

# **Wilder Penfield in the age of YouTube: Visualizing the sequential activation of sensorimotor areas across neocortex**

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**The flow of electrical activity between different areas of neocortex is essential for many sensorimotor tasks. Whether this flow is localized or spreads widely is unknown. Ferezou et al., imaging activity across the bulk of the cortical mantle in awake mice, show that touch by a single vibrissa leads to a rapid depolarization in primary sensory and motor areas that subsequently spreads across most of cortex.**

Propagation of information between different areas of cortex is a critical element in the construction of a motor response based on sensory input. Investigations of information flow have often used measurements of extracellular potentials and neuronal spiking in primates to infer communication between different regions of the brain concurrent with decision making. For example, the role of feedback from higher- to lower-level visual areas during a visual discrimination task has been explored through electrophysiology in primates (Supèr et al., 2001) and psychophysics in humans (Murray et al., 2002; Watanabe et al., 1998). Similarly, there is evidence for high-level control of sensorimotor tasks. For example, Cauller and Kulics (1991) showed that the variation in choice during a discrimination task depends on signaling from secondary to primary somatosensory areas. These authors further identified a central “[...] paradox of neuroscience: while the goal may be to understand the conscious operation of the brain,

only brains that are unconscious may be thoroughly analyzed.” This situation is now changing with emerging studies that emphasize large-scale neuronal signaling in awake animals, in addition to those that emphasize underlying neuronal computations.

In this issue of *Neuron*, Petersen and colleagues (Ferezou et al., 2007) explore the sequential activation of the vibrissa primary somatosensory area (S1) in parietal cortex and the vibrissa primary motor area (M1) in frontal cortex in response to deflection of facial macrovibrissae in mice. These investigators used the voltage-sensitive dye technique of Cohen and coworkers (Orbach et al., 1985) to observe changes in membrane polarization and a uniquely large craniotomy to expose the entirety of the somatosensory and motor areas and most of the cortical mantle, including both hemispheres. Ferezou et al. (2007) were able to image single-trial responses in the awake animal, as has been reported previously in the awake (Ferezou et al., 2006) and anesthetized (Arieli et al., 1995; Petersen et al., 2003) animal using smaller craniotomies. The acquisition of reliable single-trial data rests on the use of dyes whose absorption spectra have minimum overlap with the absorption by hemoglobin (Shoham et al., 1999), the use of head-restrained animals (Ono et al., 1986) trained to contact a sensor with their vibrissae (Bermejo and Zeigler, 2000), and the realization that vasomotor fluctuations, which comprise the dominant noise source in optical imaging experiments (Mayhew et al., 1996), are minimal in mice (Kalatsky and Stryker, 2003).

Past work with both primates (Wannier et al., 1989) and rodents (Kleinfeld et al., 2002) have characterized the nature of sensory-driven responses in motor cortex. Ferezou et al. (2007) go beyond these studies and identify the sequence of activation that occurs in response to stimulation of a single vibrissa (Figs. 1A and 1B). A region of depolarization appears initially in vibrissa S1 cortex and is followed by depolarization of vibrissa M1 cortex. Unexpectedly, the depolarization in S1 cortex spreads to a neighboring region whose neurons do not spike in the anesthetized animal (unresponsive zone in figure 1B). This is followed by continued expansion of the loci in S1 and M1 cortices to regions that include non-vibrissa areas of somatosensory and motor cortices, eventually enveloping much of both hemispheres.

In line with past work by Petersen and coworkers (Ferezou et al., 2006), the amplitude of the dye response and the extent of spatial spread depend on the behavioral state of the animal prior to deflection of the vibrissa. For example, the relative amplitude of the dye signal in different regions depends on whether or not a passive deflection evokes active whisking. If whisking is evoked, substantial signals are observed in both S1 and M1 cortices. If whisking is not evoked, or if the animal was whisking before the applied deflection, the dye signal is relatively weak in S1 cortex and essentially absent from M1 cortex.

How is the flow of information across cortex controlled? Ferezou et al. (2007) show that suppression of activity in S1 cortex by the local injection of glutamate receptor antagonists largely suppresses depolarization of M1 cortex. This result could reflect direct activation of M1 cortex via monosynaptic connections from S1 cortex (Porter and White, 1983), but is also consistent with activation of M1 cortex via an ascending pathway through the posterior medial thalamus (PO in figure 1C). The pathway through PO thalamus is enabled, in the sense that it can relay spikes to cortex, by two mechanisms: a descending input from S1 cortex (Diamond et al., 1992) and relief of inhibition of PO thalamus via a descending projection from M1 cortex through zona incerta (Urbain and Deschênes, 2007) ( $ZI_v$  in figure 1C). It is of interest that an ascending sensory pathway that flows through cerebellar circuitry and ventral lateral thalamus (VL in figure 1C) (Huerta et al., 1983; Miyashita et al., 1994) does not appear to have a strong role in the large-scale depolarization of M1 cortex. Thus, as noted by Ferezou et al. (2007), the depolarization of M1 cortex appears to be dominated by direct input from S1 cortex. Finally, while Ferezou et al. (2007) observe depolarization that is gated by vibrissa movement, they do not report rhythmic modulation of depolarization that is phase-locked to exploratory whisking. The reason for this discrepancy needs to be understood, as extracellular current flow that is locked to whisking occurs in both S1 (O'Connor et al., 2002) and M1 (Ahrens and Kleinfeld, 2004) cortices.

We now consider the possible interaction of stimulus- or movement-evoked responses

with ongoing electrical activity. The studies of Lamme and colleagues (Supèr et al., 2001) on awake primates suggest that the ongoing multi-unit activity interacts with sensory input to reach a threshold for perception. Can such an interaction be observed through optical imaging experiments? The data of Ferezou et al. (2007) is equivocal on this topic as few examples are given. However, Grinvald and colleagues (Arieli et al., 1995) previously addressed this issue by imaging ongoing and stimulus-evoked activity in the primary visual area (V1) of occipital cortex in the halothane-anesthetized cat. Their initial analysis of this data suggested that “[...] an individual response is the sum of two components: the reproducible [stimulus-evoked] response and the ongoing activity” (Arieli et al., 1996), although further analysis of this and additional data (Tsodyks et al., 1999) led to the revised claim that the ongoing activity is not random, but has a strong overlap with the patterns that are evoked by the set of sensory stimuli used in this experiment (Kenet et al., 2003). A parsimonious conclusion is that the evoked response can be stronger when the ongoing pattern is close to that of the evoked pattern (Tsodyks et al., 1999), consistent with the conclusions reached by Lamme and colleagues (Supèr et al., 2001).

In a recent issue of *Neuron*, Wu and colleagues (Xu et al., 2007) further considered the relationship between evoked and ongoing activity in primary visual (V1) and secondary visual (V2) areas of occipital cortex in isoflurane-anesthetized rats. Evoked activity appeared initially in V1 cortex, then propagated towards the border between V1 and V2 cortices, where it was partially reflected. In contrast, ongoing activity neither followed the directionality of the evoked response nor was it reflected at the border of V1 with V2 cortex. This result does not support the notion that evoked and ongoing activities produce spatially similar patterns of activation. One possible explanation of this difference is that the patterns of ongoing activity reported by Grinvald and colleagues (Arieli et al., 1995; 1996; Tsodyks et al., 1999) represent states with highly synchronous spiking, whose form is a consequence of the level of anesthesia as much as the underlying neuronal connectivity (Destexhe et al., 2003). Complementary imaging approaches are likely to help resolve whether, and how, evoked activity is shaped by ongoing activity in awake animals. One approach is the use of bulk-loaded intracellular

calcium indicators to record the spiking behavior of large numbers of individual neurons (Dombeck et al., 2007; Kerr et al., 2005; Ohki et al., 2005). The large amplitude of calcium signals, compared to voltage-sensitive dye signals, should also allow subtle, state-dependent changes in neuronal activity to be resolved. Hence in the near future we expect a plethora of new data and insights on neuronal signaling between cortical regions in trained, behaving animals.

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## Figure Legend

**Figure 1. Interactions between somatosensory and motor cortices.** **(A)** Map of a dorsal view of the left hemisphere of the rodent cortex, with several prominent somatosensory and motor regions highlighted (Chapin and Lin, 1984). The arrow labeled R points rostral and L points lateral. **(B)** Summary of the spread of membrane depolarization, as reported by Ferezou et al. (2007) for active touch in whisking mice. Times indicate the approximate latency from when a single vibrissa touched an immobile bar. **(C)** Schematic of afferent sensory pathways and thalamocortical sensorimotor pathways for the flow of spike-based signaling in the rodent (Kleinfeld et al., 2006; Urbain and Deschênes, 2007). Open arrows mark inhibitory pathways. Symbols: VPM, ventral posterior medial thalamus; PO, posterior medial thalamus, VL, ventral lateral thalamus;  $ZI_v^{mot}$  and  $ZL_v^{vib}$ , motor and vibrissa subdivision, respectively of ventral zona incerta, respectively. The slice, cut along the M1-S1 axis (Rocco and Brumberg, 2007), shows anterograde axon labeling two days after an injection of biotinylated dextran amine (BDA) in vibrissa S1 cortex. The axons that originate in S1 cortex course primarily through the deep layers and are visualized as a black reaction product of labeled BDA in M1, as well as S1 cortex. The pathway involving VPM thalamus had three subdivisions (dots). The tear in M1 cortex results from implantation of a stimulation electrode. Note the columnar subdivision (barrels) in S1 cortex. We thank J. C. Brumberg for supplying the photomicrograph.

