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ORIGINAL PAPER

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Intracortical circuitry: One of psychiatry's missing assumptions

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Abstract The brain operates as a constellation of modular functions focused on processing information. Neurons are arranged into repetitive circuits called minicolumns which themselves are assembled into macrocolumns. Most of the attention in neuroscience has focused on the experiences of organization – neuronal cellular function at one end and signal cascades and macrocolumns at the other. However, the search for pathological substrates of varied mental conditions are leading to a reassessment of the role of minicolumns in mental disorders. An appreciation of the modular framework of the brain provides a better insight as to how minicolumns contribute to the larger scope of information processing in the normal and pathological state.

Key words psychiatry · neurology · neuropathology · minicolumns · macrocolumns

"There are two ways of coming to know a machine:
one is that the master who made it should show us its artifice;
the other is to dismantle it and examine its most minute parts
separately and as a combined unit … But since the brain is a
machine, we need not hope to discover its artifice by methods
other than those that are used to find such for other machines.
There remains to be done; therefore, only what would be done
for all other machines. I mean the dismantling of all its
components, piece by piece, and consideration of what they
can do separately and as a whole"
Nicolas Steno, 1669. Quoted in Swanson, 2003, page 1.

The doctrines held by a branch of medicine define how its practitioners think and feel about themselves, the conditions they deal with, and the therapies they administer. Neurologists focus on diagnosis, treatment and prevention of neuronal damage or dysfunction in disorders of the central nervous system. In contrast, decades of failed attempts at uncovering neuropathological changes have left psychiatrists defining a group of conditions characterized by anatomical intangibles: mental, emotional, and behavioral disorders.

Neurology follows the neuronal doctrine.[1] This principle portends that in order to understand the function of the nervous system one needs to look at those interactions that focus on the neuron (Barlow 1972). The term neuron has therefore acquired an important connotation: that it is the basic anatomical and physiological unit of the brain. In accord with this concept, neuropathological research has largely concerned itself with defining specific neuronal changes such as cell loss, homogenization of cytoplasm or nucleoplasm, eosinophilia, etc. None of these changes characterize psychiatric conditions. Consequently, for most of the last century, neuropathology has been divorced from psychiatry. Arguably, a neuronocentric view of pathology has clouded rather than broaden our understanding on mental illnesses. We tend to accept a priori assertions that clinical disorders such as schizophrenia and autism have an underlying organic substratum. Paradoxically such conditions are presently classified as infirmities of the mind rather than of the brain.

Has psychiatry erred in following neurology's lead? Is the neuron truly the fundamental unit of the brain? Contemporary research invoke an a fortiori argument: what applies to other organs must apply to the brain. Hepatocytes, one cell identical to the next, do aggregate to form liver. Skeletal muscle fibers, one cell identical to the next, do aggregate to form muscle. However, the inference that neurons are the representative cellular element of the

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1 A principle stating that "the nerve cell is the anatomical, physiological, metabolic and genetic unit of the nervous system" [Waldeyer (1891), quoted in Shepherd, 1991, p. 4]. The phrase has been generalized to postulate the neuron as the framework of neurosciences including among others neuropathology, learning, and theory of mind.

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brain is no more than convenient fiction. First, neurons are not reiterative elements. Neurons, one identical to the next, do not aggregate to form brain. Instead, the brain comprises assemblies of various information-processing cells, each one differing in size, shape, connectivity, location, and function. Neuroscience recognizes these differences by characterizing brain cells with adjectives and eponyms. Neurons are variously termed GABAergic, pyramidal, horizontal, a cell of Martinotti, etc. These names describe differences in kind rather than degree. GABAergic cells will not transform into dopaminergic cells any more than Martinotti cells morph into horizontal cells of Cajal. Second, although highly differentiated, both hepatocytes and myofibers exhibit a variety of functions that reflect the role of their respective organs. Hepatocytes excrete the diverse components of bile, and muscle cells contract. On the other hand, the cascade of molecular and electrophysiological events within selected neurons in tissue slices or simpler species only caricaturize some of the functions of the brain, for example, long-term potentiation and memory. Single neurons do not produce higher cognitive functions or a mind. A great gap remains between neuronal pathology and clinical features of disease. Lastly, hepatocytes comprise approximately 60 % of the total population of liver cells. Moreover, these cells account for 90 % of the volume of the organ (Rubin and Farber 1994). Muscles may consist of an even higher proportion of myofibers. Yet the brain is a far more complex organ, containing 2 to 10 times as many glia cells as neurons.

A surprising discovery from recent neuroscience is the fact that a particular type of glia cell, the astrocyte, exhibits functions previously regarded as proprietary of neurons. Astrocytes provide some of the energy substrates of neurons and account for a significant portion of the signal in those functional neuroimaging studies reflective of cellular metabolism (Magistretti and Pellerin 1996). These cells have a high-capacity transport that inactivates glutamate within the synaptic cleft (Coyle and Schwarcz 2000), they modify serine into its optically active enantiomer (an agonist at the glycine modulatory site) (Wolosker et al. 1999), and they exhibit the potential to express all receptors and ion channels found in neurons (Gallo and Russell 1995). Furthermore, astrocytes synthesize and release a host of trophic factors that modulate synaptic plasticity and efficacy (Choi-Lundberg et al. 1997; Kotzbauer et al. 1996; Lindsay et al. 1994).

It can be seen that in marked contrast to many other organs, the brain lacks a uniquely representative cellular element. From a reductionist point of view, the neuron is a broken molecule or a split phoneme, an element no longer representative of any component, let alone the brain as a whole. Quite possibly, one gains insight into the brain's workings by looking outside and beyond the neuron. Various types of neurons provide complexity to larger ensembles called minicolumns.

The cell minicolumn is a self-contained ecosystem of neurons and their connections that reiterates itself throughout the neocortex. The term ecosystem is used to denote two facts about minicolumns: a) during development they may induce an orderly pattern of connections (Favorov and Kelly 1994a, b). William H. Calvin (1996) described it best, "It's almost like a club that self-organizes out of a crowd at a party, where people of similar interests tend to cluster together". Self-organization may explain how the apical dendrites and myelinated axons of pyramidal cells come together as bundles to provide visible components to the cell minicolumn.[2] b) The aggregate of functionally related components (that constitute minicolumns) provides for emergent properties (Casanova et al. 2003a). In these arrangements, connectivity within minicolumns is stronger than between them and their constituent cells share similar stimulus/response properties (Mountcastle 1998).

The minicolumn is the unit of cortical organization in all mammals (Buxhoeveden and Casanova 2002a). Minicolumns throughout the neocortex may follow the same anatomical and physiological template. The fact that all minicolumns may stem from a primordial template is exemplified by the unvarying use of layers II and III for association (e. g., corticocortical integration), layer IV for reception, and layers V and VI for efferent connectivity, regardless of anatomical location. Since there are some 600 million minicolumns in the neocortex, small defects in the basic template of the minicolumn may provide for significant symptomatology.

The cell minicolumn is a composite of 80 to 100 neurons arranged along an almost imperceptible scaffolding (Buxhoeveden and Casanova 2002b). The thickness dimension of the somewhat imprecise juxtaposition of cells within this columnar arrangement is easily missed in thin paraffin section. Thick Golgi sections provided the first medium in which researchers recognized minicolumns: "All of the elements of the cortex are represented in it, and therefore it may be called an elementary unit, in which, theoretically, the whole process of transmission of impulses from the afferent fiber to the efferent axon may be accomplished" (Lorente de Nó 1938).

The minicolumn arises during development when symmetrical divisions of precursor germinal cells, at the surface of the lateral ventricles, multiply their total number. Later, asymmetrical divisions form the cellular constituency of the minicolumn. Recent studies suggest that in some pervasive developmental disorders of childhood and in schizophrenia there may be defects in the morphology of minicolumns as well as in their temporal binding (co-activation of neural assemblies) (Brock et al. 2002; Buxhoeveden et al. 2000; Casanova et al. 2002a, b, c, d; Casanova et al. 2003a, b; Grive et al. 2001; Lee et al. 2003; Shergill et al. 2000).

2 Self-organization has been offered as an explanation to the complexity of the brain. The information needed to construct a brain with some 10^{10} neurons, each one capable of performing some 10^4 synapses, and more than 50 neurotransmitters is far larger than what is stored in DNA. Rather, genes appear to act as specific constraints on laws of self-organization (Scott Kelso, 1999).

Some researchers have argued that encephalization, i. e., the difference in brain size across species when taking into account body size, is due to increases in the total number of radially disposed minicolumns rather than neurons. This would explain why the surface area of the human brain is a thousand times greater than that of a mouse while only a two or three fold increase in cortical thickness separates any of the mammalian species (Rakic and Kornac 2001). If encephalization had simply occurred through a multiplication of neurons, both width and surface area would have increased concomitantly.

Contrary to neurons, minicolumns repeat themselves in a geometrically predictable fashion. A putative hexagonal pattern to the minicolumn may serve to accommodate tracts and cells without wasting space (Favorov and Diamond 1990; Tommerdhal et al. 1993). This geometric predictability applies to the different components of the minicolumn: apical dendrite bundles (Peters and Sethares 1991), myelinated axon bundles (Peters and Sethares 1996), double bouquet axon bundles (DeFelipe et al. 1990), and the interrelationship of all of the previous structures with a core of pyramidal cells (Peters and Sethares 1996). Aggregates of 40–80 minicolumns are themselves hexagonally arranged into "macrocolumns" (Favorov and Diamond 1990; Favorov and Kelly 1994b). In sensory cortex, macrocolumns are variously named barrel fields, hypercolumns or segregates (Buxhoeveden and Casanova 2002a, b). The anatomical basis of a macrocolumn is the termination of thalamic afferents that occur in focal clusters (Mountcastle 1997). Because these larger units have feature extraction capacities, they provide the basic building blocks of mental perception. A signpost as to where to look for pathology in psychiatric conditions is the fact that mental processes have a correlate within the construct of the mini- and macrocolumn.

When we step back to examine the hexagonal arrangements of mini- and macrocolumns we acquire an inkling of a fractal[3] pattern that is repeated throughout the body. The highest level of modularity within the brain is a network of macrocolumns (Fuster 2003). Interarea (cortico-cortico) connections linking macrocolumns have been noted to terminate in vertical patches several hundred microns in width (Jacobson and Trojanowski 1977; Schwartz and Goldman-Rakic 1984). These networks are geographically noncontiguous and widely distributed throughout the neocortex. The lowest level of neocortical modularity is the minicolumn.

A significant portion of our knowledge regarding mini- and macrocolumns is based on electrophysiological experiments of the first somatic sensory cortex of various species. In these brain regions, electrode penetration studies have shown vertical blocks of neocortical tissue where each neuron shares a receptive field to a given sensory modality. The size of the receptive field along with the underlying (macro)column of cortex varies according to the behavioral state of the animal, e. g., alert vs anesthesized. Studies on the minimum somatosensory receptive field have shown corresponding cortical transitions every 40–50 um (Favorov and Diamond 1990). These "minimal" columns (or minicolumns) provide for sharp shifts in receptive fields without evidence of overlap (Kaas et al. 1981). Studies using C-2-deoxyglucose and intrinsic optical signaling (IOS) have now established the minicolumn as the smallest anatomical division within the larger domain of the macrocolumn (Buxhoeveden and Casanova 2002b) and the smallest neocortical module capable of information processing (Mountcastle 1998).

The impetus established by recent research has recast crucial issues. Is the minicolumn the fundamental unit of the brain? Is a positive interpretation relevant and fair? The problem of defining the basic unit of the brain is of great importance not only in psychiatry but for neurosciences in general. We have now the ability to clone large number of stem cells that have the potential of becoming neurons. Neuroscientists are studying the viability of stem cell grafts in certain neurological conditions. Thus far, side effects from the surgical intervention have been significant and improvements, if any, appear to be mediated by an increased expression of neurotrophic factors (Corti et al. 2003). Transplantation of single cells in the context of the modular organization of the brain may provide for iatrogenically induced heterotopias. The latter situation could well be worse than no medical intervention at all (Swanson 2003). Similarly, we must question the usefulness of stereological cell counts when results are given independently from the modular organization of the brain. Trying to understand the existence of a neuronal change would be pointless unless seen as part of the complex whole from which it is an interdependent and interrelated component. For now, a focus on minicolumns simplifies and illuminates our understanding of an otherwise complex information processing chain within the neocortex. It allows us to link abnormalities of information processing to signs and symptoms of mental disorders (Casanova 2002b) and to explain numerous and often-contradictory perturbing neurochemical events as attempts at modulating a primary minicolumnar defect. More importantly, minicolumns offer a paradigm shift in the way we perceive the organic nature of mental conditions. In the end psychiatry will investigate that anatomical and physiological unit of the brain that best explains all its disparate findings and establishes coherence within the field.

3 Fractal geometry models the recurrence of similar patterns at different scales. The respiratory, circulatory, and digestive systems are considered as fractals.

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