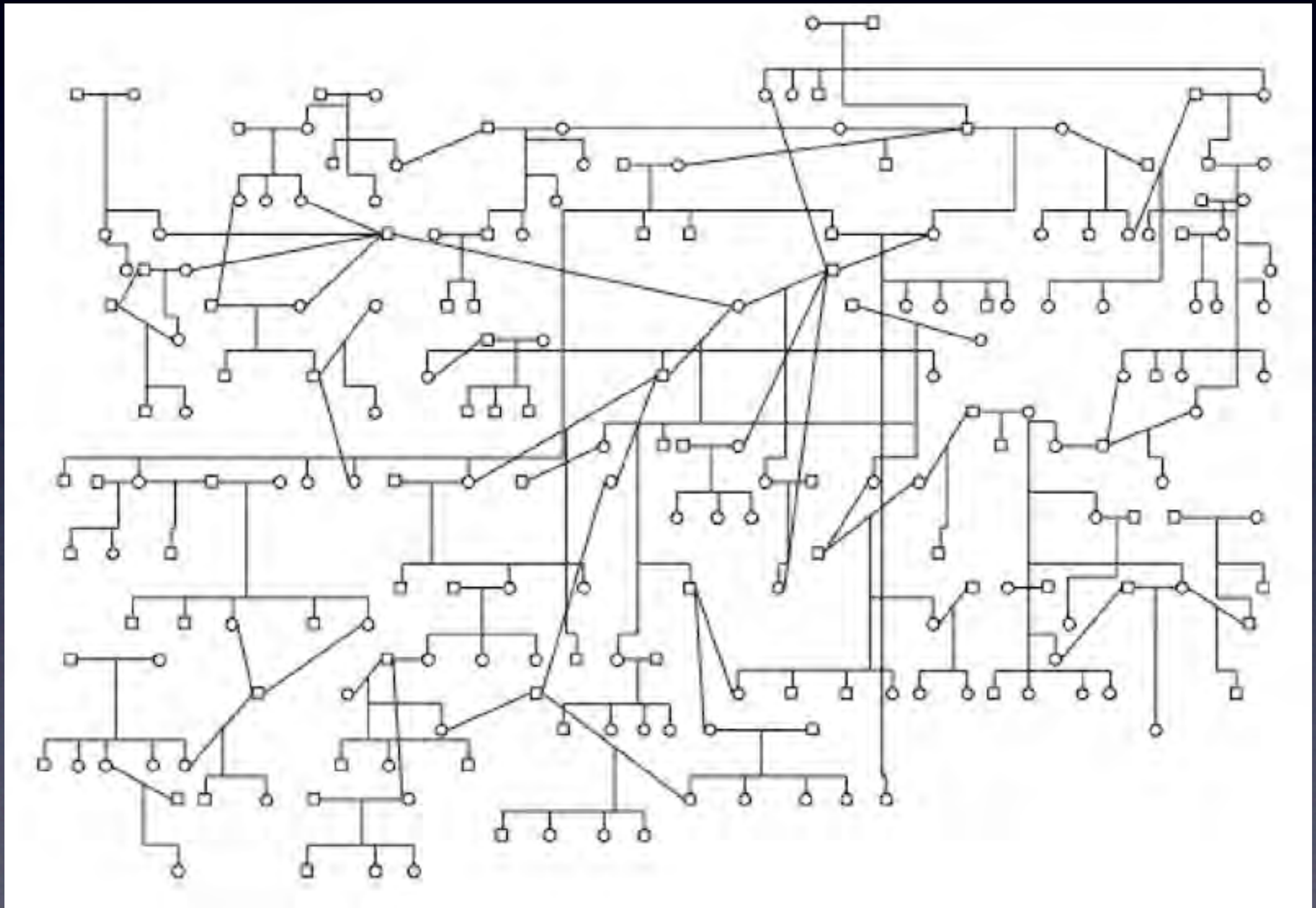




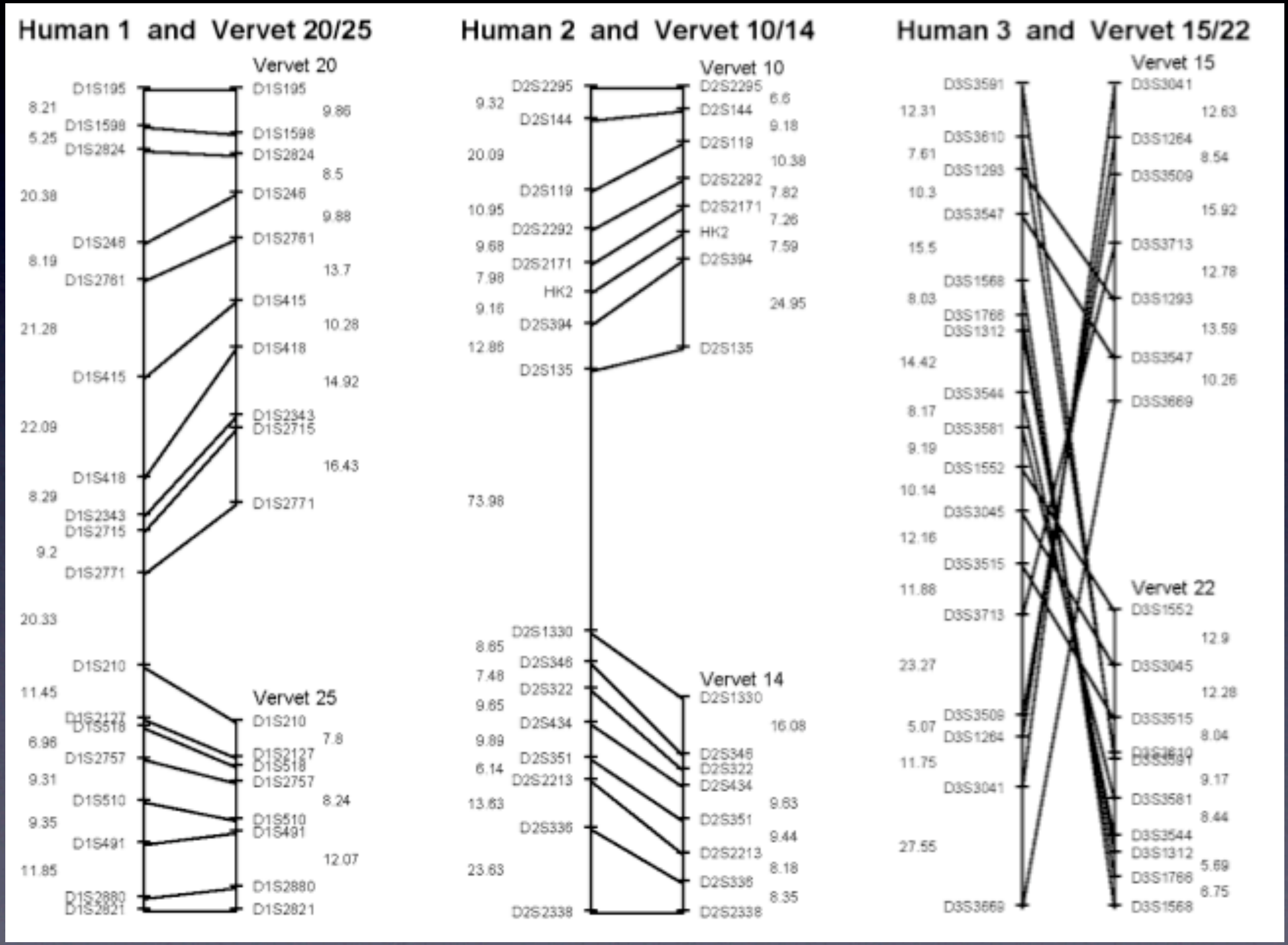
Cryomacrotome Atlas:
http://labs.pharmacology.ucla.edu/mellab/vervet_atlas/

Vervet Research Colony

- Descended from 57 wild-caught vervets (29 females; 28 males) trapped on St. Kitts from 1975 to 1985
- 24 matrilines currently in 3rd to 8th generations



Vervet Genetic Map



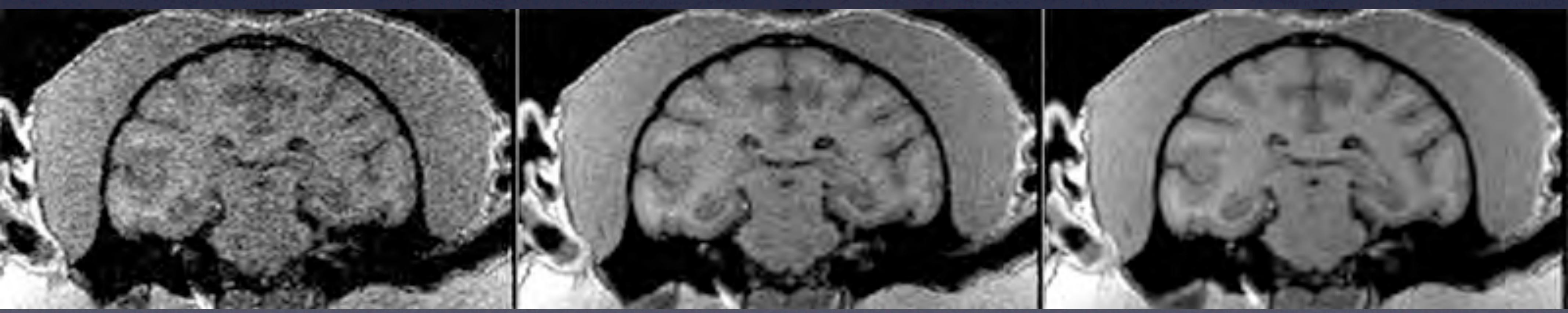
T-1 Weighted Acquisition

MPRAGE sequence

TR=1900 msec; TE=4.3 msec

Voxels 0.5 x 0.5 x 0.5 mm

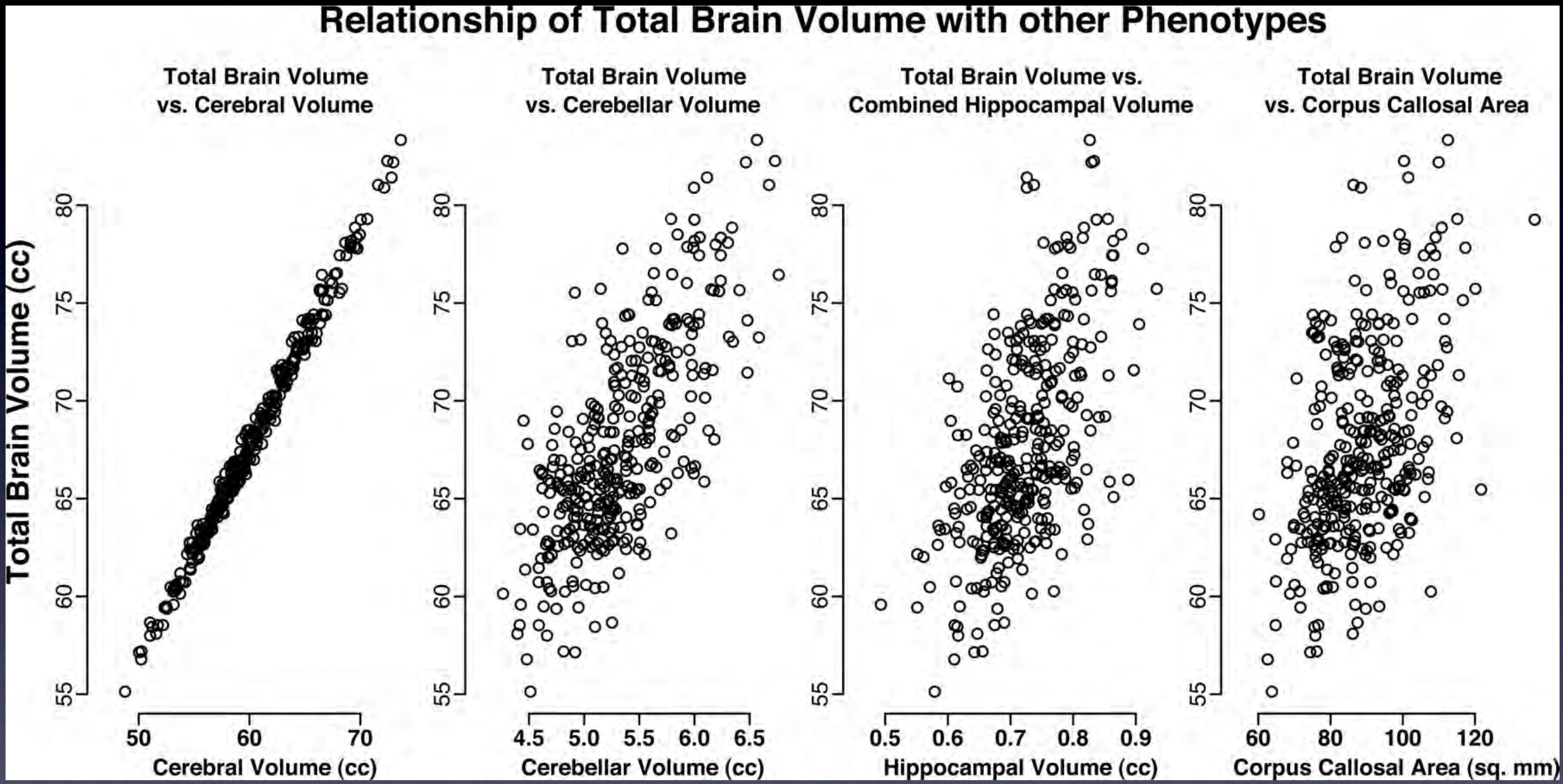
9 Independent acquisitions, registered and averaged



1 Average 4 Averages 9 Averages

Clinically Unsuspected Abnormalities

Nine animals identified with major abnormalities

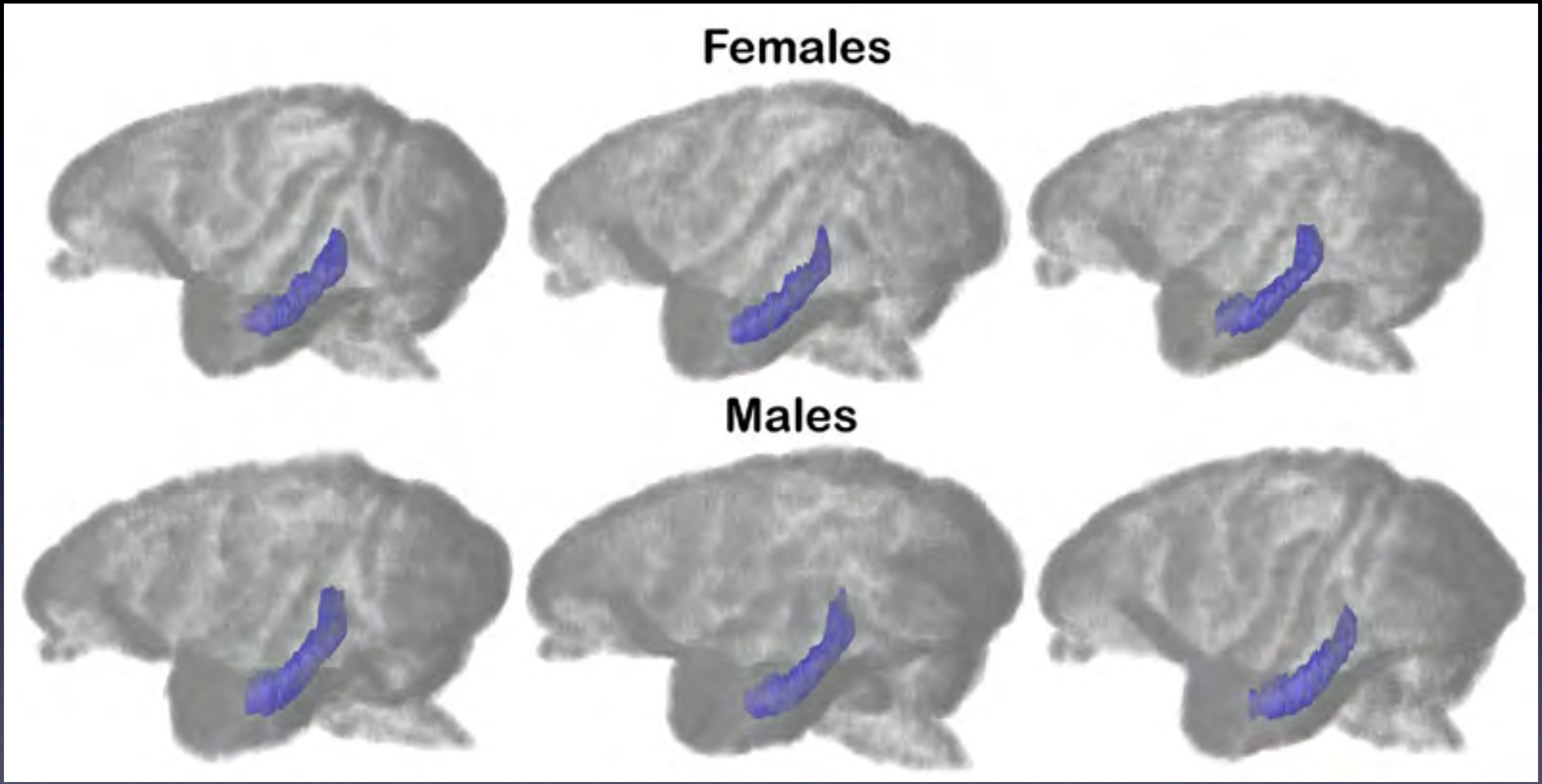


Scott C. Fears et al. J. Neurosci. 2009;29:2867-2875

The Journal of Neuroscience

Committed MRI Phenotypes

- Total Brain Volume
- Cerebellar Volume
- Ventricular Volume
- Hippocampal Volume
- Corpus Callosum Cross Sectional Area


Females
Males

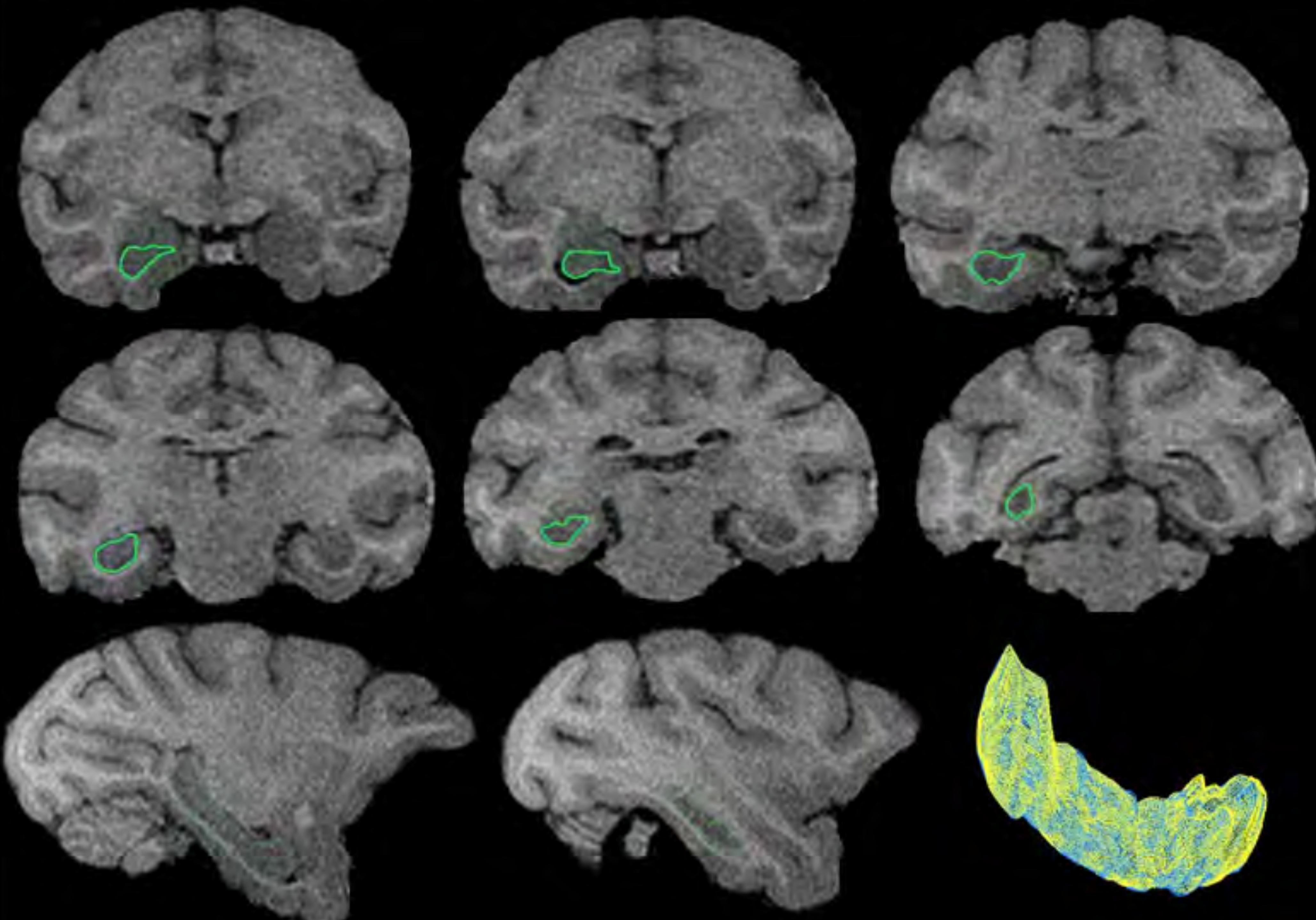


Table 5. Summary of heritability estimates for brain phenotypes

	h^2* (SE)	95% confidence interval	Included covariates	h^2 (SE) after including a factor for log total brain volume
Total brain volume	0.99 (0.06)	0.87–1.0	Sex	NA
Cerebral volume	0.98 (0.06)	0.86–1.0	Sex	0.77 (0.08)
Cerebellar volume	0.86 (0.09)	0.68–1.0	Sex, weight	0.85 (0.07)
Combined hippocampal volume	0.95 (0.07)	0.81–1.0	Sex, weight	0.86 (0.08)
Corpus callosal area	0.89 (0.07)	0.75–1.0	Sex, age, weight	0.58 (0.09)

*$p < 10^{-16}$. NA, Not applicable.