Primary Somatosensory and Motor Cortex

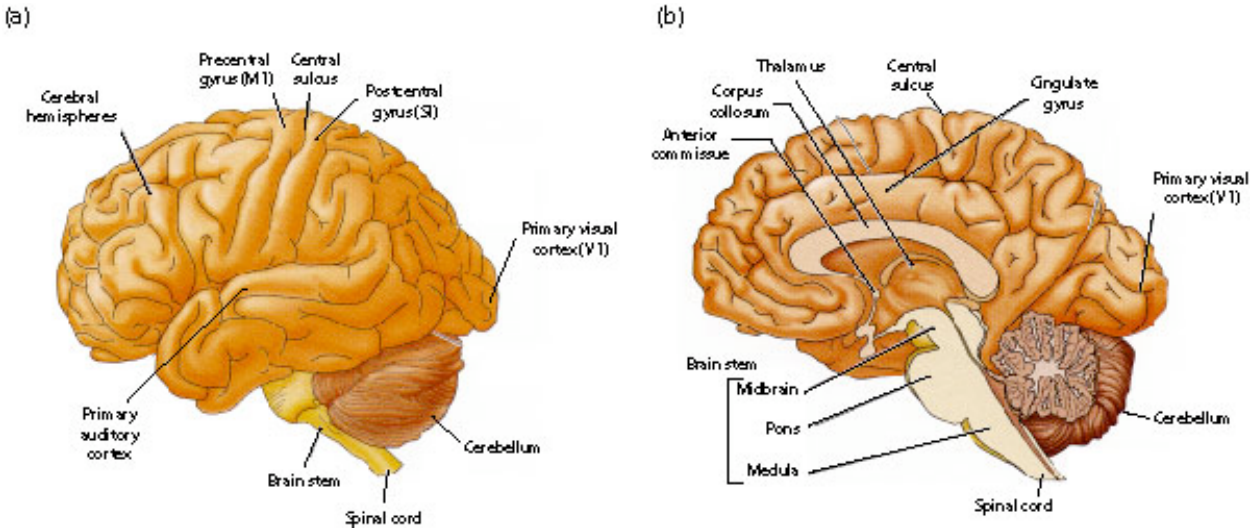

Figure 1. The gross anatomy of the brain is shown from a lateral (a) and medial (b) view. The wrinkled outer surface that covers the majority of the brain is the cerebral cortex. In panel (a) labels illustrate some of the areas of localized function including primary motor cortex on the precentral gyrus (M1) and primary somatosensory cortex on the postcentral gyrus (S1). Other primary sensory cortex areas for vision and audition are also shown.

Introduction

The well-recognized outer surface of the human brain with its associated fissures (sulci) and folds (gyri) is the cerebral cortex (Figure 1). This sheet of neurons if unfolded and flattened out would occupy an area of about 2600 cm^2 with a thickness varying between 2-4 mm housing an estimated 10-30 billion neurons. About 90% of this sheet of neurons has six histologically defined layers and is called the neocortex; our focus will be on two specialized areas of the neocortex, the primary motor and somatosensory cortex (M1 & S1, Figure 1a).

The neocortex of all mammals, not just primates, has identifiable areas of localized function for visual, auditory and somatic senses and most also have a separate motor area as well. The increase in size of the mammalian brain, from mouse to man, results from a disproportionate increase in the size of the neocortex. The thickness of the neocortex is only moderately larger in man and the number of neurons per unit volume is not significantly different from the mouse (with the notable exception of the primary visual cortex in anthropoids). However, there is a massive increase in the surface area of the neocortex resulting in the formation of fissures and gyri that characterize the surface of the primate brain. This increase in surface area gives rise to new identifiable cortical areas; thus in mammals with the smallest neocortices there are 10-20 areas but this number reaches upwards of 100 in humans [1,2]. Today we take for granted that separate areas of the brain have different functions, but it was not always so.

Two hundred years ago at the beginning of the 19th century, a new *science* was born whose central tenet was that different functions of the brain were anatomically localized. This theory of localized brain function was introduced by Gall as the science of phrenology. While the phrenological system of the 19th century was never formally recognized as an accredited science, it did influence Broca (1861) who demonstrated that an area of the left frontal cortex was essential for articulate speech. In the early 20th century Campbell (1905) and Brodmann (1906) painstakingly subdivided the neocortex into different regions based on the differences in the histological appearance. At the same time Sherrington (1906) emerged as a champion of localization by meticulously “mapping” the relationship between electrical stimuli applied to the surface of the brain to motor responses (in chimpanzees,

gorillas and orangutans, references for these historical papers can be found in 1). The collaboration between Sherrington and Campbell on the same brains led to the conclusion that the region immediately in front of the central sulcus, which had the lowest stimulation threshold for evoking motor responses, was histologically unique. This result made the localization of specific brain functions demonstrable beyond doubt and modern brain imaging techniques, such as functional magnetic resonance imaging (fMRI), have corroborated this result.

The importance of localization for neuroprosthetics is that different functional information maybe recorded in the electrical activity of neurons in different locations of the neocortex. In addition, stimulation of the cortex through a bioelectric interface will produce different behavioural outcomes related to the localized function of the area stimulated. For example, by recording from pyramidal neurons in layer V of the primay motor cortex one can eavesdrop on a final output of the motor areas of the brain to the brainstem and spinal cord. These recordings can be used to predict the movement of an arm and then control a robot [3] or control cursor movement in a closed loop brain machine interface [4,5]. An excellent example of a neuroprosthetic using stimulation is the *robotrat* that can be navigated by implanting stimulating electrodes in the somatosensory neocortex paired with stimulating electrodes in another area of the brain responsible for reward [6].

I. STRUCTURE

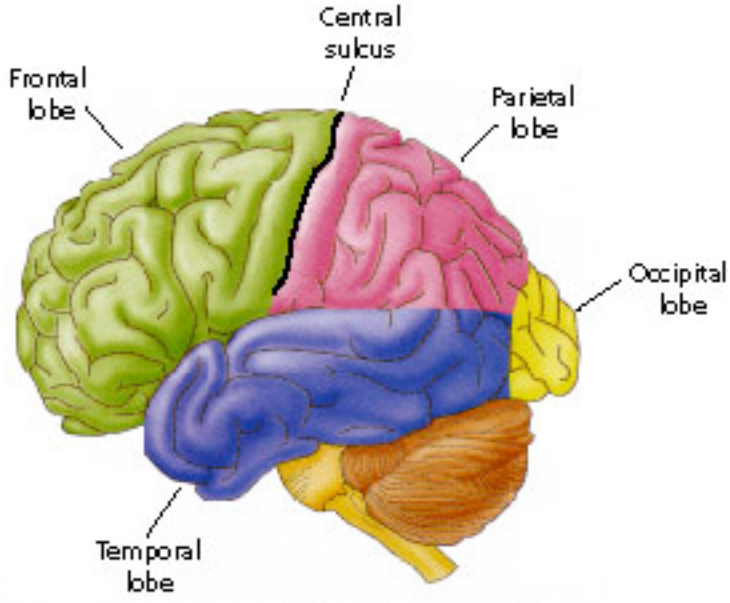

Figure 2. At the most general level of division the cerebral cortex has four lobes: frontal, parietal, occipital and temporal. Motor areas are located in the frontal lobe, in front of the central sulcus, while the somatosensory cortex lies in the parietal cortex immediately behind the central sulcus.

A. Gross anatomical features and location

The cerebral cortex is divided into 4 major lobes: frontal, parietal, occipital, and temporal (Figure 2). The central sulcus divides the frontal and parietal lobes and is the key landmark for locating the primary motor and somatosensory cortices. Directly in front of the central sulcus in the frontal lobe is an area of agranular cortex (i.e. lacking granule cells) that has been called the precentral gyrus, Brodmann's area 4, Rizzolatti's F1 and the primary motor cortex (M1). This is the area that Sherrington found could produce movement of the contralateral limbs with the lowest threshold stimulation. The mapping revealed that there was a sequence of body regions associated with stimulation of different regions of the M1: lower limb movements near the top of the gyrus and the head movements toward the bottom. This somatotopic organization of the motor map in subhuman primates was the foundation for similar motor mapping experiments done by Wilder Penfield and colleagues in human cortex during neurosurgical procedures. It was Penfield (1952) [7] who introduced this somatotopic map in caricature style that has been widely reproduced as the motor homunculus (Figure 3).

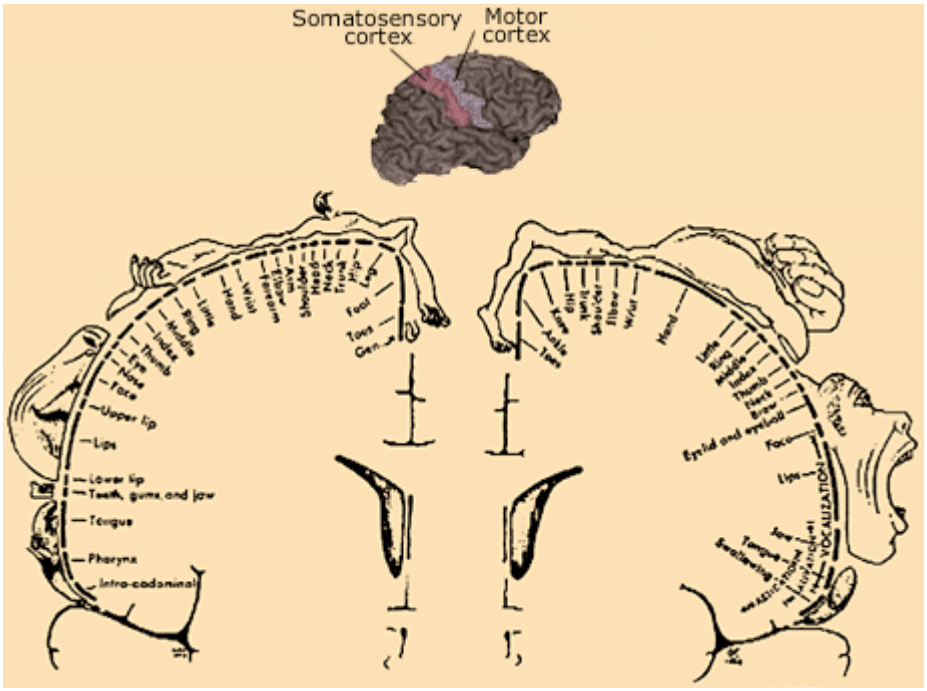

Figure 3. The homunculi in S1 (left) and M1 (right) as mapped by Penfield and colleagues is useful for illustrating the gross somatotopic organization of the cortex in these areas.

Directly behind the central sulcus in the parietal lobe is an area of granular cortex that has been called the postcentral gyrus, Broadmann's areas 3, 1, 2 and the primary somatosensory cortex (S1, Figure 1a). S1 can be subdivided into 4 subregions based on afferent inputs and Brodmann's classification. The muscle afferents project to area 3a, which is continuous with M1; cutaneous afferents, both fast and slow adapting, project to areas 3b and 1; and joint afferents make up the major input to area 2. In each of these areas there is a somatotopic arrangement of the sensory input, i.e. a sensory homunculus, with sensory responses from the foot area at the top of the hemisphere and the face toward the bottom (Figure 3). None of the afferents projecting to S1 are first order sensory neurons; the information has been relayed across at least 2 synapses with the final projection coming from the thalamus. [2]

B. Cell types, cortical layers and columns

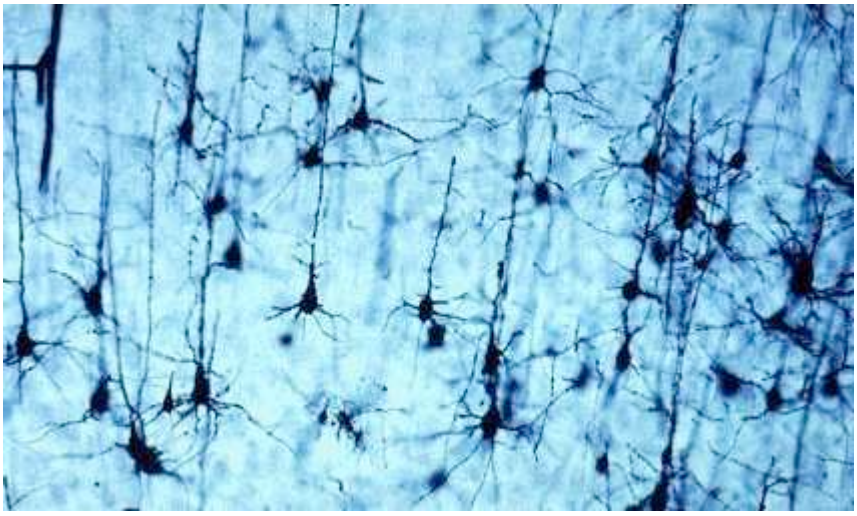

Figure 4. This is a stain that selectively marks pyramidal neurons. The tissue was taken from primate M1 area. Growing out of the top of the soma is the apical dendrite and the shorter branches extending horizontally from the base of the soma are the basilar dendrites.

There are two basic neuron types in the neocortex: spiny (excitatory) and non-spiny (inhibitory). Spiny neurons are glutamatergic neurons that have nodules on their dendrites and include both pyramidal and stellate (or granular) neurons. The pyramidal neurons, shown in Figure 4, comprise about 75% of the cortical neurons and are the only neurons that project their axons outside of the immediate vicinity to other cortical and subcortical targets. Non-spiny interneurons have smooth dendrites are inhibitory GABAergic cells that may also co-release neuropeptides. The most studied inhibitory interneurons are the large basket, double bouquet and

chandelier cells. Other classes of non-spiny cortical interneurons include the peptide, small basket as well as the neurogliaform cells.

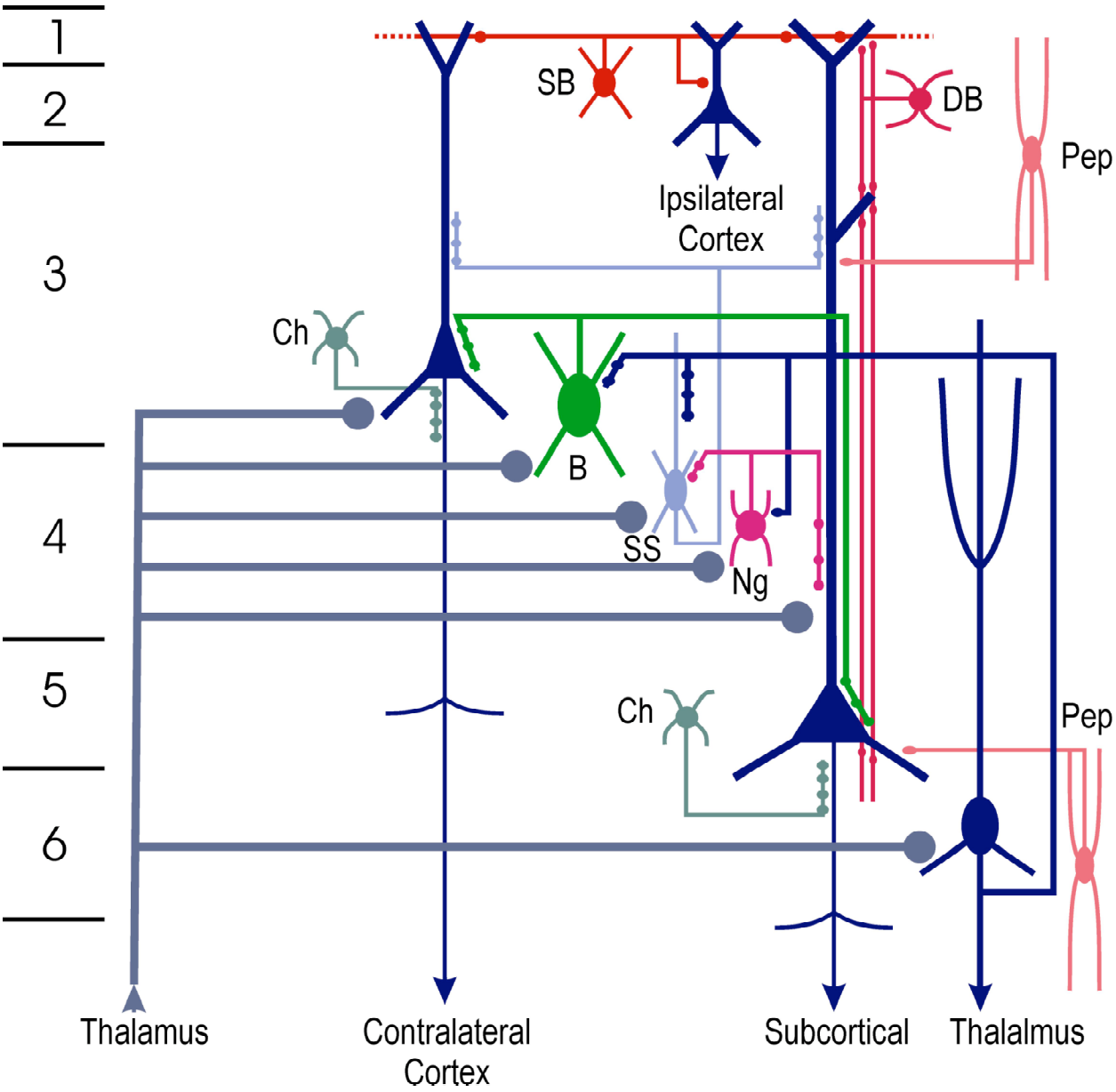

Figure 5. On the left side of the figure the boundaries between the 6 layers are shown. Excitatory neurons that use glutamate are illustrated in blue and include the afferent input from the thalamus, pyramidal neurons and spiny stellate (SS) neurons. Perisomatic inhibitory neurons are shown in green and include the chandelier (Ch) and large basket (B) neurons. The other inhibitory interneurons contacting the dendrites are shown in red and include the small basket (SB), double bouquet (DB), neurogliaform (Ng) and peptide (Pep) cells. The output targets of pyramidal neurons in different layers is also shown. (Adapted from ref 8)

Classification of the cells in the neocortex uses multiple criteria such as the cell shape and pharmacology but also localization of synapses on target cells (e.g. pyramidal cells) and the location of the cell body in the six layers of the

neocortex. Currently there are two types of cortical inhibitory cells based on the spatial location of their synapses: perisomatic and dendritic. The basket and chandelier cells preferentially contact the pyramidal neuron soma, initial segment and axon hillock and thus fall in the category of perisomatic. Inhibitory synapses in this region can have a strong effect on the final electrical output of the pyramidal neuron. In contrast the double bouquet cells contact the branches of the dendritic arborization where they have a more localized effect on dendritic integration (Figure 5).

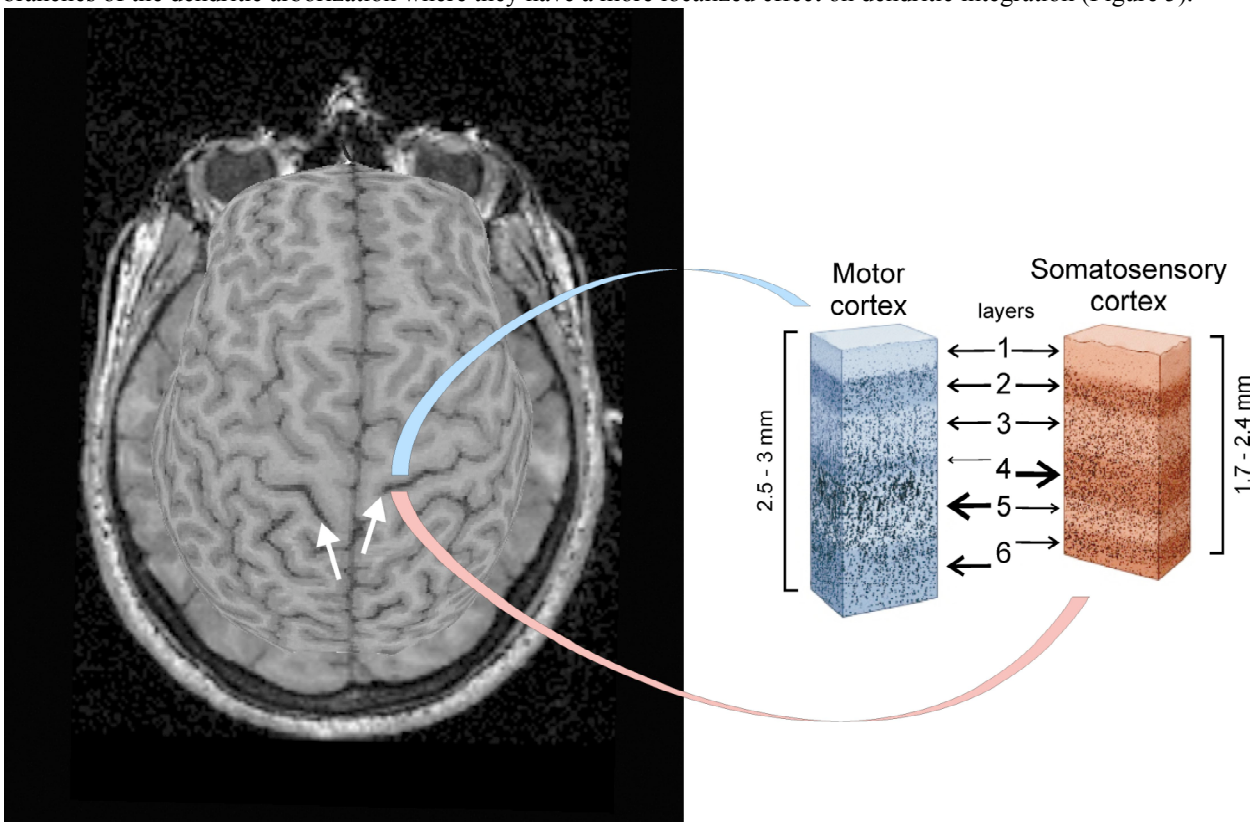

Figure 6. The MRI on the left is a combination of a 2D MRI slice through the head at the level of the eyes superimposed with a 3D MRI using curvilinear image processing. (Courtesy of AC Bastos [16]) The 3D image is a curvilinear slice 6 mm down from the cortical surface to illustrate the deep and complex convolutions of the cerebral cortex and highly curved boundary between the gray and white matter. Arrows in each hemisphere indicate the location of the central sulcus. The right panel illustrates the layered nature of the cortex on either side of the central sulcus. The dark spots in the layers indicate the position of neuron soma. The thickness in the precentral cortex (M1) is slightly greater than that in postcentral cortex (S1). The indicated thickness is for human and non-human primates. [2]

The border between the gray and white matter along the contours of the cortex is easily distinguished in the MRI illustration (Figure 6). The gray matter of the neocortex is divided into six layers over its thickness of 2-4 mm. Different layers have different cell types and densities ranging from virtually no cells in layer I (immediately adjacent to the cortical surface) to the high-density packing of cells in layer 4 of S1. The density of cells in the different layers of the cortex is illustrated in the right panel of Figure 6. The major difference in the structure and distribution of cell types in M1 and S1 is an exaggerated layer 5 (output) versus layer 4 (input) respectively. The layers are formed during development with layer 6 neurons migrating to their final destination first followed by neurons migrating to layer 5 then 4 and so on. The layers of the cortex have functional significance and the same cell type in different layers may have a distinct functional role. For example, pyramidal cells found in layer 2 project to other ipsilateral cortical areas, 3 project to contralateral cortex, 5 project to subcortical targets and the layer 6 pyramidal neurons project to the thalamus [8] (Figure 5). Layer 4 is the primary input layer that receives sensory

afferent input from the thalamus and is also the location of a high density of spiny stellate cell bodies. Thus it is layer 4 that initiates the information processing of a circumscribed region of neocortex to produce output from the pyramidal cells.

During development, following migration of neurons to different cortical layers, the neurons differentiate and mature, which involves the extension of dendrites and axons. There is a strong tendency for all of the cortical cell types to extend their processes in a vertical orientation at right angles to the surface of the brain, the most striking of which is the apical dendrite of the pyramidal cells. The vertical, or columnar, organization of the cortex is reflected not only in dendritic and axonal bundles but also in the distribution of the cell bodies of neurons [9]. Thus in many areas of the cortex, including M1 and S1, the density of cell bodies varies parallel to the surface of the cortex with regions of high density separated by regions of sparse density of cell bodies. These vertically organized structures are the minicolumns of the neocortex and measure about 50 um in diameter containing 80-100 neurons. Fifty to eighty minicolumns are linked together by thalamic projections and short-range horizontal connections to form a column, 300-500 um in diameter [2]. The neurons of a column share common features such as similar receptive fields in S1 and similar motor output in M1.

Neocortex circuitry

Afferent input to the neocortex can come from three general sources: thalamus, ipsilateral cortex & contralateral cortex. The thalamic input is directed primarily to layer 4 and the principle target is the spiny stellate cells though there are also connections to the inhibitory interneurons and directly to pyramidal neurons. In M1 it is often not possible to identify layer 4 as there is a marked absence of the spiny stellate cells that normally form this layer (Figure 6, right). In M1 then, the thalamocortical input tends to terminate directly on the spines of the pyramidal dendrites in layers 3 and 5. Input from the other areas of the cortex, both ipsi and contralateral, synapses with neurons in layers 2 through 4. Areas M1 and S1 are connected in the same hemisphere by long horizontal projections from layer 2/3 pyramidal neurons. The contralateral input from the opposite hemisphere projects via the corpus callosum to terminate primarily on dendritic spines in layers above those where the thalamocortical connections are most dense. One notable exception for contralateral inputs is the hand area of M1 that has few, if any, callosal afferents. The thalamocortical input to layer 4 that initiates the information processing proceeds upwards to layers 2/3, then downward to layer 5 followed by layer 6 and finally upward to all uppers layers again. This gross overview of the progression of the processing of the thalamic afferent input via the intrinsic circuits can be followed through in the circuit diagram of Figure 5.

II. Function

Primary Motor Cortex, M1

The exact function of M1 and the other areas of the frontal lobe associated with motor function remains a mystery. At the heart of this mystery are the numerous experimental examples of correlation between the electrophysiological activity of neurons recorded in M1 and various parameters of movement including muscle force [10,11], direction [12], speed [13] and the modulation of activity with different postures. [14, 15] The classical description of M1 held that this area of the cortex was the chief origin for descending cortical control of spinal cord circuitry with a direct connection to the motoneurons supplying distal muscles of the hand. Thus movements requiring a high level of dexterity, like a pincer grasp, are severely disrupted by damage to M1. Originally, M1 was thought to function at a subordinate level of a motor control hierarchy in which M1 specified the low level details of movements (i.e. which muscles to activate, when and how strongly) that have been planned in other higher order motor areas of the frontal lobe such as the ventral and dorsal premotor cortex (PMv & PMd), supplementary motor area (SMA) and the cingulate motor areas on the medial surface of the cortex. However, more recent findings have resulted in significant changes in the conceptual thinking about the function of M1 and the related motor areas of the cerebral cortex.

One requirement for M1s involvement in controlling motor action is a physical link between the cortex and the spinal cord. The main descending tract carrying action potentials from the cortex to the spinal cord is the corticospinal tract. The axons that make up the corticospinal track have their origin in wide spread areas of the

cerebral cortex in both the frontal and parietal lobes. The primary motor cortex contributes the largest number of axons to this tract compared to any other region, just under 40% [1], but there are important contributions of axons from S1 and other parietal lobe areas (roughly 24%) with the remainder coming from the premotor areas in the frontal lobe. [17, 18] This suggests that M1, in primates, has a significant number of physical connections that could influence the spinal cord circuitry for generating muscle contractions.

The influence of M1 in generating muscle contractions has been studied using primarily two methods: stimulation and recording. We have already discussed the finding by Sherrington and Penfield that M1 required the least amount of stimulating current to generate muscular contractions. Asanuma and his colleagues did more detailed work using intracortical microstimulation (ICMS). [19] This method used a metal microelectrode to penetrate the cortex to different depths, i.e. different layers, and deliver a weak electrical stimulus within a restricted area. The most salient findings were that single muscles or small groups of muscles with similar actions were excited with near threshold stimulation and that within a circumscribed area (about 300 um wide) the same muscle(s) were stimulated as the electrode was advanced through the cortical layers, i.e. columnar organization. The ICMS method also allowed a more detailed mapping of M1 compared to the gross somatotopy of the Penfield homunculus (Figure 3). Rather than smooth continuous distributions of muscles across M1, the same muscles or movements were stimulated with the microelectrode in multiple discontinuous regions of M1 intermingled with areas where different muscles or movements were generated. [20] Another result from the ICMS studies was that stimulation in a local area could cause excitation of multiple synergist muscles with inhibition of antagonist muscles. [1] The data supporting this coordinated activation about a single joint did not predict the most recent findings to emerge from M1 stimulation.

Graziano and colleagues [21] used relatively long duration stimulation (0.5 sec) to evoke coordinated, complex movements involving multiple joints. Perhaps even more surprising, stimulation resulted in a stereotyped final arm posture regardless of the position of the arm at the initiation of stimulation. These findings are incompatible with the idea that M1 controls either muscles or higher order kinematic variables such as direction and speed of movements as the stimulation results in movement to a final posture regardless of the muscles activated or the direction of movement required. These authors have suggested that the division of M1 as a separate motor area apart from other premotor areas in the frontal lobe is artificial. Instead they suggest that the motor areas of the frontal lobe fit together into a holistic map of the reachable workspace. [22] However, some caution is warranted when considering how much "functional" information can be gained from artificially activating the nervous system by means of stimulation. The spatiotemporal pattern of single neuron discharges resulting from stimulation is not equivalent to the pattern of activity that occurs during natural movements.

The other method for deducing M1 function is recording the electrophysiological activity of single neurons during while primates engage in different motor tasks. The logic in these studies has been to design tasks that isolate dynamic and kinematic variables of movement to determine which variables have a stronger correlation to the electrical activity of the neurons. For example, movements of the same extent at the same speed but against different loads maintain constant kinematics in the face of changes in the dynamic requirements of the task. If the neuron is encoding muscle force the activity will be significantly different depending on the load. Alternatively, if the neuron encodes kinematic variables then the activity will be independent of the load. Investigators have found evidence for neurons fitting both of those descriptions within M1 and the emerging consensus seems to be that muscles, movements and posture are functionally represented by single neuron activity in M1. [23, 24]

Thus activity of neurons in M1 seems to satisfy requirements for both low level coding of muscles and high level coding of spatial parameters. In closing it is stressed that the encoding of a given neuron or region of M1 is not static but can be modified based on experience or learning. [5, 25, 26] Thus any attempt to decode the activity of the same neuron over long periods of time must include an adaptive algorithm that can respond to these changes in neuronal activity.

Primary Somatosensory Cortex, S1

The function of S1 is intimately connected to the input it receives from mechanoreceptors in the skin, muscle and joints. The function of S1 is processing this afferent information resulting in the detection of the mechanical stimuli giving rise to a sense of touch, position and movement. Not only is S1 responsible for detecting the presence and magnitude of a sensory stimulus but also locality on the body surface. The most complex processing occurs when

the afferent information from different sensory sources is integrated to produce a coherent perception of a sensory experience such as sterognosis, the ability to recognize and object's size and shape by touch alone.

III. Summary

Blah blah blah

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