Chapter 8
Columnar Organization of the Motor Cortex: Direction of Movement

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Abstract The discovery by Vernon B. Mountcastle of the columnar organization of the cerebral cortex (Mountcastle VB, J Neurophysiol 20:408–434, 1957, Brain 120:701–722, 1997) was the single most important discovery of the twentieth century in cortical physiology. Not only did it serve as the framework for the orderly arrangement of knowledge concerning cortical organization and function (Edelman and Mountcastle, The mindful brain. MIT Press, Cambridge, MA, 1978) but also as a framework for exploring and investigating new ideas and for revisiting old ones about the organization of particular cortical areas. Here I review the history of facts and ideas about the organization of the motor cortex and discuss the evidence that the direction of movement is the principle governing motor cortical columnar organization.

Keywords Columnar organization • Motor activity • Motor cortex • Directional tuning

8.1 Introduction

Motor cortex controls movement. Hughlings Jackson put it elegantly in his paper titled "On some implications of dissolution of the nervous system" in 1882, as follows: "Nervous centres represent movement, not muscles. From negative lesions of motor centres there is not paralysis of muscles, but loss of movements." (Jackson 1882, p. 411). Unfortunately, Jackson's insight into the motor cortical representation of *integrated* movements gradually faded and was replaced by an "atomistic" perspective, namely that *components* of movements (about a joint) or just "musculature" are represented, rather than whole movements. In the famous "motor figurine chart" of Woolsey et al. (1952; Fig. 122, p. 239) "each of the figurines indicates the peripheral location of the musculature activated by stimulating electrically the cortical point to which the figurine corresponds" (Woolsey et al. 1952,

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p. 239). I think there were two main conceptual reasons for this regressing to simple components. The first reason had to do with the general emphasis on the neuron as the structural and functional element of organization of the central nervous system: a component-based structural framework extended conceptually to encompass a component-based cortical mapping of function. The work and views of Sherrington (1906, 1940), Lashley (1933), Hebb (1949), and Pitts and McCulloch (1947) were notable exceptions, which failed, however, to shift the mainstream thinking from an atomistic to an integrative perspective. The second reason was a carry-over from the somatosensory system where sensation began by stimulation of discreet receptors in the skin and was ultimately integrated in higher cortical areas, such as the posterior parietal cortex. However, at the level of the first somatosensory cortex (S1), the representation of the sensory stimulus was discreet and atomistic, in the sense that cells there responded to stimulation of specific-modality receptors located in discreet receptive fields. It was natural, then, to assume implicitly that representations in the primary motor cortex (M1), separated from S1 only by the central sulcus, would similarly correspond to some atomistic motor attribute, such as motion about a joint. It was no wonder then that Woolsey's maps of S1 and M1 (Woolsey et al. 1952) strived to illustrate the correspondence between the sensory and motor atomistic representations in the two areas, respectively. Although somatotopically correct in the general sense of body part representation, the point as to *what* is represented in the two areas was missed, and M1 representations became as distinctly atomistic as those of S1, a viewpoint exemplified later by Fetz (1984). At the other extreme, protracted electrical stimulation of the motor cortex (Graziano et al. 2002) elicits a small number of stereotyped movement sequences, reflecting massive, simultaneous activations and apparently unrelated to specific cortical columns.

The work of Mountcastle on the columnar organization of S1 drew the attention of Asanuma and his colleagues who used their newly developed intracortical microstimulation (ICMS) technique (Asanuma and Sakata 1967) to investigate the matter in M1 of the cat (Asanuma and Sakata 1967) and monkey (Asanuma and Rosén 1972). It was found that ICMS elicited localized muscle contractions of the same muscles along anatomical columns. It was argued that this is the organizing principle of M1 columns and was attributed to the excitation of cells of origin of the pyramidal tract. However, it was shown later that "a weak intracortical stimulation is relatively ineffective in a direct excitation of pyramidal tract cells and that the effects of such a stimulation are mainly indirect, especially when repetitive stimuli are used." (Jankowska et al. 1975, p. 617). In fact, Jankowska (1975), after reviewing the then available literature on the effects of surface or ICMS electrical stimulation of the motor cortex, concluded that "that there is no satisfactory evidence for location of the pyramidal tract (PT) cells which project directly (monosynaptically) to motoneurones of one muscle in primates within small and separate cortical areas; such evidence is even weaker for PT cells which exert their effects via polysynaptic pathways in other species. *The available evidence shows in contrast a very pronounced overlap of cortical areas of projection to different motor nuclei.*" (Jankowska 1975, p. 699; italics mine). This conclusion is very much in accord with a re-representation of muscles in various overlapping combinations underlying the representation of movement direction in motor cortex, as discussed below.

Other mapping studies in the motor cortex focused explicitly on joint movements. For example, in one study "The Movement about a joint was selected as the index of response." (Kwan et al. 1978, p. 1120). Unfortunately, this *a priori* focus restricted severely the possibility of exploring other hypotheses and ideas. The joint-focused research culminated in a paper by Murphy et al. (1982) titled "Precentral unit activity correlated with angular components of a compound arm movement" in which 3-D arm motions at various joints were recorded simultaneously with single activity in M1 of monkeys reaching to targets in 3-D space, an engineering feat at that time. The neuronal discharge rates were analyzed with respect to angular joint motions and muscle activity, with essentially negative results. The main conclusion was that "No simple relation between the EMG and single precentral neuron activities was observed in these experiments, even in those cases where the muscles recorded were activated by ICMS at the unit recording site. A similar lack of a simple relationship has been noted for presumed single joint movements . . . Although the motions occurring at the two joints were produced quite differently, shoulder and elbow units tended to behave very similarly in this task." (Murphy et al. 1982, p. 144). Obviously, an analysis of M1 cell activity during multijoint movements using motion/muscle components as a reference did not lead to any meaningful insights. Ironically, it was that same year that our paper was published, reporting on the orderly relations between motor cortical activity and direction of arm movement in 2-D space (Georgopoulos et al. 1982).

8.2 Movement in Space

A different, integrative perspective was employed in studies of cell activity in the posterior parietal cortex (areas 5 and 7) (Mountcastle et al. 1975), recordings in which I was privileged to participate as a postdoctoral fellow in the early 1970s. Mountcastle's fame then was as a somatosensory neurophysiologist with a keen interest in cortical organization and the quantitative bridging of sensation and neural activity (Mountcastle 1967). His adoption of the behaving monkey experimental paradigm was the ultimate step in his attempt to explore, study and elucidate the neural mechanisms of sensation and perception. The natural step in this direction was to record cell activity in posterior parietal cortical areas 5 and 7, where integration of somatic perception was thought to occur, as suggested by the higher-order deficits seen in people with damage to the posterior parietal cortex (Critchley 1969) and by the convergence model of cortical organization put forward by Jones and Powell (1970) based on detailed neuroanatomical studies. The first aim in those recordings was to explore and identify adequate conditions for cell activation by examining the monkey and eliciting movements towards rewards (e.g. pieces of fruits). We then discovered a class of cells Vernon called "reach" neurons which became active when the monkey reached for a reward (Mountcastle et al. 1975), even in total darkness (Mountcastle et al. 1980). In classical Mountcastle style, we studied their activity in exquisite quantitative detail by designing a special apparatus that we called the “electric train” (Mountcastle et al. 1975, Fig. 2, p. 875). It had a semicircular rail on which a box (“train”) with a light could move at different speeds; the box was also a press-switch. The monkey would initiate the train’s motion by depressing a key at lap level. At some point along its travel, the light would dim, and this served as the “go” signal to the monkey to let go the key, reach towards the moving train, press its switch by hitting it, get a juice reward and return to the key to initiate a new trial. To our surprise, we found that the profile of cell activity was very similar when the train was hit at different locations along its travel, i.e. with reaching movements even when their motor profile was very different across those trials. We discussed those finding in the paper as indicating neural control of overall reaching movements, irrespective of their particular components (Mountcastle et al. 1975, Figs. 7–9, pp. 883–884). This was the first instance of relating neuronal cortical activity to a holistic, integrative aspect of arm movement *in extrapersonal space*. Now, since these were recordings from the parietal cortex, they did not influence concurrent studies by other groups in the motor cortex, which continued unabated on the atomistic platform.

8.3 The Importance of Movement Direction in Space

It was during that time that I made the basic observation about the direction of arm movement in space as the important variable for cell activity, as follows. Naturally, we used the electric train to study those cells that were active with reaching movements. Fortunately, we continued spike collection for a few hundred milliseconds after the delivery of reward, that is, while the arm was returning to the key in front of the monkey. Now, this return movement was in a direction opposite to that of the forward reach. I plotted the time course of cell activity during that return movement and saw that very frequently cell firing was very reduced: it seemed that cell firing was related to the direction of movement in space, and that in our forward reach paradigm we were using only a portion of the direction space. In fact, my colleagues and I confirmed that hypothesis when, several years later, we recorded cell activity in area 5 in the center → out task, where movement direction was varied systematically over the whole 2-D, 360 deg space (Kalaska et al. 1983, Fig. 3, p. 251). The broad directional tuning explained the finding of relative invariance of cell firing with reaching in the earlier study (Mountcastle et al. 1975): cell firing was consistently high around the cell’s preferred direction, and the electric train design employed movements spread rather narrowly around the preferred direction, hence the apparent invariance.

8.4 The Center → Out Design

In 1978, I established my own laboratory next to Dr. Mountcastle's, in what used to be Clinton Woolsey's lab, where he had done his mapping experiments! I was keen to study systematically the relations of motor cortical cell activity to the direction of movement in space. Ideally, we needed to monitor free reaching movements in 3-D space but at that time I did not have the means to do that. So, I settled for the next best, namely drawing movements in 2-D space, on a tablet (Georgopoulos et al. 1981; Georgopoulos and Massey 1991). The essence of the design was for the monkey to make movements of the same amplitude whose direction would be equally (isotropically) distributed in 2-D space. Naturally, this suggested center → out movements, starting from the center of the tablet and ending at the circumference. It seemed that sampling 360 deg every 45 deg would be adequate, hence the 8-movement, starfish design (Georgopoulos et al. 1981, Fig. 1, p. 728; Georgopoulos et al. 1982, Fig. 1). Interestingly, a similar design had been employed by Fitts and Deininger (1954) in their study of stimulus-response compatibility; somehow, that paper reinforced my choice.

It should be realized that in 1978 planning an experiment on motor cortical control of movement outside the atomistic "box" of muscles and/or single-joint movements was unheard of, simply because the conceptual framework was so rigid and dominant. Nevertheless, I went ahead with the 2-D movement plan using a device constructed specially for this experiment at the Applied Physics Laboratory of the Johns Hopkins University (Georgopoulos and Massey 1991). The results were stunning: the activity of single cells in the motor cortex varied in an orderly fashion with the direction of movement *in space,* cell after cell (Georgopoulos et al. 1982). I remember how impressed Elwood Henneman (Dr. Mountcastle's old friend and collaborator) was when he visited us from Harvard (always wearing his bowtie), and sat in a recording session and couldn't believe his eyes at the regularity of this directional variation, as spike trains were plotted one after another at our large analog Tektronix screen and printed as hard copies. The regularity in the variation of cell discharge with direction in those plots (Figs. 8.1 and 8.2) were scientifically amazing and esthetically beautiful. Scatterplots of that orderly variation established the *directional tuning curve* (Figs. 8.2 and 8.3) and the findings were reported at the Annual meeting of the Society for Neuroscience in 1980 (Georgopoulos et al. 1980). Remarkably, that time a new wind started blowing in my direction(!). Two other, different labs were focusing on the planning and control of arm movements in 2-D space, claiming *space* as the proper framework: one lab was in Minnesota (Viviani and Terzuolo 1982) and the other at MIT (Abend et al. 1982). This was a conceptual meeting of minds. I presented our results at a conference in Henniker, NH in July 1981 (Engineering Foundation Conference on "Biomechanics and neural control of movement") where I was encouraged by Peter Strick to pursue this line of work. Another ideological supporter was Andras Pellionisz from New York University, who, with Rodolfo Llinás, had proposed an integrative role of the cerebellum in motor control (Pellionisz and Llinás 1979).

From within the neurophysiology field, Vernon Brooks was an enthusiastic supporter of the new idea and, surprisingly, motor physiologists of the spinal cord, including Anders Lundberg and Sten Grillner. The spinal cord is a hotbed of integrative motor functions, including central pattern generation, sensorimotor integration, online sensory control of locomotion, etc. So, spinal cord physiologists were more at home endorsing my integrative notion of movement direction as a basic motor parameter than were motor cortical neurophysiologists who were thinking mostly within the atomistic, movement component framework. The confluence of spinal and motor cortical integrative mechanisms resulted in a *Perspectives* paper in *Science* jointly authored by Sten Grillner and myself (Georgopoulos and Grillner 1989). Finally, it should be noted that, although in 1980 movement direction in space struck as a purely spatial measure, research during the subsequent 30 years showed that it captures many key motor attributes, including torques and EMG activity. We have reviewed these studies in detail in a recent "theory and hypothesis" paper (Mahan and Georgopoulos 2013) in which we also reviewed the evidence for the presence of directional tuning in all cortical and subcortical areas where it has been investigated ("directional motor resonance").

Since the 2-D device we used in those early experiments involved motion by the monkey of an articulated manipulandum, and took a few months to train the monkeys to use it, I was concerned as to what extent directional tuning would hold in 3-D space for free reaching movements. Indeed, it held amazingly well, as it was shown in several studies (Georgopoulos et al. 1986; Schwartz et al. 1988; Caminiti et al. 1990; Naselaris et al. 2006a, b). The 3-D tuning curve was also esthetically beautiful (Fig. 8.4).

8.5 Directional Columns

Directional tuning became firmly established during the 1980s. Two key issues were raised and began to be addressed during that period. The first had to do with the unique neural coding of movement direction: given that the directional tuning curve is broad and symmetric, it can provide unambiguous information only at its peak (i.e. at the cell's preferred direction), but it is unreasonable to suppose that only that point in the curve is used and all else discarded. This problem was solved by the neuronal population vector, an ensemble coding scheme (Georgopoulos et al. 1983, 1986, 1988) which became a nodal factor for the resurgence of computational neuroscience. The neuronal population vector has proved an effective way for decoding directional tuned motor cortical recordings currently used in neuroprosthetics (Collinger et al. 2013; Courtine et al. 2013) and for monitoring dynamic, time-varying cognitive operations (Georgopoulos et al. 1993; Pellizzer et al. 1995).

The second problem had to do with the cortical representation of the preferred direction (PD). Cells had different PDs which covered the whole directional range (Figs. 8.3 and 8.5) (Schwartz et al. 1988). Naturally, we asked the question of

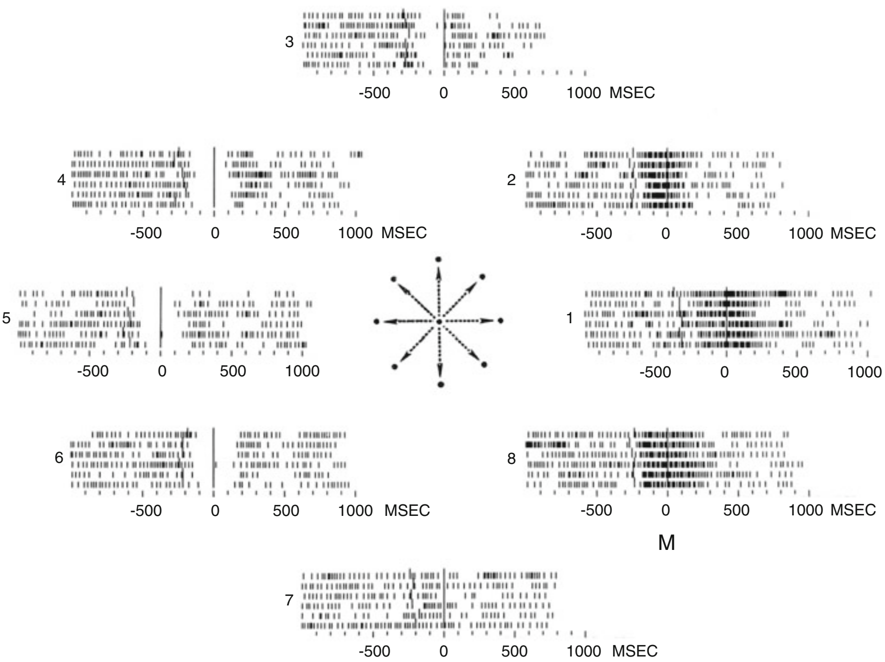

Fig. 8.1 Orderly variation of neuronal activity with movement direction in the center → out task (Georgopoulos et al. 1982), as indicated in the insert. Trials are aligned to the onset of movement (*M*); longer bars prior to movement onset denote the time of target onset. (Georgopoulos AP, Kalaska JF and Caminiti R, unpublished observations)

whether the preferred direction would be a feature (or, rather, *the* feature) of motor cortical columnar organization. Our first approach was similar to that used by Powell and Mountcastle (1959), namely to note the location of cells with specific PD along histologically identified penetrations and then observe possible *en block* changes in PD in penetrations at an angle with anatomical cortical columns. I presented our first results (Georgopoulos et al. 1984) at a meeting of the Neuroscience Research Program (NRP) held at the Salk Institute in 1983, after the NRP moved from the Rockefeller University to the Neurosciences Institute in La Jolla, CA. The results provided strong evidence for a columnar organization of the PD: in penetrations at the exposed cortex, PDs stayed very similar (Fig. 8.6), whereas they changed *en block* in penetrations at an angle with the anatomical columns (Amirikian and Georgopoulos 2003, Fig. 1). We went a step further and analyzed this relation quantitatively. For that purpose, we correlated two measures: one was this angle φ between the penetration and the anatomical columns that it crossed (Fig. 8.7) and the other was the spread of PDs along that penetration, measured as the circular standard deviation s_0 (Mardia 1972) of the PD distribution. If the columnar organization of PD holds, we argued that, at the one extreme, when $\varphi \approx 0$ (i.e. for penetrations along a column), then $s_0 \approx 0$, whereas, at the other extreme, when $\varphi \approx 90°$ (i.e. for penetrations perpendicular to columns, as in a

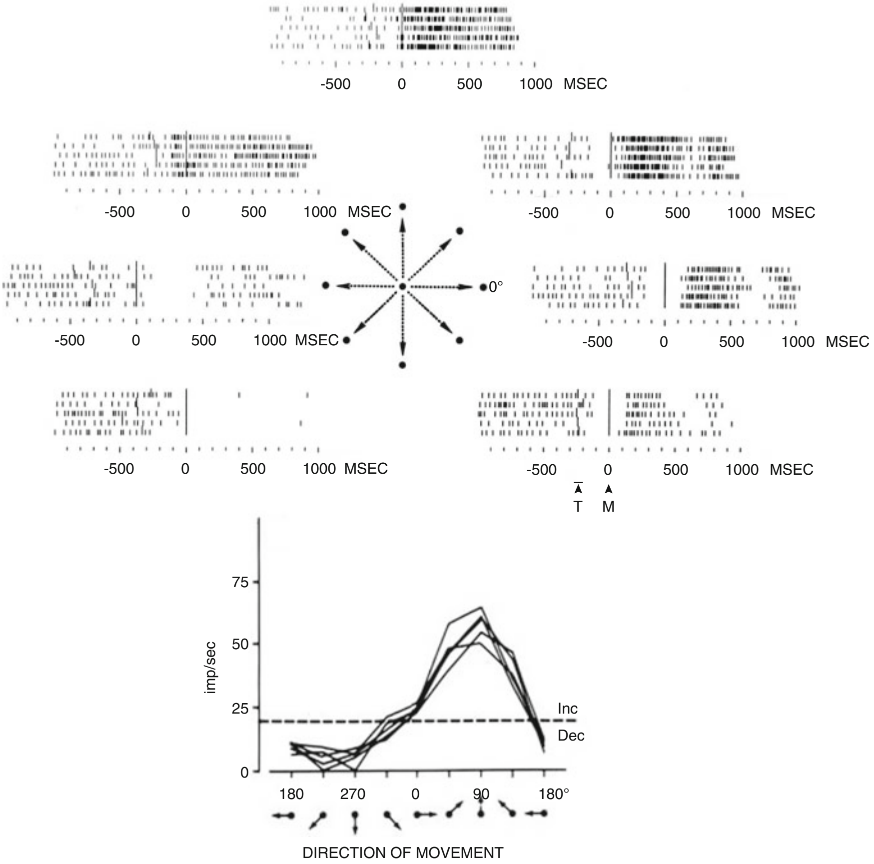

Fig. 8.2 Directional tuning of single cell activity and directional tuning curve. Five tuning curves, one for each trial (*raster row*) are plotted superimposed to illustrate their similarity. Conventions as in Fig. 8.1. The *dotted line* in the lower panel indicates the discharge rate preceding stimulus onset (Inc, Dec: increase, decrease of cell activity from that level) (Georgopoulos AP, Kalaska JF and Caminiti R, unpublished observations)

bank), then $s_0 \approx 180°$, with intermediate values in-between. Indeed, we found a statistically significant positive correlation between φ and s_0 ($r = 0.756$, $p < 0.01$) (Georgopoulos et al. 1984). This finding provided strong support for the columnar organization of the PD. Interestingly, at the same meeting, Bruce Dow presented the results of a similar analysis done for orientation selectivity in the visual cortex; their correlation coefficient was $r = 0.6$ (Dow et al. 1984). Therefore, our quantitative evidence for a columnar organization of the PD in the motor cortex was as good as, or better than, that for orientation selectivity in the visual cortex!

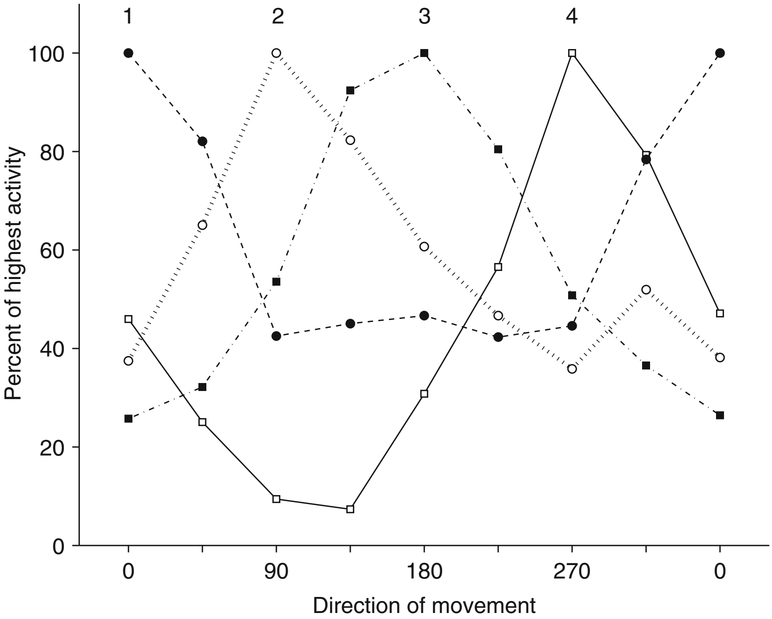

Fig. 8.3 Four directional tuning curves, normalized to their maximum, to illustrate the range of the preferred direction across the 360 deg direction space (Georgopoulos AP, Kalaska JF and Caminiti R, unpublished observations)

8.6 3-D Reaching Movements

The next major step was to extend the testing of the columnar hypothesis for PD to 3-D reaching movements. Our first attempt provided clear quantitative evidence in that direction (Amirikian and Georgopoulos 2003). However, it was clear that we needed an experimental arrangement designed specifically for this problem. Specifically, we needed to (a) have a 3-D reaching task, (b) insert microelectrodes in a regular grid on motor cortical surface, (c) identify (or approximate) the trajectory of microelectrode penetrations, and (d) record neural activity during 3-D reaching at regular spatial intervals (depths) along a penetration. We successfully implemented those objectives as follows (see Naselaris et al. 2005, 2006a for details). We (a) employed the original 3-D reaching task (Schwartz et al. 1988), (b) constructed precise location-aligned templates for inserting and advancing 16 microelectrodes simultaneously using the Eckhorn Multielectrode matrix, (c) used dyes to identify the edges of the penetration matrix, (d) recorded neural activity simultaneously from 16 electrodes every 150 μm during task performance, (e) approximated the location of recording sites along the penetrations, (f) flattened the cortex, and (g) projected the PD in the recording sites onto the flattened cortical surface (Fig. 8.8). Thus, a 2-D cortical map was constructed with the PD color coded, after they were binned to octants (Fig. 8.9). Figure 8.9 shows that PDs were

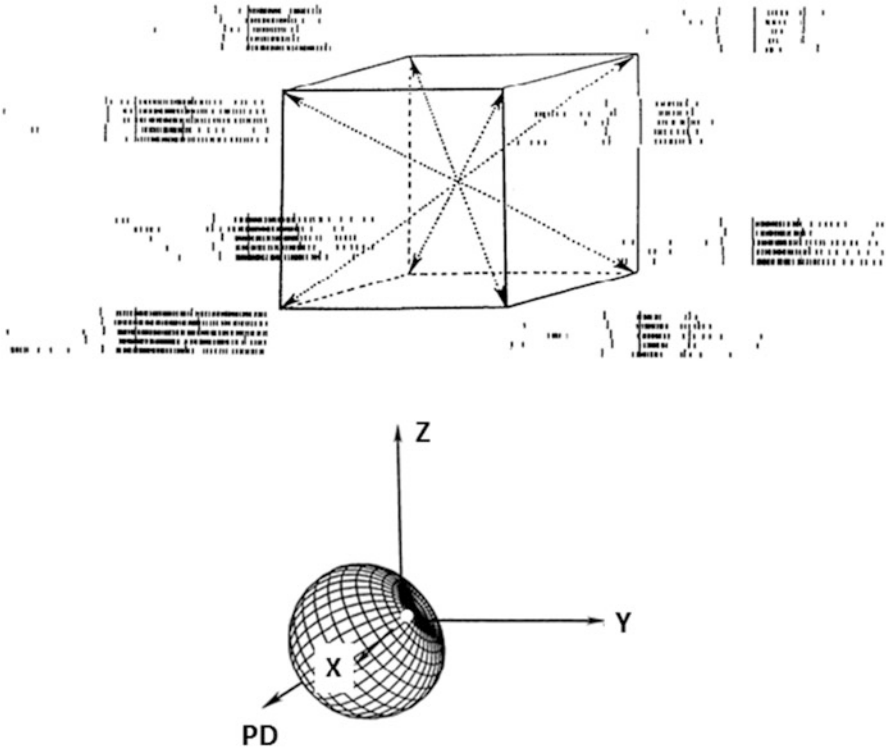

Fig. 8.4 Directional tuning in the 3-D reaching task and associated 3-D fitted tuning curve (Adapted from Schwartz et al. 1988)

repeatedly represented on the motor cortical surface such that, within a given locale, practically the full range of the PD continuum was represented. This meant that an accurate neuronal population estimate of the movement direction could be derived from within any one of these locales (Naselaris et al. 2006b).

The next challenge, of course, was to find out whether PDs are organized in a columnar fashion. For that purpose, we used the full precision of the PD determination (i.e. without binning) and carried out a spectral analysis of the distribution of the PDs on the cortical surface (Georgopoulos et al. 2007). We identified 3 major peaks in the periodogram, namely one at a period of ~240 µm, another at a period of ~90 µm, and a smaller peak at ~30 µm (see Figs. 8.4 and 8.5 in Georgopoulos et al. 2007). These findings suggested a columnar organization of the PD with an estimated unit-column width of ~ 30 µm and a repetition of the full PD range every ~240 µm (Fig. 8.10). In fact, a regression analysis revealed an orderly increasing angular difference of PDs away from a given locus, up to 120 µm, suggesting an orderly representation of a series of PDs on the cortical surface (Georgopoulos et al. 2007). Altogether, these findings suggested a lattice representation of PDs, as illustrated in Fig. 8.10.

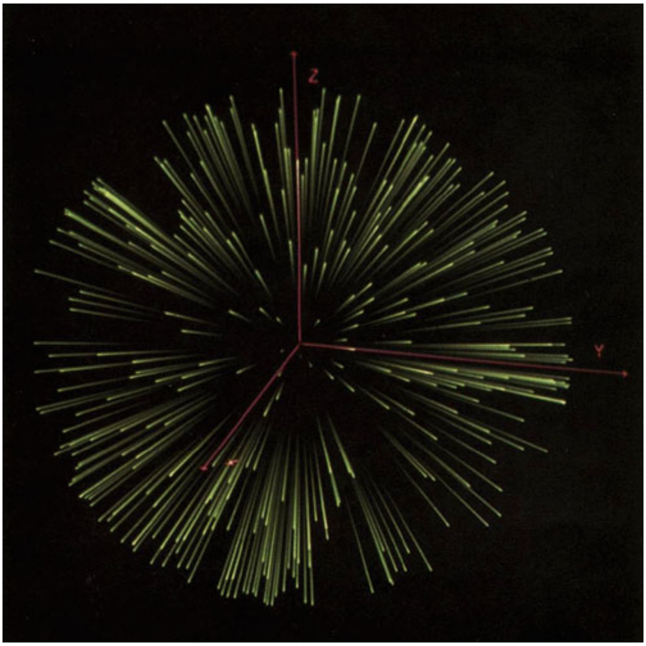

Fig. 8.5 Distribution of 475 3-D preferred directions (From Schwartz et al. 1988)

8.7 Concluding Remarks

There is no doubt that the column is *the* organizing unit of the cerebral cortex. Although the computer metaphor of the brain has been discredited in many attempts, prominently fought against relentlessly by the late giant of neuroscience and dear friend Gerry Edelman, there is something to be said for the operational usefulness of the analogy.[1] Assuming the metaphor for the sake of argument, one can consider the cortical column as a microprocessor, and the brain as a set of massively interacting such microprocessors, i.e. a high-performance computer cluster. Accordingly, intra-columnar processing (Anderson et al. 2010; Opris et al. 2011; Apicella et al. 2012; Chadderdon et al. 2014) would correspond to operations within the microprocessor, whereas inter-columnar operations would correspond to serial and parallel operations in the cluster. The most immediate case concerns local inter-columnar operations, i.e. within an area of a radius of ~500 μm around a column (Gatter and Powell 1978; Georgopoulos and Stefanis 2010). Such local interactions would serve, e.g., to shape the directional tuning curve (Lee

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[1] I argued in favor of the resurgence of this idea, playing the Devil's advocate, at a meeting of the Neuroscience Research Program in La Jolla, CA in 2013. Dr. Edelman was incredulous and hardly believed his ears. Nevertheless, in his usual grand style, humor and compassion, he counter argued, and we had a lot of intellectual fun.

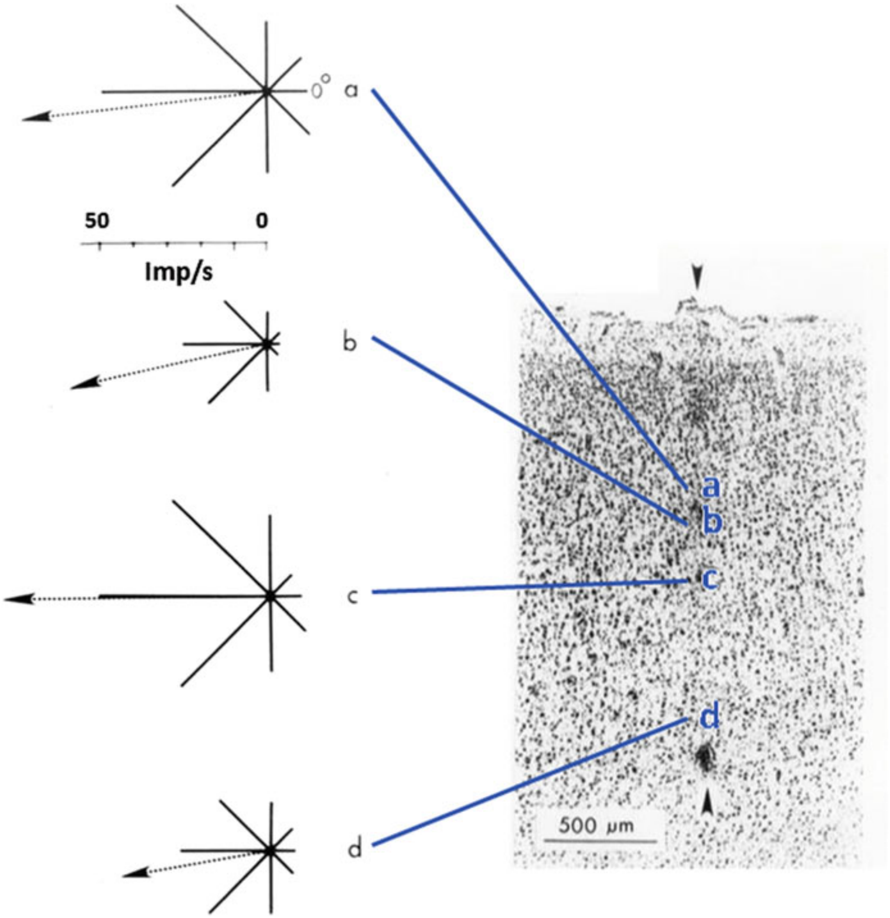

Fig. 8.6 Directional tuning of 4 neurons recorded along the histologically identified penetration shown. Preferred directions are very similar for this penetration, parallel to the cortical columns (Adapted from Georgopoulos et al. 1984)

et al. 2012; Mahan and Georgopoulos 2013; Georgopoulos 2014). Long-range interactions among columns (Caminiti et al. 1985, 1988), and with spinal systems (Georgopoulos 1996), would correspond to large-scale, parallel computer-cluster type of operations. Figure 8.11 gives an overall picture of columnar and intercolumnar/hemispheric organization, based on known anatomical and physiological facts, as follows. (a) Cortical layers (laminae) are color-coded and labeled with Roman numerals (layer IV is omitted for this agranular cortex). (b) Neurons in different layers of the same column interact and are also synchronized (Opris et al. 2011). (c) Neurons from different layers project predominantly to different targets: layer II → ipsilateral cortex; layer III → contralateral cortex; layer V → subcortical structures (basal ganglia, brainstem, spinal cord); layer VI → thalamus.

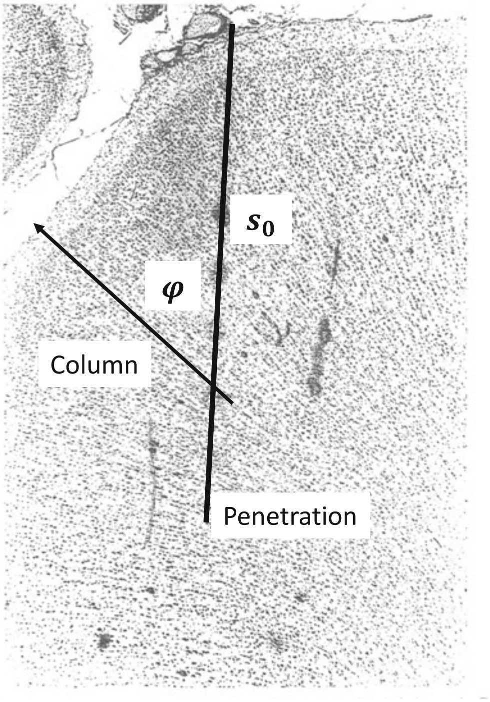

Fig. 8.7 Diagram to illustrate angle φ and a histologically identified penetration traversing the anterior bank of the central sulcus; s_0, circular standard deviation of the preferred directions of cells recorded at different depths along the penetration (See text for details)

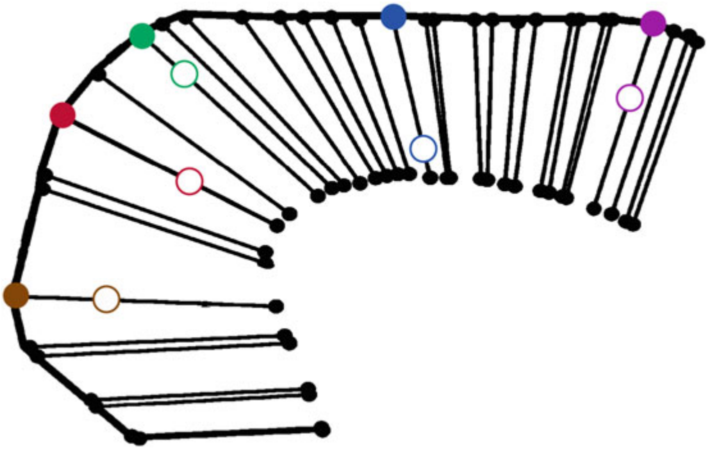

Fig. 8.8 Schematic diagram to illustrate the projection of the preferred direction from a recording site on the cortical surface, along the anatomical column of the recording site (From Georgopoulos et al. 2007)

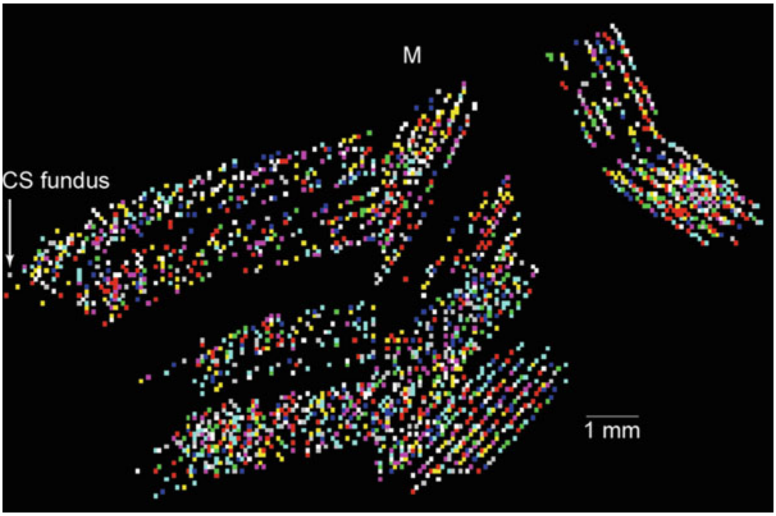

Fig. 8.9 Motor cortical map of preferred directions, constructed as indicated in Fig. 8.8. Colors denote preferred directions within an octant in the unit sphere (From Georgopoulos et al. 2007)

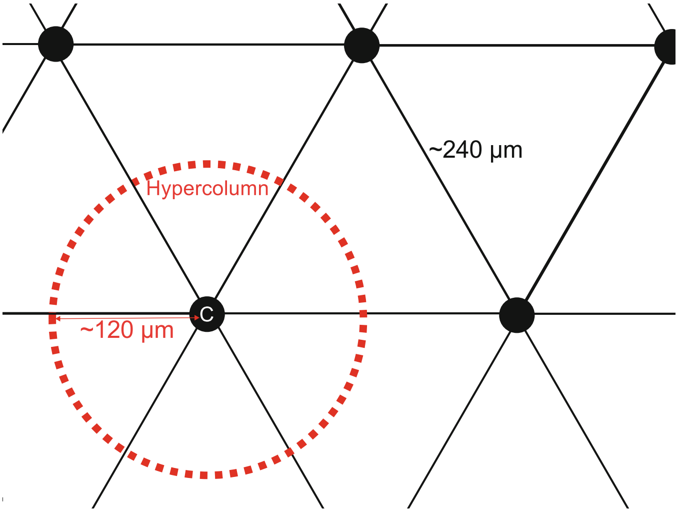

Fig. 8.10 A hypothesized lattice model of the repeated, regular mapping of the preferred direction in the motor cortex, based on the results of the spectral analysis of the distribution of preferred directions on the motor cortical surface (See text for details; from Georgopoulos et al. 2007)

The extensive cortical synchronization observed in studies using various technologies, including fMRI (Christova et al. 2011), magnetoencephalography (Leuthold et al. 2005; Langheim et al. 2006) and local field potentials (Merchant et al. 2014), is probably due to multiple factors, namely (i) local mechanisms (Stefanis and

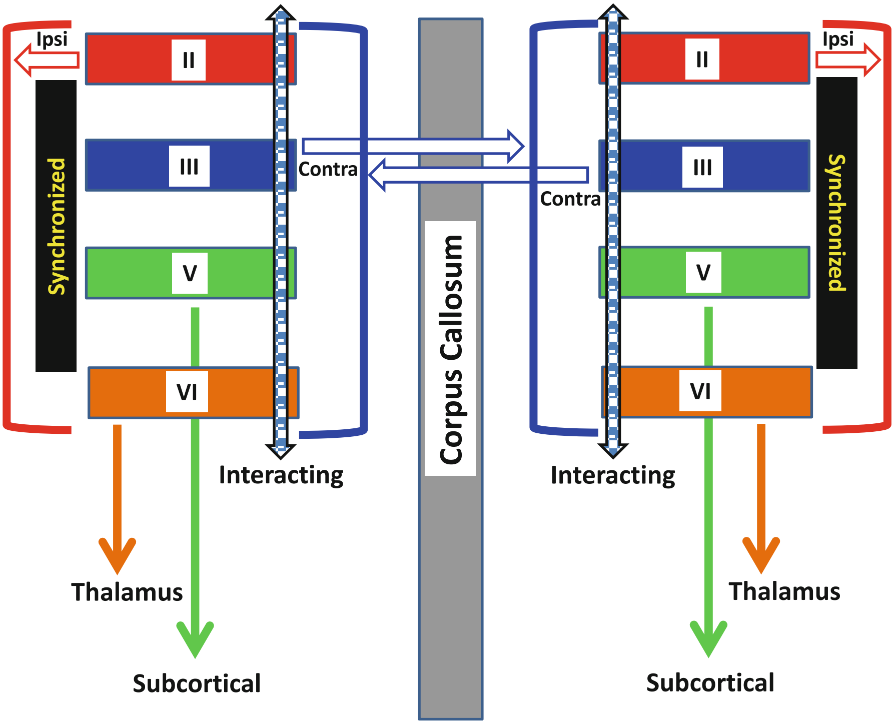

Fig. 8.11 Schematic diagram of intralaminar and inter-columnar interactions, based on known anatomical and physiological findings (See text for details)

Jasper 1964a, b), (ii) specific and non-specific thalamic afferents (Jones 2001), and (iii) synchronization among cortical layers, carrying over to their projections (Opris et al. 2011).

Finally, although the aspect of large-scale intercolumnar interactions has been extensively investigated, mainly by analyzing the effects of brain lesions or electrophysiological interventions (e.g. electrical stimulation, transcranial magnetic stimulation, etc.), possible behavioral consequences arising from disturbances in intra-columnar processing are gradually being recognized and investigated (Opris and Casanova 2014). The term "mini-columnopathy" has been coined to columnar abnormalities observed in autism (Casanova 2007), the beginning of a new era in connecting cortical columns to disease.

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