Chapter 8

Minicolumnar Patterns in the Global Cortical Response to Sensory Stimulation

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Introduction

In 1978 Mountcastle [1] hypothesized that the smallest functional unit of neocortical organization (the “minicolumn”) is a radial cord of cells about 30–50 µm in diameter, and that sensory stimuli activate local groupings of minicolumns (called “macrocolumns”). This hypothesis subsequently received support from multiple lines of experimental evidence, leading to its substantial elaboration.

Structurally, minicolumns are attributable to the radially-oriented cords of neuronal cell bodies evident in Nissl-stained sections of cerebral cortex. It is likely that they also are related to ontogenetic columns [2] and to the radially-oriented modules defined by the clustering of the apical dendrites of pyramidal neurons [3]. Among the various elements of neocortical microarchitecture, spiny-stellate cells and double-bouquet cells [4–6] are most directly relevant to Mountcastle’s concept of the minicolumn. Spiny-stellates are excitatory intrinsic cells that are especially prominent in layer 4 of primary sensory cortex. They are the

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major recipients of thalamocortical connections and, in turn, they (especially the star pyramid subclass of spiny-stellates) distribute afferent input radially to cells in other layers. Double-bouquet cells are GABAergic cells whose somas and dendritic trees are confined to the superficial layers. The axons of double-bouquet cells descend in tight 50 µm diameter bundles across layers 3 and 4 and into layer 5, making synapses along the way on the distal dendrites of pyramidal and spiny-stellate cells, but avoiding the main shaft of apical dendrites [4,5,7,8]. Because the double-bouquet cells are more likely to inhibit cells in adjacent minicolumns rather than in their own, they offer a mechanism by which a minicolumn can inhibit its immediate neighbors.

Overall, the detailed features of primary sensory cortical microarchitecture are clearly suggestive of a **structural** substrate for the minicolumns hypothesized by Mountcastle. But it remains unproven that these structurally-defined units act as **functional** entities—that is, that there is a minicolumnar dimension to primary sensory cortical information processing and representation. In this paper we review some of the experimental evidence that supports the proposal that primary sensory cortical information processing and representation exhibits a minicolumnar nature, and consider the possible functional utility of this dimension of the primary sensory cortical response to natural stimulation of peripheral receptors.

**Minicolumnar Receptive Field Organization**

Receptive field (RF) mapping studies carried out in primary somatosensory cortex (SI) of cats and monkeys obtained experimental evidence that strongly supports Mountcastle’s minicolumnar hypothesis [9,10]. These studies found that the receptive fields (RFs) of neurons within fine (~50 µm in diameter) radial cords are very similar in size, shape, and position on the skin. In contrast, the same studies found that neurons located in adjacent minicolumns typically have RFs that differ significantly in size and shape, and frequently overlap only minimally on the skin (on average, RFs of neurons in adjacent minicolumns overlap by only 22% in cat, and 28% in macaque monkey). Comparable results have been reported in the primary auditory and visual cortical areas of cat and monkey [11–13]. These findings are schematically summarized in Figure 1.
RF similarity as a function of the tangential distance separating neurons in primary sensory cortex. The plots show that neurons that are near neighbors in the tangential plane of the cortex have very similar RF properties, and that similarity declines with increasing distance. The decline in RF similarity with increasing tangential separation has two distinct phases: In the first phase, at separations less than 50 µm, average RF similarity declines very quickly with distance; in the second phase, at separations greater than 50 µm the rate of decline is much slower. In contrast, neurons with very similar RFs are found at much greater separations in the radial dimension of sensory cortex—a finding that suggests the presence of radially-oriented strands of cells, <50 µm in diameter, within each there is relatively limited RF diversity (see refs. 9 and 10 for in-depth discussion). (A) Ordinate indicates the average degree of RF overlap of pairs of neurons in somatosensory cortex (reproduced, with modifications, from Favorov and Whitsett [9]). (B) Ordinate indicates the ratio of optimal stimulus frequencies of pairs of cells in auditory cortex (higher frequency/lower frequency; reproduced with permission from Abeles and Goldstein [11]). (C) The ordinate is the frequency of encountering 2 visual cortical neurons with optimal stimulus orientations differing by less than 7.5° (reproduced, with modifications, from Albus [13]).

Most of the experimental literature that has addressed the topographical organization within the primary somatosensory, visual, auditory, and motor cortical areas (and association cortex as well) at high resolution shows that while neighboring neurons exhibit a remarkable uniformity from the standpoint of some RF property (e.g., stimulus orientation in visual cortex), they tend to differ prominently in other properties (for review see ref. [14]). In fact, when sensory cortical neuron RF dimensions are considered in toto, neighboring neurons typically have little in common—that is, a stimulus optimal for one cell frequently activates its neighbor much less effectively. The studies reviewed above [9–13,15] suggest, however, that this prominent diversity in the receptive field properties of neurons located in the same locale in sensory cortex is constrained substantially in the radial dimension—that is, cells that occupy the same radially-oriented minicolumn have very similar RF properties. In other words, the tendency for the RF properties among neighboring sensory cortical neurons to be different is mainly attributable to the diverse RF properties of neurons that occupy neighboring minicolumns. Figure 2 illustrates the minicolumnar organization of single
neuron RF properties that published studies have identified within cat and monkey primary sensory cortex.

Figure 2. Summary of minicolumnar RF organization in SI somatosensory cortex. Left: Drawing of cross-section of Nissl-stained cortical tissue showing darkly-stained cell bodies organized in radially oriented cords, interpreted as minicolumns. Filled circles labeled a–g—sequence of neurons located within a single minicolumn; 1–30—sequence of neurons located in series of adjacent minicolumns. Right: Sequences of RF centers (connected dots) mapped by neuron sequences a–g and 1–30. Note that RF centers for SI neurons that occupy the same minicolumn stay close together, whereas the RF centers for pairs of neurons located in neighboring minicolumns shift back and forth over large distances, and occupy totally non-overlapping skin regions when the pair of neurons occupies different SI macrocolumns. Based on Favorov and Whitsel [9], and Favorov and Diamond [10].

Model of Minicolumnar RF Formation

The predominance of radially-oriented intrinsic connectivity within cerebral cortex clearly predicts that cells lying in a particular minicolumn will have very similar RFs. But why are the RFs of neurons in adjacent minicolumns so different? Favorov and Kelly [16,17] suggested in a modeling study that during perinatal development minicolumns might actively drive their neighbors to establish afferent connections with different, only partially overlapping sets of thalamic neurons. This might be accomplished via the lateral inhibitory interactions among adjacent minicolumns expressed via the connectivity attributable to double-bouquet cells. In the model of Favorov and Kelly [16,17] (shown schematically in Figure 3) each minicolumn is driven during self-organization of the network by inhibitory interactions with adjacent minicolumns (mediated by double-bouquet cells) to acquire a set of afferent (thalamic) connections different from those of its immediate neighbors. On the other hand, each minicolumn also is driven by excitatory interactions with neurons in a larger circle
of neighboring minicolumns (mediated by spiny-stellate cells) to make its set of afferent connections similar to theirs. According to this model these opposing pressures are satisfied by the achievement (during early development) of a permuted arrangement of the minicolumns in the macrocolumn. To achieve this arrangement the RFs of adjacent minicolumns in the macrocolumn move farther apart, and at the same time the RFs of the entire macrocolumn are prevented from diverging too widely. In this way the model of Favorov and Kelly [16,17] generates complex patterns of RFs across the macrocolumn similar to those observed experimentally in microelectrode penetrations through SI cortex in adult subjects [10,16,17].

![Diagram of minicolumnar connections modified from Favorov and Kelly (16).](image)

**Figure 3.**
Pattern of minicolumnar connections (modified from Favorov and Kelly [16]). Shown is a section across an idealized cortical region, represented as a tightly packed field of cylinder-shaped minicolumns, each containing one representative spiny stellate, pyramidal, and double bouquet cells. Afferent, intra-minicolumnar, and local inter-minicolumnar connections are shown for one minicolumn.
In Vivo Stimulus-evoked Minicolumnar Activity Patterns

Because of the prominent differences in RF properties that exist among neighboring minicolumns in sensory cortex in adults, even the simplest sensory stimulus should evoke a spatially complex minicolumnar pattern of activity in the engaged cortical region—such a pattern consisting of a patchwork of active and inactive minicolumns [17]. This expectation is in accord with experimental observations obtained in high-resolution 2-deoxyglucose (2-DG) metabolic studies of mouse (barrel field) and monkey SI [18–20]. Those studies revealed not only that the distribution of stimulus-evoked 2-DG labeling in somatosensory cortex is modular on a macrocolumnar scale, but is highly non-uniform within such a macrocolumnar module. Analysis of the spatial distribution of activity within the characteristic column-shaped patches of 2-DG label evoked in primary somatosensory cortex by natural skin stimuli suggested that such patches are made up of groupings of highly active minicolumns interdigitated with less active minicolumns. The experimental evidence that led the authors to propose this concept is summarized in Figure 4.

More recently our laboratory has employed a very different imaging modality to continue our investigation of the response of primary somatosensory cortex at the minicolumnar level of resolution—in these studies we used near-infrared (830 nm) imaging of the optical intrinsic signal (OIS) evoked by mechanical stimulation of the skin [21,22]. The spatial resolution of this imaging method is fine enough to enable direct visualization of stimulus-evoked patterns of active/inactive minicolumns in local cortical territories viewed from above. An example of such a minicolumnar activity pattern within SI cortex of the cat is shown in Figure 5.
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Figure 4.
Minicolumnar pattern of stimulus-evoked activation in monkey SI cortex: Spatial frequency analysis of stimulus-evoked 2-DG labeling (modified from Tommerdahl et al. [20]). Discrete Fourier transforms were computed across linear, tangentially-oriented sectors of middle and upper cortical layers, and plotted as periodograms. Top-left: Average periodograms for optical density data sampled from Nissl-stained sections of SI cortex. Note that distribution of spatial frequencies is the same in the upper and middle layers, and that the radial striation of Nissl-stained sections is reflected by the prominent peak near the minicolumnar frequency of 20 cycles/mm. Top-right: Average periodograms of 2-DG labeling in an unstimulated region of SI. Note close similarity of periodograms for 2-DG labeling to those obtained from Nissl-stained sections: both demonstrate prominent minicolumnar periodicity of 20 cycles/mm. Bottom: Outline of a patch of above-background 2-DG labeling in a section through stimulus-activated SI region. Fourier transforms were computed across the two rectangular regions and plotted as periodograms on the right. Note that the periodogram of the middle layers is similar to those obtained from both the unstimulated region and the Nissl-stained sections, in that its peak is near to the minicolumnar frequency. In contrast, in the upper-layer periodogram the peak is prominently shifted to lower spatial frequencies, indicating that in the upper layers the activated SI column consists of interdigitated radial strands of elevated and near-background 2-DG labeling. This outcome suggests that neighboring minicolumns were differentially activated by the stimuli that were used.
Figure 5.
Minicolumnar pattern of activation in cat SI cortex: OIS imaging of the stimulus-evoked intrinsic signal (B & C) and modeling prediction (D). The response in B and C was evoked by 400 µm amplitude 25 Hz vibrotactile stimulation of the ulnar eminence on a contralateral foreleg. Image in B shows two activated cortical regions, the bottom one in area 3b, top one in area 3a. Upon closer inspection shown in C, each active region appears to consist of a patchwork of minicolumn-sized spots. Note that the spots tend to be organized in short parallel strings, and that orientation of the strings varies across the activated region. Image in D was generated by the minicolumnar model of Favorov and Kelly, [16,17] It shows a spatial pattern of active minicolumns, driven by a punctate stimulus. This model-generated pattern is similar to the one on the left in that minicolumns activated by the stimulus are also organized in short parallel strings which run in different directions in different parts of the pattern.
The optical intrinsic signal (OIS) is an activity-dependent change in the light scattering properties of neural tissue. Although both the OIS evoked in cortical tissue by natural stimulation and the OIS evoked in a cortical slice by electrical stimulation co-localize with stimulus-evoked neuronal activity, and increase in magnitude with increasing stimulus intensity, the OIS recorded \textit{in vivo} or \textit{in vitro} is primarily non-neuronal in origin. That is, the OIS mainly reflects the changes in the extracellular space and cell swelling attributable to glia and neurons. Specifically, repetitive activity in a neuronal population leads to a local excess of potassium and glutamate in the extracellular space that, after a brief delay, is restored to normal by the surrounding glia. The movement of potassium from the extracellular space into glial cells (via ion pumps, transporters and channels), is accompanied by glial uptake of water and swelling. The resultant decrease in extracellular space causes the stimulus-activated region in a brain slice to increase its light transmittance, and the stimulus-activated region in the cortex of an intact subject to undergo an increase in light absorbance. Since the glial swelling that results from uptake of the activity-related excesses in extracellular potassium and glutamate are highly correlated with the degree and spatial extent of neuronal activity, the change in light transmittance \textit{in vitro} can be used to characterize the spatial characteristics of the distributed response of the neocortical slice to controlled afferent drive, and the increase in absorbance observed \textit{in vivo} can be used to evaluate the spatially distributed response of the intact sensory cortex to natural skin stimulation.

\textit{In Vitro} Stimulus-evoked Minicolumnar Activity Patterns

Optical imaging has been used extensively to study the global patterns of response to natural tactile stimulation [21–24]. However, only a few studies have evaluated the minicolumnar patterns of activity evoked by skin stimulation (e.g., Figure 5). \textit{In vitro} studies of the sensory cortical response to controlled afferent drive at the minicolumnar level of resolution are also relatively rare, but the few studied of this type that have been carried out have provided observations that make it evident that the column-shaped SI response evoked by stimulation at layer VI/WM border is not spatially homogenous (Figure 6). Instead, spatial frequency analysis revealed that although all minicolumns are activated at the level of the cortex at which most direct thalamocortical afferents terminate (i.e., layer IV), at more superficial levels (in layers II-III) activated groupings of minicolumns in the responding macrocolumn are separated from one another by less active minicolumns [25].
Figure 6.
Measures of OIS minicolumnar SI activity patterns in vitro in rat somatosensory cortical slice preparation. (A) Image of column-shaped OIS evoked by a threshold pulse stimulus delivered to the layer VI/WM junction. (B) Evoked potential evoked from the same layer VI/WM locus by single pulse at same intensity. (C) Spatial intensity histogram obtained by averaging all pixel values sampled radially across middle layers. (D) Power spectrum of the spatial intensity histogram in C. Note a prominent peak at approximately minicolumnar frequency of 24 cycles/mm, or 42 µm period, as well as a second peak at ~8 cycles/mm. (E) Image of a Nissl-stained section from the same slice that yielded the OIS response in A. (F) Power spectrum of the distribution of optical densities in layer IV of the Nissl-stained section. Note the presence of a peak at the minicolumnar frequency, but not at the frequency of ~8 cycles/mm. This difference in power spectra of OIS and Nissl images suggests that the stimulus activated the cortical macrocolumn non-uniformly, preferentially driving on average every third minicolumn.
The above-described spatial variations in OIS intensity indicate the presence of a repeating radially-oriented structure within layer IV of the responding column with a center-to-center spacing equal to that of the cortical minicolumn. That these spatial variations correspond to activated minicolumns is supported by the observation that no change in spatial frequency occurred in the radial direction. More recently, we have investigated the patterns of SI minicolumnar activation detected under different stimulus conditions in vitro. Figure 7 exemplifies the influence of increasing stimulus intensity of electrical stimulation in the sensorimotor cortical slice on the spectral content of the stimulus evoked OIS.

![Figure 7](image)

**Figure 7.**
Stimulus intensity influences the pattern of minicolumnar activity within the responding SI macrocolumn. *A:* 3 OIS images obtained in response to 3 different intensities of stimulation (1×, 2×, and 3× threshold) delivered to the layer VI/WM junction. *B:* Left column: Power spectra of OIS activity across the columnar response evoked by stimuli of two different intensities (2× and 3× threshold). Right Column: Histograms showing spatial distribution of the response at each stimulus intensity. Note that at both stimulus intensities the spectrum contains two peaks—one at the minicolumnar frequency of 25 cycles/mm, or 40 µm period, the other at 13 cycles/mm, or 80 µm period. However, the relative powers of these two peaks change with stimulus intensity, with 13 cycles/mm frequency growing in power at stronger stimulus.
While prominent power is observed at the minicolumnar spatial frequency (~25 cycles/mm) when using relatively low intensities of layer VI/WM stimulation, a consistent leftward shift in the power spectrum occurs when higher intensities of stimulation are used. We interpret this enhanced low-frequency component at higher intensities of stimulation to be a result of increased local lateral interactions among minicolumns, resulting in significant numbers of minicolumns becoming inhibited, or “turned off,” by their neighbors.

We also have initiated an examination of the patterns of SI minicolumnar activity evoked by multi-site afferent drive more representative of the spatially distributed input patterns evoked in vivo by natural skin stimuli. Figure 8 demonstrates a method which provides detailed information about this more complex, but probably much more realistic pattern of afferent drive. Arrays consisting of 3–5 electrodes placed at the layer VI/WM junction were used to deliver input to the SI slice. In the example shown in Figure 8, the stimulus intensity in the central electrode was maintained at threshold while the intensity at the 2 electrodes positioned to either side of the central electrode were systematically modified.

While the observations obtained to date in our in vitro studies are preliminary, they clearly indicate that competitive (inhibitory) minicolumnar interactions leading to a “checkerboard-like” interleaved pattern of local groupings of activated and non-activated minicolumns occurs under 2 conditions: (1) when the afferent drive evoked by a single electrode placed at VI/WM border is strong; and (2) when the minicolumns within a large cortical territory receive simultaneous, equal-intensity (suprathreshold) afferent drives from a linear array of layer VI/WM sites. On the other hand, when the afferent drive provided at the same multiple layer VI/WM sites is unequal (for example, the 4×-1×-4× condition in Figure 8) activity in the minicolumns within the weakly-driven macrocolumn is suppressed by lateral inhibitory influences arising in the neighboring, more strongly activated macrocolumns.
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Figure 8.
Lateral influence of adjacent cortical territories on stimulus-evoked minicolumnar activity patterns. In this experiment, threshold for each stimulating electrode was set independently. Responses shown in this figure were those obtained when stimuli of the indicated intensities (1× = threshold) were delivered at each of the electrodes simultaneously. (A) Left panel: Image of a neocortical slice with 3 stimulating bipolar electrodes located at layer VI/white matter border. Right panel: OIS image evoked by all three stimulating electrodes simultaneously. For this particular response the stimulus condition used was 4× threshold intensity at the left electrode, 1× threshold at the central electrode, and 4× threshold at the right electrode (denoted by 4×-1×-4×). (B) Stimulus conditions are denoted at far right. Right column: Spatial intensity histograms obtained by sampling OIS data tangentially across the region of slice activated by the three electrodes. Left column: Power spectra of the spatial intensity histograms sampled above the central stimulating electrode. Note the presence of a peak at the minicolumnar frequency of ~21 cycles/mm (48 µm period) under 0.5×-1×-0.5× and 4×-1×-4× stimulus conditions, and another peak at lower spatial frequency of 12 cycles/mm (83 µm period) under all three stimulus conditions. The relative magnitudes of these two peaks vary depending on the stimulus conditions. In particular, the minicolumnar frequency peak completely disappears when a larger cortical region is driven by the stimulus (1×-1×-1×), even though the stimulus intensity here is near threshold, which in the case of single-electrode stimulation produces a prominent peak at the minicolumnar frequency (see for example Figure 7).
Discussion

What picture of sensory information processing in somatosensory cortex has emerged from the studies reviewed in this paper? Most fundamentally, it is apparent that cortical processing is modular on at least two different scales, macrocolumnar and minicolumnar.

With regard to macrocolumns, according to Favorov et al. [9,10,18], the mystacial vibrissa region of rodent somatosensory cortex is not unique in being organized as a mosaic of discrete macrocolumns; i.e., barrel-based columns. Favorov and colleagues demonstrated a similar honeycomb-like pattern made up of discrete place-defined macrocolumns—“segregates”—in the region of cat and monkey somatosensory cortex that receives input from forelimb skin, and proposed that discrete place-defined macrocolumns are a common mode of topographic organization throughout somatosensory cortex. Within such discrete macrocolumns, as one moves from one minicolumn to the next, the RFs of neurons shift back and forth on the skin, displaying local RF diversity without yielding any overall RF shift across the entire macrocolumn. Only at a border separating adjacent macrocolumns do RFs shift en masse in a single step to a new skin position (see Figure 2 for a graphic illustration).

The studies of Pearson et al. [26], Montague et al. [27], Senft and Woolsey [28], and Xing and Gerstein [29] suggest that such discrete macrocolumns—either barrels or segregates—emerge during perinatal development when small (0.3-0.5 mm diameter) cortical regions become innervated each by a selected group of thalamic neurons, sharing similar RFs, whose axons all terminate extensively throughout the territory of that macrocolumn. Within a macrocolumn, according to Favorov and Kelly [16], thalamocortical axons do not connect to all the minicolumns uniformly, but connect selectively so that each minicolumn receives afferent connections from a unique subset of the thalamic neurons projecting to that macrocolumn. The differences in afferent inputs to neighboring minicolumns in a macrocolumn are further amplified by lateral inhibitory interactions among adjacent minicolumns. As a result, in response to a tactile stimulus (even a simple punctate stimulus), an activated macrocolumn generates a complex, spatially heterogeneous pattern of activity that consists of active minicolumns interdigitated throughout the macrocolumn with much less active minicolumns. Furthermore, tactile stimuli, even the most spatially restricted ones, usually activate not a single macrocolumn but a local group of macrocolumns [20]. Each macrocolumn in such an active group generates its own pattern of minicolumnar activation. Thus, the SI response to a skin stimulus takes the form of a patchwork of active minicolumns that extends across multiple macrocolumns (as illustrated in Figure 5). The Favorov and Kelly model predicts that the richly-detailed spatiointensive minicolumnar patterns evoked by tactile stimuli should be very stimulus-specific, exhibiting exquisite sensitivity to stimulus location, shape, and temporal characteristics (such as direction of motion for moving stimuli). One demonstration of such sensitivity is provided in Figure 9.
Figure 9.
Minicolumnar activity patterns generated by Favorov and Kelly [16,17] model in response to spatially detailed stimulus patterns in a shape of letters H and U. *Top row:* on the right, the field of minicolumns (small hexagons) organized into larger groups, macrocolumns (large hexagons). On the left, locations on the model skin of the RF centers (dots) of the minicolumns shown in the right panel. *Middle row:* on the left, the shape and location on the skin of the stimulus pattern. On the right, the pattern of activities evoked by the stimulus in the minicolumns (activity level is grayscale-coded from white—no activity—to black—maximal activity). *Bottom row:* minicolumnar response pattern evoked by another stimulus. Note the prominent differences in spatial details of the two minicolumnar activity patterns throughout the activated cortical field, despite the fact that the two stimuli were quite similar to each other (the change from H to U is merely a small downward shift of the horizontal bar).
In conclusion, while the subject of the existence and functional significance of minicolumns has received relatively little experimental exploration, primarily due to profound technological difficulties associated with addressing it, the combination of experimental and modeling studies reviewed in this paper suggest that cortical networks respond to sensory stimulation with spatially complex patterns of differentially activated minicolumns. An intriguing possibility is that such spatial patterns of activities among minicolumns in an activated cortical field might function to encode highly detailed information about stimulus properties such as, for example, its location, motion, and various spatiotemporal features.

References


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