CROTCHETS & QUIDDITIES

What Stamps the Wrinkle Deeper on the Brow?

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Science often relies on simplified diagrams to convey information, but these can embed tacit assumptions. A good example is provided by the surface convolutions of the cerebral cortex. It is surprisingly difficult to know what these features mean, and which deserve evolutionary explanation.

In a noteworthy 1935 book, Ludwik Fleck wrote that what science accepts and interprets as "fact" is not purely objective, but is a product of the history and underlying theory of the science at the time.[1,2] Contextual and even subjective factors drive, mold, and constrain scientific inference more than we may realize. Fleck showed how scientific illustrations serve as *ideograms* that reflect but also subtly promote the prevailing worldview. This conveys information but also channels thought, because in deciding how to represent a phenomenon some features are made more obvious while others disappear. The resulting presentation can have seductively proliferating effects. What we see in graduate school can stay with us a *long* time!

Fleck was not an evolutionary biologist but historical sciences may be more vulnerable to being prisoners of their theory—interpretive preferences—than experimental sciences like chemistry or physics. This certainly pertains to evolutionary anthropology, where our endless arguments about what is or isn't visible in a fossil specimen generally depend on visual presentation and assessment. Multiregional continuity, or replacement? Human ancestor or side branch? Robust or gracile? Bipedal?

Fleck singled out anatomic illustration to make his points. One example was the depiction of the surface anatomy of the cerebral cortex. Even something so seemingly straightforward shows how ambiguous or theory-dependent a simple illustration can be, in regard both to function and evolution. Interpreting past representations is problematic because we can't really know what preconceptions the authors might have built into them (intentionally or otherwise). But the same is true today. What evidentiary criteria might we apply to determine what can, or should, be included in a modern representation?

FROM VESALIUS TO NOW

In his gloriously illustrated 1543 anatomy text, Vesalius[3,4] drew the surface patterns of the brain to show "the appearance of coils of intestine or even more to clouds outlined by schoolboys or unskilled art-students," giving little importance to specific features (Figure 1). Fleck notes that Vesalius and even ancient classical authors had portrayed schematic, rather than literal, details of the cerebral surface. Today, we dismiss a disregard for detail as art rather than science, less "real" than modern illustrations (http://www.nlm.nih.gov/exhibition/dreamanatomy/index.html). But are more literal representations more correct than Vesalius was?

One need look at no more than two brains—even if they are identical twins—or even just left and right sides of the same brain to see that the surface features vary considerably from person to person (Figure 2).[5] Both the overall convolutional complexity and the details vary. Not surprisingly, variation among species is even greater (Figure 4). But it is not clear what aspects of this variation are important to include, and how less important features should be presented so as not to *mis*represent the brain. Perhaps we should turn to evolution, because if functionally relevant traits have been molded by natural selection they should have a genetic and specific developmental basis today.

We can frame such a search around some rather general aspects of the brain about which there is at least widespread implicit agreement: 1) The brain has multiple distinct functional capabilities; 2) being distinct, these could be expected to "map" (be localized) in the brain; 3) broadly speaking, the size of the relevant area will reflect aspects of function; 4) local size variation should affect the overall shape of the brain; and 5) because the skull and brain develop together, they may influence their respective shapes.

DEVELOPMENT: SULCI AND GYRI

Developmental studies have shown that the surface of the cerebrum is smooth until the appearance of the lateral sulcus (Sylvian fissure) in the 4th gestational month, followed rapidly by the other primary sulci (e.g., central pre- and post-central sulci, intraparietal, frontal). Secondary and tertiary convolutions continue to ap-

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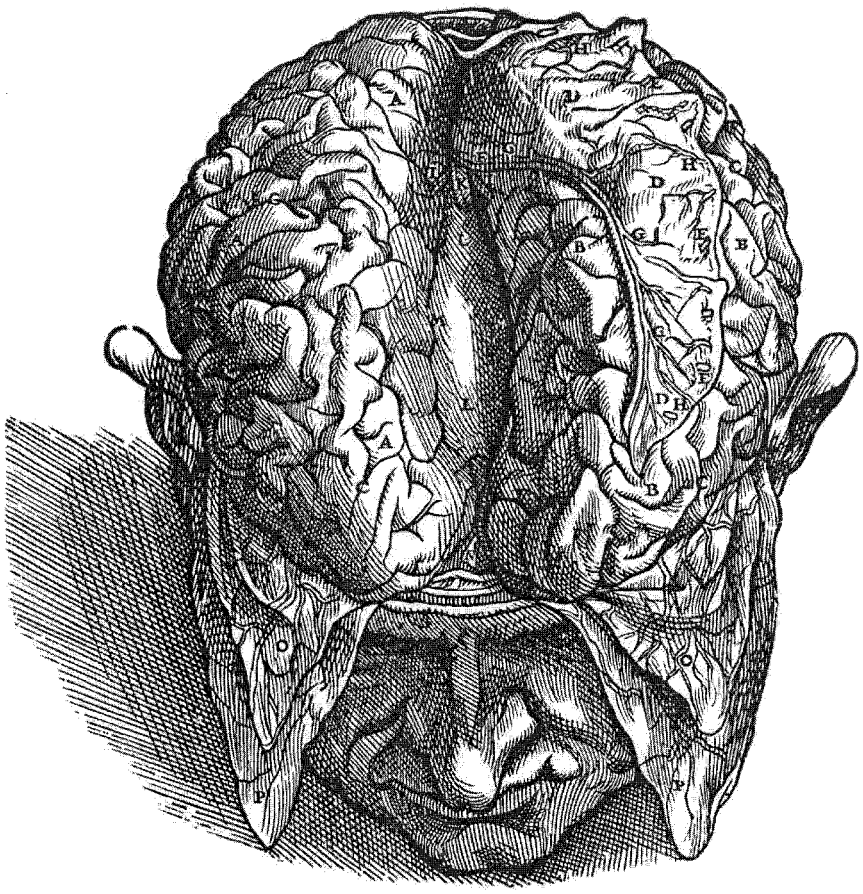

Figure 1. Ideograms or truth? Vesalius captured impressions. Was he wrong? (Source: Vesalius, 1543)

pear long into the postnatal period. The primary sulci tend to be deeper and are generally the most stable within and among species, and develop earliest ontogenetically (Figure 3). Compared to these, the other features are the dirt roads of the brain atlas, some being too variable to be depicted accurately in a single illustration, while others are deemed—rightly or wrongly—too unimportant to be specifically named.

Despite some conserved features, there is still a remarkable degree of variability among primate brains, as suggested by Figure 4, picturing MRIs (magnetic resonance images) of 10 anthropoid species. There are differences in size, the degree of convolution, presence of specific sulci, and depth of sulci present. However, these variables do not show entirely clear or consistent relationships with each other, or with phylogenetic distance, so their adaptive interpretation or importance are unclear. Some authors have suggested that convolutions appear to be located in different places in humans than other species, or that a given sulcus is longer or deeper. The human brain is somewhat more convoluted, which under the assumption that increased convolution leads to increased cortical surface area, has been inferred as implying greater intellect. This is an understandable inference given our anthropocentric obsession with the brain as our evolutionary *raison d'etre* (whatever happened to the thumb?).

However, it is not obvious what these observations mean because, beyond the primary features, the amount of variability makes it unclear how many sulci are homologous across species, as opposed to just being in roughly the same location, and bigger brains are not inevitably more convoluted within a given taxon or group. Depending on what biological process causes the sulcus, location *per se* may not even be a good criterion for assigning homology; for example, homology might more properly be associated with the underlying function, cytological cortical structure, or developmental processes that resulted in a given fold. These questions have not yet been answered, but every line in

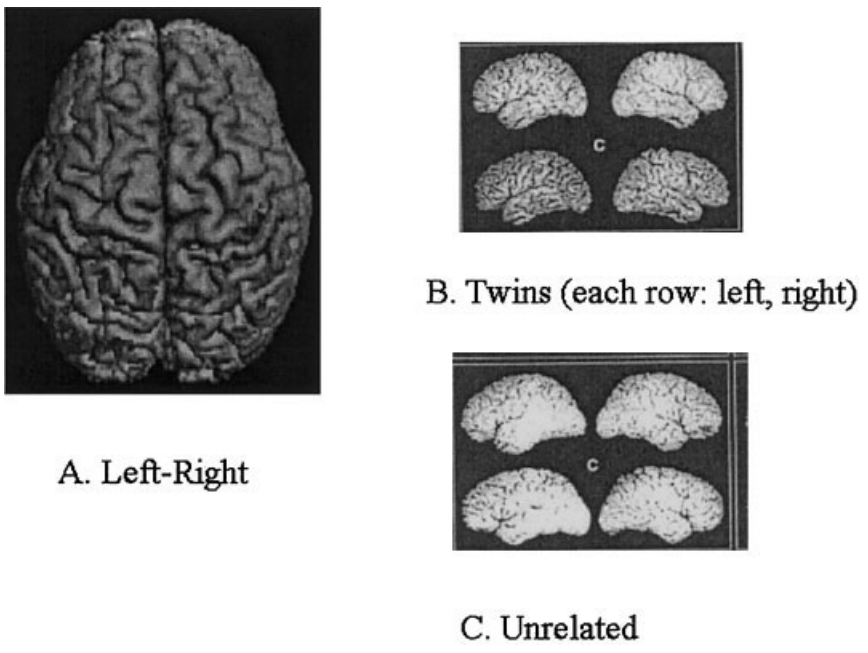

Figure 2. Variation in brain surface anatomy. (A) Left-right variation; (B) Identical twins; (C) Unrelated individuals. (Credits: B, C.[5])

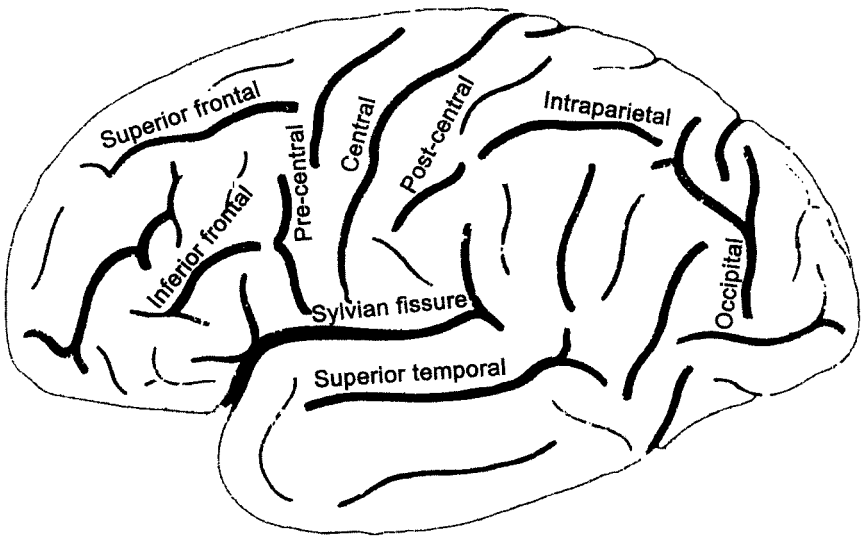

Figure 3. Some primary sulci of the human brain.

an illustration is a statement about them.

Stuff and Nonsense?

The major lobes of the telencephalon (forebrain) are produced by an early developmental patterning mechanism involving the expression and quantitative interactions among signaling and gene-expression factors.[6] But is the developmentally later formation of the sulcal/gyral pattern an elaboration of that same process? It is generally thought that sulci are produced by differential growth of the cortex, with some areas expanding faster than others. The reason is a matter of debate, and several plausible alternatives have been suggested.

One hypothesis is that gyri are formed through localized growth spurts of cortex, leaving valleys of slower growing cortex between them. In this view, the convolutions are simply a random "stuffing" phenomenon: as the brain grows inside the constraining braincase, it folds much as would occur when cramming more and more clothing into a laundry bag (this may also change the shape of the bag itself). The random-like appearance of tertiary convolution had been noted by the early 1900s. Tertiary sulci develop during the early postnatal period when the braincase has essentially closed; however it is not completely clear that the braincase is a constraint, because both it and the brain grow during this period. Alternatively, the locations of sulci may be determined by growth of the subcortical structures. This idea is that the cortex is "anchored" by adjacent subcortical structures (creating a depression—sulcus), with surrounding areas allowed to experience growth (creating a bulge—gyrus). One might think of this as cords constraining the billowing brain growth, much as cords restrain the shape of a billowing parachute, or as the frontalis muscle (literally) furrows the brow. A third possibility is that the cortex "buckles" in various places, based upon differential growth of the internal versus external layers of the cortex itself.

These three views are not mutually exclusive; different convolutions might be produced by different processes. Demonstrating a random component, if it exists, may not be easy because it would require specification of reliable landmarks, and hence homology, about which there is not universal agreement.

GENETICS: VAGUE BUT SIGNIFICANT EFFECTS

Whatever their developmental cause, if the pattern is of evolutionary importance, its basis should be genetic—transmitted from parent to offspring, rather than just being the ephemeral products of chance during an individual's lifetime. If the tertiary or even the secondary convolution pattern is just a random stuffing phe-

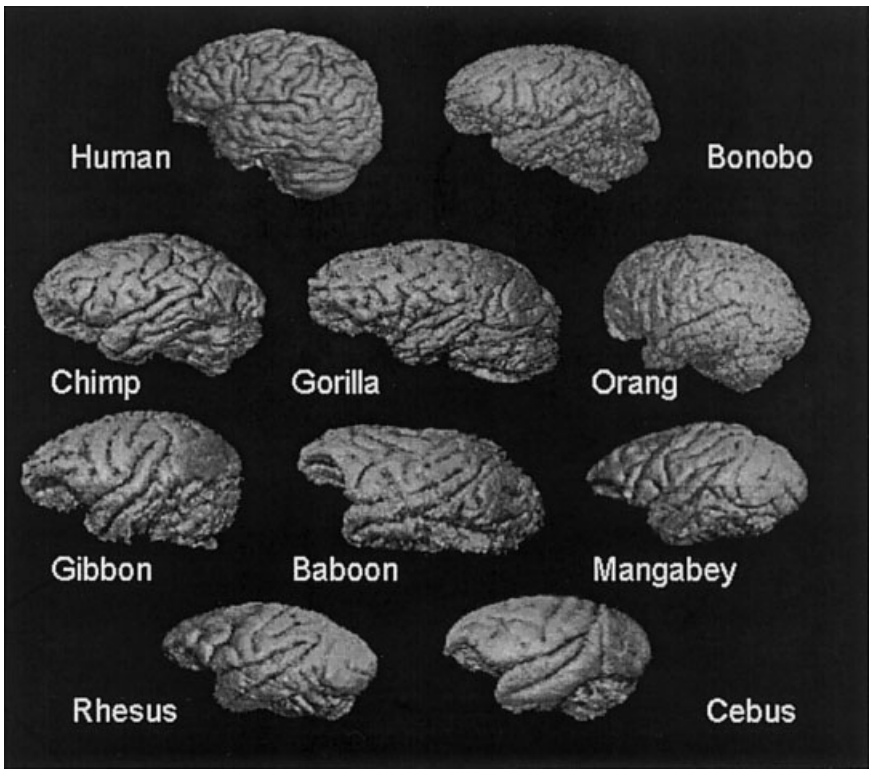

Figure 4. Variation among primates. Not to scale. (Credits listed in the acknowledgments.)

nomenon, it may have no functional consequences and have been of no concern to selection. If so, then most biologists would consider it not to be an evolutionary trait. But this would not be the usual assessment, because cortical convolution is so pronounced, and it is generally agreed that both localized function and its variation are evolutionarily important. A number of studies have sought to find genetic effects by comparing related and unrelated individuals (typically identical twins to unrelated people or pairs of dizygous siblings). The tested traits have included multivariate metric scoring of cortical thickness, volume, or overall shape, sulcal mark-points, sulcal depth, or underlying MRI-scored brain shape.

Sample sizes have been small but results are broadly consistent.[5,7,8] Brain size, volume, and overall shape seem to be under strong genetic control. The most heritable convolution structures are those that develop earliest, formed by the major lobal divisions. These deeper, longer, traditionally named sulci seem highly genetic (although in one study of macaques sulcal *length* did not seem heritable.[9]) This is satisfying because it is consistent with their shared presence within humans and among primates.

The story is less clear for the subtler features. Heritability estimates for tertiary gyri and sulci are lower, though they can be statistically significant. Convolutional complexity is roughly correlated with overall shape, which is statistically heritable. Tertiary features vary more than other features between left and right sides in the same person and between identical twins (Figure 2), but contralateral features are correlated when comparing MZ twin sets,[5] suggesting genetic effects. Numerous localized areas of the cortex have been shown to have detectable heritability.[10,11] However, their relationship to specific structure of the overlying gyri is difficult to evaluate, in part because heritability is an *overall* statistical measure: individual gyri occur in variable locations among individuals, making comparison difficult. Nonetheless, measures of overall sulcal similarity have shown statistically significant heritability.[7]

So much for location. Do these genetic effects on shape have anything to do with brain *function*? MZ twins vary in the left-right asymmetry associated with handedness.[12] Variation between MZ twins isn't genetic, but some brain asymmetry does appear to be affected by genes.[11] Genetic influence has also been reported in Broca's and Wernicke's areas associated with speech and language, and in frontal areas plausibly related to other behavioral traits including intelligence.[11]

The specific nature of morphological variability associated with the locations of these functions is rather unclear, even if they *are* genetically localized. Do the heritable features span sulcal boundaries? Are they in the same place in each person? On the surface or underlying it? We know that functions can re-map in the brain (e.g., in injured persons). While there is a tendency to think of the cortex as being the seat of all function, it is actually just a depot in many more dispersed functional pathways. For example, visual function is accorded three pathways, one via the thalamus on its way to the visual cortex in the occipital lobe, one via the superior colliculus, the thalamus, the brainstem, visual cortex, and frontal cortex, and a third via the pretectal brainstem and the thalamus. Combinations of these three pathways ensure actually seeing an object, locating it in space, and following it with your eyes. Though the cortex is involved, the other subcortical regions play equally important roles in these pathways. Should we expect sulcal or gyral structures to be tightly associated with these functions?

It is not easy to infer from heritability studies what genes might be involved. A bit of light may be shed by a couple of experimental results. Over-expression of the β-catenin gene in mice generated a sulcated surface, but the normal mouse brain is smooth,[13] a finding interpreted as being relevant to functional (intelligence?) differences between mouse and human brains.[14] Abnormal mutations in a gene called ASPM can be responsible for greatly reduced brain size and convolution complexity in humans.[15]

EARLIER VIEWS WE LOVE TO HATE

In a broad evolutionary sense brain size is correlated with function and we've seen that human brain size variation has been shown to have a genetic component. Still, Gould's *Mismeasure of Man*[16] is perhaps the best-known demonstration that brain size has been notoriously misused. He recounts how the American anatomist E. Spitzka collected brains of the intelligentsia and compared them with the not-so. Spitzka and others attempted a size-based hierarchy from Animal to Man, but what they really found was Animal to Anatole—Anatole France, that is, the small-minded author who famously showed that size does not always matter.

To save the mental hierarchy in the Great Chain of Braining, Spitzka turned to convolutional complexity. As shown in Figure 5, it seemed obvious that savage brains *must* be less complex than those of great mathematicians. This drawing—if true—is interesting because the other evidence we've cited suggests that size is correlated with convolution complexity (whether by stuffing or billowing constraints), and Gauss did not have a particularly large brain. Given the complexities of relationships among convolution, size, and function, we cannot know if these diagrams were accurate for the specimens examined or to what extent they were filtered through the sieve of their illustrator's expectations. Ideogram or fact?

These issues persist to the present day. Investigators have combed (so to speak) over Albert Einstein's cadaverous brow on the assumption that his brain must have been different from that of us ordinary mortals.[17] Using assumptions about the tricks of Einstein's trade (having to do with visuospatial reasoning), one somewhat enlarged area with enhanced sulcal complexity in a temporal lobe was indeed claimed to have been found. Responses to this necessarily *post hoc* study of a sample of size 1 are highly instructive (*The Lancet,* 1999, 354:1821–23), because the discussion is precisely about the kinds of features we've been discussing here. Can Einstein's vast intellect be attributed to this particular regional size enhance-

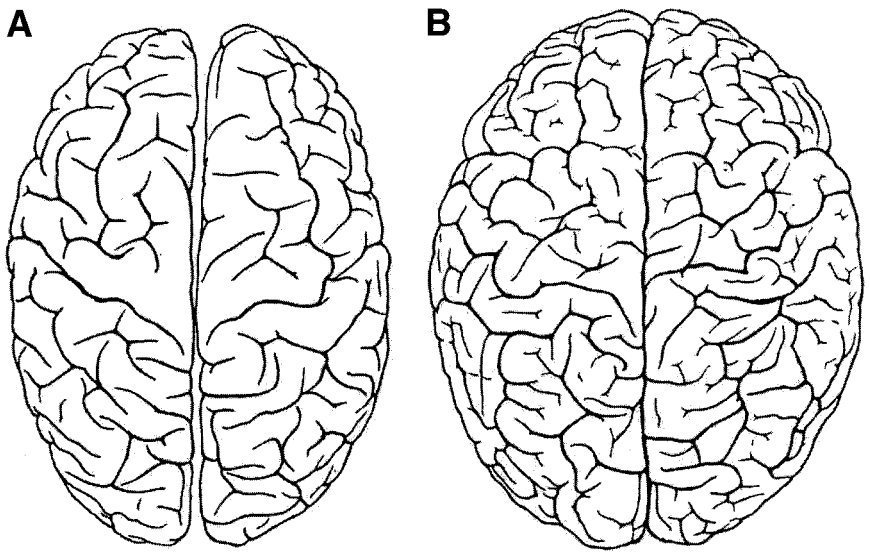

Figure 5. Spitzka's convoluted reasoning (A) Papuan, (B) the famous mathematician K.F. Gauss (from[16]).

ment or sulcal length? Some portion of it? Anything visible at all, or just a biochemical difference? Or might it be merely attributable to individual variability that need not be related to a specific localized feature? My Sylvian fissure's bigger than your Sylvian fissure!

In 1798 Franz Josef Gall founded the science of phrenology. Phrenologists mapped functional locations (Figure 6A), whose relative size they thought could be discerned even through the skull. They were scientists working with what they had at the time, but their idea that the furrows of the brow reveal the inner person is not considered scientific today because it did not have what we consider adequate evidentiary criteria.

That was then. Today we insist instead on molecular furrows. We use sophisticated electro-stimulation studies in primates, observations of human pathology, and fMRI and PET imaging to demonstrate localized function in the brain as in Figure 6B–C.[18] This is a replicable kind of direct physiological response measure, but we're too sophisticated today to think of trying to map traits like an "imitation" area of the brain (Figure 6A, arrow)—aren't we? Well, that's exactly what is done in Figure 6B–C. By this modern test, the "imitation" area curiously differs between left and right sides on the surface, but deep down, scanning shows "imitation" to be right under where the phrenologists said it was! What are we supposed to make of that?

There is humor here but this is not just a joke. We've used this selected example not to defend phrenology, which clearly wandered into cultish never-never land, but to ask that you re-read our earlier list of generally accepted characteristics of the brain, in the paragraph just before the "Sulci and gyri" section above. Those are the premises with which Gall first articulated the science of phrenology, and phrenologists used data (of their time) and reasoning similar to what we use today (http://pages.britishlibrary.net/phrenology/other texts/retzer.htm). They established brain regions in rather *post hoc* ways, on small opportunistic samples, and rationalized contrary or inconsistent observations. But we do that, too, and their idea was not different in principle from the study of Einstein's brain—a serious attempt published in the world's leading medical journal in 1999. Modern scanning methods permit greater experimental control by real-time monitoring, and brain-mapping studies often find variable and/or distributed rather than exceedingly focused map locations in the brain. However, it is not obvious how much more informative or long-lasting these results will be compared to past efforts. In any case, they tell us little more about the nature of sulcal/gyral patterns *per se* than a phrenology map could. This is especially true given the amount of interperson variation, and the unknown degree to which functional location itself is really fixed.[20]

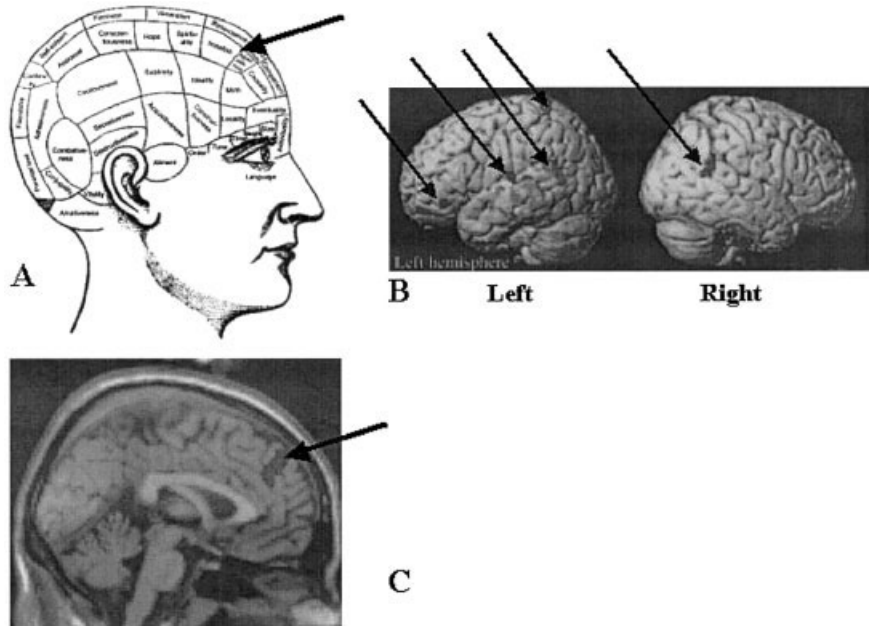

Figure 6. Phrenology old and new? Areas associated with the trait *imitation* by (A) the old palpable phrenology, (B, C) the new molecular kind (a PET scan), arrows indicate left and right superficial, and medial excitation areas for "imitation" test, respectively. (Source: A: public domain, relabeled for text readability; B, C.[18])

LEFT BRAIN, RIGHT BRAIN

Genetic variation influences functional areas of the cortex, localized but with unclear relationship to gyral structure. Genes may help account for common left-right asymmetries in brain function—male and female sides, spatial right, analytic left, and all that. However, both developmental and genetic studies suggest that much if not most of the observed variability is randomly generated. But does "random" mean not worth worrying about in diagrams of brain structure? That's rather subtle. We give high importance to the human brain specifically as having evolved to be flexible, *not* pre-programmed. Perhaps what evolved was the means to produce the *random* variation that we see in sulcal patterns. Maybe that has the key functional implications for human culture and behavior, much as the immune system has evolved specifically to generate variation in disease response capability.

If so, "stuffing" and chance is the right metaphor. That, rather than coarser measures like size or multidimensional shape, may be what explains the variation in musical or athletic ability, intelligence, and personality that capture so much attention. In such a view the relevant genes might have to do with growth and timing, not specific functional attributes. This could be what the ASPM and β-catenin studies mean (if they mean anything), because these are intracellular spindle fiber, and general transcription factor genes, respectively, not, for example, neurotransmitter genes.

At best, current data show that it is not so obvious what should be depicted in a "scientific" drawing of the brain surface, and the same issues apply to other representations in science. What is the trait we want to portray, and how do we give the right information? If some variation is genetic and other chance, and *both* can have functional consequences in the *same* brain region, how can we show that? Indeed can we represent "the" brain, or just "a" brain? One recent paper suggests that we should develop a "probabilistic atlas" of the sulcal locations,[19] but that would be inherently sample-dependent. Perhaps when art imitates life it conveys an erroneous sense of specificity. Maybe Vesalius was more right to keep the convolutions schematic than we are to be more literal. These are not easy questions to answer, and the reason is Fleck's: whatever our answer, it will embed within it judgments about what counts as a "fact" and who's counting.

Our title is from Lord Byron's once-popular poem *Childe Harold's Pilgrimage*. He used the wrinkled brow as a metaphor for "the worst of woes that wait on age," the passing of loved ones during a person's life. Here we ask whether it is the passing chance events in this life, or the accumulated events of ancestral ages, that stamped the developmental wrinkles on our brow. As we have tried to indicate, whether this is a metaphorical or true biological question is something to worry over.

NOTES

We welcome comments on this column: kenweiss@psu.edu. Crotchety-Comments are maintained on: www.-anthro.psu.edu/rsrch/weiss lab.htm. We thank Anne Buchanan, Joan Richtsmeier, John Fleagle, and an anonymous reader for helpful comments, and Jim Rilling, Tom Insel, Patrick Barta, and Godfrey Pearlson for the MR images.

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