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
In 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 account 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 shaking 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.

“In general, then, our measurement method yields cranial capacities that are circa 50 cm\(^3\) less than, or are on average 96\% of, those produced by Morton’s.”

“Biased Scientists Are Inevitable, Biased Results Are Not”

Table 1. Densities of randomly packed spheres

<table>
<thead>
<tr>
<th></th>
<th>Friction†</th>
<th>Loose</th>
<th>Close packed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\mu_s$</td>
<td>$\mu_k$</td>
<td></td>
</tr>
<tr>
<td>Steel balls</td>
<td>0.24</td>
<td>0.17</td>
<td>0.608</td>
</tr>
<tr>
<td>Steel (in oil)</td>
<td>0.24</td>
<td>0.17</td>
<td>0.611</td>
</tr>
<tr>
<td>Plexiglass (polished)</td>
<td>0.44</td>
<td>0.28</td>
<td>0.605</td>
</tr>
<tr>
<td>Nylon (ground)</td>
<td>0.63</td>
<td>0.25</td>
<td>0.575</td>
</tr>
</tbody>
</table>

Brain Size and Sex

Rhesus

Rhesus

Human


Will Rogers Phenomenon

• “When the Okies left Oklahoma and went to California, the average intelligence of both states went up.”

Brain Size and Height: Single Population

FIG. 4. Brain weight as function of height, ages 28–41, Pakkenberg and Voigt (1964) study. Females, $r = -0.1$ (ns); males, $r = 0.1$ (ns).

Brain Size and Height Across Populations

Brain/body in humans (WM)

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)
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

**MCPH1**

MCPH1 Selection

ASPM

abnormal spindle-like microcephaly associated

ASPM Selection

MCPH1 D Distribution

MCPH1 Introgression

Evans PD, et al., PNAS 2006;103:18178-83
Roth G, Dicke U. 
*Trends in Cognitive Sciences* 
2005;9:250-257

Brain Volume (cc)

Caucasian
Asian
Hispanic
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)

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
Nutrition and Brain Size

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

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

<table>
<thead>
<tr>
<th>Step</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>skull stripping</td>
<td>&lt;10 sec</td>
</tr>
<tr>
<td>bias field correction</td>
<td>1-10 mins</td>
</tr>
<tr>
<td>tissue classification</td>
<td>&lt;20 sec</td>
</tr>
<tr>
<td>cerebrum identification</td>
<td>&lt;1 min</td>
</tr>
<tr>
<td>topology correction</td>
<td>&lt;1 min</td>
</tr>
<tr>
<td>tessellation</td>
<td>&lt;5 sec</td>
</tr>
<tr>
<td>pial surface generation</td>
<td>20-30 mins</td>
</tr>
</tbody>
</table>

- 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
Statistical maps showing significant regional differences in cortical gray matter concentration (i) in patients with first episode schizophrenia (sz) compared with healthy subjects (nc) after covarying for sex (top row); (ii) between male and female subjects across diagnostic groups (second row); (iii) for interactions between sex and diagnosis (third row); and (iv) between diagnostic groups with in males (right) and females (left).

Genetic Variance and Vervet Migration

\[ \sigma^2_{GQTL_i} + \sigma^2_{G_{\text{residual}}} \]

UCLA

\[ \sim 1975-1985 \]
UCLA Vervet Colony
\[ n=57 \]

\[ \sim 1600 \]
Trading Ships
\[ n=50-100 \]

Africa

St. Kitts
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
T1-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
Clinically Unsuspected Abnormalities

Nine animals identified with major abnormalities
Relationship of Total Brain Volume with other Phenotypes

Committed MRI Phenotypes

- Total Brain Volume
- Cerebellar Volume
- Ventricular Volume
- Hippocampal Volume
- Corpus Callosum Cross Sectional Area
<table>
<thead>
<tr>
<th>Brain Phenotype</th>
<th>$h^2$ (SE)</th>
<th>95% Confidence Interval</th>
<th>Included Covariates</th>
<th>$h^2$ (SE) after including a factor for log total brain volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total brain volume</td>
<td>0.99 (0.06)</td>
<td>0.87–1.0</td>
<td>Sex</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebral volume</td>
<td>0.98 (0.06)</td>
<td>0.86–1.0</td>
<td>Sex</td>
<td>0.77 (0.08)</td>
</tr>
<tr>
<td>Cerebellar volume</td>
<td>0.86 (0.09)</td>
<td>0.68–1.0</td>
<td>Sex, weight</td>
<td>0.85 (0.07)</td>
</tr>
<tr>
<td>Combined hippocampal volume</td>
<td>0.95 (0.07)</td>
<td>0.81–1.0</td>
<td>Sex, weight</td>
<td>0.86 (0.08)</td>
</tr>
<tr>
<td>Corpus callosal area</td>
<td>0.89 (0.07)</td>
<td>0.75–1.0</td>
<td>Sex, age, weight</td>
<td>0.58 (0.09)</td>
</tr>
</tbody>
</table>

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