

## Introduction

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Every neuroscientist has a list of those he considers the most important unsolved problems in brain science. Surely high on the list of many will be that considered in this issue of *Cerebral Cortex*. Namely, what are the transforming operations imposed in a local region of neocortex, a cortical column, upon its input to produce its several outputs? The essays included here provide a cross-section of this large field, written by investigators using methods that include Golgi studies, slice recording with multiple intracellular microelectrodes and multiple microelectrode recording in intact cortex; several include theoretical modeling. While no one of these authors would venture that the problem is solved, their contributions and those of others in the field indicate that significant progress has been made in constructing an intra-columnar flow diagram, and in understanding the dynamic neuronal operations within it.

When in 1955–1959 I described the columnar organization of the somatic sensory cortex on the basis of observations made in single neuron recording experiments in cats and monkeys (Mountcastle *et al.*, 1955; Mountcastle, 1957; Powell and Mountcastle, 1959), the report was met with disbelief by many neuroanatomists. This was so because the histological methods available at the time revealed no structural counterpart to match the physiological observations. Lorente de No had described, in 1949, synaptically linked, trans-laminar, chains of neurons in the rodent cortex, which he postulated to be an elementary unit of the neocortex. Several anatomists had described cords of cells oriented normally to the pial surface, like those in the human auditory cortex described by von Economo, who first used the word column to describe them (von Economo and Koskinas, 1925). The Golgi method Lorente de No used revealed no sign of the horizontal disjunctions in functional properties we now know to characterize columnar organization, and to group sets of minicolumns into columns. I quote him directly, for Fulton's textbook of Neurophysiology is not now widely available.

If use is made of the elementary unit introduced previously, it may be said that the cortex is composed of an enormous number of elementary units, *not simply juxtaposed but overlapping* [my emphasis]. Each elementary unit has a series of axonal and dendritic plexuses, where the synapses between intracortical elements and afferent fibres with cortical cells are established. The bodies of the cells which form similar links in the intracortical chains are grouped in horizontal layers. Therefore any change in the constitution of the intracortical chains must produce a variation in the density of the plexuses, i.e., in the Nissl pattern, in the size of the empty [*sic*] intracellular spaces, and likewise in the number of cells in each layer. (Lorente de No, 1949)

It is clear from these perceptive generalizations, and the more detailed descriptions given in Lorente de No's essay, that he

recognized what we now term the cortical minicolumn, and he envisaged how variations of cell number and type at different depths in different areas could account for the cytoarchitectural differences then well known for many decades. However, Lorente de No could not recognize the abrupt transitions in functional properties which separate one column from the next.

Perhaps disbelief should have been expected, for the proposals were foreign to prevailing views of cortex. They were, firstly, that a vertical organization exists at cross-axis to and indeed accounts for the laminar organization of the cortex, and, secondly, that the cortex consists of a large number of units much smaller than cytoarchitectural areas. The concepts of laminar organization and the division of the cortex into 'cortical organs' defined by cytoarchitectural differences were dominant. The idea was then widely held, and still is by some, that different laminae might be specialized for different functions. The physiological observations made in the somatic sensory cortex in cats and monkeys, and in the visual cortex of both species by Hubel and Wiesel (Hubel and Wiesel, 1959, 1968, 1977) suggested two facts then unknown. Firstly, that the terminations of afferent systems to the cortex, whether from the thalamus or from other cortical areas, are arranged in clusters of sub-millimeter dimensions. Secondly, it was postulated on the basis of the latency measurements that the imposed cortical input is relayed rapidly in the vertical dimension, but restricted in the horizontal (i.e. parallel to the pial surface) dimension, and that it engages both pyramidal cells and interneurons after no more than one or two intracortical synapses. Evidence was presented that a pericolumnar inhibition might lend a dynamic tone to columnar isolation, although the cortical inhibitory interneurons were then unknown.

In the years since 1955–1959 the columnar or modular organization of the neocortex has been documented in studies of sensory, motor and homotypical areas under many experimental conditions and in many species, including the waking, behaving monkey. The requirements given above have been met in many anatomical and physiological experiments. The generally agreed state of knowledge can be summarized in a series of brief statements, as follows. The basic unit of cortical operation is the *minicolumn*, Lorente de No's 'elementary unit'. It contains of the order of 80–100 neurons, except in the primate striate cortex, where the number is more than doubled. The minicolumn measures of the order of 40–50  $\mu\text{m}$  in transverse diameter, separated from adjacent minicolumns by vertical, cell-sparse zones which vary in size in different cortical areas. Each minicolumn has all cortical phenotypes, and each has several output channels. The minicolumn is produced by the iterative division of a small set of progenitor cells in the neuroepithelium, probably via the interim ontogenetic unit described by Rakic (Rakic, 1972, 1988, 1995). By the 26th gestational week the human neocortex is composed of a large number of

minicolumns in parallel vertical arrays. This remarkable regularity is revealed in histological sections closely aligned with the vertical axes of minicolumns; see Figure 3 in (Buxhoevedan and Casanova, 2002). Moreover, optical density measurements reveal the oscillating changes in cell density in the horizontal dimension, with periods at the minicolumn diameter of 40–50  $\mu\text{m}$  (Schlaug *et al.*, 1995).

Cortical columns are formed by the binding together of many minicolumns by common input and short range horizontal connections. The number of minicolumns per column varies, probably because of variation in size of the cell sparse interminicolumnar zones; the number varies between 50 and 80. Long-range, intracortical projections link columns with similar functional properties. Columns vary between 300 and 500  $\mu\text{m}$  in transverse diameter, and do not differ significantly in size between brains that vary in size over three orders of magnitude (Bugbee and Goldman-Rakic, 1983). Cortical expansion in evolution is marked by increases in surface area with little change in thickness; how columns are recruited to form new areas is a matter of much study and speculation, but is still uncertain. Columnar organization allows for intermittently recursive mapping, so that two or more variables can be mapped to the single  $x$ - $y$  dimension of the cortical surface (Mountcastle, 1997, 1998; Buxhoevedan and Casanova, 2002).

#### **Are Properties Identical For All Neurons in a Minicolumn?**

Certainly not! The defining properties of minicolumns and columns are set by afferent input from several sources, concatenated with the results of intracolumnar processing. In primary sensory cortices, like the koniocortex of area 3b and other primary sensory areas of the postcentral somatic sensory cortex, the defining properties of place and mode are set strongly for all neurons of minicolumns by thalamocortical input. These properties are invariant over a wide range of behavioral conditions, ranging from deep anesthesia and natural sleep, to intensive attention during somatic sensory discrimination tasks (Mountcastle, 1990). Many other properties vary between neurons at different vertical levels of the elementary unit: among them are differences in small-molecule and peptide transmitters, gene expressions, receptor molecules, differential projections of non-primary thalamocortical fibers to neurons in superficial layers, etc. Even ontogenetic lineage differs for some, for about one-third of inhibitory interneurons are generated in the ganglionic eminence; all other interneurons and all projection neurons derive from the germinative neuroepithelium (Letinic *et al.*, 2002). Dynamic activity patterns also differ between different neurons, generated by different spike-generating mechanisms. One might predict, for example, that the discharge patterns of pyramidal cells projecting from layer III to other cortical areas will differ from those of pyramidal cells of layers V and VI projecting to subcortical structures. The important point is that columnar organization depends upon a certain set of properties common to all neurons in the elementary unit, but that other properties may vary between different neurons in the same minicolumn.

#### **Are Minicolumns in Different Cortical Areas All the Same?**

Certainly not! The similarity between the vertical processing chains in different cortical areas indicates a basic similarity in cortical structure. This has led to the idea that the intrinsic function of the neocortex is similar from place to place, and that what we regard as the different functions of cortical areas are due wholly to differences in afferent inputs. I believe this

appealing idea is not compatible with the evidence that the processing chains are not everywhere identical, and indeed that new cell phenotypes appear in some areas in some species and not in others, notably in the frontal and limbic cortex of humans and chimpanzees (Nimchinsky *et al.*, 1999). There is now growing evidence that chemical labels and biochemical mechanisms differ in minicolumns in different cortical areas; e.g. the role of nitrous oxide as a transmitter agent (Barone and Kennedy, 2000). It seems likely that the differences in afferent input are convolved with different intrinsic operations in different cortical areas to produce what we call different functions.

#### **How Can the Intrinsic Function of the Cortex Be Studied?**

Current answers are given in the essays which follow. A major problem is how to study the dynamic operations within a large-numbered neuronal circuit intimately interconnected with other circuits of equal complexity, from which it cannot be decoupled for partial analysis. The ideal experiment, of course, would be to observe the activity of all the neurons in a column, individually, either directly or from a distance, without tissue intrusion. This seems impossible at the present time. Efforts to obtain images of the total activity by surface recording of electrical events, or of changes in oxygen consumption or blood flow, or of changes in light emission, have yielded information of great value, but until now little concerning intrinsic operations at the level of single neurons or small groups of neurons. These records cannot be devolved, at least with present methods of analysis, to unique solutions for each of the neuronal elements producing them.

A second problem is the choice of experimental preparation. Most of the essays in this issue describe studies of the rodent barrel cortex, or the striate cortex of cats or monkeys, which are among the most highly specialized cortical formations in all of cortex. Moreover, some of the experiments described were made in slice preparations, and bear the further shadow that most were done in immature cortex. Yet we know that intracortical connectivity changes in major ways between birth and maturity. The answer to many problems may come from studies of the primate homotypical cortex, now under way in many laboratories.

#### **What Generalizations Can Be Made?**

These vary from those well established on the basis of present knowledge to those still hypothetical and subject to revision in the light of new discoveries.

1. The basic unit of the neocortex is the minicolumn of 40–50  $\mu\text{m}$  transverse measure. Minicolumns are linked into columns which contain an uncertain number of minicolumns, perhaps 50–80. The number varies with the distribution of thalamocortical axons, and with the sizes of the cell-sparse, neuropil-rich regions between minicolumns. Columns vary in size by a factor of ~1–2 in brains which vary in total surface area by three orders of magnitude.
2. Neurons in minicolumns possess a certain set of properties in common, like those of place and mode in 3b, but different cell phenotypes possess other properties which differ.
3. Minicolumns show considerable similarity between different neocortical areas, but they are not identical. They differ in connectivity, synaptic transmitters, other biochemical determinants, etc. The inference is that the intrinsic cortical operations are not identical between different cortical areas in the same brain.

4. Cytoarchitectural differences between different cortical areas are the result of sometimes sudden and in other cases gradual differences in the vertical, i.e. the laminar, distributions of neuronal phenotypes, changes commonly concurrent with changes in thalamic projections. Cortical laminae as such are not functional entities.
5. As demonstrated in this special issue, a major objective of current research is to determine the intrinsic operations in minicolumns and columns. Looming ahead, however, is an even greater question, which investigators have only begun to tackle: how are these elementary units in different cortical areas linked dynamically in the distributed systems of the neocortex?

## Notes

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