Published in final edited form as:

Trends Neurosci. 2015 May ; 38(5): 259–261. doi:10.1016/j.tins.2015.03.005.

Motor cortex layer 4: less is more

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Abstract

The stratified motor cortex is variously thought to either lack or contain layer 4. Yamawaki et al. described a functional layer 4 in mouse motor cortex with properties and connections similar to layer 4 in sensory areas. Their results bolster a theoretical framework suggesting all primary cortical areas are equivalent.

The motor cortex in mammals is situated in the frontal lobe, immediately in front of the primary somatosensory area. Both areas have a complete map of the body—the primary motor cortex for movement and the somatosensory area of the body surface and proprioception. These neighboring areas differ by the relative prominence of their different layers. Such differences across the cortical mantle provided the basis to map the cortex into architectonic areas. The most famous architectonic map of the human cortex was made by Brodmann [1], which is still used today.

The idea that the cortex has six layers also dates back to Brodmann, who thought that all areas have six layers in development but some areas subsequently lose layers while others gain layers. Brodmann thought that the motor cortex loses its middle layer 4 postnatally. When paper thin sections are cut through the cortex and stained with a cellular stain, layer 4 looks granular because it is composed of small neurons. Areas that lack layer 4 are thus called agranular.

In contrast to Brodmann, others saw a layer 4 in the motor cortex [2, 3]. For example, Ramón y Cajal in 1899 described a layer 4 in the human motor cortex but indicated that it is small and buried in a dense thicket of neuronal processes from the layers above and below. The adjacent layer 5 is particularly prominent in the primate motor cortex: the specialized Betz cells found there are gigantic, and all neurons have extensive dendritic trees that invade layer 4, dwarfing the granular neurons [4]. Thus, finding layer 4 in the motor cortex is like finding a row of violets flanked by weeds.

Layer 4 is of particular interest because it receives a robust pathway from the thalamus. If the motor cortex lacks layer 4, which neurons does the thalamic pathway influence? In a recent paper, Yamawaki et al [5] addressed this issue. Using optogenetic methods the

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authors stimulated the ventrolateral nucleus—a motor thalamic nucleus—and recorded evoked activity in a corridor between layers 3 and 5A in the motor cortex in live brain slices from mice. This pathway is reminiscent of the classic pathways from the relay thalamic nuclei to the primary sensory areas in mammals [6]. The authors also found that these layer 4 neurons have largely one-way excitatory connections with neurons in layers 2/3 and receive sparse long-distance connections besides the thalamic input. These features are typical of neurons in layer 4 in sensory cortices, considered to be the gold standard.

Layer 4 may be hidden in the motor cortex of mice or men, but is brought out by markers that selectively label neurons in layers 3 and 5 [7, 8] (Figure 1). The identified layer 4 in the motor cortex has neurons with cellular features of local neurons whose axons remain in the cortex [4]. The findings of Yamawaki et al thus signify that the basic wiring of the motor cortex is not fundamentally different from the sensory areas, as previously espoused [9].

The controversy about the status of layer 4 in the motor cortex may be rooted in a sensory-centric interpretation of cortical organization. Layer 4 is readily visible and specialized in the primary sensory areas. Primates rely heavily on visual input. The visual world is mapped topographically in layer 4 in primate visual cortex, which has several subdivisions in primates, (reflecting a gain of layers, according to Brodmann [1]). In rats and mice, which live in dark and narrow spaces, it is the whisker system that is specialized. Each whisker is represented in a separate cluster within layer 4 of somatosensory cortex.

In the motor cortex it is layer 5 that is most prominent, which gives rise to pathways that innervate lower motor neurons which innervate the muscles that move the body. The dendritic trees of layer 5 neurons in motor cortex become increasingly elaborate after birth, a process that is based on activity. When movement is limited by disease, the granular layer 4 in the motor cortex is evident beyond development, as seen in the brains of children with cerebral palsy [10].

Unlike the sensory relay nuclei that receive input from the periphery—the eyes, the ears, the body surface—the motor-related thalamus receives the output of the cerebellum and the basal ganglia, two large structures associated with motor and other functions. Pathways from the motor thalamus reach layer 4 as well as parts of layers 3, 5 and 1 [11], a pattern seen for other cortical areas as well [12]. These thalamic pathways vary in density and layer(s) of termination across the cortical mantle, reflecting the structural and functional specialization of cortical areas [13].

The term agranular has implications beyond missing the violets for the weeds in the motor cortex: it places the motor cortex with areas that are truly agranular—the phylogenetically ancient limbic cortices, which differ significantly from the motor cortex. The limbic areas have a rudimentary lamination and are poorly myelinated. The motor cortex has six layers and is strongly myelinated. Among a series of motor-related cortices, the cingulate limbic areas have the simplest laminar structure. The motor cortex has the most elaborate structure. Premotor areas situated between the motor cortex and the limbic areas show an intermediate pattern of lamination. The graded changes across these areas are evident by the content of myelin and label for a cytoskeletal protein (Figure 1). The limbic areas also differ from the

primary areas by the extent and laminar pattern of their connections [14, 15]. Limbic areas have widespread connections—they are the cortical generalists. The primary areas have comparatively restricted connections—they are the specialists. In the scheme of graded changes in architecture the motor cortex is the most specialized. It is thus no wonder that the subtle layer 4 of the motor cortex identified in the work of Yamawaki and colleagues [5] functions much like layer 4 of the primary sensory areas. The motor cortex and the primary sensory areas differ by their local laminar features but they are sister areas in the broader scheme of the systematic variation of the cortex and its evolution.

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Figure 1.

Architecture of motor-related cortices. (A) Nissl stain (blue) shows laminar differences between an agranular (limbic) area (far left) and the motor cortex (area 4, far right) photographed from coronal sections through the rhesus monkey brain. The sections between them show gradual changes in laminar architecture through a series of premotor areas (preSMA to 6DC). (B) Matched sections through the same areas were processed to see SMI-32, a neurofilament protein (brown label). Note gradual changes from low to high expression from agranular area 24a to the motor cortex (also known as area 4). Silhouette

arrows in A and B (far right) point to the giant Betz cells of the primate motor cortex (area 4). **(B')** Low magnification photographs show clearly the transitions from an agranular area (24a) to the motor cortex (area 4). SMI-32 labels neurons in layers III and V but not in layer IV; black arrows (right) show the non-labeled zone between layers III and V that demarcates layer IV. **(C)** Matched sections show the low myelin content (dark brown fibers) in an agranular limbic area (24a) and gradual transitions through premotor areas to the motor cortex (area 4), which has the highest myelin content. **(D)** lateral, and **(E)** medial views of the frontal lobe show the motor cortex, premotor and limbic areas and the levels (arrows) of the three sections shown in B'. See [7] for further details.