

DEAD TISSUE, LIVING IDEAS: FACTS AND THEORY FROM NEUROANATOMY

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Modern neuroscience is based on ideas derived from neuroanatomy dating back to the neuron doctrine in 1888, when Ramon y Cajal demonstrated with the Golgi stain that the nervous system is not a syncytium but consists of individual neurons (DeFelipe and Jones, 1988). When the electron microscope was introduced about 50 years later, the gaps between neurons could be seen at high resolution and neuroscience acquired a powerful tool to probe the intricate structure of the synapse, and more recently its modification in learning and in disease.

The organization of the cortex into layers and columns is fundamental for neural function. Brodmann relied on differences in the shape and arrangement of neurons in cortical layers to divide the cortex into architectonic areas (Brodmann, 1909). Superimposed on the laminar (horizontal) organization, is a vertical organization into columns of neurons with similar features (Mountcastle et al., 1955). This dual organization of the cortex considerably increases its computational capacity (Grossberg, 1999), providing the structural basis for segregation and interaction of inputs and outputs, local inhibitory control, and parallel and distributed processing.

Columns mapped in physiologic studies were first thought to span the entire depth of the cortex. Evidence that this is not true in all cases emerged when a simple histochemical procedure for cytochrome oxidase fractionated columns of the primate primary visual area by intensely labeling 'blobs' in layers 2-3, setting them apart from sites with low intensity. A re-evaluation of the response properties indicated that neurons in blobs had distinct physiology as well (Livingstone and Hubel, 1984).

It wasn't until the introduction of neural tracers that columns could be seen in brilliant clarity and their organization understood, as ocular dominance columns in the primate primary visual cortex, or barrel fields in the rodent somatosensory cortex. Neural tracers replaced the pioneering but difficult and limited ablation-degeneration mapping methods, and offered exciting new possibilities. No other technique has comparable power and flexibility to show at once the spectrum of inputs and outputs of small or large brain areas, a column, layer, or single neurons. Using tracers we learned, for example, that connections between any two structures are generally reciprocal. Initially all but

ignored in functional studies, it is now clear that reciprocal connections have a fundamental role in all neural systems, ranging from simple sensory perception to complex cognitive processes [for review (Barbas et al., 2002)].

Neural tracers have made it possible to study the interactions of prefrontal association areas, which were not easily amenable to physiologic study and remained 'silent' until recently [review in (Goldman-Rakic, 1996)]. A conceptual advance was made when anatomic data showed that the prefrontal cortex, long thought to be the seat of cognition, also has a limbic component, a system classically associated with emotions (Nauta, 1979; Yakovlev, 1948). The limbic cortex, situated on the medial and basal surfaces, has expanded in primate evolution along with the association cortices and maintains strong connections with them, inextricably linking areas associated with cognition and emotion [for review (Barbas et al., 2002)]. This evidence challenges the classic idea of Plato that thoughts and emotions are entirely separate. In fact, disconnection of pathways associated with cognition and emotion likely is at the core of psychiatric diseases characterized by inability to attach the appropriate emotion to a situation. Such pathology disproportionately affects limbic areas, and by extension, feedback communication, the predominant pattern of projections of limbic areas (Barbas et al., 2002).

In spite of its empirical and conceptual contributions, neuroanatomy is often underestimated for its power to understand neural function. This perception stems from a fundamental misunderstanding that information obtained from 'dead tissue' is limited, as a colleague physiologist once suggested. For him a change of mind came fortuitously, when we were examining histological slides from the brain of one his monkeys and saw that a large part of the lateral geniculate nucleus on one side had degenerated. Paradoxically, the monkey's partial blindness had escaped notice during the behavioral training and physiologic recording, but was now inferred from a set of slides.

Beyond such perceptions, however, problems exist in neuroanatomy, weighed down with long lists of terms, confusing variations in maps, and architectonic borders that most cannot easily see. Can the problems be resolved? I believe so. Take, for instance, variations in maps. We now have a host of molecular markers that are differentially

distributed in the cortex, making it possible to construct quantitative profiles and characterize architectonic areas objectively. Figure 1 (left) shows one such example, where a dozen quantitatively assessed architectonic features were considered simultaneously using multidimensional analysis. Prefrontal limbic areas clustered to the left, and the eulaminate to the right, because they differ structurally. Objective approaches eliminate the need to rely on subjective analysis and can resolve differences in maps in the literature.

Reliable maps are needed, now more than ever, to localize activity and interpret functional imaging studies in humans. However, the value of maps transcends the need to localize because structure affects the pattern of connections. Thus, systematic variations in architecture underlie the graded laminar pattern of corticocortical connections [see (Barbas et al., 2002)]. Patterns of connections have variously been interpreted to reflect the direction of processing in sensory areas, or the distance between connected areas [for review (Felleman and Van Essen, 1991)]. However, just as columns are not unique to sensory areas but represent fundamental organizing units in the cortex (Fig. 1, right), so is cortical structure, whose systematic variation can be used to explain and predict the pattern of connections equally well in sensory, association, and limbic cortices.

A frequently voiced criticism of neuroanatomy is that it's descriptive. But accurate quantitative description is the *sine qua non* for the life sciences, whether it's labeled boutons, firing properties of neurons, or expression of genes. Darwin used it, and so did Ramon y Cajal, and the mappers of the human genome. Darwin's meticulous descriptions of finches, barnacles and rock formations were necessary for the inductive process, giving rise to

the theory of evolution. Quantitative empirical data provide the opportunity to reveal relationships, derive principles, perform computations, model, predict normal function and dysfunction in disease. And this is where the excitement and challenge lies in neuroanatomy – fortified with quantitative tools and analyses it is at the core of neuroscience.

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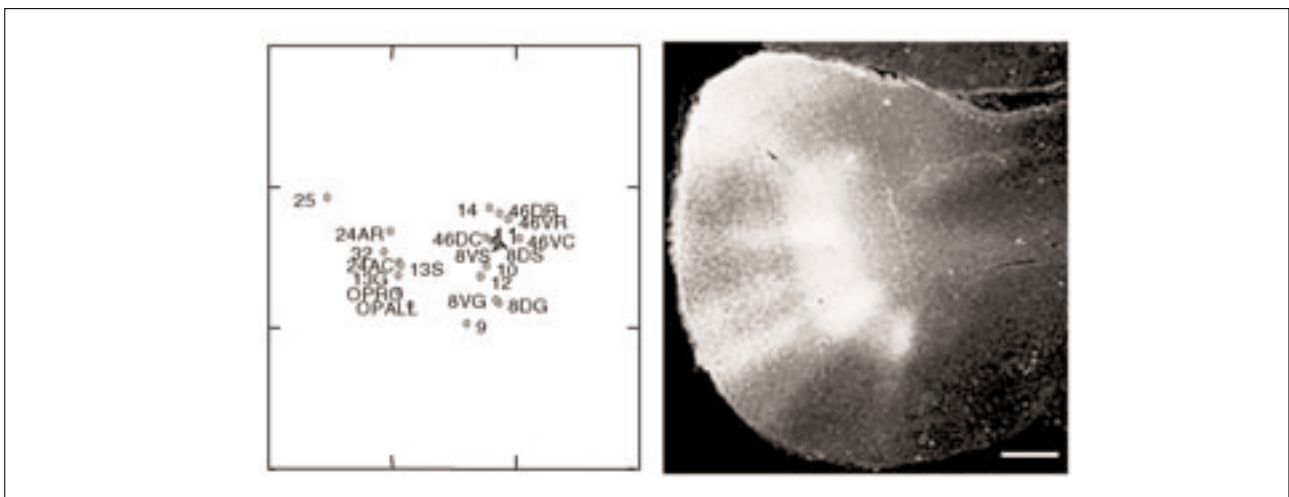


Fig. 1 – Analysis of architectonic features and pattern of connections in the prefrontal cortex in the rhesus monkey. (Left) Quantitative architectonic features of prefrontal cortices (neuronal density, glial density, thickness for layers 1, 2-3 and 5-6, and for the calcium binding proteins parvalbumin, calbindin and calretinin for layers 1-3) were considered simultaneously using nonmetric multidimensional scaling (NMDS). The plot indicates the relative similarity of prefrontal areas according to normalized laminar profiles across the quantitatively obtained experimental measures. In this analysis the limbic prefrontal areas cluster to the left and the eulaminate to the right. (Right) Columns formed by the termination of axons (white) emanating from area 46 and terminating in area 12 of the prefrontal cortex. Scale = 1 mm. (The figure on the left was adapted from Dombrowski, Hilgetag and Barbas, *Cerebral Cortex* 11:975-988, 2001.)