Confusing cortical columns

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The late developmental neurobiologist, and a member of the National Academy of Sciences, Victor Hamburger told me during one of our discussions about the distinction between boring data and exciting concepts, “one can spend an entire lifetime correcting a flawed paper published in reputable journal and still lose the battle if people like the basic idea” (V. Hamburger, personal communication). An example of the longevity of basically incorrect information is the phenomenon of “The basic uniformity in structure of the neocortex,” published in 1980 by Rockel, Hiorns, and Powell (1). This highly influential paper had obvious problems at almost every level: The authors selected an arbitrary 30-μm-wide, 25-μm-deep vertical cortical “column” between the pia and the bottom of the cortex, because the ruler in the graticule of the oil-immersion eyepiece on their microscope had a 30-μm marker and their histological sections were 25 μm thick; then, they estimated that the number of neurons within this “minicolumn” is 110 in all cytoarchitectonic areas examined, without any correction for the cell size; and finally, based on this dubious finding, they made a broad generalization that the magic number of 110 is constant in all mammalian species (rodents, carnivore, and primates, including human) in all cytoarchitectonic areas (except the primary visual cortex in primates). This finding led them to conclude that, “the intrinsic structure of the neocortex is basically more uniform than has been thought and that differences in cytoarchitecture and function reflect differences in connections.”

Most neuroscientists recognized the problems with both the method used and the data obtained, but many found the simple concept of the uniformity of the cortex across various modalities as well as during evolution of neocortical expansion highly attractive. Although at least six research articles have directly refuted the accuracy of the data of Rockel et al. as well as the validity of their generalization (e.g., ref. 2), according to the Institute of Scientific Information (ISI), their article has been cited 500 times. It is discussed often in the major reference books of neuroscience and brain evolution, and is used widely in computational models of cortical operations. The concept of uniformity across all species appealed to philosophers who liked the idea that the difference between animals and human are just quantitative. It also provided the scientific basis of the so-called “tabula rasa hypothesis” of cortical development, which assumes that all cytoarchitectonic areas are specified from the initially homogeneous and equipotential cortex by input from the periphery.

This is why the article by Herculano-Housel et al. (3) in this issue of PNAS serves a useful purpose, even though it does not report any unexpected results. Using a state-of-the-art unbiased stereology method, the authors show convincingly that the density of neurons in the neocortex varies as much as three times even among the highly related primate species. The results from the two studies are difficult to compare because Rockel et al. (1) counted the number of neurons in very small vertical cylinders (minicolumns), whereas Herculano-Housel et al. estimated the density of neurons in a larger volume of cortical tissue that can be more affected by the amount of neuropile. However, the main goal of the work of Herculano-Housel et al. seems to be to dispel the lingering perception that the data reported by Rockel et al. are basically valid and to emphasize, once again, that the simple concept of basic uniformity of the cortex, which may appear attractive, is basically incorrect. I, however, feel that Herculano-Housel et al. did not go far enough in addressing the related problem that is caused by the frequent misuse of the term “cortical column.”

Classical anatomists have emphasized the laminar deployment of the neocortex but were also aware of the prominent columnar organization as visualized in Golgi impregnated material and as is particularly compelling in the Nissl-stained sections of the human cerebral cortex (4). However, the concept of functional columns received deserved attention only after Vernon Mountcastle (5) discovered that the neurons arranged vertically (or radially in the convoluted cerebrum) in the form of columns spanning the width of the primary somatosensory cortex respond to a single receptive field at the periphery. This, and subsequent research by many others, has shown that the cortical columns consist of an array of iterative neuronal groups (also called modules) that extend radially across cellular layers VI to II with layer I at the top (6–10). The neurons within a given column are stereotypically interconnected in the vertical dimension, share extrinsic connectivity, and hence act as basic functional units subserving a set of common static and dynamic cortical operations that include not only sensory and motor areas but also association areas subserving the highest cognitive functions (8, 9, 11).

Although the anatomical and functional columnar unity of the neocortex has never been in doubt, the size, cell composition, synaptic organization, expression of signaling molecules, and function of various types of “columns” are dramatically different. Columns could be defined by cell constellation, pattern of connectivity, myelin content, staining property, magnitude of gene expression, or functional properties. For example, there are ocular dominance columns, orientation columns, hypercolumns, and color columns, to mention only those described in the primary visual cortex (12), that differ from each other as well as from the columns of the alternating callosal and ipsilateral projection in the frontal lobe (8) or various minicolumns advocated by Szentgahotai (7), Eccles (9), Buxhoeveden and Casanova (10), and a more recent detailed reconstruction of barrel field columns by Sakmann and colleagues (13) and their visibility in vivo by neuroimaging (14). The only connections between these diverse structures and concepts is that they refer to the vertical or radial columnar organization of its elements as opposed to the horizontal or laminar organization that is more explicit in histological preparations of the mature neocortex. Thus, the term cortical “column” is used in so many ways that it can be very confusing to the nonspecialist.

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many ways that it can be very confusing to the non-specialist if not more precisely defined. The term and concept of radial cortical columns is also used in developmental neurobiology of the cerebral cortex. Thus, I have used the term “ontogenetic column” in designating the cohorts of cortical neurons that originate, over time, from a single neuronal progenitor (15). The clonally related postmitotic neurons are initially deployed in a geometrically perfect columnar pattern in the embryonic primate cerebral cortex where the temptation to use the term column was irresistible (see figure 1 in ref. 15). The ontogenetic columns are also evident in slice preparations (16) and in vivo labeling of neuronal lineages using gene transfer tracing (17). Columnar organization is particularly evident in the developing primate cerebral cortex where neurons are positioned into a radial array with crystalline regularity that depends on a sequential production and the directed migration of neurons that requires the orchestration of multiple molecular events and complex cell–cell interactions (11).

The relationship between ontogenetic and various functional columns has not been adequately investigated. However, it has been clear from the beginning that any functional column in the adult cerebral cortex must consist of several ontogenetic columns (polyclones), depending on their function; and that neurons from different clones intermix with the adjacent columns as they migrate across the intermediate zone (18). It was initially evident and clearly stated that the ontogenetic columns in various cytoarchitectonic areas are different and thus contradict the notion of the homogeneity of the neocortex (15). This variability can explain both the differential expansion of individual functional areas and the introduction of new areas during evolution as formulated in the protomap hypothesis (15, 19). The concept of polyclones was supported by the finding of wider alternating columns of gene expression in transgenic and chimeric mice (19–21). The morphological variability of ontogenetic columns is diminished after arrival of the interneurons, glial cells, and afferents, which all participate in the formation of the neocortex with a myriad of synaptic connections that constitute diverse types of functional columns described by the anatomists and physiologists (11).

The longevity of the concept of the basic uniformity in structure of the neocortex is in part due to the high regard for Tom Powell, a professor at Oxford and a leading neuroanatomist at the time. The other part is that the conclusions of Rockel, Hiorns, and Powell (1), that the cortex consists of columns and that it expands during evolution more in surface than in thickness, are obvious and still stand. Also still standing, as clearly pointed out by Herculano-Houzel et al. (3), is the existence of ontogenetic columns and the validity of the radial unit hypothesis as the basis for understanding its evolutionary expansion at the cellular and molecular level. A new challenge is to reconstruct the complete cellular and synaptic circuits and develop model cortical columns that are dedicated to each function to determine how deviation of this pattern affects behavior.

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COMMENTARY. For the article “Confusing cortical columns,” by Pasko Rakic, which appeared in issue 34, August 26, 2008, of Proc Natl Acad Sci USA (105:12099–12100; first published August 20, 2008; 10.1073/pnas.0807271105), the authors note that, due to printer’s errors, three references were omitted and a phrase appeared incorrectly. On page 12099, left column, second paragraph, line 11, “(e.g., ref. 2)” should appear as “(e.g., refs. 2, 22, and 23).” Also on page 12099, right column, line 6, “single receptive field” should instead read: “single modalities in the receptive field.” Finally, on page 12100, center column, line 21, “(15, 19)” should appear as “(15, 24);” and in line 25, “(19–21)” should appear as “(21–24).” In addition to these errors, the authors note that in ref. 3, the author names “Herculano-Housel S, Collins CE, Wang P, Kaas J” should have appeared as “Herculano-Houzel S, Collins CE, Wong P, Kaas JH, Lent R.” The corrected and omitted references appear below.


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CELL BIOLOGY. For the article “Dual-color superresolution imaging of genetically expressed probes within individual adhesion complexes,” by Hari Shroff, Catherine G. Galbraith, James A. Galbraith, Helen White, Jennifer Gillette, Scott Olenych, Michael W. Davidson, and Eric Betzig, which appeared in issue 51, December 18, 2007, of Proc Natl Acad Sci USA (104:20308–20313; first published December 12, 2007; 10.1073/pnas.0710517105), the authors note that on page 20312, right column, in Materials and Methods, under Sample Preparation, line 4, “Cell Line Nucleofector Kit SF” should have appeared as “Cell Line Nucleofector Kit SE.”

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GENETICS. For the article “Fine structure mapping of a gene-rich region of wheat carrying Ph1, a suppressor of crossing over between homoeologous chromosomes,” by Gaganpreet K. Sidhu, Sachin Rustgi, Mustafa N. Shafqat, Diter von Wettstein, and Kulvinder S. Gill, which appeared in issue 15, April 15, 2008, of Proc Natl Acad Sci USA (105:5815–5820; first published April 8, 2008; 10.1073/pnas.0800931105), the authors note that “a part of our Fig. 1 was reproduced from figure 1 of the paper by Simon Griffiths et al. [Griffiths S, et al. (2006) Nature 439:749–752]. In our paper we neglected to reference this figure as adapted from the original work.”

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