

spindle orientation and the cytoplasmic distribution of cell fate determinants in dividing cells. Future studies will be needed to show how the orientation of cell divisions relates to the distribution of cell fate determinants, and whether these factors are related to cell cycle length and cell fate choice. We anticipate that further work in this field will continue to shed light on the intricate mechanisms of neural progenitor cell division.

REFERENCES

Fietz, S.A., Kelava, I., Vogt, J., Wilsch-Bräuninger, M., Stenzel, D., Fish, J.L., Corbeil, D., Riehn, A., Distler, W., Nitsch, R., and Huttner, W.B. (2010). *Nat. Neurosci.* 13, 690–699.

Fishell, G., and Kriegstein, A.R. (2003). *Curr. Opin. Neurobiol.* 13, 34–41.

Hansen, D.V., Lui, J.H., Parker, P.R., and Kriegstein, A.R. (2010). *Nature* 464, 554–561.

Knoblich, J.A. (2008). *Cell* 132, 583–597.

Konno, D., Shioi, G., Shitamukai, A., Mori, A., Kiyonari, H., Miyata, T., and Matsuzaki, F. (2008). *Nat. Cell Biol.* 10, 93–101.

Kriegstein, A., and Alvarez-Buylla, A. (2009). *Annu. Rev. Neurosci.* 32, 149–184.

Lui, J.H., Hansen, D.V., and Kriegstein, A.R. (2011). *Cell* 146, 18–36.

Noctor, S.C., Martínez-Cerdeño, V., Ivic, L., and Kriegstein, A.R. (2004). *Nat. Neurosci.* 7, 136–144.

Postiglione, M.P., Jüschke, C., Xie, Y., Haas, G.A., Charalambous, C., and Knoblich, J.A. (2011). *Neuron* 72, this issue, 269–284.

Reillo, I., de Juan Romero, C., Garcia-Cabezas, M.A., and Borrell, V. (2010). *Cereb. Cortex* 21, 1674–1694.

Shitamukai, A., Konno, D., and Matsuzaki, F. (2011). *J. Neurosci.* 31, 3683–3695.

Wang, X., Tsai, J.W., LaMonica, B., and Kriegstein, A.R. (2011). *Nat. Neurosci.* 14, 555–561.

Yu, F., Kuo, C.T., and Jan, Y.N. (2006). *Neuron* 51, 13–20.

Zigman, M., Cayouette, M., Charalambous, C., Schleiffer, A., Hoeller, O., Dunican, D., McCudden, C.R., Firnberg, N., Barres, B.A., Siderovski, D.P., and Knoblich, J.A. (2005). *Neuron* 48, 539–545.

Movement, Confusion, and Orienting in Frontal Cortices

Michael Brecht^{1,*}

¹Bernstein Center for Computational Neuroscience, Humboldt University, Berlin 10115, Germany

*Correspondence: michael.brecht@bccn-berlin.de

DOI 10.1016/j.neuron.2011.10.002

In this issue, two studies, by Ehrlich et al. and Hill et al., address the role of the frontal motor cortices in behavior of the rat and suggest a potential role for this structure in high-level control of diverse behaviors. Hill et al. show that motor cortical neurons predict whisker movements even without sensory feedback and that their activity reflects efferent control. Surprisingly, Ehrlich et al. report the participation of this same cortical region in the preparation and execution of orienting behaviors.

The inadequate access of young scientists to funding and university resources predates shrinking NIH budgets. In the late 1860s two young physicians, Fritsch and Hitzig, were associated with the Berlin Physiological Institute but did not have working space available there. They went home, tied down their experimental animals on Fritsch's wife's dressing table, and performed perhaps the greatest neurophysiological experiment of all times. They analyzed the electric excitability of cerebral cortex, first of an awake rabbit, then of awake dogs, and finally of anesthetized dogs. The scientists employed a primitive current generator and adjusted current strength by attaching the platinum stimulation electrodes to

the tongue and choosing currents that evoked tickling sensations. At some frontal stimulation sites they made an incredibly spooky observation. Currents evoked a wide variety of movements of the experimental animals, whereby the type of evoked movement varied with the cortical location of the stimulation site. Fritsch and Hitzig then went on and lesioned cortical sites representing forelimb movements. Such lesions resulted in a partial inability to do forelimb movements and greatly strengthened the conclusions of the stimulation experiments. The investigators correctly concluded that motor functions were localized at discrete sites in the cerebral cortex. The results shook the world.

Cortical function could be studied scientifically. The neurophysiologist's electrodes replaced the phrenologist's fantasies. The Scottish physiologist Ferrier reproduced Fritsch and Hitzig's results in monkeys. By 1875—just five years after the initial publication—it was clear that neural activity in motor cortices is both necessary and sufficient for motor control.

Confusing Motor Map Complexity

Even though Fritsch and Hitzig's experiment was immensely illuminating and once and for all clarified our thinking about the brain, their motor mapping approach also elucidated a complexity of cortical organization that we are still struggling with today. When more and more motor

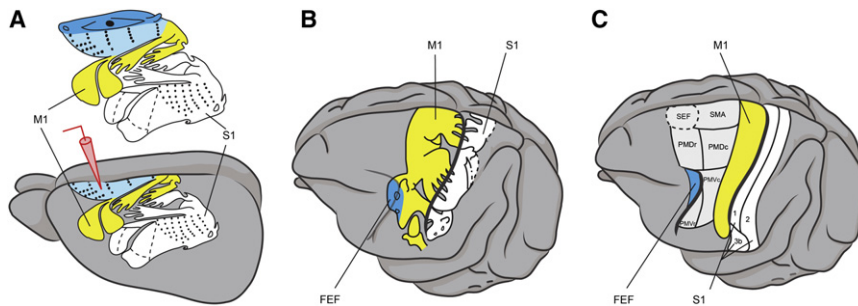


Figure 1. Partitioning Schemes of Rat and Macaque Monkey Motor Cortices

(A) Schematic of rat primary somatosensory (S1, white) and motor (M1, color) cortex as a flat map (top) and superimposed on the rat brain (bottom). The red electrode indicates the recording site of the studies by Hill et al. (2011) and Erlich et al. (2011).

(B) A schematic of the precentral motor and postcentral somatosensory map derived by Woolsey et al., 1958 in the macaque monkey. The supplementary motor area also identified by these authors is not shown. FEF, frontal eye field.

(C) A recent (see Preuss et al., 1996) more fine-grained map of monkey cortex as derived by intracortical microstimulation and single-cell recording.

maps from different investigators and different species became available it became clear—much to the surprise of early investigators—that motor maps differed between species and that there is not one universal mammalian cortical motor organization. Today it is a commonplace that the different motor capacities and habits of the different mammalian species are reflected in the different motor maps of these species. Even worse, it turned out that motor maps derived from the same species by different investigators could differ considerably. It was also observed that motor maps are not even entirely consistent within experiments, an observation referred to “functional instability of cortical motor points” by Sherrington. Finally, it was found that muscletomy captures the complexity of cortical motor organization only partially (Schieber, 2001) and that motor cortex might contain multiple entirely different maps. In particular, when long and intense stimulation trains are used, one can evoke from single motor cortical sites complex, “goal-directed” motor behaviors (Graziano et al., 2002). As these movements include sequences of very different muscle activation patterns, they require some kind of remapping of motor output during behavior. Behaviors map in an orderly fashion onto motor cortex and are organized according to “ethological” categories, i.e., defensive behaviors, reaching behaviors, etc.

Ultimately, investigators started to integrate cytoarchitectonic, connectional,

recording, and lesion data in their concepts of cortical localization, but—while it greatly expanded our knowledge of cortical circuitry—it also led to novel disagreements and an even wider variety of cortical partitioning schemes. This has led to a Babylonian confusion about how to label cortical areas. Thus, two studies published in this issue of *Neuron* report data from exactly the same area in rodent cortex, but they refer to it under different names, namely as vibrissae primary motor cortex (vM1; Hill et al., 2011) or frontal orienting field (FOF; Erlich et al., 2011). If there were just two names for this area, we would probably deal with it, but the reality is that this exact same piece of cortex has also been referred to as anteromedial cortex, dorsomedial prefrontal cortex, medial precentral cortex, frontal eye field (FEF), vMC (vibrissa motor cortex), agranular medial area (AgM), frontal area 2 (F2), and secondary motor cortex (M2). This cacophony of names fundamentally impairs our ability to communicate our findings.

Consensus Views on Cortical Motor Organization

There is hope, however. First, investigators have taken up the challenge posed by cortical complexity. Specifically as reported in this issue, Hill et al. (2011) and Erlich et al. (2011) performed sophisticated recording, blocking, and deafferentation experiments in rats. Perhaps most importantly, the researchers overcame the temptation to be original and

performed experiments very similar to those that had been done before in other cortical areas and species. As discussed in depth below, the results reveal both intriguing similarities and crystal-clear differences between cortical areas; collectively, the experiments make one feel that we are on the road of clarification about motor cortices. Second, the challenging organizational diversity of motor maps will ultimately make comparative cortical localization much more interesting. Third, there is much more consensus about motor organization than suggested by the plethora of area names. For example—even though everyone refers to it by a different name—there is excellent agreement between studies about the stereotaxic coordinates of whisker motor cortex. We thus know that vibrissae motor cortex is a large frontal/medial cortical area. Recent work that incorporated cytoarchitectonic data (Neafsey et al., 1986) and identified neurons (Brecht et al., 2004a) suggested that there is one major motor map in rodent frontal cortex (Figure 1A). This scheme is not unlike the motor map identified by early investigators such as Woolsey and Penfield in primates (Figure 1B). This scheme recognized in monkeys and humans a major motor map along the precentral sulcus and a smaller, medially situated motor field referred to as supplementary motor area (not shown in Figure 1B). When Asanuma and colleagues introduced a novel method of brain stimulation for which they used microelectrodes (originally developed for extracellular single-cell recordings), which they inserted directly into the cortical tissue rather than apply surface stimulation as Fritsch and Hitzig did, a much more fine-grained picture of primate motor cortices emerged (Figure 1C). In those recent maps the major precentral motor field is divided into a primary motor cortex M1, premotor cortices, and a frontal eye field (FEF), which is spatially segregated from M1. It is noteworthy, however, that eye movements are conspicuously absent from M1 as defined in this scheme. It seems possible that the primate frontal eye fields are simply a segregated part of what once was a single major precentral motor map. Thus, the different views of motor organization outlined in Figures 1A–1C are not all too incompatible (for

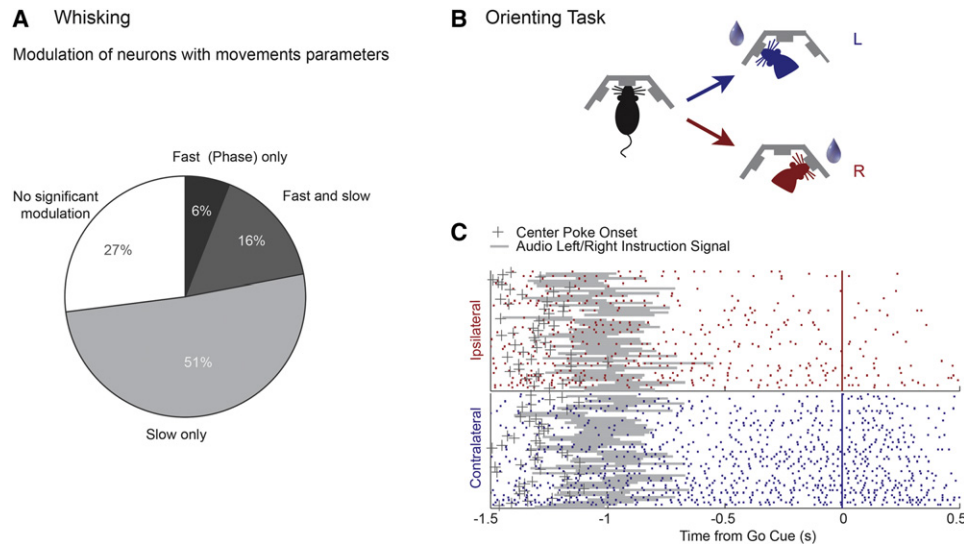


Figure 2. Covariation of Cortical Activity with Whisking and Orienting in the Rat

(A) Covariation of cortical activity with whisking parameters.
 (B) Orienting task.
 (C) Activity during and prior to orienting, dots indicate spikes. Note the differential activity preceding the different turning movements.

a review of the full complexity in assessing frontal cortex homologies between primates and rodents, see [Preuss, 1995](#)).

Cortical Control of Whisker Movements

How then does the vibrissa motor cortex control whisker movements? How is motor control through motor cortex different from activity in somatosensory cortex, whose stimulation also evokes movements? Addressing this question has been remarkably difficult, not the least because whisker movements are among the fastest movements performed by mammals. Hill and et al. (2011) tackle this problem by performing recordings in vibrissa motor cortex combined with high-speed videography and electromyographic recordings of whisker muscle activity. They find that a large fraction of neurons in vibrissa motor cortex is modulated in their activity during whisker movements ([Figure 2A](#)). Interestingly, only a few neurons appear to be involved in the precise timing of movements (the phase of the whisking rhythm). Most cells covary in their activity with slow movement parameters such as the envelope of the movement or the midpoint of movements around which the whiskers oscillate ([Figure 2A](#)). The predominance of cells concerned with slow movement

time scales is in line with an earlier recording study, which also showed that cells did not covary 1:1 with the whisking rhythm and that cells would globally turn off and on with whisking ([Carvell et al., 1996](#)). [Hill et al. \(2011\)](#) also show that motor cortical neurons accurately predict whisker movements. Most interestingly, this covariation of motor cortical activity and whisker movements persist after removal of sensory feedback, implying that it reflects efferent control rather than afferent modulation. This finding differs from data in somatosensory cortex, where the removal of sensory feedback disrupts the comodulation of activity and whisking ([Fee et al., 1997](#)). This result is of great significance, because it presents one of the clearest dissociations of vibrissae motor and somatosensory cortical activity in sensorimotor integration discovered so far. The modulation of neural activity associated with whisking is fairly weak. Overall there is only a temporal redistribution of neural activity during whisking and no net firing rate increase during whisking!

Does such weak modulation argue against a motor role of these neurons? Almost certainly not. In most mammalian motor cortices the activity during spontaneous behaviors is rather modest. The situation changes when tasks become

complicated or when animals are trained on certain movements. One might guess that for most of the day motor cortex is not in the driver's seat, and instead acts like a mastermind of complicated, unusual, or very significant movements. As for the lesions to the motor cortical forelimb representation performed by [Fritsch and Hitzig](#), damage to vibrissa motor cortex does not fully abolish whisker movements. The persistence of whisking after cortical ablation suggested early on the existence of a brain stem pattern generator for whisking. Lesions to vibrissa motor cortex do affect the amplitude distribution of whisker movements, a result much in line with the current results from [Hill et al. \(2011\)](#). The characteristics of stimulation-evoked movements in vibrissa motor cortex strongly depend on methodology of stimulation and the identity of the stimulated neurons ([Brecht et al., 2006](#)). Stimulation of pyramidal neurons and interneurons evokes movements of opposite directions. While movements evoked by brief trains of extracellular stimulation pulses are brief and restricted to few whiskers, movement fields observed with single-cell stimulation are large and single-cell-evoked movements persist for seconds ([Brecht et al., 2004b](#)). Single-cell stimulation effects are in line with the conclusion of [Hill et al.](#)

(2011) that vibrissa motor cortex controls movements on long timescales. Vibrissa motor cortex distributes output to a wide variety of subcortical targets. Inputs to vibrissa motor cortex arrive from a wide variety of brain regions in an intricate extremely orderly laminar pattern.

Orienting and Working Memory in Frontal Cortices

As firmly indicated by the stereotaxic coordinates of their recordings, Erlich et al. (2011) study the same cortical region as Hill et al. (2011) (vibrissa motor cortex), but their investigation takes a very different angle and they refer to the recorded region as frontal orienting field (FOF). They show that blocking neural activity in FOF/vMC interferes with a memory guided orienting task. Recordings demonstrate that a large fraction of neurons in FOF/vMC show delay activity that predicts upcoming orienting movements and this activity occurs without an obvious relation to whisker movements (Figures 2B and 2C). They conclude that such findings corroborate a similarity between the primate frontal eye fields and the rat FOF/vMC. How similar is FOF/vMC to the primate frontal eye field? A major similarity that links both FEF/vMC and the primate FEF to orienting behaviors is that both areas project heavily to deep layers of the superior colliculus, a key subcortical integration site for orienting responses. Lesion data in monkeys showed that combined lesions to the superior colliculus and the FEF result in much more devastating effects on orienting than lesions to one of the two structures alone (Schiller et al., 1980). Earlier

lesion studies in rats had already indicated that FOF/vMC damage can cause neglect-like symptoms and orienting deficits (Crowne et al., 1986). The deficits in memory-guided orienting observed by Erlich et al. (2011) mirror deficits induced by interference with primate frontal eye fields, which causes lasting problems in orienting toward remembered target locations (Dias and Segraves, 1999). Overall, frontal cortices seem to have a key function in generating delayed responses, which require working memory. The presence of delay activity (as demonstrated by Erlich et al., 2011; Figure 2B) is a prominent physiological characteristic of neurons in primate frontal cortices and is often regarded as a neural correlate of working memory. In summary, the work of Erlich et al. (2011) lets it appear that—in the midst of all the aforementioned confusion—decades of work on the frontal and rodent cortices are beginning to converge.

Conclusion

Sensor movements of eyes, pinnae, or whiskers are relatively simple movements, yet motor mapping implicates large parts of the frontal cortices in their control. Activity in frontal motor cortices is associated less with the fine detail of orienting movements and more so with the overall control of movements and their preparation. Modulation of neural activity is weak for simple sensor movements. The attentional/orienting deficits imposed by lesions of cortices involved in sensor movements reveal that the function of these cortices goes way beyond pure motor control. That said, a homology of

rodent eye, whisker, pinna motor cortex, and primate frontal eye and pinna fields is plausible but remains to be definitively proven.

REFERENCES

- Brecht, M., Krauss, A., Muhammad, S., Sinai-Esfahani, L., Bellanca, S., and Margrie, T.W. (2004a). *J. Comp. Neurol.* 479, 360–373.
- Brecht, M., Schneider, M., Sakmann, B., and Margrie, T.W. (2004b). *Nature* 427, 704–710.
- Brecht, M., Grinevich, V., Jin, T., Margrie, T., and Osten, P. (2006). *Pflugers Arch.* 453, 269–281.
- Carvell, G.E., Miller, S.A., and Simons, D.J. (1996). *Somatosens. Mot. Res.* 13, 115–127.
- Crowne, D.P., Richardson, C.M., and Dawson, K.A. (1986). *Behav. Brain Res.* 22, 227–231.
- Dias, E.C., and Segraves, M.A. (1999). *J. Neurophysiol.* 81, 2191–2214.
- Erlich, J.C., Bialek, M., and Brody, C.D. (2011). *Neuron* 72, this issue, 330–343.
- Fee, M.S., Mitra, P.P., and Kleinfeld, D. (1997). *J. Neurophysiol.* 78, 1144–1149.
- Graziano, M.S.A., Taylor, C.S.A., and Moore, T. (2002). *Neuron* 34, 841–851.
- Hill, D.N., Curtis, J.C., Moore, J.D., and David Kleinfeld, D. (2011). *Neuron* 72, this issue, 344–356.
- Neafsey, E.J., Bold, E.L., Haas, G., Hurley-Gius, K.M., Quirk, G., Sievert, C.F., and Terberry, R.R. (1986). *Brain Res.* 396, 77–96.
- Preuss, T.M. (1995). *J. Cogn. Neurosci.* 7, 1–24.
- Preuss, T.M., Stepniewska, I., and Kaas, J.H. (1996). *J. Comp. Neurol.* 371, 649–676.
- Schieber, M.H. (2001). *J. Neurophysiol.* 86, 2125–2143.
- Schiller, P.H., True, S.D., and Conway, J.L. (1980). *J. Neurophysiol.* 44, 1175–1189.