Chapter 9
Discrete, Place-Defined Macrocolumns in Somatosensory Cortex: Lessons for Modular Organization of the Cerebral Cortex

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Keywords Minicolumn • Macrocolumn • Receptive field • Segregate

9.1 Introduction

In 1957 Mountcastle introduced the concept of the *cortical column* as the vertical processing unit of the cerebral cortex. This idea, the "columnar hypothesis," was based on the then prevailing view that the cortex is most richly interconnected in its vertical dimension (Lorente de No 1949) and on Mountcastle's demonstration in single-unit recording experiments in cat (and later monkey; Powell and Mountcastle 1959) primary somatosensory cortex (SI) that neurons in ~0.5 mm wide vertical columns are activated by peripheral stimuli of the same submodality and have similar receptive fields (RFs). Mountcastle (1957) and Powell and Mountcastle (1959) also showed that their cortical columns – later named "macrocolumns" to distinguish them from single-cell-wide "minicolumns" (Mountcastle 1978) – can be separated from each other by abrupt boundaries, on the opposite sides of which neurons respond to stimuli of different submodalities and/or have prominently different RFs.

This paper reviews the evidence that SI cortex of cats and monkeys is partitioned into a honeycomb-like mosaic of discrete macrocolumns. The review then draws

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upon the lessons derived from studies of these columnar entities to update and clarify the original Mountcastle's definition of the macrocolumn and advance the possibility that macrocolumns constitute fundamental functional units of the cerebral cortex, as envisioned by Mountcastle (1978).

9.2 Columnar Organization of SI Cortex

9.2.1 SI Cortex is Partitioned into a Mosaic of Discrete Macrocolumns

The simplest way to demonstrate the sharp boundaries separating discrete macrocolumns is to use the "minimal RF" mapping method (Favorov and Diamond 1990). This method is designed to identify the skin locus that provides the strongest input to a local cluster of neurons (for practical details of this RF mapping method, which are critical for detecting macrocolumnar borders, see Favorov and Diamond 1990).

Figure 9.1 shows typical sequences of minimal RFs encountered in near-radial microelectrode penetrations of cat or monkey SI cortex. The penetrations shown in Fig. 9.1 were inserted into the forelimb region of cat SI and minimal RFs were mapped every 100–150 μm along the electrode track. In the penetration in Fig. 9.1a, all the minimal RFs mapped from the pial surface to the white matter occupy the same position on the skin and do not show any somatotopic drift. In the penetration in Fig. 9.1b, the first 4 minimal RFs occupy one position on the skin, whereas the last 3 minimal RFs occupy a new, prominently displaced skin position. The 5th minimal RF was mapped right at the obviously very sharp topographic transition, signaling a boundary separating two cortical columns. Similarly abrupt jumps of minimal RFs are also reliably observed in penetrations that travel tangentially through the SI cortex (Favorov et al. 1987; Favorov and Diamond 1990).

Minimal RFs mapped in arrays of closely spaced penetrations reveal the shape and size of macrocolumns delineated by such sharp minimal RF discontinuities (Favorov and Diamond 1990). An exemplary array of such penetrations is illustrated in Fig. 9.2. Twenty five penetrations were inserted in this experiment approximately perpendicular to the cortical surface and in each penetration two or three minimal RFs were mapped at or near layer 4 (Fig. 9.2a). Figure 9.2b shows the outlines of all 62 mapped minimal RFs on a single drawing of the skin of the forearm, revealing that they form 10 nonoverlapping clusters, labeled from *a* to *j*. Figure 9.2c shows a two-dimensional surface-view reconstruction of the cortical region sampled by the 25 penetrations. Positions of all the recording sites, projected radially onto layer 4, are indicated by filled circles. Recording sites mapped in the same penetration are connected by thin lines, and each recording site is assigned the letter of the RF cluster to which its minimal RF belongs. The reconstruction in Fig. 9.2c clearly shows that recording sites with the same minimal RF form

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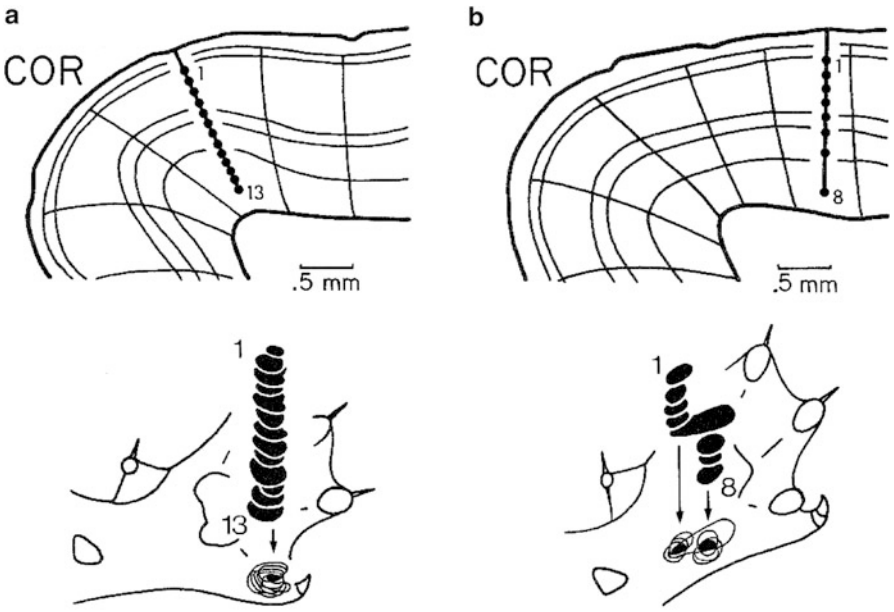

Fig. 9.1 Typical near-radial penetrations of cat SI. In this and the following figures illustrating histological sections, orientations of radial cords of cells are indicated by thin lines and recording sites are indicated by circles. Minimal RFs are drawn stacked in the order in which they were mapped in the penetration. *COR* coronal sulcus (From Favorov and Diamond 1990)

nonoverlapping groups up to 350 μm in width, separated from other such groups by just a few tens of micrometers in the plane of cortical surface. The most probable arrangement of the columnar boundaries is indicated in Fig. 9.2c by the set of solid and dotted lines, revealing a mosaic of sharply delineated topographic units, within each of which the minimal RF does not change, but jumps to a new skin location when crossing into another such unit.

To summarize, the minimal RF mapping method reveals sharp somatotopic discontinuities that subdivide SI cortex into a mosaic of 300–600 μm-diameter irregular hexagonally-shaped columns. The same minimal RF is mapped at any site within a column. In adjacent columns, minimal RFs occupy prominently displaced, nonoverlapping positions on the skin. The columns with more distally located minimal RFs tend to be larger in size. To emphasize their discrete nature, Favorov and colleagues called such place-defined macrocolumns "segregates."

9.2.2 RF Diversity Within SI Macrocolumns

A minimal RF is determined jointly by multiple neurons in a vicinity of the electrode tip and is the skin site that provides the most effective afferent drive to

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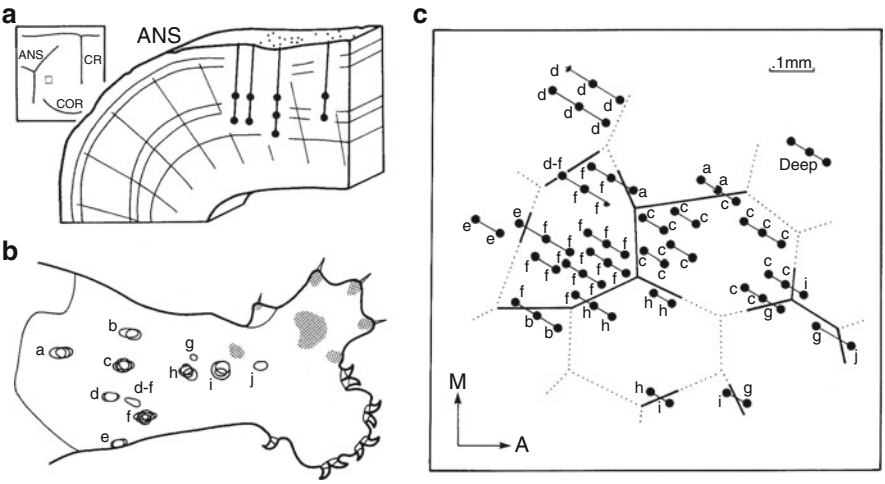

Fig. 9.2 Array of 25 closely spaced penetrations reveals discrete columns in cat SI (From Favorov and Diamond 1990)

those neurons as a group. Individual neurons in the recorded group obviously are driven from skin areas larger than their common minimal RF. For a single neuron, its *maximal* RF can be defined as the full extent of the skin area that provides suprathreshold input to that neuron (Favorov et al. 1987). Neurons located within a single macrocolumn/segregate all share in their maximal RFs that segregate's minimal RF, but also each neuron receives afferent input from some additional – and frequently very extensive – surrounding territories, which are different for different neurons (Favorov et al. 1987; Favorov and Whitsel 1988ab).

Figure 9.3 offers an example of the diversity of maximal RFs of neurons found in a single segregate. Shown in Fig. 9.3a, 21 single neurons were isolated in a near-radial penetration of a single segregate in area 3b in cat and their maximal RFs were mapped. All 21 maximal RFs are drawn in Fig. 9.3b, revealing prominent diversity of their sizes, shapes, and skin positions across the length of the penetration and even among close neighbors. However, there is one very small skin locus that is common to all 21 RFs (Fig. 9.3c). This skin locus coincides with the minimal RF mapped in this penetration.

To summarize, maximal RFs of all neurons in a segregate include a common skin locus (the minimal RF) and, in addition, extend for variable distances outward in all directions from that common locus. Neurons in a segregate differ from one another in how much their maximal RFs extend in each and every direction from the common skin locus (Favorov and Whitsel 1988b). Because of its central importance to segregate organization, the common skin locus of a segregate – its minimal RF – was given a special name, "segregate RF center" (Favorov and Whitsel 1988a).

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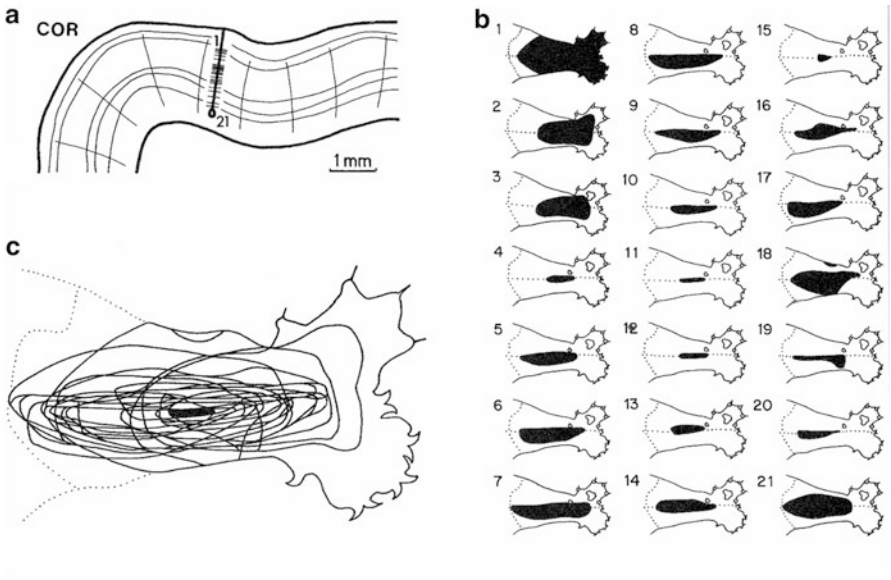

Fig. 9.3 Maximal RFs collected in a typical radial penetration of cat SI. Cortical locations of studied single units are indicated in panel A by tics (From Favorov and Diamond 1990)

9.2.3 Minicolumnar Organization of Maximal RFs

Mountcastle (1978) hypothesized that a radial cord of cells about 30–50 μm in diameter – a "minicolumn" – might be the smallest functional unit of neocortical organization. Structurally, minicolumns are attributable to the radially-oriented cords of neuronal cell bodies evident in Nissl-stained sections of cerebral cortex. Population analysis of maximal RFs of neurons isolated within the same SI segregate supports Mountcastle's minicolumnar hypothesis (Favorov and Whitsel 1988a; Favorov and Diamond 1990). According to this analysis, the maximal RFs of neurons within minicolumns are most similar in size, shape, and position on the skin. In contrast, neurons located even in adjacent minicolumns typically have RFs that differ significantly in size and shape, and frequently overlap only minimally on the skin. In other words, local RF diversity within segregates is mostly attributable to diversity *among* minicolumns and much less to within minicolumns.

For example, Fig. 9.4 plots the average degree of overlap of maximal RFs as a function of the tangential distance separating neurons within a segregate. The plot shows that neurons that are the closest neighbors in the tangential plane of the cortex have the most similar RFs, and that similarity declines with increased distance. At separations larger than 50 μm, RF overlap within segregates is independent of the distance between neurons. Instead, moving from one minicolumn to the next within a segregate, maximal RFs shift back and forth on the skin without yielding a net RF shift across the entire segregate. Only at a border separating

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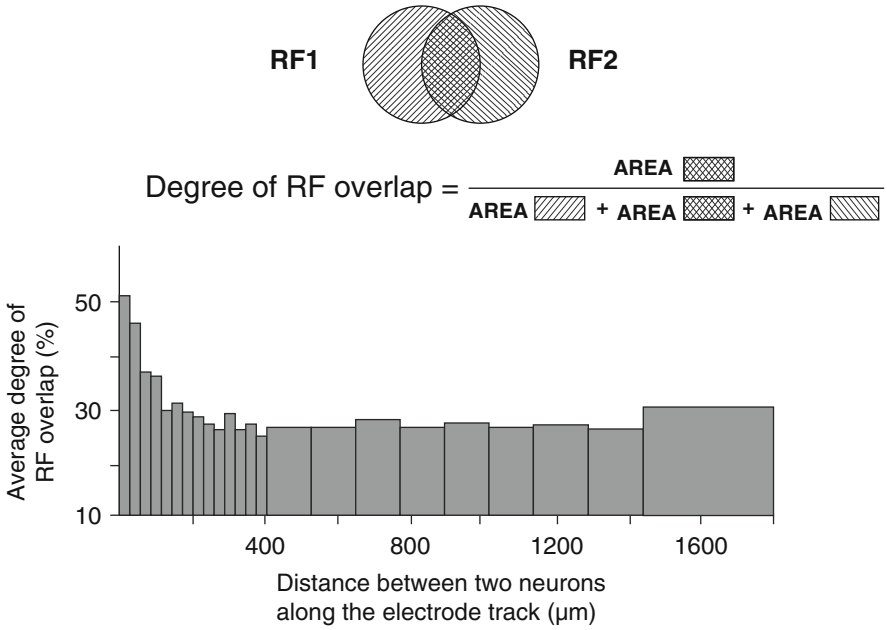

Fig. 9.4 Similarity of maximal RFs as a function of distance separating two neurons in the plane of the cortical surface in monkey SI (From Favorov and Whitsel 1988a)

adjacent segregates do RFs shift *en masse* to a new skin territory (Favorov and Whitsel 1988a; Favorov and Diamond 1990).

Because of the prominent differences in RF properties among neighboring minicolumns, even a point-like tactile stimulus ought to evoke a spatial pattern of activity in the responding SI region consisting of a mix of active and inactive minicolumns. High-resolution 2-deoxyglucose (2-DG) metabolic studies of monkey SI (Tommerdahl et al. 1993) indeed showed that column-shaped patches of 2-DG label evoked in SI cortex by natural skin stimuli comprise groupings of highly active minicolumns interdigitated with less active minicolumns.

9.3 Functional Significance of Discrete Place-Defined Macrocolumns

Mountcastle originally defined columns as functional entities comprising groups of minicolumns bound together by common input and short-range lateral connections. Since then, however, the term "column" has been frequently used more broadly to refer to any vertical cluster of cells that share the same tuning for any given RF attribute, not necessarily of any functional significance (Horton and Adams 2005). At the same time the functional significance of Mountcastle's cortical columns has

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been questioned (Swindale 1990; Purves et al. 1992; Horton and Adams 2005; Da Costa and Martin 2010). For example, Horton and Adams (2005) conclude their comprehensive critique of Mountcastle's columnar hypothesis by stating that "one must abandon the idea that columns are the basic functional entity of the cortex. It now seems doubtful that any single, transcendent principle endows the cerebral cortex with a modular structure. Each individual area is constructed differently..."

The minimal and maximal RF organization of SI segregates – Mountcastle's original macrocolumns – however offers a number of insights that counteract the criticism and clarify the nature of macrocolumns as functional entities:

1. **The structural evidence of discreteness associated with macrocolumns should be sought at the level of cell bodies, rather than at the level of dendrites and axon terminals**

The basal dendrites of pyramidal cells have a large horizontal spread – up to 400–500 μm in diameter (Feldman 1984). This means that a portion of the basal dendritic fields of the majority of pyramidal cells in an SI segregate invades neighboring segregates. If there were no restrictions on the inputs the dendrites of pyramidal and spiny stellate cells can receive from elements outside their own segregate, then the majority of the cells in a segregate would reflect the activity from the neighboring segregates invaded by their dendrites. Neurons in different parts of a given segregate would be influenced by activity of different surrounding segregates, and the RFs of a linear array of neurons across a segregate would show an orderly, gradual and continuous shift in skin position. In reality, segregates show no such somatotopic gradients within their confines (see above), thus indicating that although some dendritic branches of cells in one segregate invade the territories of adjacent segregates, they do not receive opportunistic synaptic contacts there from neurons residing there or from afferents innervating those segregates. On the other hand, the afferents innervating a given segregate and the local axon collaterals of neurons residing in that segregate will follow the dendritic branches originated in that segregate into the territories of the adjacent segregates. As a result, the systems of afferent and intrinsic connections wiring adjacent segregates can remain functionally separate while physically intermingled in each other's neuropil.

2. **Definition of the macrocolumn by common input and short-range connections should not be taken to imply that neurons making up the macrocolumn all have uniform RFs**

Instead of uniformity, neurons making up an SI segregate possess prominently diverse maximal RFs (see above), with each maximal RF differ in how much it extends in different directions away from the segregate RF center (i.e., the skin locus common to RFs of all the cells in the segregate). Thus, the segregate is recognized on statistical grounds by its possession of a certain assortment, or *distribution*, of maximal RFs centered on a particular skin point. Neurons in different sectors of the same segregate apparently have the same distribution of maximal RFs. The reason why the border between adjacent segregates can be detected is because RF distributions immediately across the border have clearly

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different central tendencies and occupy different, only partially overlapping skin territories (the RF center of one segregate is included in only 50 % of the maximal RFs found in an adjacent segregate). The reason why minimal RF mapping method is highly effective in detecting segregate borders is that it is designed to estimate the central tendency of the distribution of maximal RFs of a local group of neurons picked up by the tip of the recording electrode, and thus it directly reveals where in the course of an SI penetration the central tendency of local maximal RFs stays the same and where it jumps to a new skin location.

These statistical properties of segregate maximal RFs are depicted schematically in Fig. 9.5. It shows hypothetical distribution of maximal RFs across two adjacent segregates. For graphic clarity, the skin and RFs are treated as unidimensional. Hypothetical maximal RFs are plotted in Fig. 9.5b for 200 neurons sampled along a continuous path that spans the two segregates (Fig. 9.5a). The random variations in the size (length) of the RFs reflect the diversity of sizes of maximal RFs sampled in cat and monkey experiments (Favorov and Whitsel 1988a; Favorov and Diamond 1990). The first 100 RFs belong to neurons located in the first segregate. They all share in common skin point A, but otherwise they vary randomly how far they extend to the left and to the right from this central point of their distribution. The next 100 RFs belong to neurons located in the second segregate. Their distribution is similar to that of the first 100 RFs, except that it is centered on skin point B. The change in the central tendency occurs at the transition from the first segregate to the second, between the 100th and 101th RFs. The distance between the two central skin points, A and B, is such that the central point of one segregate is included in 50 % of RFs of the other segregate. This Fig. 9.5b plot captures the essential characteristics of the segregate organization of maximal RFs in cat and monkey SI cortex.

3. **The afferent input to the macrocolumn is provided by neurons in lower-level cortical areas and/or thalamic nuclei via axons all terminating extensively over the same territory**

Individual thalamocortical axons projecting to Layer 4 in SI have terminal arbors varying in size from 350 to 800 μm (~600 μm average) in macaque (Garraghty and Sur 1990; Raussel and Jones 1995) or from 300 to 600 μm (~500 μm average) in cat (Landry and Deschenes 1981; Landry et al. 1987). Such arbor sizes match or slightly exceed the range of widths of SI segregates in these species. The most parsimonious interpretation is that each thalamocortical axon targets a particular segregate and arborizes throughout its territory and also follows dendrites of the spiny stellate cells near the segregate borders into the adjacent segregates. Any given segregate is innervated in this manner by a group of thalamocortical neurons, which are expected to possess similar RFs. Because of their non-identical, partially shifted RFs, such a group of thalamocortical neurons together will cover a skin area greater than the size of an individual RF; we can call this total skin area the segregate's "*afferent RF*." By their axons all terminating over more or less the full extent of the segregate, while avoiding synaptic contacts with cells in the adjacent segregates, the group of thalamocortical neurons innervating a

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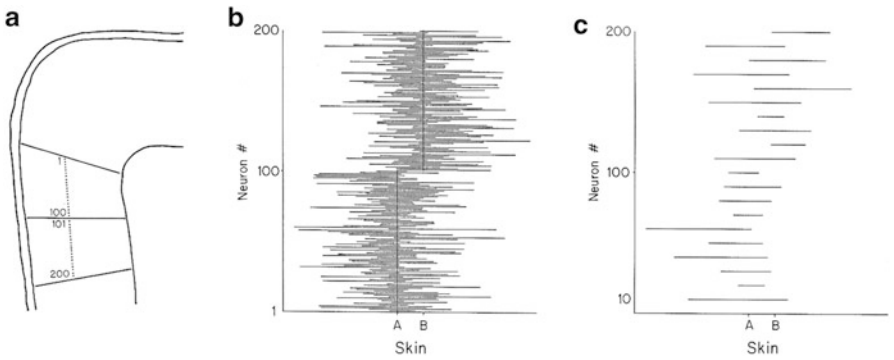

Fig. 9.5 The segregate plan of topographic organization of SI cortex. (**a**) A hypothetical track of a microelectrode penetration down the posterior bank of the central sulcus. The *solid lines* indicate the boundaries of two adjacent segregates. The *line of dots* indicates the locations of 200 single units mapped in the two segregates. (**b**) Hypothetical maximal RFs of the 200 mapped single units. Each maximal RF is drawn as a horizontal line showing its full extent and position on the skin. RFs of successive single units are drawn in a vertical order according to the single unit's position along the electrode track. Maximal RFs from 1 to 100 belong to the top segregate and they all share in common skin point A (indicated by a vertical line segment). Maximal RFs from 101 to 200 belong to the next segregate and they all share in common skin point B. (**c**) 1 out of 10 subsample of the maximal RFs plotted in panel B. While the *en masse* shift of RFs at the segregate border is clearly noticeable in panel B, it is unrecognizable in the smaller RF sample in panel C (From Favorov 1991)

segregate in fact creates that segregate: it gives that segregate its sharp boundaries while avoiding somatotopic gradients across its territory. Adjacent segregates are supplied by different groups of thalamocortical neurons.

4. **Having discrete macrocolumns might be a strategy used by cortical areas to devote larger numbers of cells to recognizing significant spatiotemporal patterns of activity in a reduced number of chosen subsets of afferent neurons innervating an area**

According to this strategy, a group of afferent neurons terminating over a particular macrocolumn constitutes one of the "chosen" subsets. In SI cortex, each segregate has as its chosen subset a group of thalamic neurons terminating over it, through which it receives information about patterns of tactile events taking place in that segregate's afferent RF (defined above). The spatiotemporal patterns of activity in the segregate's set of afferent neurons are first processed by the segregate in its layer 4 by roughly 1,000–1,500 spiny stellate cells residing there, and then by 2,500–3,500 pyramidal cells residing in the upper layers (estimated based on Beaulieu and Colonnier 1989, and Favorov and Diamond 1990). Layer 4 cells tune to different afferent input patterns as a step to generalization, which takes place in the upper layers (Poggio and Bizzi 2004). If we think of the segregate's set of N afferent neurons as defining an N-dimensional "*afferent pattern*" space of the segregate, each dimension of which corresponds to one of

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the afferent neurons, then each layer 4 cell in the segregate can be thought of as a functional analog of a Radial Basis Function (RBF) in that space (Favorov and Kursun 2011). The 1,000–1,500 layer 4 cells in the segregate have their RBFs distributed throughout the afferent pattern space of the segregate and together they create a 1,000–1,500-point map of that space. The 2,500–3,500 pyramidal cells in the segregate's upper layers next integrate the outputs of the segregate's layer 4 cells to compute 2,500–3,500 different functions over the segregate's *N*-dimensional afferent pattern space, thereby creating a new, higher-level representation of significant patterns of tactile events taking place on the territory of the segregate's afferent RF (Favorov and Kursun 2011).

In the absence of such discrete macrocolumnar compartmentalization of a cortical area, we can expect individual minicolumns or small groups of minicolumns to create their own afferent pattern spaces, but these spaces will be mapped by many fewer layer 4 cells/RBFs and will be much more redundant than afferent pattern spaces of macrocolumns. Whether having fewer, more densely mapped afferent pattern spaces is functionally advantageous and offers the functional rationale for existence of discrete macrocolumns will have to be determined in future studies.

5. Segregate-like discrete macrocolumns might be present in the visual cortex, V1 and V2

Visuotopic organization of the visual cortex has received much less experimental attention than its other properties, such as ocular dominance and orientation tuning. Nevertheless, Roe and Ts'o (1995) found prominent topographic discontinuities at the borders separating the thin, thick and pale stripes in macaque V2. Furthermore, they found topographic discontinuities not only between but also within stripes, where RF jumps were coincident with other signs of functional partitioning of individual stripes into discrete macrocolumn-scale domains. This is very suggestive that V2 – similar to SI – is partitioned into a mosaic of discrete place-defined macrocolumns.

V1 of cats and monkeys has a well-developed map of orientation tuning. This map has local regions in which the preferred orientation changes relatively slowly and monotonically, but these regions are separated by fractures and singularities where the orientation preference changes rapidly. The fracture lines tend to enclose ~400 μm-wide columnar regions, which Blasdel and Salama (1986) – who were the first to generate orientation maps using the voltage-sensitive dye technique – described as modular units of V1 organization. Studying the relationship between orientation and retinotopic maps in cat V1, Das and Gilbert (1997) found that orientation fractures are associated with retinotopic discontinuities, suggesting that Blasdel and Salama's (1986) fracture-defined modular units can also be place-defined as discrete macrocolumns comparable to SI segregates.

In disagreement with Das and Gilbert (1997), the map of visual space in V1 has been consistently described as smooth, although at a local level neighboring cells do exhibit prominent, but seemingly random, scatter in the positions of their RFs (Hubel and Wiesel 1974; Albus 1975; Bosking et al. 2002; Buzas et al. 2003; Yu

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et al. 2005). The magnitude of such local RF scatter is comparable to that observed in cat and monkey SI. However, as we see in SI, such RF scatter effectively hides topographic discontinuities at segregate boundaries in SI cortex. As is illustrated in Fig. 9.5b, an abrupt shift in the central tendency of local groups of maximal RFs at a segregate border is easy to see in plots involving large numbers of RFs. But such a high density of RF sampling is not practically achievable and a limited sample of RFs obtainable in an experiment is not likely to reveal any jumps in RF central tendency upon visual inspection. For example, in Fig. 9.5c only one out of every ten RFs shown in Fig. 9.5b is plotted and now, because of large RF variability, it is no longer apparent that RFs actually were sampled from two different, displaced distributions. A common practice in V1 studies of using the geometric centers of RFs to map the progression of RFs across a cortical territory would only further obscure topographic discontinuities. A much more effective approach to detecting topographic discontinuities is to use the minimal RF mapping method (see above), but it has not been popular in visual cortical studies.

To conclude, the studies of visuotopic organization of the visual cortex carried out up to date have not been suited for detection of topographic discontinuities and discrete place-defined macrocolumns. However, the limited evidence of Roe and Ts'o (1995) and Das and Gilbert (1997) suggests that such discontinuities and macrocolumns responsible for them are present in V1 and V2.

9.4 Conclusion

Mountcastle's concept of the discrete macrocolumn as a group of minicolumns bound together by common input and short-range lateral connections has been best exemplified so far by segregates, which are the discrete place-defined columns found in cat and monkey SI (Favorov et al. 1987; Favorov and Whitsel 1988a, b; Favorov and Diamond 1990). The available knowledge of segregate dimensions, morphological properties of thalamocortical axon arborizations in SI, dendritic and axonal fields of SI neurons, and RF composition of segregates allow us to refine the definition of Mountcastle's macrocolumn in terms of its common input and local connections. That is, the macrocolumn is as a group of 40–80 minicolumns that form a structural and functional union by imposing the following constraints on their connectivity:

1. The ascending input to this group of minicolumns is provided by a set of afferent axons each of which terminates on layer 4 cells across all the minicolumns (although not uniformly, but varying in the strength of its individual connections);
2. While dendrites and axons of the cells belonging to this group of minicolumns penetrate into the neuropil space of the neighboring minicolumns outside the group, they stay functionally isolated by avoiding indiscriminate connections with local neurons and afferent axons there;

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3. Horizontal connections between macrocolumns are organized on the principle of functional relatedness and not simple physical proximity.

We propose that the reason for exposing all the layer 4 cells in a macrocolumn to the same set of afferents is to enable them, as a large group, to map at high resolution the state space, or the "afferent pattern" space, of this set of afferents (Favorov and Kursun 2011). Whether the functional benefits of such mapping strategy are limited to somatosensory and possibly visual cortex (Roe and Ts'o 1995; Das and Gilbert 1997; Favorov and Kursun 2011) or whether such strategy is used universally throughout the cerebral cortex remains to be determined. Unfortunately, because of interpenetration of dendritic and axonal fields of adjacent macrocolumns, direct visualization of the macrocolumnar segregation of afferent projections and of local connections is problematic. Instead, functional discontinuities, which are a telltale sign of macrocolumnar borders, offer a more practical means of detecting discrete macrocolumns. However, in a note of caution, not all discontinuities might be associated with macrocolumnar borders. In principle, feature maps, such as orientation or ocular dominance maps in V1, do not have to have a simple relationship to macrocolumns. Any feature map will comprise local maps developed by individual macrocolumns in a possible coordination across macrocolumnar borders. The maps of particular features, as well as relationships between maps of different features, might vary across cortical areas, mammalian species and even in different regions of the same area (Horton and Adams 2005), but this does not necessarily have to mean that these areas do not contain discrete macrocolumns.

References

Albus K (1975) A quantitative study of the projection area of the central and the paracentral visual field in area 17 of the cat: I. The precision of the topography. Exp Brain Res 24:159–179

Beaulieu C, Colonnier M (1989) Number of neurons in individual laminae of areas 3b, 4γ, and 6aα of the cat cerebral cortex: a comparison with major visual areas. J Comp Neurol 279:228–234

Blasdel GG, Salama G (1986) Voltage-sensitive dyes reveal a modular organization in monkey striate cortex. Nature 321:579–585

Bosking WH, Crowley JC, Fitzpatrick D (2002) Spatial coding of position and orientation in primary visual cortex. Nat Neurosci 5:874–882

Buzas P, Volgushev M, Eysel UT, Kisvarday ZF (2003) Independence of visuotopic representation and orientation map in the visual cortex of the cat. Eur J Neurosci 18:957–968

Da Costa NM, Martin KAC (2010) Whose cortical column would that be? Front Neuroanat 4:16

Das A, Gilbert CD (1997) Distortions of visuotopic map match orientation singularities in primary visual cortex. Nature 387:594–598

Favorov OV (1991) Detection and characterization of the mosaic body representation in SI cortex. In: Franzen O, Westman J (eds) Information processing in the somatosensory system. Macmillan Press, London, pp 224–232

Favorov OV, Diamond M (1990) Demonstration of discrete place-defined columns, segregates, in cat SI. J Comp Neurol 298:97–112

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Favorov OV, Kursun O (2011) Neocortical layer 4 as a pluripotent function linearizer. J Neurophysiol 105:1342–1360
Favorov O, Whitsel BL (1988a) Spatial organization of the peripheral input to area 1 cell columns: I. The detection of "segregates". Brain Res Rev 13:25–42
Favorov O, Whitsel BL (1988b) Spatial organization of the peripheral input to area 1 cell columns: II. The forelimb representation achieved by a mosaic of segregates. Brain Res Rev 13:43–56
Favorov OV, Diamond ME, Whitsel BL (1987) Evidence for a mosaic representation of the body surface in area 3b of the somatic cortex of cat. Proc Natl Acad Sci U S A 84:6606–6610
Feldman ML (1984) Morphology of the neocortical pyramidal neuron. In: Peters A, Jones EG (eds) Cerebral Cortex. Vol. 1. Plenum, New York, pp 123–200
Garraghty PE, Sur M (1990) Morphology of single intracellularly stained axons terminating in area 3b of macaque monkeys. J Comp Neurol 294:583–593
Horton CH, Adams DL (2005) The cortical column: a structure without a function. Philos Trans R Soc Lond B Biol Sci 360:837–862
Hubel DH, Wiesel TN (1974) Uniformity of monkey striate cortex: a parallel relationship between field size, scatter, and magnification factor. J Comp Neurol 158:295–305
Landry P, Deschenes M (1981) Intracortical arborizations and receptive fields of identified ventrobasal thalamocortical afferents to the primary somatic sensory cortex in the cat. J Comp Neurol 199:345–371
Landry P, Diadori P, Leclerc S, Dykes RW (1987) Morphological and electrophysiological characteristics of somatosensory thalamocortical axons studied with intra-axonal staining and recording in the cat. Exp Brain Res 65:317–330
Lorente de No R (1949) Cerebral cortex: architecture, intracortical connections, motor projections. In: Fulton JF (ed) Physiology of the nervous system, 3rd edn. Oxford University Press, New York, pp 288–312
Mountcastle VB (1957) Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 20:374–434
Mountcastle VB (1978) An organizing principle for cerebral function: the unit module of the distributed system. In: Mountcastle VB, Edelman GM (eds) The mindful brain. MIT Press, Cambridge, MA, pp 7–50
Poggio T, Bizzi E (2004) Generalization in vision and motor control. Nature 431:768–774
Powell TPS, Mountcastle VB (1959) Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture. Bull Johns Hopkins Hosp 105:133–162
Purves D, Riddle DR, La Mantia A-S (1992) Iterated patterns of brain circuitry (or how the cortex gets its spots). Trends Neurosci 15:362–368
Raussel E, Jones EG (1995) Extent of intracortical arborization of thalamocortical axons as a determinant of representational plasticity in monkey somatic sensory cortex. J Neurosci 15:4270–4288
Roe AW, Ts'o DY (1995) Visual topography in primate V2: multiple representation across functional stripes. J Neurosci 15:3689–3715
Swindale NV (1990) Is the cerebral cortex modular? Trends Neurosci 13:487–492
Tommerdahl M, Favorov OV, Whitsel BL, Nakhle B, Gonchar YA (1993) Minicolumnar activation patterns in cat and monkey SI cortex. Cereb Cortex 3:399–411
Yu H, Farley BJ, Jin DZ, Sur M (2005) The coordinated mapping of visual space and response features in visual cortex. Neuron 47:267–280

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Chapter 10
Prefrontal Cortical Microcircuits for Executive Control of Behavior

Ioan Opris, Ioana L. Popa, and Manuel F. Casanova

Abstract During the perception-to-action cycle, our cerebral cortex mediates the interactions between the environment and the perceptual-executive systems of the brain. At the top of the executive hierarchy, prefrontal cortical microcircuits are assumed to bind perceptual and executive control information to guide goal-driven behavior. Here, we discuss new results that show the involvement of prefrontal cortical inter-laminar microcircuits in the executive control of behavior. Recent results show that during perception and executive selection phases, cell firing in the localized prefrontal layers and caudate-putamen region exhibited a similar location preference on spatial-trials, but less on object- trials. When the perceptual-executive microcircuit became facilitated by electrically micro-stimulating the prefrontal infra-granular-cell layers with signal patterns previously derived from neuron firing in the supra-granular-layers, it was shown to produce stimulation-induced spatial preference (similar to neural tuning) in the percent correct performance only during spatial trials. These results suggested that inter-laminar prefrontal microcircuits play causal roles to the executive control of behavior across the perception-to-action cycle.

Keywords Cortical microcircuits • Executive control • Minicolumn • Prefrontal cortex • Primates • MIMO model • Causal relationship • Perception-to-action

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10.1 Introduction

As it was initially proposed by Mountcastle, the primate neocortical circuitry has a modular architecture that sub-serves a multitude of sensory (visual, auditory, touch), motor, cognitive (attention, memory, decision) and emotional functions (Barbas et al. 2005; Buschman et al. 2012; Buxhoeveden et al. 2002; Favorov et al. 1987; Gilbert and Wiesel 1989; Mountcastle 1957, 1997; Shepherd and Grillner 2010; Opris and Bruce 2005). These modules are composed of elementary building blocks formed by vertical arrangements of cortical neurons, called minicolumns (Casanova et al. 2008; Mountcastle 1997; Szentágothai and Arbib 1975; Hubel and Wiesel 1969). Within minicolumns, cortical neurons are aggregated into six horizontal layers (or laminae): three supra-granular layers (L1-L3), a granular layer (L4) and two infra-granular layers (L5/L6) (Fig. 10.1a). The granular layer receives sensory input from thalamus (Constantinople and Bruno 2013), while the minicolumnar outputs in the infra-granular layers send top-down signals to the subcortical structures (including striatum and thalamus; Alexander et al. 1986; Mountcastle et al. 1955, 1957; Opris et al. 2013). The supra-granular layers consist of small pyramidal neurons that form a complex network of intra-cortical connections, particularly the connections to the infra-granular layers of larger pyramidal neurons that generate most of the output from cerebral cortex to other parts of the brain (Buxhoeveden and Casanova 2002). According to this three stratum functional module, infra-granular layers execute the associative computations elaborated in supra-granular layers (Buxhoeveden and Casanova 2002; Casanova et al. 2011).

10.2 Prefrontal Cortical Minicolumns

Vernon Mountcastle described for the first time the electrophysiological basis of the cortical minicolumn and suggested it as an elemental unit of information processing (Mountcastle 1998, 1957, 1997; DeFelipe et al. 2012). According to this model of cortical organization, neurons and their connections form part of a vertical system which unites the cells of each minicolumn (Fig. 10.1a, b) into a coordinated functional unit (Mountcastle 1978, 1997). In this context, the smallest unit of cortical organization is the minicolumn, usually defined in Nissl stained sections by a narrow radial array of pyramidal neurons traversing laminae II-VI (Rakic 1988; Mountcastle 1997). Minicolumns are composed of vertical chains of excitatory neurons surrounded by inhibition (Fig. 10.1c, d) in cylindrical arrangement that constitutes the smallest module capable of information processing (Mountcastle 1957, 1998; Rakic 2008). The human neocortex is composed of a large number of minicolumns in parallel vertical arrays (Casanova et al. 2007). Minicolumns are the first step in a nested ensemble of nodes or "echelons" of increasing complexity (Opris and Casanova 2014). Other levels of modular organization include multiple minicolumns, macrocolumns, and large-scale networks of macrocolumns that are interconnected with the entire brain (Buxhoeveden and

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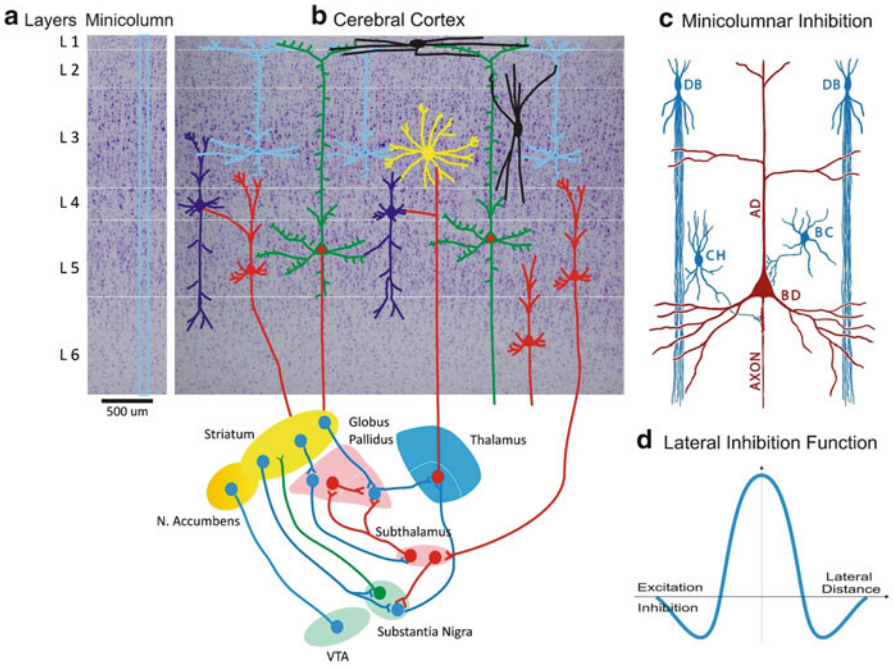

Fig. 10.1 Illustration of prefrontal cortical minicolumns, layers and loops. (**a**) Prefrontal cortical minicolumn highlighted in a human brain slice. (**b**) Laminar and columnar display of the major cell types in prefrontal cortex together with its connections to basal ganglia and thalamus. The six-layered cortex is showing on a Nissl background the pyramidal cells and the cortical interneurons. The cells are connected to the thalamus and basal ganglia, as shown on the lower panel. VTA is ventral tegmental area; N. accumbens is nucleus accumbens. (**c**) Pyramidal cell surrounded by interneurons illustrates the minicolumnar curtain o inhibition. AD is apical dendrite, BC is basket cell, BD is basal dendrite, CH is chandelier cell, DB is double bouquet cell. (**d**) Lateral inhibition function shows the neural activation (excitation and inhibition) with horizontal distance from a minicolumn's center (Adapted from Opris and Casanova, 2014)

Casanova 2002). The somas of pyramidal cells are not randomly distributed in space; rather, they are organized into layers and different-sized columns or modules. Similarly, some dendritic and axonal ramifications that begin or end in these somas are wired in parallel groups of fibers (Mountcastle 1997, 2003). Minicolumns are often considered highly repetitive, even clone-like, units; however, they display considerable heterogeneity between areas and species, perhaps even within a given macrocolumn.

10.2.1 Columns and Minicolumns

Minicolumns are arranged within larger columns or macrocolumns (e.g., barrel somatosensory cortex of the rodent) bound together by short-range horizontal connections (Jones 2000; Zhang and Alloway 2006; Jones and Rakic 2010;

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DeFelipe et al. 2012). The different echelons are semi-independent of each other, a function of the limited number of information channels between them (Casanova 2005). According to Buxhoeveden and Casanova (2002), and in agreement with Favorov and coworkers (1987, 1990) and Mountcastle (1957, 1997), the estimated width of cortical macrocolumns is 350–600 μm. Hubel and Wiesel (1974) found that optimal orientation tuning changes systematically through 180° with an electrode advance of between 0.5 and 1.0 μm. The term "hypercolumn" refers to a complete rotation of columns (e.g. 0°, 10°, 20°,. . .,180°; Hubel and Wiesel 1974; Wiesel and Hubel 1974). Recently, Opris and collaborators (Opris et al. 2011, 2012b, c) suggested that interlaminar interaction in prefrontal cortical minicolumns take an active role in sensorimotor integration and the selection of behaviorally relevant targets. Sparse distributed representations of inputs flowing from visual cortex to the higher association areas in prefrontal cortex appear to be part of distributed networks, named "cognits" by Fuster (Fuster and Bressler 2012). However, the specific role of prefrontal macrocolumns in prospective coding and representation storage is yet to be demonstrated (Bastos et al. 2012).

A sparse distributed representation is one where items are encoded by activation of a small set of the available representing units. Sparse encoding does not reduce to a straight majority vote scheme. Anatomically, sparse encoding may be enforced by variability between minicolumns which themselves suggest differences in their internal architecture (Casanova 2008; Rinkus 2010). This variability among components of a minicolumn may contribute to the fault tolerance of larger networks such as macrocolumns. McCulloch (1959) has shown that when failure of individual components occur under a certain threshold (e.g., cell loss at the beginning stages of Alzheimer's disease) redundant networks of unstable nets could be designed for greater reliability than redundant systems of stable nets of the same size.

10.2.2 Cortical Modules and Maps

Early studies by (Mountcastle et al. 1955; Mountcastle 1957, 1997) and Hubel and Wiesel (Hubel and Wiesel 1974; Wiesel and Hubel 1974) showed that neurons with similar response properties are grouped in vertical columns, about 0.5–1 mm in diameter, with each column oriented perpendicular to the surface of the cortex and spanning its thickness. Correspondingly, anatomical studies (using histological staining for the enzyme cytochrome oxidase) showed a modular organization in the primate visual cortex with periodically spaced patches about 350 μm apart (Horton and Adams 2005). In the primate prefrontal cortex the diameter of columns vary between 300 and 500 μm, but it does not differ significantly in size between brains with over three orders of magnitude difference in volume (Bugbee and Goldman-Rakic 1983). This common periodicity means that any block of cortex, approximately the size of a single hypercolumn, contains cells tuned to all values of every receptive field variable (Swindale et al. 2000). Hubel and Wiesel

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(Hubel 1982; Katz et al. 1989) applied the term "module" to this tissue block comprising multiple, overlapping hypercolumns. Mountcastle (1997) has used the term 'module' interchangeably with 'column'.

The most salient feature of cortical organization is the presence of an orderly topographic map of visual space that is remapped sequentially as information flows from visual cortex to prefrontal cortex (Salinas 2004). Neighboring neurons tend to have receptive fields in similar positions in visual space, and these positions "change predictably" as a function of position on the cortex (Swindale et al. 2000). In addition to orientation, visual neurons vary in their preference for the direction of motion of an oriented bar or edge, in their preference for stimuli delivered to one eye or the other (ocular dominance), and in their preference for low versus high spatial frequencies in the visual image (Swindale 1998). All of these properties have been found to vary in an orderly way with position on the cortical surface, so that, typically, a complete set of values occurs at least once every mm or so.

10.3 Prefrontal Cortical Microcircuits

As proposed by Mountcastle, the primate neocortical circuitry has a modular architecture that subserves a multitude of sensory (visual, auditory, touch), motor, cognitive (attention, memory, decision) and emotional functions (Mountcastle 1957, 1997; Shepherd and Grillner 2010; Opris and Bruce 2005). According to this "modular" view of the prefrontal cortex, Goldman-Rakic (1996) provided evidence from experimental studies in nonhuman primates that the central executive decomposes into segregated information processing modules each with its own sensory, mnemonic, and motor control features.

Inter-laminar microcircuits, consisting of interconnected pyramidal neurons between the supra- and infra-granular layers, form a three stratum functional module that connects both worlds via sensory and motor circuits, in which infra-granular layers execute the associative computations elaborated in supra-granular layers (Buxhoeveden and Casanova 2002; Casanova et al. 2011; Thomson and Bannister 2003; Opris et al. 2011, 2012b, 2013). These microcircuits receive input from neurons in layer L4, which project to L2-L3, or through direct thalamic projections to the supra-granular layers in the higher-order cortical areas. Neurons in L2-L3 then project top-down to L5, where they target specific types of pyramidal cells and inhibitory interneurons. Some L5 neurons project back to L2-L3 neurons, forming an inter-laminar loop (Weiler et al. 2008) back to L4, targeting mostly interneurons (Thomson and Bannister 2003). The outputs from cortical microcircuits, cortico-striatal projections arise mostly from L5, whereas cortico-thalamic projections arise from L6.

Cortical microcircuits are connected by cortico-cortical connections into a macro-network that links areas within the same hemisphere, as well as across hemispheres (Van Essen et al. 1982). This super network subserves the

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'perception-to-action' cycle – a group of processes that handle environmental stimuli and convert them into actions (Fuster and Bressler 2012; Romo et al. 2002). Microcircuits within the same hemisphere are interconnected (from low level sensory to high level associative processes) through horizontal connections in lamina 2/3, spanning over many cortical areas (Das and Gilbert 1995; Kritzer and Goldman-Rakic 1995; Fuster and Bressler 2012).

Inter-area connectivity of cortical microcircuits preserves spatial topography suggesting a column-to-column match from one area to another (Goldman-Rakic 1996). Additionally, the topography is preserved within minicolumns owing to the inter-laminar projections (Opris et al. 2013). Interhemispheric connectivity is formed by neural interconnections of lamina 3b (Jones 2000; Van Essen et al. 1982). Cortical microcircuits are also interconnected across the two hemispheres through cortico-cortical connections from lamina 3b (Jones 2000; Van Essen et al. 1982). This implies that the firing of a single callosal neuron might influence several cortical columns within the opposite hemisphere. However, microcircuits in each hemisphere are symmetrically interconnected (from low level sensory to high level associative processes) through horizontal connections in lamina 2/3 across many cortical areas (Das and Gilbert 1995; Kritzer and Goldman-Rakic 1995; Fuster and Bressler 2012). This imply a bottom-up remapping of a spatial topography with a column-to-column match from one area to another on the dorsal visual stream from V1 to prefrontal cortical area 46 (Goldman-Rakic 1996). In the same time each topography is preserved across layers through top-down inter-laminar projections within minicolumns (Opris et al. 2013).

Recent research conducted in nonhuman primates indicates that a variety of sensory, motor and executive functions emerge from the interactions between frontal, parietal, temporal and occipital cortical microcircuits (Atencio and Schreiner 2010; Buffalo et al. 2011; Opris et al. 2012b, c, 2013; Mahan and Georgopoulos 2013; Hirabayashi et al. 2013a, b; Takeuchi et al. 2011; Hansen et al. 2012). This suggests that cortical microcircuits perform elementary computations while cognitive functions are sub-served by a broader network comprising multiple cortical areas (Fuster and Bressler 2012). This implies that cortical microcircuit integrate, represent or select the relevant signals from a multitude of incoming inputs.

10.4 Integration, Representation and Selection in Cortical Microcircuits

The functional role of the cortical minicolumn is a continuing source of research and debate more than half a century after it was identified as a component of brain organization (Mountcastle 1957, 1997; Mountcastle et al. 1955). Nevertheless, the cognitive ability of prefrontal cortical mechanism is hypothesized to emerge from the "laminar-columnar" architecture of the prefrontal cortical minicolumns, that are

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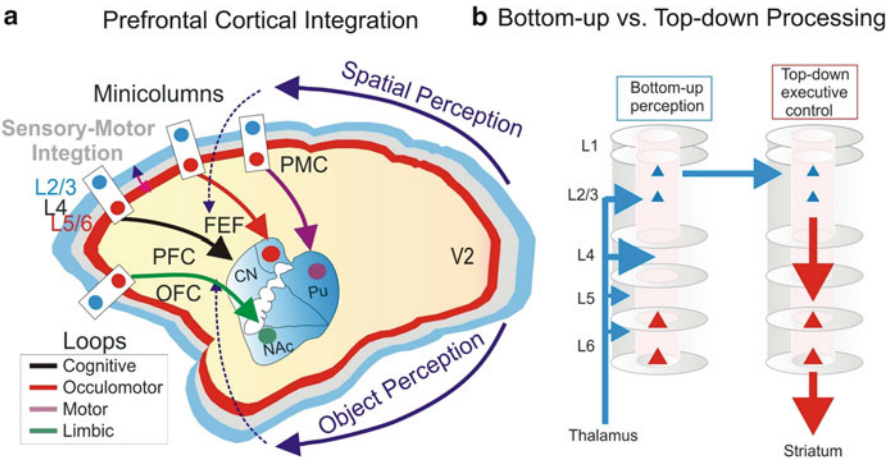

Fig. 10.2 Inter-laminar microcircuits for integration, representation and selection. (**a**) Prefrontal cortical integration of cognitive, oculomotor, motor and limbic structures in four loops. (**b**) Illustration of bottom-up and top-down processing within cortical microcircuits

interconnected (Fig. 10.2) with basal ganglia and thalamus in recurrent loops (Bugbee and Goldman-Rakic 1983; Goldman-Rakic 1996; Opris et al. 2011, 2012d, 2013). Such columnar recurrent 'microcircuit' may be regarded as the 'basic functional unit' of the cognitive function. Its cognitive relevance emerges from the 'computational' ability of the inter-laminar microcircuit to: (a) integrate incoming signals of the input layers, (b) store information through feedback connections in reverberatory loops, and (c) to compare input signals to a threshold criterion, triggering an output response i.e. the ability to make a decision.

10.4.1 Integration

The integrative role of cortical minicolumns as a module (Leise 1990) stems from connecting the horizontal and vertical components of the cortex within the same columnar space. The supragranular layers L2/3 which are the major source of corticocortical projections also receive sensory information, while the infragranular layer L5 is the output to subcortical structures involved in behavior (Miller and Cohen 2001). Thus, interlaminar connections form microcircuits that bind sensory-related signals with behavior/movement related outputs (Opris et al. 2011). This sensorimotor integration (Fig. 10.2a) was demonstrated by Opris et al. (2011, 2013) by means of interlaminar correlated firing between supragranular layers that carry perceptual/visual spatial information and the infragranular layers that carry action related information. Such transformations of neural signals may likely reduce the output degrees of freedom within the cortical minicolumn by selecting only the relevant signals for action/behavior. This

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integrative process that occurs in canonical microcircuits binds/segregates parallel streams of minicolumnar processing within the 'executive cognit' network (Fuster and Bressler 2012; Miller and Cohen 2001).

Prefrontal microcircuits are in a unique and privileged position at the top of sensory-to-motor hierarchy network because they coordinate a multitude of stimuli, perceptions, biases and actions related to such functions as attention, decision making, and working memory. As such, prefrontal microcircuits integrate and synthetize signals over a broad spectrum of perceptual stimuli and various modalities (Wilson et al. 1993). This integration is performed in supra-granular layers, whereas the output of the infra-granular layers provides selection-related signals, which are sent back to the infra-granular layers and the other areas comprising the network. As a matter of fact, signals can reverberate within inter-laminar loops. Thus, microcircuits in entorhinal cortex and hippocampal formation employ such reverberating signals (Takeuchi et al. 2011) to integrate relevant information over time (Fuster 2001). For example, microcircuits of the temporal cortex use such synchrony to maintain items in long term memory (Takeuchi et al. 2011; Hirabayashi et al. 2013a), while the microcircuits in the prefrontal cortex perform elementary computations for the executive control of behavior (Opris et al. 2012b, c);

10.4.2 Representation

The prefrontal cortex is crucial for the representation of stimulus properties (spatial, object features) in working memory and the hippocampus is essential for the long term memory (Funahashi et al. 1989; Miller and Cohen 2001; Takeuchi et al. 2011; Naya and Suzuki 2011). Prefrontal cortical "modules" (minicolumns) are composed of neurons with "memory fields" (Goldman-Rakic 1996), with isodirectional tuning for minicolumnar cells (Rao et al. 1999). Prefrontal neurons exhibit persistent "delay period" activity with enhanced firing rate in animals performing delay response tasks, being regarded as a neural "signature" of working memory (Funahashi et al. 1989). Such persistent firing of prefrontal cortical neurons is hypothesized to emerge from functional interactions between cells in different cortical layers, wired together in reverberatory loops (inter-laminar and/or thalamo-cortical) (Alexander et al. 1986). As a matter of fact, signals can reverberate within inter-laminar loops (Weiler et al. 2008). Thus, cortical microcircuits for long term memory in entorhinal cortex employ such reverberating signals (Takeuchi et al. 2011) to represent relevant information over time (Fuster 2001). Takeuchi et al. (2011) demonstrated a "reversal" of interlaminar signal between sensory and memory processing in monkey temporal cortex. Thus, during the sensory "cue" epoch, the canonical microcircuit signals flowed "feed-forward" from granular to supragranular layers and from supragranular to infragranular layers, while during the "memory" delay epoch, however, the signal flow reversed to the "feed-back" direction: from infragranular to supragranular layers. Such

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reversal of signal flow highlights a neat dissociation of the sensory and mnemonic processing in the temporal cortex that differentially recruits its laminar circuits.

10.4.3 Selection and Decision Making

The available evidence suggests that the prefrontal cortical minicolumn might be the first stage bottleneck in the cortical-striatal-palidal-thalamo-cortical loop (Alexander et al. 1986). It is obvious that layers 2/3 and 4 cells integrate a lot of inputs from virtually all of the brain, while the number of outputs from layer 5/6 pyramidal cells to subcortical structures participating in behavior is much less. Also, a key role in selection is played by the GABAergic interneurons of minicolumns (Raghanti et al. 2010) that shape the tuning for preferred direction/location by means of lateral inhibition. The minicolumnar role in plasticity is associated not only with the tuning (Fig. 10.3) of synaptic activity states but also with optimal selection among alternate subnetworks of microcircuits developing within a given context. Such parallel subnetworks may process complementary submodalities within a defined receptive/memory field; alternatively they may provide overlapping response characteristics to a common input. Competition among networks allows for circuit optimization (selection), in particular by means of learning.

We hypothesize that minicolumnar diversity provides the substrate for this competition and the basis for adapting learned behavior to context. During development, neurogenetic programs interact with epigenetic factors to regulate formation of cortical microcircuit templates (Rakic 1988; Jones 2000; Jones and Rakic 2010; Kaas 2012), which are then shaped and pruned by differential patterns of sensory activity. Thus, increased minicolumnar diversity may give rise to greater potential for combinatorial activity of microcircuits within overlapping networks, resulting in enhanced learning and behavioral flexibility (Casanova 2008). Cortical minicolumns may therefore play a crucial role in behavioral selection that is in fact the substrate of executive function (e.g., attention, decision making).

Is cortical minicolumn a decision module? A decision circuit is defined as a closed neural network that measures the probable value of a signal element and makes an output signal based on the value of the input signal and a predetermined criterion or threshold (Ratclif et al. 2003; Opris and Casanova 2014). Minicolumns in PFC are interconnected to each other through horizontal "long range" projections in layer 2/3 (Kritzer and Goldman-Rakic 1995; Rao et al. 1999) and interlaminar mini-loops (Weiler et al. Takeuchi et al. 2011). The loop is then closed ("reverberatory loops") through projections to the subcortical basal ganglia nuclei and thalamus (Alexander et al. 1986; Swadlow et al. 2002). Such "reverberatory loops" may be regarded as the "basic functional unit" of cognitive/executive mechanism because they: (i) combine incoming signals of the different input layers (Casanova et al. 2007); (ii) store mnemonic information through feedback connections in "persistent" spiking activity (Wang 2012); (iii) compare input signals to a threshold criterion triggering an output response (selection), which constitutes the

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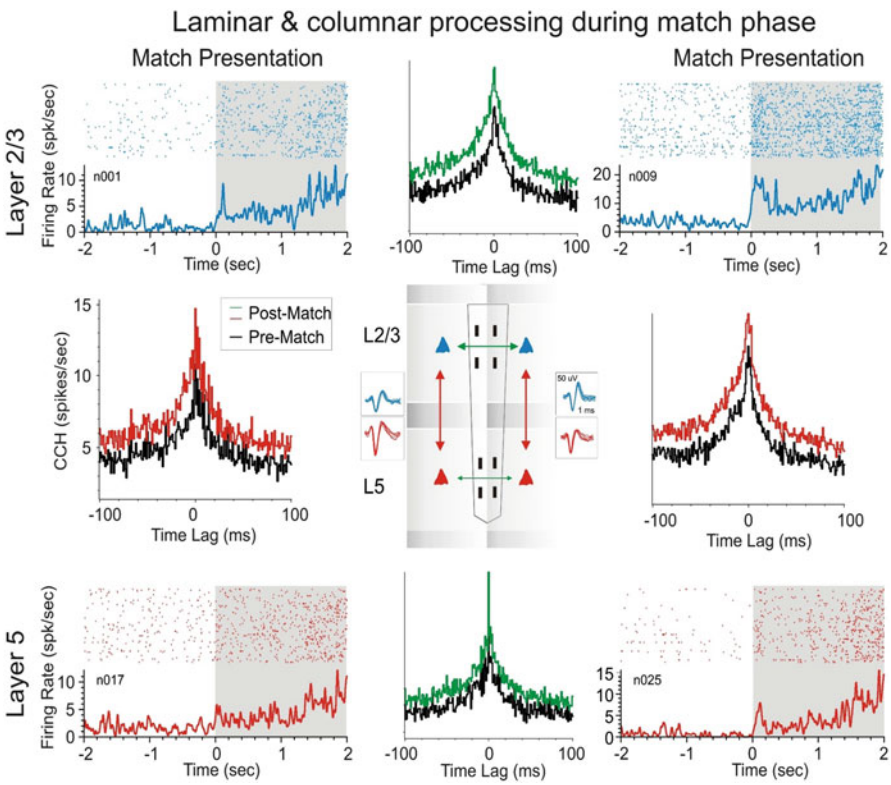

Fig. 10.3 Simultaneous recordings of cortical minicolumns. Minicolumnar interlaminar processing of target selection during the match phase of the task. Peri-event and cross-correlation (post- vs. pre-match) histograms depict the functional role in integration/selection of prefrontal cortical layers and minicolumns

ability to make a decision (Ratcliff et al. 2003). Thus, a cortical minicolumn with integrative, selective and threshold abilities can play the role of a decision module.

10.5 Correlated vs. Causal Relationships to Executive Control

Several approaches based on microcircuits have been implemented. These advances have been possible owing to of the development of new multi-electrode arrays (MEA) fitted for recordings from neural elements of cortical columns (Hampson et al. 2004; Moxon et al. 2004). Thus, MEAs with linear or bi-linear geometry have been successfully employed for simultaneous recordings from supra- and infragranular cortical laminae in adjacent minicolumns, resulting in

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unprecedented insights into the function of cortical microcircuits (Mo et al. 2011, Opris et al. 2011, 2012b, c, 2013).

10.5.1 Inter-laminar Interactions and Emergence of Executive Control

The relevance of minicolumnar activity to executive function has been investigated with different approaches under several conditions (Hirata and Sawaguchi 2008; Opris et al. 2011, 2012b, c, 2013; Hampson et al. 2012). Our recent results in nonhuman primates show for the first time interlaminar processing in PFC (Fig. 10.3) during target selection (Opris et al. 2011, 2012b, c) and sensorimotor integration (Opris et al. 2011). An example of this interlaminar interaction during target selection (Opris et al. 2012b, c) in delay match to sample (DMS) task is shown in Fig. 10.3 for two cell pairs with rasters and perievent histograms (PEHs) bracketing the temporal interval of image presentation (Match Phase onset) and completion of the target selection Match Response (0–2 s). The cell pairs were recorded on appropriate sets of adjacent pads (minicolumns 1&2) in the conformal multiple electrode array (MEA) shown in the illustration (Opris et al. 2011, 2012b, c) of both interlaminar cell pairs in L2/3 and L5 (Fig. 10.3 center). Neurons in both layers showed significant increases in mean firing in supra- and infragranular layers as a function of Match presentation (Post Match: 0 to +2 s) and during subsequent movements associated with target selection. Demonstration of precise functional connections between individual cells within each minicolumn was provided by cross correlation histograms (CCHs; Opris et al. 2011, 2012b, c); constructed for individual L2/3 and L5 cell pairs recorded on vertically positioned pads of the MEA. Normalized CCHs for both minicolumn cell pairs and between minicolumns are shown in Fig. 10.3 for cell firing in the displayed PEHs: (i) prior to (black) Match phase onset (2 s to 0, Pre) or (ii) after (green) Match phase onset (0 to +2 s, Post) for the same cell pairs. Both CCHs show significantly correlated firing (Opris et al. 2012b).

10.5.2 Causal Relations Involving Inter-laminar Microcircuits

The unique properties of conformal MEAs (Fig. 10.4a; Moxon et al. 2004) together with prior microstimulation work (Opris et al. 2001, 2005; Hampson et al. 2004) has provided a basis for showing functional relationships to executive function in prefrontal cortex of nonhuman primates. The conformal multi-electrode array (MEAs) also provide the basis for applying a system specific model to control firing of cells via application of electrical stimulation (Opris et al. 2012c; Hampson

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et al. 2012) to the same loci in which columnar firing has been detected and analyzed with respect to DMS task performance (Opris et al. 2012c; Hampson et al. 2012). This same model was implemented to test whether it could facilitate performance on trials that show a distinctive difference in correct performance (Hampson et al. 2012) as a function of the prior instructions as to type of response to make in the Match phase (i.e. Object *vs.* Spatial trials). Figure 10.4 shows the integration of a multi-input multi-output (MIMO) nonlinear math model to assess the patterns of firing in L2/3 and L5 cells recorded in the columnar manner with the MEA shown with adjacent vertical pads (Opris et al. 2011, 2012b; Hampson et al. 2012). Figure 10.4b reflects the type of input and output firing patterns recorded and analyzed by the MIMO model and also illustrates how the output pattern of L5 cell firing is duplicated via a multichannel stimulator that is capable of delivering predetermined patterns of pulses to the same L5 pads to mimic firing on correct trials. The advantage of the MIMO model is that the online recording provides the means to detect when the inappropriate L2/3 firing pattern occurs which triggers the delivery of the appropriate L5 stimulation pattern providing the means to override errors and enhance performance (Hampson et al. 2012). Stimulation consisted of 1.0 ms bipolar pulses (20–50 μA) delivered to L5 recording locations following presentation of the Match phase screen and prior to the completion of the Match Response.

The results of microstimulation delivery are shown in Fig. 10.4c, d, in which the effects on performance are compared to trials in which stimulation was not delivered, respective of trial type. Figure 10.4c compares the change in % correct performance as a function of processing time (reaction time + movement time) on stimulation (Stim) trials with respect to the no stimulation (No stim) case. Figure 10.4d showed for the first time the increase in correct performance on trials as a function of the number of distracter images in the Match phase. The results indicate that MIMO derived stimulation induces enhanced cognitive processing (Opris et al. 2012c, 2013; Hampson et al. 2012) required to retrieve the "rule for successful selection" of the appropriate item. The distribution of microstimulation induced spatial bias (Fig. 10.4e) will be shown in Fig. 10.5 of the next section.

10.6 Prefrontal Microcircuits Bind Perception to Executive Control

A broad range of brain functions, from perceptual to executive actions encode, represent, monitor and select information that is either spatial- and/or object-specific for effective behavioral performance (Quintana and Fuster 1999; Goldman-Rakic 1996; Posner and Snyder 1975; Shallice and Burgess 1996; Botvinick et al. 1999; Selemon and Goldman-Rakic 1988; Opris and Bruce 2005). Such constellations of brain abilities use large scale neural circuits consisting of thalamo-cortical loops and cortical microcircuits with functional roles in the integration, representation and selection of information (Fuster and

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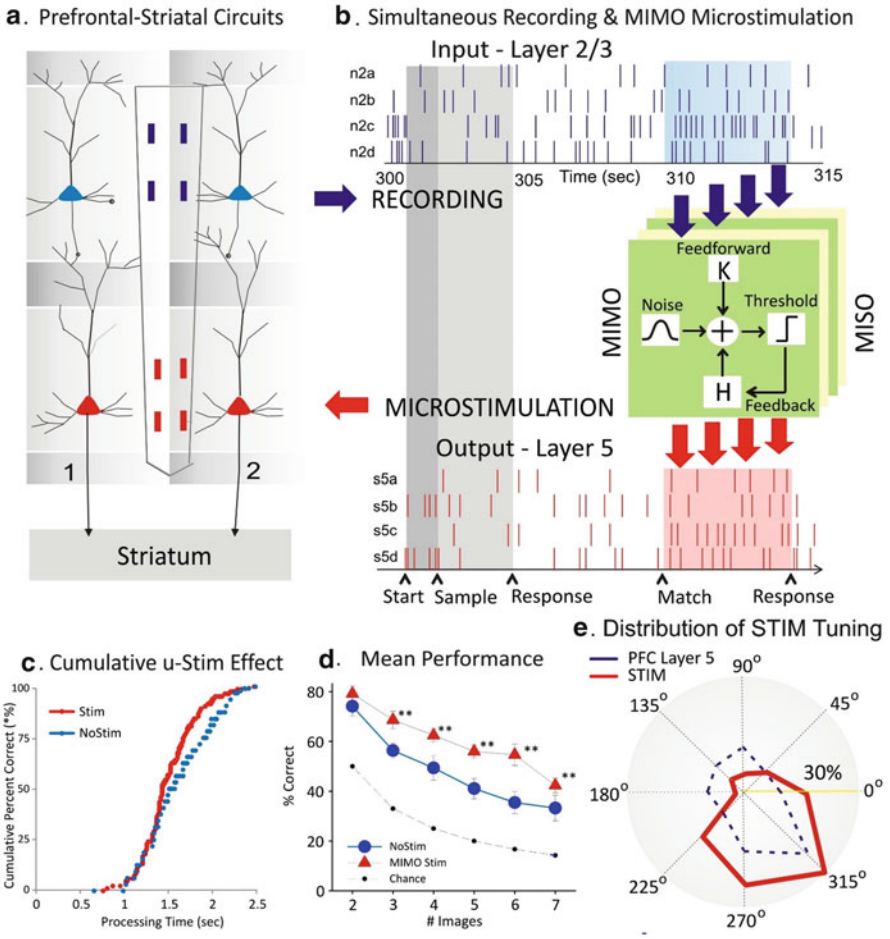

Fig. 10.4 Manipulation of executive control in PFC microcircuits. (**a**) Prefrontal striatal neuronal circuits. (**b**) Simultaneous recording and MIMO model microstimulation. (**c**) Cumulative microstimulation effect neuronal circuits. (**d**) Population mean performance as a function of the number of images in the task. (**e**) Distribution of stimulation induced tuning vectors

Bressler 2012; Alexander et al. 1986; Opris et al. 2011). Cortical microcircuits topographically connected by cortico-cortical and subcortical connections into a super network subserves the 'perception-to-action' cycle – an ensemble of processes that sense/perceive the environmental stimuli and convert them into actions (Fuster and Bressler 2012; Romo et al. 2002).

As previously shown the dorsal visual stream from the striate cortex to the posterior parietal region carries the spatial information (Fig. 10.5a) required for sensorimotor transformations in visually guided actions, while the ventral stream

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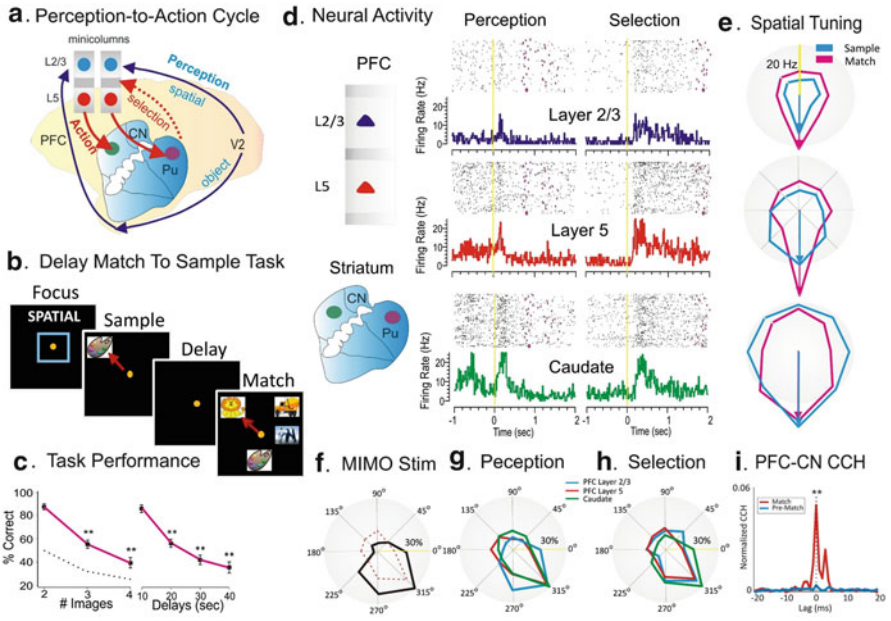

Fig. 10.5 Prefrontal cortical microcircuits and the perception to action cycle. (**a**) Perception to action cycle. (**b**) Behavioral DMS task. (**c**) Task performance as a function of the number of images and delays in the DMS task. (**d**) Neural activity in prefrontal cortical layers *L2/3*, *L5* and caudate during perception and selection. (**e**) Spatial tuning during the perception and selection phases of the task. (**f**) Distribution of MIMO stimulation induced tuning. (**g**) Distribution of neural tuning in prefrontal cortical layers *L2/3*, *L5* and caudate during perception. (**h**) Distribution of neural tuning in prefrontal cortical layers *L2/3*, *L5* and caudate during executive control/selection. (**i**) Population cross-correlation between prefrontal layers *L5* and caudate nucleus during match vs. pre-match phase. Compiled figure from Opris et al. 2013

projections from the striate cortex to the inferior temporal cortex is primarily responsible for perceptual identification of objects (Goodale and Milner 1992; Ungerleider and Mishkin 1982). Thus, a visual object's qualities and its spatial location depend on the processing of different types of visual information in the inferior temporal and posterior parietal cortex, respectively. However, object and spatial information carried in these two separate pathways has been shown to be integrated into a unified 'visual percept' in prefrontal cortex which receives connections from both circuits (Goodale and Milner 1992; Ungerleider and Mishkin 1982; Rao et al. 1997).

Basal ganglia participate in multiple parallel segregated circuits or 'thalamo-cortical loops' that make connections with motor, sensory and cognitive areas of the cerebral cortex (Alexander et al. 1986; Middleton and Strick 2002; Hoover and Strick 1993). Prefrontal cortical areas seem to be the target of extensive, topographically organized outputs from the basal ganglia (Middleton and Strick 2002). Such thalamo-cortical projections from basal ganglia to the superficial and deep prefrontal cortical layers can directly activate specific inputs to the re-entrant loop

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(McFarland and Haber 2002; Swadlow et al. 2002). Thus, the outputs from the inter-laminar microcircuits of prefrontal cortex are in ideal position to support the decision to act via the synchronous excitation of the constellation of circuits in the executive hierarchy (Quintana and Fuster 1999; Fuster and Bressler 2012).

Executive control is a fundamental function of the brain that mediates the integration of perception and action during behaviorally relevant environmental events. It has been proposed that executive control involves a broad network of brain areas, including frontal and parietal/temporal cortex, as well as striatum and other subcortical structures (Fuster and Bressler 2012). These structures have been consistently associated with roles in sensorimotor integration and selection of task specific behavioral responses, commonly considered to be the regions necessary for 'executive decisions' (Opris et al. 2012b, d). However, recent evidence has shown that these brain structures are part of functional loops in which inter-laminar microcircuits or 'minicolumns' in dorsolateral prefrontal cortex 'bind' perception and executive selection of spatial targets to guide goal-specific behavior.

To demonstrate this Opris et al. (2013) have trained nonhuman primates (rhesus monkeys) to perform a delayed match to sample (DMS) task with the instruction to select the remembered spatial location of the image on the screen, each presented in the Sample phase of the task (Fig. 10.5b). Subjects made hand tracking movements to the appropriate visual targets for rewards in the Match phase of the task (Fig. 10.5b). The DMS task incorporated key features like the number of distracter images (2–4) which could appear in any of eight locations on the screen in the Match phase after variable durations of the intervening delay period (1–40 s). These factors were reflected in the animal's behavioral performance levels during encoding and selection of spatial or object stimuli as shown in Fig. 10.5c.

Neurons were recorded simultaneously in PFC (in layer L2/3 and in layer L5) and in the striatum (caudate and putamen) while the animals performed the DMS task. Consistent with previous reports (Opris et al. 2012b, d) firing of cells in prefrontal layers and minicolumns reflected differential encoding of spatial location in the DMS task. Figure 10.5d shows raster and peri-event histograms of cells recorded in prefrontal cortical layers 2/3 and 5, together with cells recorded simultaneously in caudate/putamen. For each of these cells (Fig. 10.5d) firing patterns were compared during (a) encoding of sample target's location of sample presentation on the screen (Perception), and during: (b) selection of the spatial location of the sample image presentation on the screen (spatial trials), in the Match phase of the task (Selection). The polar plots in Fig. 10.5e show that neurons in layer 2/3 and 5 fired similarly with caudate neurons and were synchronized and spatially tuned to the same screen locations (black arrows). When compared during match phase presentation (Match Tuning) neural tuning directions for the 3 regions were again similar.

To further test whether inter-laminar firing links spatial perception to executive selection we applied a novel type of closed loop patterned MIMO stimulation previously shown to facilitate performance of the same task (Opris et al. 2012b; Hampson et al. 2012). This is shown in Fig. 10.4 as a functional diagram in which neural firing in PFC layer 2/3 was recorded with a multielectrode array (Opris

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et al. 2012b, d) and fed into a nonlinear multi-input–multi-output (MIMO) math model (Fig. 10.3a), which processed and simultaneously delivered a pattern of electrical pulses from a multi-channel stimulator that mimicked the correlated firing of PFC layer 5 cells on successful trials (Hampson et al. 2012). MIMO stimulation methods and associated control procedures proving columnar activation have been previously published in detail (Opris et al. 2012d; Hampson et al. 2012). These controls included delivery of stimulation pulse patterns that were different than what the MIMO model derived for correct trials. In this case the intensity and the number of pulses, plus the area (L5) that was stimulated were identical.

The effectiveness of MIMO stimulation delivered to this particular region of PFC is shown in Fig. 10.5f where the preference effect on stimulated (Stim) vs. nonstim trials is compared for all Spatial (n = 40 sessions) trials within the same session. The difference in mean % correct performance for all stim vs. nonstim trials (ALL) is shown in comparison to stim vs. nonstim trials in which performance at locations was significantly above that at all other locations (Facilitated; see also Opris et al. 2013). The marked difference in the degree of increase in % correct trials produced by MIMO stimulation at preferred vs. non-preferred (ALL) locations indicates that in addition to facilitating performance at all response locations, the stimulation enhanced the innate directional preference (spatial tuning) which corresponded to the anatomic location of the PFC layer 2/3 minicolumn. This demonstrated that the MIMO stimulation delivered during the match/selection phase of the task was likely to have facilitated discharge of Layer 5 neurons in the same recorded minicolumns and that is what improved spatial target selection in this phase of the task.

The unique feature of these experiments is that they allow us to tap into the perception-to-action cycle (Quintana and Fuster 1999). As a final validation of microcircuit tuning in PFC and caudate we compared polar firing across the same three nodes in the perception and selection phases on spatial trials in which MIMO stimulation induced increases in performance. Figure 10.5g, h shows nearly complete overlap (between 81 % and 91 %) in spatially tuned firing indicating that the majority of neural tuning vectors for the preferred microcircuit target location (315°) facilitated task performance when subjected to MIMO stimulation during spatial trials. The anatomic link between prefrontal cortex and striatum is demonstrated physiologically through normalized cross-correlations pairs of cells in PFC layer 5 and Caudate displaying synchronized firing during Match target presentation epoch (0, 2 s; red) compared to the pre-Match epoch (−2 s,0; blue). Therefore, such synchronized firing of PFC and Caudate neurons during the match phase (dealing with target selection and executive control; Fig. 10.5i) is telling us that these key nodes in the prefrontal cortical striatal loop show the modulation of executive control signals in the cortical-striatal executive loop (Alexander et al. 1986).

These novel findings demonstrate a robust involvement of cortical layers and striatum in the perception-to-action cycle (Quintana and Fuster 1999; Fuster and Bressler 2012). This is supported by implementation of the MIMO model which extracts the percept from prefrontal layer 2/3 and imparts the appropriate signal to

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columnar related layer 5 cells, thereby strengthening activation via the executive loop through the caudate nucleus (shown in Fig. 10.4a) to manifest selection of a particular target location. Given these findings, the functional specificity of the perceptual circuit is likely determined via "tuned" inter-laminar microcircuits connected to executive prefrontal cortico-striatal, thalamo-cortical loops, that are translated into action via "cognits" that coordinate information in large scale networks (Fuster and Bressler 2012; Alexander et al. 1986; Fuster 2007).

The enhancement in cognitive performance by the MIMO stimulation may be explained by induced changes in the balance between excitation and inhibition in cortical-striatal loop (Hampson et al. 2012; Opris et al. 2005) and by the temporal specificity of the PFC layered L2/3-L5 firing pattern (Hampson et al. 2012), since stimulation in a "scrambled" (random) pattern with the same pulses impaired performance in prior studies (Opris et al. 2012d; Hampson et al. 2012). The microstimulation current activates the neighboring minicolumns around the microelectrode pad/tip causing the preference of this group of minicolumns to win the competition for the behavioral output (Opris et al. 2005). Therefore, these results clearly indicate the need for inter-laminar microcircuits to bind perception and action.

10.7 Implications for a Modular Approach to Neuroscience

Recent developments in nanotechnological tools and in the design and synthesis of nano-materials have generated optical, electrical, and chemical methods that can be adapted for use in neuroscience. Nanotechnology was instrumental to nanofabricated planar electrode arrays for high-density neuronal voltage recording (Du et al. 2011; Suyatin et al. 2009). Nanofabrication technology raises the prospect for creating vastly greater numbers of electrodes and smaller, less invasive implantable devices. Among the promising tools for the study of brain microcircuits is the planar electrode array (Viventi et al. 2011; Alivisatos et al. 2013), which can be patterned on a crystalline, ceramic, or polymer support structure. The recording of neuronal activity with three-dimensional (3D) microelectrode arrays (Zorzos et al. 2012) represents a major advance in brain activity mapping techniques, by providing a tool to probe how intra and inter-laminar/regional neural circuits cooperate to process information. In the next decade or so, the modular approach to neuroscience research will gain an unprecedented momentum.

One reason would be the building of prosthetic minicolumns as basic modules to repair the damaged cortical tissue. Microcircuit-based approaches could be implemented in various cortical areas for building cognitive prosthetics (Berger et al. 2011) in order to reverse cognitive deficits in a broad spectrum of diseases like schizophrenia (Dobbs 2010; Casanova 2007), dementia (Chance et al. 2006, 2008, 2011; Di Rosa et al. 2009), autism (Casanova 2012; Casanova et al. 2002a, b, 2003a, 2006a, b, 2010, 2012, 2013; Sokhadze et al. 2010, 2012), ADHD (Brennan and Arnsten 2008), addiction (Tomasi et al. 2010), aging (Wang et al. 2011;

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Opris et al. 2009) and executive dysfunction (Duncan et al. 1997; Shallice and Burgess 1991) in which inter-laminar processing is likely disrupted due to cortical tissue damage or malfunction (Opris et al. 2012a, d; Casanova et al. 2003a; Duncan et al. 1997; Shallice and Burgess 1991). Therefore, a better understanding of the function of inter-laminar microcircuits across the neocortex is needed to develop treatments for neurological disorders, as well as to develop methods for brain augmentation.

10.8 Conclusion

In summary, these concepts provide support for modular approaches to executive brain functions in key nodes of the prefrontal loop (including PFC layer 2/3, layer 5 and caudate nucleus), as well as causal relationships involving the inter-laminar microcircuits across neocortex. These findings suggest that prefrontal inter-laminar microcircuits play a causal role in linking perception to the executive selection of spatial targets to spatial locations to which such microcircuitry has been tuned via past experience. The fact that activation of an innate PFC minicolumnar bias (shown via MIMO model-controlled stimulation) resulted in improved performance provides the real support for extending the modular approach across many areas/regions of the brain. This modular approach provides an important basis for building cognitive prosthetics (Berger et al. 2011) in order to reverse cognitive deficits in a broad spectrum of diseases.

References

Alexander GE, DeLong ME, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381

Alivisatos AP, Andrews AM, Boyden ES, Chun M, Church GM, Deisseroth K, Donoghue JP, Fraser SE, Lippincott-Schwartz J, Looger LL, Masmanidis S, McEuen PL, Nurmikko AV, Park H, Peterka DS, Reid C, Roukes ML, Scherer A, Schnitzer M, Sejnowski TJ, Shepard KL, Tsao D, Turrigiano G, Weiss PS, Xu C, Yuste R, Zhuang X (2013) Nanotools for neuroscience and brain activity mapping. ACS Nano 7:1850–1866

Atencio CA, Schreiner CE (2010) Columnar connectivity and laminar processing in cat primary auditory cortex. PLoS One 5(3), e9521

Jones EG (2000) Microcolumns in the cerebral cortex. A historical overview of the concept of micro- or minicolumns. Proc Natl Acad Sci U S A 97(10):5019–5021

Barbas H, Hilgetag CC, Saha S, Dermon CR, Suski JL (2005) Parallel organization of contralateral and ipsilateral prefrontal cortical projections in the rhesus monkey. BMC Neurosci 6:32

Bastos AM et al (2012) Canonical microcircuits for predictive coding. Neuron 76:695–711

Berger TW et al (2011) A cortical neural prosthesis for restoring and enhancing memory. J Neural Eng 8(4):046017

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999) Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402(6758):179–181

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Brennan AR, Arnsten AF (2008) Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann N Y Acad Sci 1129:236–245
Buffalo EA, Fries P, Landmanc R, Buschman TJ, Desimone R (2011) Laminar differences in gamma and alpha coherence in the ventral stream. Proc Natl Acad Sci U S A 108:11262–11267
Bugbee NM, Goldman-Rakic PS (1983) Columnar organization of corticocortical projections in squirrel and rhesus monkeys: similarity of column width in species differing in cortical volume. J Comp Neurol 220:355–364
Buschman TJ, Denovellis EL, Diogo C, Bullock D, Miller EK (2012) Synchronous oscillatory neural ensembles for rules in the prefrontal cortex. Neuron 76(4):838–846
Buxhoeveden DP, Casanova MF (2002) The minicolumn hypothesis in neuroscience. Brain 125 (5):935–951
Buxhoeveden D, Fobbs A, Roy E, Casanova MF (2002) Quantitative comparison of radial cell columns in children with Down syndrome and controls. J Intellect Disabil Res 46(1):76–81
Casanova MF (2005) An apologia for a paradigm shift in neurosciences. In: Casanova MF (ed) Neocortical modularity and the cell minicolumn. Nova Biomedical Publishers, New York, pp 33–55
Casanova MF (2007) Schizophrenia seen as a deficit in the modulation of cortical minicolumns by monoaminergic systems. Int Rev Psychiatry 19(4):361–372
Casanova MF (2008) The significance of minicolumnar size variability in autism: a perspective from comparative anatomy (ch. 16). In: Zimmerman A (ed) Autism current theories and evidence. Current clinical neurology. The Humana Press, Totowa, pp 349–360
Casanova MF (2012) The minicolunopathy of autism. In: Buxbaum JD, Hof PR (eds) The neuroscience of autism spectrum disorder. Academic, Amsterdam, pp 327–334
Casanova MF, Buxhoeveden DP, Switala AE, Roy E (2002a) Minicolumnar pathology in autism. Neurology 58:428–432
Casanova MF, Buxhoeveden DP, Switala AE, Roy E (2002b) Neuronal density and architecture (gray level index) in the brains of autistic patients. J Child Neurol 17(7):515–521
Casanova MF, Buxhoeveden D, Gomez J (2003a) Disruption in the inhibitory architecture of the cell minicolumn: implications for autism. Neuroscientist 9(6):496–507
Casanova MF, Buxhoeveden D, Switala A, Roy E (2003b) Rett syndrome as a minicolumnopathy. Clin Neuropathol 22:163–168
Casanova MF, van Kooten I, Switala AE, van Engeland H, Heinsen H, Steinbusch HWM, Hof PR, Trippe J, Stone J, Schmitz C (2006a) Minicolumnar abnormalities in autism. Acta Neuropathol 112(3):287–303
Casanova MF, van Kooten I, Switala AE, van Engeland H, Heinsen H, Steinbusch HWM, Hof PR, Schmitz C (2006b) Abnormalities of cortical minicolumnar organization in the prefrontal lobes of autistic patients. Clin Neurosci Res 6(3):127–133
Casanova MF, Trippe JT II, Switala AE (2007) A temporal continuity to the vertical organization of the human neocortex. Cereb Cortex 17(1):130–137
Casanova MF et al (2008) Neuronal distribution in the neocortex of schizophrenic patients. Psychiatry Res 158(3):267–277
Casanova MF, El-Baz A, Vanbogaert E, Narahari P, Switala A (2010) A topographic study of minicolumnar core width by lamina comparison between autistic subjects and controls: possible minicolumnar disruption due to an anatomical element in-common to multiple laminae. Brain Pathol 20:451–458
Casanova MF, El-Baz A, Switala AE (2011) Laws of conservation as related to brain growth, aging, and evolution: symmetry of the minicolumn. Front Neuroanat 5:66
Casanova MF, Baruth JM, El-Baz A, Tasman A, Sears L, Sokhadze EM (2012) Repetitive TMS (rTMS) modulates ERP indices of attention in autism. Transl Neurosci 3(2):170–180
Casanova MF, El-Baz A, Kamat SS, Dombroski BA, Khalifa F, Elnakib A, Soliman A, Allison-McNutt A, Andrew AE (2013) Focal cortical dysplasias in autism spectrum disorders. Acta Neuropathol Commun 1:67. doi:10.1186/2051-5960-1-67

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Chance SA, Casanova MF, Switala AE, Crow TJ, Esiri MM (2006) Minicolumn thinning in temporal lobe association cortex but not primary auditory cortex in normal human ageing. Acta Neuropathol 111(5):459–464
Chance SA, Casanova MF, Switala AE, Crow TJ (2008) Auditory cortex asymmetry, altered minicolumn spacing and absence of ageing effects in schizophrenia. Brain 131:3178–3192
Chance SA, Clover L, Cousijn H, Currah L, Pettingill R, Esiri MM (2011) Microanatomical correlates of cognitive ability and decline: normal ageing, MCI, and Alzheimer's disease. Cereb Cortex 21(8):1870–1878
Constantinople CM, Bruno RM (2013) Deep cortical layers are activated directly from thalamus. Science 340(6140):1591–1594
Das A, Gilbert CD (1995) Long-range horizontal connections and their role in cortical reorganization revealed by optical recording of cat primary visual cortex. Nature 375(6534):780–784
DeFelipe J, Markram H, Rockland KS (2012) The neocortical column. Front Neuroanat 6:22
Di Rosa E, Crow TJ, Walker MA, Black G, Chance SA (2009) Reduced neuron density, enlarged minicolumn spacing and altered ageing effects in fusiform cortex in schizophrenia. Psychiatry Res 166(2–3):102–115
Dobbs D (2010) Schizophrenia: the making of a troubled mind. Nature 468:154–156
Duncan J, Johnson R, Swales M, Freer C (1997) Frontal lobe deficits after head injury: unity and diversity of function. Cognit Neuropsychol 14:713–741
Du J, Blanche TJ, Harrison RR, Lester HA, Masmanidis S (2011) Multiplexed, high density electrophysiology with nanofabricated neural probes. PLoS One 6(10), e26204
Favorov OV, Diamond ME (1990) Demonstration of discrete place-defined columns-segregates-in the cat SI. J Comp Neurol 298:97–112
Favorov OV, Diamond ME, Whitsel BL (1987) Evidence for a mosaic representation of the body surface in area 3b of the somatic cortex of cat. Proc Natl Acad Sci U S A 84(18):6606–6610
Funahashi S, Bruce CJ, Goldman-Rakic PS (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol 61(2):331–349
Fuster JM (2001) The prefrontal cortex–an update: time is of the essence. Neuron 30:319–333
Fuster JM (2007) Jackson and the frontal executive hierarchy. Int J Psychophysiol 64:106–107
Fuster JM, Bressler SL (2012) Cognit activation: a mechanism enabling temporal integration in working memory. Trends Cogn Sci 16(4):207–218
Gilbert CD, Wiesel TN (1989) Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. J Neurosci 9:2432–2442
Goldman-Rakic PS (1996) The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philos Trans R Soc Lond B Biol Sci 351:1445–1453
Goodale MA, Milner AD (1992) Separate visual pathways for perception and action. Trends Neurosci 15(1):20–25
Hampson RE, Coates TD Jr, Gerhardt G,A, Deadwyler SA (2004) Ceramic-based micro-electrode neuronal recordings in the rat and monkey. Proc Annu Int Conf IEEE Eng Med Biol Soc (EMBS) 25:3700–3703
Hampson RE, Gerhardt GA, Marmarelis V, Song D, Opris I, Santos L, Berger TW, Deadwyler SA (2012) Facilitation and restoration of cognitive function in primate prefrontal cortex by a neuroprosthesis that utilizes minicolumn-specific neural firing. J Neural Eng 9(5):056012
Hansen BJ, Chelaru MI, Dragoi V (2012) Correlated variability in laminar cortical circuits. Neuron 76(3):590–602. doi:10.1016/j.neuron.2012.08.029
Hirabayashi T, Takeuchi D, Tamura K, Miyashita Y (2013a) Microcircuits for hierarchical elaboration of object coding across primate temporal areas. Science 341(6142):191–195
Hirabayashi T, Takeuchi D, Tamura K, Miyashita Y (2013b) Functional microcircuit recruited during retrieval of object association memory in monkey perirhinal cortex. Neuron 77(1):192–203
Hirata Y, Sawaguchi T (2008) Functional columns in the primate prefrontal cortex revealed by optical imaging in vitro. Neurosci Res 61(1):1–10

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Hoover JE, Strick PL (1993) Multiple output channels in the basal ganglia. Science 259 (5096):819–821
Horton JC, Adams DL (2005) The cortical column: a structure without a function. Philos Trans R Soc Lond B Biol Sci 360(1456):837–862
Hubel DH (1982) Cortical neurobiology: a slanted historical perspective. Annu Rev Neurosci 5:363–370
Hubel DH, Wiesel TN (1969) Anatomical demonstration of columns in the monkey striate cortex. Nature 221:747–750
Hubel DH, Wiesel TN (1974) Sequence regularity and geometry of orientation columns in the monkey striate cortex. J Comp Neurol 158(3):267–293
Jones EG (2000) Microcolumns in the cerebral cortex. A historical overview of the concept of micro- or minicolumns. Proc Natl Acad Sci U S A 97(10):5019–5021
Jones EG, Rakic P (2010) Radial columns in cortical architecture: it is the composition that counts. Cereb Cortex 20(10):2261–2264
Kaas JH (2012) Evolution of columns, modules, and domains in the neocortex of primates. Proc Natl Acad Sci U S A 109(Suppl 1):10655–10660
Katz LC, Gilbert CD, Wiesel TN (1989) Local circuits and ocular dominance columns in monkey striate cortex. J Neurosci 9:1389–1399
Kritzer MF, Goldman-Rakic PS (1995) Intrinsic circuit organization of the major layers and sublayers of the dorsolateral prefrontal cortex in the rhesus monkey. J Comp Neurol 359:131–143
Leise EM (1990) Modular construction of nervous systems: a basic principle of design for invertebrates and vertebrates. Brain Res Brain Res Rev 15(1):1–23
Mahan MY, Georgopoulos AP (2013) Motor directional tuning across brain areas: directional resonance and the role of inhibition for directional accuracy. Front Neural Circ 7:92. doi:10.3389/fncir.2013.00092
McCulloch WS (1959) Agatha Tyche of nervous nets – the lucky reckoners. In: McCulloch WS (ed) Embodiments of mind. MIT Press, Cambridge, 1965, pp 203–215 (Reprint of: National Physical Laboratory. Mechanisation of thought processes. London: H.M. Stationery Office, pp 611–625)
McFarland NR, Haber SN (2002) Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. J Neurosci 22 (18):8117–8132
Middleton FA, Strick PLB-g (2002) Projections to the prefrontal cortex of the primate. Cereb Cortex 12(9):926–935
Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202
Mo J, Schroeder CE, Ding M (2011) Attentional modulation of alpha oscillations in macaque inferotemporal cortex. J Neurosci 31(3):878–882
Mountcastle VB (1957) Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 20:408–434
Mountcastle VB (1978) An organizing principle for cerebral function: the unit module and the distributed system. In: Edelman GM, Mountcastle VB (eds) The mindful brain. MIT Press, Cambridge, MA, pp 7–50
Mountcastle VB (1997) The columnar organization of the neocortex. A comprehensive review of the literature indicating the modular architecture of the cortex. Brain 120(4):701–722
Mountcastle VB (1998) Perceptual neuroscience. The cerebral cortex. Harvard University Press, Cambridge
Mountcastle VB (2003) Introduction. Cereb Cortex 13:2–4
Mountcastle VB, Berman A, Davies P (1955) Topographic organization and modality representation in the first somatic area of cat's cerebral cortex by method of single unit analysis. Am J Physiol 183:464

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Mountcastle VB, Berman AL, Davies P (1957) Response properties of neurons of cats' somatic sensory cortex to peripheral stimuli. J Neurophysiol 20(4):374–407
Moxon KA, Leiser SC, Gerhardt GA, Barbee KA, Chapin JK (2004) Ceramic-based multisite electrode arrays for chronic single-neuron recording. IEEE Trans Biomed Eng 51:647–656
Naya Y, Suzuki WA (2011) Integrating what and when across the primate medial temporal lobe. Science 333:773–776
Opris I, Bruce CJ (2005) Neural circuitry of judgment and decision mechanisms. Brain Res Rev 48:509–526
Opris I, Barborica A, Ferrera VP (2001) A gap effect during microstimulation in the prefrontal cortex of monkeys. Exp Brain Res 138:1–7
Opris I, Barborica A, Ferrera VP (2005) Microstimulation of dorsolateral prefrontal cortex biases saccade target selection. J Cogn Neurosci 17(6):893–904
Opris I, Hampson RE, Deadwyler SA (2009) The encoding of cocaine vs. natural rewards in the striatum of nonhuman primates: categories with different activations. Neuroscience 163 (1):40–54
Opris I, Hampson RE, Stanford TR, Gerhardt GA, Deadwyler SA (2011) Neural activity in frontal cortical cell layers: evidence for columnar sensorimotor processing. J Cogn Neurosci 23 (6):1507–1521
Opris I, Santos LM, Song D, Gerhardt GA, Berger TW, Hampson RE, Deadwyler SA (2012a) Prefrontal cortical microcircuits bind perception to executive control. Sci Rep 2013 3:2285
Opris I, Hampson RE, Gerhardt GA, Berger TW, Deadwyler SA (2012b) Columnar processing in primate pFC: evidence for executive control microcircuits. J Cogn Neurosci 24(12):2334–2347
Opris I, Fuqua JL, Huettl PF, Gerhardt GA, Berger TW, Hampson RE, Deadwyler SA (2012c) Closing the loop in primate prefrontal cortex: inter-laminar processing. Front Neural Circuits 6:88
Opris I et al (2012d) Closing the loop in primate prefrontal cortex: inter-laminar processing. Front Neurosci 6
Opris I, Santos L, Gerhardt GA et al (2013) Prefrontal cortical microcircuits bind perception to executive control. Sci Rep 3:2285. doi:10.1038/srep02285
Posner M, Snyder C (1975) Attention and cognitive control. In: Solso R (ed) Information processing and cognition: the Loyola symposium. Lawrence Erlbaum, Hillsdale
Quintana J, Fuster JM (1999) From perception to action: temporal integrative functions of prefrontal and parietal neurons. Cereb Cortex 9:213–221
Raghanti MA, Spocter MA, Butti C, Hof PR, Sherwood CC (2010) A comparative perspective on minicolumns and inhibitory GABAergic interneurons in the neocortex. Front Neuroanat 4:3
Rakic P (1988) Specification of cerebral cortical areas. Science 241(4862):170–176
Rakic P (2008) Confusing cortical columns. Proc Natl Acad Sci U S A 105(34):12099–12100
Rao SC, Rainer G, Miller EK (1997) Integration of what and where in the primate prefrontal cortex. Science 276:821–824
Rao SG, Williams GV, Goldman-Rakic PS (1999) Isodirectional tuning of adjacent interneurons and pyramidal cells during working memory: evidence for microcolumnar organization in PFC. J Neurophysiol 81:1903–1916
Ratcliff R, Cherian A, Segraves M (2003) A comparison of macaque behavior and superior colliculus neuronal activity to predictions from models of two-choice decisions. J Neurophysiol 90(3):1392–1407
Rinkus GJ (2010) A cortical sparse distributed coding model linking mini- and macrocolumn-scale functionality. Front Neuroanat 4:17
Romo R, Hernández A, Zainos A, Lemus L, Brody CD (2002) Neuronal correlates of decision-making in secondary somatosensory cortex. Nat Neurosci 5(11):1217–1225
Salinas E (2004) Fast remapping of sensory stimuli onto motor actions on the basis of contextual modulation. J Neurosci 24(5):1113–1118

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Selemon LD, Goldman-Rakic PS (1988) Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J Neurosci 8:4049–4068
Shallice T, Burgess PW (1991) Deficits in strategy application following frontal lobe damage in man. Brain 114(2):727–741
Shallice T, Burgess P (1996) The domain of supervisory processes and temporal organization of behaviour. Philos Trans R Soc Lond B Biol Sci 351:1405–1411
Shepherd G, Grillner S (2010) Handbook of brain microcircuits. Oxford University Press, New York
Sokhadze E et al (2010) Impaired error monitoring and correction function in autism. J Neurother 14:79–95
Sokhadze E et al (2012) Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. Appl Psychophysiol Biofeedback 37:91–102
Suyatin DB, Hallstram W, Samuelson L, Montelius L, Prinz CN, Kanje M (2009) Gallium phosphide nanowire arrays and their possible application in cellular force investigations. J Vac Sci Technol B 27:3092–3094
Swadlow HA, Gusev AG, Bezdudnaya T (2002) Activation of a cortical column by a thalamocortical impulse. J Neurosci 22:7766–7773
Swindale NV (1998) Cortical organization: modules, polymaps and mosaics. Curr Biol 8:R270–R273
Swindale NV, Shoham D, Grinvald A, Bonhoeffer T, Hübener M (2000) Visual cortex maps are optimized for uniform coverage. Nat Neurosci 3:822–826
Szentágothai J, Arbib MA (1975) Conceptual models of neural organization. MIT Press, Cambridge, MA
Takeuchi D, Hirabayashi T, Tamura K, Miyashita Y (2011) Reversal of interlaminar signal between sensory and memory processing in monkey temporal cortex. Science 331:1443–1447
Thomson AM, Bannister AP (2003) Interlaminar connections in the neocortex. Cereb Cortex 13(1):5–14
Tomasi D, Volkow ND et al (2010) Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers. PLoS One 5:e10815
Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW (eds) Analysis of visual behavior. MIT, Cambridge, MA, pp 549–586
Van Essen DC, Newsome WT, Bixby JL (1982) The pattern of interhemispheric connections and its relationship to extrastriate visual areas in the macaque monkey. J Neurosci 2(3):265–283
Viventi J, Kim D-H, Vigeland L, Frechette ES, Blanco JA, Kim Y-S, Avrin AE, Tiruvadi VR, Hwang S-W, Vanleer AC, Wulsin DF, Davis K, Gelber CE, Palmer L, Van der Spiegel J, Wu J, Xiao J, Huang Y, Contreras D, Rogers JA, Litt B (2011) Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. Nat Neurosci 14:1599–1605
Wang XJ (2012) Neural dynamics and circuit mechanisms of decision-making. Curr Opin Neurobiol 22(6):1039–1046
Wang M et al (2011) Neuronal basis of age-related working memory decline. Nature 476:210–213
Weiler N, Wood L, Yu J, Solla SA, Shepherd GM (2008) Top-down laminar organization of the excitatory network in motor cortex. Nat Neurosci 11:360–366
Wiesel TN, Hubel DH (1974) Ordered arrangement of orientation columns in monkeys lacking visual experience. J Comp Neurol 158(3):307–318
Wilson FA, O'Scalaidhe SP, Goldman-Rakic PS (1993) Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 260:1955–1958
Zhang M, Alloway KD (2006) Intercolumnar synchronization of neuronal activity in rat barrel cortex during patterned airjet stimulation: a laminar analysis. Exp Brain Res 169(3):311–325
Zorzos AN, Scholvin J, Boyden ES, Fonstad CG (2012) Three-dimensional multiwaveguide probe array for light delivery to distributed brain circuits. Opt Lett 37:4841–4843

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