

transport or retention). In fact, the two sushi repeats in 1a have strikingly different structural properties and participate in protein interactions with multiple partners (Blein et al., 2004), which may generate additional heterogeneity in the GABA_B receptor system. It is possible that the extracellular domain of GABA_{B1} isoforms may interact with proteins not only on the same cell but also those on the synaptic partners or in the extracellular matrix to achieve proper subcellular localization. Second, are different isoforms of GABA_B receptors at different subcellular locations (e.g., dendritic shaft versus spine of CA1 pyramidal neurons) also preferentially exposed to distinct subtypes of GABA terminals? There is evidence that only certain subtypes of interneurons activate GABA_B receptors. Neurogliaform cells in the neocortex are such an example and appear to preferentially innervate GABA_B receptor-containing dendritic spines (Tamas et al., 2003). Is it possible that GABA_{B1} isoforms might contribute to a matching of pre- and postsynaptic sites through organizing extracellular protein interactions? Third, the learning and memory deficits in 1a^{-/-} mice may have resulted from altered developmental plasticity processes due to constitutive germ-line knockout. To further pin-point the precise physiological and behavioral functions of GABA_{B1} isoforms, conditional inactivation of 1a and 1b in specific neural circuits in the mature brain is necessary. Finally, although the molecular identities and functions of two distinct GABA_B subtypes are finally recognized by these studies, it is still difficult to explain the apparently more diverse GABA_B physiological responses in vivo (Kerr and Ong, 1995). It is possible that further functional variations of GABA_B receptors may arise from the modification of these two "prototype" GABA_{B1} isoforms, for example, by auxiliary proteins and post-translational mechanisms. Identification of GABA_B receptor-interacting proteins and characterization of their expression will undoubtedly provide further insight into the finer organization of the GABA_B system.

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Seeing What the Mouse Sees with Its Vibrissae: A Matter of Behavioral State

The behavioral state of an animal is accompanied by ongoing brain activity that primes neuronal circuitry to sensory inputs. While it should come as no surprise that the pattern of cortical activation is tied to behavioral states, only now has this dependence been imaged. In this issue of *Neuron*, Ferezou, Bolea, and Petersen show that the level and spatial extent of activation of vibrissa sensory cortex critically depend on behavioral context and mode of stimulation, i.e., passive versus active contact.

The central focus of systems neuroscience is to relate behavior to the underlying neuronal circuitry. Yet, for reasons of experimental convenience and control, the issue of behavior is often dropped, as the vast majority of neurophysiological studies on sensory encoding are performed on anesthetized (nonbehaving) animals. While this approach quenches neuronal feedback and thus exposes patterns of afferent inputs, the use of anesthetized preparations introduces biases in understanding the nature of sensory systems. Consider obvious differences between sensory processing in awake and anesthetized animals. First, brain dynamics during wakefulness are modified by an array of neuromodulators that are selectively released according to behavioral state (McCormick and Bal, 1997). Second, active positioning of sensors, such as tracking in vision or touch, or active changes in the sensory stream, such as sniffing in olfaction or tapping in touch, directly influence how stimuli are encountered and thus encoded by the nervous system. Third, attentional mechanisms, which depend on prior experiences and the expectation of reward, dynamically alter the manner in which neuronal circuits respond to stimuli.

Why is the use of awake behaving preparations still the exception rather than the rule for the study of cortical dynamics? To be fair, much primate research involves the use of awake animals. This reflects the *relative* ease with which primates can be trained both to do tasks and to sit comfortably with their head fixed so that electrodes may be inserted and removed. But the focus on awake animals has, for the most part, not filtered down to the rodent sensory community, despite the beautiful pioneering work of Chapin and Woodward (1982) on motor control of somatosensory input in free-ranging rats. Part of the problem is technical. However,

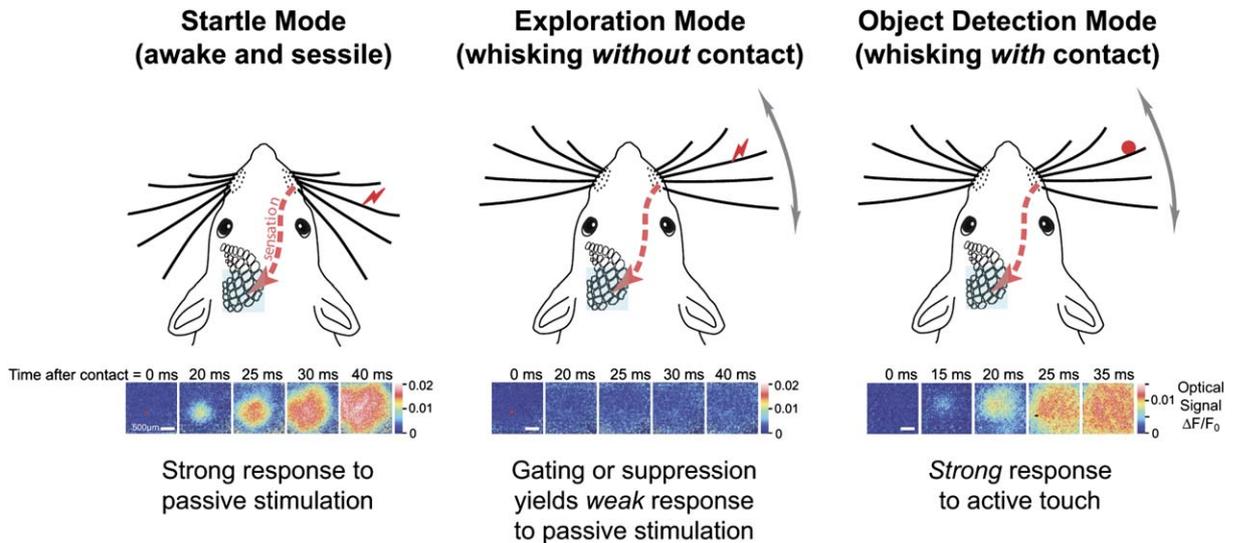


Figure 1. Summary of Behavioral States and Associated Cortical Responses Reported by Ferezou, Bolea, and Petersen

The upper panels are caricatures of the behavior of the mouse in three different awake states: a “startle mode” that corresponds to immobility, a “exploration mode” that is accompanied by rhythmic sweeps of the vibrissae in air, and an “object-detection mode” that corresponds to palpation of an object with the vibrissae. A sequence of images, in which each pixel reports the spatially averaged change in the membrane potential of neurons in superficial layers of vibrissa S1 cortex, corresponds to a typical response for each of the three awake states. Note the large difference between active and passive stimulation in the two whisking states.

advances in head-mounted devices allow one to monitor cortical activity in a manner that does not impede the ability of the animal to behave in a natural manner, even for mice (Luo et al., 2003). The other problem is the realization of an environment in which the relevant behavior and sensory input to the animal can be quantitatively tracked and manipulated concurrent with physiological measurements. Only when these two challenges are met can neuronal activity be reliably related to the sensory stream. In this issue of *Neuron*, Ferezou, Bolea, and Petersen (Ferezou et al., 2006) describe an approach that overcomes both of these obstacles through the use of voltage-sensitive dyes (VSDs) as a reporter of neuronal activity together with a fiber optic bundle to image cortical activity across the entire vibrissa region of primary somatosensory (S1) cortex in freely behaving mice. This technique allows the investigators to record the spatially averaged transmembrane potential, a measure unique to the use of VSDs (Grinvald et al., 1982). The observed signal corresponds to correlated depolarization across many neurons in the superficial layers. With the exception of highly synchronous activity, individual spikes are not resolved with this technique.

In the paradigm of Ferezou et al., mice were placed in a behavioral chamber that was positioned within the field of view of a high-speed camera, such that body, head, and individual vibrissa movements could be recorded simultaneously with images of the VSD signal. Stimulation of a vibrissa could be passive, by magnetic deflection of a strip of metal attached to the vibrissa; or active, by coaxing the mouse to tap an object with its vibrissa. Within limitations, this technique provides a means to assess the responses of large populations of neurons to stimuli in the wake of ongoing waves of cortical activity and related behavioral states. Further, these responses could be directly compared, for the

case of passive stimulation, to the response under anesthesia with the same mouse.

The unique aspect of the Ferezou et al. study concerns the relative response to passive versus active stimulation in different behavioral states. When animals are in an awake but sessile state, i.e., one characterized behaviorally by immobility and electrically by the dominance of irregular low-frequency activity in hippocampus (Berg et al., 2005), passive deflection of a vibrissa leads to a VSD signal that spreads across all of vibrissa S1 cortex (Figure 1A). The same stimulation leads to a dramatically different response when the animal is whisking. Passive stimulation while the mouse whisks leads to a highly variable response that, on average, is reduced 4-fold in amplitude compared to the case of passive stimulation with a sessile mouse (Figure 1B). How do we interpret the differences between the sessile and active responses? One possibility is that cholinergic activation of cortex during the active state leads to adaptation of the thalamocortical inputs (Castro-Alamancos, 2004). A second is that motor control of whisking per se gates the sensory stream. One scenario for such a gate could involve the inhibition of the paralemniscal pathway to vibrissa S1 cortex (Yu et al., 2006) by high-order thalamic nuclei (Lavallee et al., 2005; Trageser and Keller, 2004).

The big question is the nature of the cortical response during active touch. Here, Ferezou et al. recorded from mice as they actively touched objects with their vibrissae as they explored the behavioral chamber (Figure 1C). In contrast to the case for passive stimulation, the cortical responses were considerably enhanced in terms of maximum amplitude, but not as strong as the case for passive stimulation while sessile. Nonetheless, the critical fact is that passive and active touch lead to dramatically different cortical responses in the active animal.

It is of interest that the VSD signal recorded in response to active contact is not so different from the response to passive touch in anesthetized animals. Despite this similarity, the response to active touch surely masks underlying neuronal dynamics that are absent in the case of anesthesia. Neurons in vibrissa S1 cortex respond to whisking motion in the absence of contact, a self-generated sensory signal, such that different neurons tend to spike with higher probability at specific phases of the whisk cycle. This encoding of movement is seen both in extracellular (Fee et al., 1997) and intracellular recordings (Crochet and Petersen, 2006), yet was unresolved in the present imaging study, most likely as a result of limited dynamic range of the detector. Another confound is that reward modulates the degree of correlations among neurons during a whisking task (Ganguly and Kleinfeld, 2004). Similarly, attention and possibly the contextual nature of a task is likely to modulate the timing among cortical spikes, as occurs in the somatosensory system of primates (Steinmetz et al., 2000). Finally, active contact incorporates the mechanics of the vibrissa and the dynamics of the mystacial motor plant. The elastic properties of the vibrissa (Hartmann et al., 2003; Neimark et al., 2003) may lead to a multiplicity of stimulus-induced spikes through mechanical resonances and subsequent multiple contacts with an object. Multiple or more intense contacts may also result from transient, positive feedback in the brainstem sensorimotor loop (Nguyen and Kleinfeld, 2005).

A general issue raised by the work of Ferezou et al. is the interpretation of cortical responses in different behavioral states of the awake animal. It appears that the widespread, large-amplitude, and long-duration electrophysiological response evoked by passive stimulation in the sessile mouse reflects a “startle mode” in which animals are highly sensitive to unexpected sensory input (Figure 1A). Behaviorally, one would expect that an unanticipated stimulus delivered during the startle mode should have a significant behavioral impact, i.e., animals may become active in order to investigate the unexpected stimulus. Ferezou et al. informally observed such changes in that mice tended switch from sessile to exploratory behaviors shortly after receiving passive and unanticipated stimuli. In contrast, Ferezou et al. did not observe any behavioral influence as a result of passive stimulation during exploratory whisking, suggestive of an “exploratory mode” in which the mouse maintains a reliable expectation of sources of tactile stimulation as it sweeps its vibrissae through space (Figure 1B). One explanation is that unanticipated passive stimuli may be confused with self-motion, as opposed to contact with an object. Finally, Ferezou et al. show that during these same periods of exploration, physical contact of the vibrissae with an object leads to a pronounced cortical response. This is suggestive of an “object-detection mode” that provides information about the location and identity of objects in the immediate environment that are of intense behavioral relevance to the animal (Figure 1C).

A final issue concerns the implication of this study for the interpretation of cortical response from anesthetized animals. One the one hand, studies that define the topology of afferents inputs, exemplified by recent maps of direction sensitivity within individual columns in vibrissa

S1 cortex (Andermann and Moore, 2006), clearly depend on the use of anesthesia to quench feedback connections. However, studies of cortical dynamics and feedback that make use of anesthetized animals may well reach incorrect conclusions. The ascent of in vivo recording from cortex of free-ranging behaving rodents during vibrissa-based tasks (Fee et al., 1997; Krupa et al., 2004) will further refine the relation between behavior and neural circuitry. Advances in in vivo imaging technologies with free-ranging rodents, such as the VSD technique utilized by Ferezou et al. and emerging techniques that exploit nonlinear optics and endogenous markers of neuronal activity (Helmchen and Denk, 2002), will further push these studies.

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Parkin Blushed by PINK1

Mutations in the PTEN-induced putative kinase 1 (PINK1) are a common cause of autosomal recessive