FORUM

TOWARDS A QUANTITATIVE, PROBABILISTIC NEUROANATOMY OF CEREBRAL CORTEX

David C. Van Essen

(Department of Anatomy and Neurobiology, Washington University School of Medicine)

Major progress was made during the past century in understanding the functional organization of primate cerebral cortex, thanks in considerable measure to several essential types of information provided by neuroanatomy. More specifically, neuroanatomy reveals cortical morphology and how cortical convolutions vary across individuals and species; it provides the basis for subdividing the cortical sheet into distinct architectonic areas, thereby establishing a structural framework for exploring functional specializations; and it provides information about cortical connectivity, which guides hypotheses about information processing in macroscopic and microscopic cortical circuits.

Despite this progress, our current understanding of cortical organization and connectivity remains fragmentary, fraught with uncertainty, and described largely in qualitative rather than quantitative terms. Three general problems are particularly glaring. (1) It has proven remarkably difficult to achieve a consensus partitioning scheme for subdividing cortex into distinct areas, even in intensively studied species such as the macaque monkey. On the one hand, it is widely agreed that the overall number of cortical areas is fairly large – for example, in the macaque there are several dozen visual areas, and perhaps 100 or more cortical areas in all (Felleman and Van Essen, 1991; Van Essen, 2002 in press, a). On the other hand, a consensus scheme is lacking for all but the primary sensory and motor areas and their close neighbors. Instead, any given region of cortex is associated with multiple partitioning schemes in current use that differ in fundamental ways, not just in terminology (Van Essen, 2002 in press, a). (2) Solid quantitative information about major anatomical pathways is notably scarce. The number of known cortico-cortical and cortico-subcortical connections in the macaque probably exceeds a thousand, but only a handful are understood quantitatively in terms of the number and spatial distribution of their origins (projection cells) and terminations (synapses). Instead, published descriptions of most pathways are typically presented in qualitative terms (e.g. "strong", "moderate" or "weak") or at best as semi-quantitative analyses, and the spatial pattern of connections is often portrayed using a few representative sections or qualitative summary sketches. In humans, our current understanding remains rather rudimentary in terms of knowing the basic arrangement of cortical areas, and it is extremely sparse in terms of information about connectivity. (3) There is marked variability across individuals in the pattern of convolutions and in the size of each cortical area. Yet individual variability has until recently been treated largely as a thorny problem to be swept under the rug, rather than a tractable issue to be embraced because its inherently great interest.

In my view, it is vitally important for cortical neuroanatomy to move quickly towards becoming a predominantly quantitative approach. An overarching aim should be to provide progressively more accurate and detailed probabilistic maps of cortical structure and connectivity that include explicit representations of uncertainty and individual variability. Such a transition will entail capitalizing more fully on a number of recent methodological advances, and it will also require major efforts to develop new methods, particularly for quantitative analyses of connectivity.

One major advance in the past decade is the emergence of structural magnetic resonance imaging (MRI) as a reliable method for noninvasively visualizing cortical morphology. This provides an invaluable anatomical substrate for dealing with individual variability in the pattern of convolutions and in the arrangement of cortical areas across the cortical surface. A corollary development is the emergence of automated methods for segmenting structural MRI data and generating surface reconstructions that faithfully represent cortical convolutions (Dale et al., 1999; Fischl et al., 1999; Kriegskorte and Goebel, 1999; Van Essen et al., 1998, 2001). Surface-based maps and analyses facilitate the visualization of areal partitioning schemes, connectivity patterns, and other spatially complex data sets. In addition, they provide the substrate for coordinate systems that respect the topology of the cortical sheet and for registration methods that take individual variability into account.

Another set of advances involves improved methods for characterizing cortical architecture. This includes methods to obtain a much richer description of the chemoarchitectonic fingerprint of

different cortical regions based on receptor binding, immunocytochemical staining, and gene expression patterns, along with conventional histochemical stains (Mazziotta et al., 2001; Zilles and Palomero-Gallagher, 2001; Ongur and Price, 2000 Heintz, 2000). An important corollary is the development of analysis methods for quantifying these characteristics and for objectively discriminating architectonic transitions (Schleicher et al., 1999; Grefkes et al., 2001). While some of these methods remain technically difficult and time-consuming, they will be vital in providing the information needed for accurate probabilistic atlases of cortical partitioning schemes.

On the pathway tracing front, the methodological news is mixed. On the one hand, there have been exciting advances in methods for tracing connections in vivo using diffusion tensor imaging, which allows tracking of fiber trajectories in white matter even in humans (Conturo et al., 1999), and using focally injected MRI susceptibility agents (Saleem et al., 2002). In addition, there are improved methods for tracing pathways with enhanced sensitivity and even transneuronally, for example, using neurotropic viral tracers (Kelly and Strick, 2000; Loewy, 1998). On the other hand, existing methods generally are not well-suited to provide accurate quantitation of absolute connection strengths. This remains a major challenge for technology development.

Finally, an increasingly important role for neuroanatomy will be to provide the spatial substrate for digital brain atlases. A new information infrastructure is needed to cope with the continuing explosion of information available about cortical structure, function, and connectivity, which far exceeds the communications capabilities of conventional scientific publications. The analogous problem in genomics and proteomics has been successfully addressed by the widespread use of sequence and protein structure databases. In systems neuroscience the problem is more challenging because of the extraordinary complexity of brain anatomy and connectivity. Spatially organized, anatomically accurate, internet-accessible databases and visualization options have the potential to reshape how information is accessed and communicated in systems neuroscience (Van Essen, in press, b). The full fruits of this effort remain many years away, but they will be vital for accelerated progress in deciphering cortical circuitry and function in health and disease.

References

Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry REC, Burton H and Raichle ME. Tracking neuronal fiber pathways in the living human brain. *Proceedings of the National Academy of Sciences,* USA, *96:* 10422-10427, 1999.

Dale AM, Fischl B and Sereno MI.Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage*, *9:* 179-194, 1999.

Felleman DJ and Van Essen DC. Distributed hierarchical processing in primate cerebral cortex, *Cerebral Cortex*, *1:* 1-47, 1991.

Fischl B, Sereno MI and Dale AM. Cortical surface-based analysis. I: Inflation, flattening, and a surface-based coordinate system. *NeuroImage*, *9:* 195-207, 1999.

Grefkes C, Geyer S, Schormann T, Roland P and Zilles K. Human somatosensory area 2: Observer-independent cytoarchitectonic mapping, interindividual variability, and population map. *Neuroimage*, *14:* 617-631, 2001.

Heintz N. Analysis of mammalian central nervous sytem gene expression and function using bacterial artificial chromosome-mediated transgenesis. *Human Molecular Genetics*, *9:* 937-943, 2000.

Herzig U, Cadenas C, Sieckmann F, Sierralta W, Thaller C, Visel A and Eichele G. Development of high-throughput tools to unravel the complexity of gene expression patterns in the mammalian brain. *Novartis Foundation Symposium*, *239:* 129-46; Discussion 146-59, 2001.

Kelly RM and Strick PL. Rabies as a transneuronal tracer of circuits in the central nervous system. *Journal of Neuroscience Methods, 103:* 63-71, 2000.

Kriegeskorte N and Goebel R. An efficient algorithm for topologically correct segmentation of the cortical sheet in anaomtical mr volumes. *Neuroimage*, *14:* 329-346, 2001.

Loewy AD. Viruses as transneuronal tracers for defining neural circuits. *Neuroscience Biobehavioural Review*, *22:* 679-684, 1998.

Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B et al. A four-dimensional probabilistic atlas of the human brain. *Journal of American Medical Informatics Association, 8:* 401-30. 2001.

Ongur D and Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex 10:* 206-19, 2000.

Saleem KS, Pauls JM, Augath M, Trinath T, Prause BA, Hashikawa and Logothetis NK. Magnetic resonance imaging of neuronal connections in the macaque monkey. *Neuron*, *34:* 685-700, 2002.

Schleicher A, Amunts K, Geyer S, Morosan P and Zilles K. Observer-independent mehthod for microstructural parcellation of cerebral cortex: A quantitative approach to cytoarchitectonics. *NeuroImage*, *9:* 165-177, 1999.

Van Essen DC, Drury HA, Joshi S and Miller MI. Functional and structural mapping of human cerebral cortex: Solutions are in the surfaces. *Proceedings of the National Academy of Sciences*. USA *95:* 788-795, 1998.

Van Essen DC, Dickson J, Harwell J, Hanlon D, Anderson CH and Drury HA. An Integrated Software System for Surface-based Analyses of Cerebral Cortex. *Journal of American Medical Informatics Association 8:* 443-459, 2001.

Van Essen DC. Organization of visual areas in Macaque and human cerebral cortex. L. Chalupa and J.S. Werner, Eds. In: *The Visual Neurosciences*. MIT Press (in press).

Van Essen DC. Windows on the brain. The emerging role of atlases and databases in neuroscience. *Current Opinion in Neurobiology*. (in press).

Zilles K and Palomero-Gallgher N. Cyto-, mylo-, and receptor architectonics of the human parietal cortex. *Neuroimage*, *14:* S8-20, 2001.

David C. Van Essen, Department of Anatomy and Neurobiology, Washington University, Shool of Medicine, 660 S. Euclid Ave., Box 8108. St. Louis, MO 63110. e-mail: vanessen@v1.wustl.edu