

# The Functional Organization of the Barrel Cortex

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The tactile somatosensory pathway from whisker to cortex in rodents provides a well-defined system for exploring the link between molecular mechanisms, synaptic circuits, and behavior. The primary somatosensory cortex has an exquisite somatotopic map where each individual whisker is represented in a discrete anatomical unit, the “barrel,” allowing precise delineation of functional organization, development, and plasticity. Sensory information is actively acquired in awake behaving rodents and processed differently within the barrel map depending upon whisker-related behavior. The prominence of state-dependent cortical sensory processing is likely to be crucial in our understanding of active sensory perception, experience-dependent plasticity and learning.

## Introduction

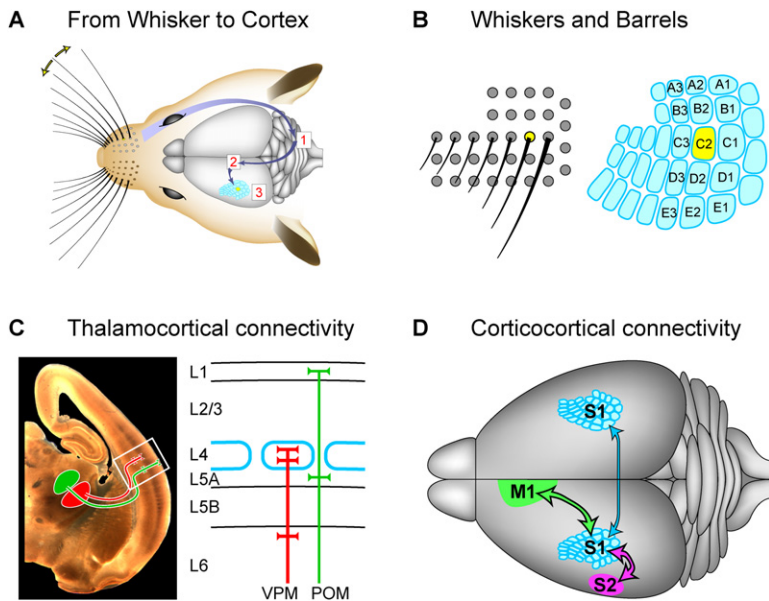
The whiskers on the snouts of mice and rats serve as arrays of highly sensitive detectors for acquiring tactile information. By using their whiskers, rodents can build spatial representations of their environment, locate objects, and perform fine-grain texture discrimination. Somatosensory whisker-related processing is highly organized into stereotypical maps, which occupy a large portion of the rodent brain. During exploration and palpation of objects, the whiskers are under motor control, often executing rapid large-amplitude rhythmic sweeping movements, and this sensory system is therefore an attractive model for investigating active sensory processing and sensorimotor integration.

Since mice and rats are nocturnal animals living in tunnels, the whisker system is likely to have evolved to compensate for the poverty of visual information during much of a rodent's life. Perhaps the most remarkable specialization of this sensory system is the primary somatosensory “barrel” cortex, where each whisker is represented by a discrete and well-defined structure in layer 4 (Woolsey and Van der Loos, 1970). These layer 4 barrels are somatotopically arranged in an almost identical fashion to the layout of the whiskers on the snout. This barrel map is in large part genetically specified and forms early in development. Within a few days of birth, the map is fixed, so that even dramatic interventions such as peripheral lesions have little effect upon the somatotopic layout of the barrels. The functional organization, postnatal development, and experience-dependent plasticity of the primary somatosensory whisker cortex can therefore be examined in the context of an invariant anatomical somatotopic map. In addition to long-term plasticity, it is also becoming increasingly clear that the functional operation of cortical circuits in behaving animals is under rapid and strong top-down control, generating highly flexible adaptive sensory processing within the same hard-wired neuronal networks (Gilbert and Sigman, 2007). It is therefore of great importance to examine the dynamic function of the

barrel cortex in the context of specific whisker-related behaviors.

## From Whisker to Cortex

The most important synaptic pathways signaling whisker-related sensory information to the neocortex have begun to be characterized (Figure 1A). Deflection of a whisker is thought to open mechanogated ion channels in nerve endings of sensory neurons innervating the hair follicle (although the molecular signaling machinery remains to be identified). The resulting depolarization evokes action potential firing in the sensory neurons of the infraorbital branch of the trigeminal nerve. A single sensory neuron only fires action potentials to deflection of one specific whisker. The innervation of the hair follicle shows a diversity of nerve endings (Ebara et al., 2002), which may be specialized for detecting different types of sensory input (Szwed et al., 2003). The sensory neurons make excitatory glutamatergic synapses in the trigeminal nuclei of the brain stem. Trigeminothalamic neurons in the principal trigeminal nucleus are organized into somatotopically arranged “barrelettes,” each receiving strong input from a single whisker (Veinante and Deschenes, 1999). The principal trigeminal neurons project to the ventral posterior medial (VPM) nucleus of the thalamus, which is also somatotopically laid out into anatomical units termed “barreloids.” VPM neurons respond rapidly and precisely to whisker deflection, with one “principal” whisker evoking stronger responses than all others (Simons and Carvell, 1989; Friedberg et al., 1999; Brecht and Sakmann, 2002). The axons of VPM neurons within individual barreloids project to the primary somatosensory neocortex forming discrete clusters in layer 4, which form the basis of the “barrel” map. The layer 4 barrel map is arranged almost identically to the layout of the whiskers on the snout of the rodent (Woolsey and Van der Loos, 1970; Figure 1B), and the barrels can be easily visualized in both living and stained brain slices (Finnerty et al., 1999; Petersen and Sakmann, 2000). Although the primary



**Figure 1. Synaptic Pathways for Processing Whisker-Related Sensory Information in the Rodent Barrel Cortex**

(A) Deflection of a whisker evokes action potentials in sensory neurons of the trigeminal nerve, which release glutamate at a first synapse in the brain stem (1). The brain stem neurons send sensory information to the thalamus (2), where a second glutamatergic synapse excites thalamocortical neurons projecting to the primary somatosensory barrel cortex (3).

(B) The layout of whisker follicles (left, only C-row whiskers shown) on the snout of the rodent is highly conserved and is identical between rats and mice. There are obvious anatomical structures termed “barrels” in layer 4 of the primary somatosensory neocortex (right), which are laid out in a near identical pattern to the whiskers. The standard nomenclature for both whiskers and barrels consists of the rows A–E and the arcs 1, 2, 3, etc. The C2 whisker follicle and the C2 barrel are highlighted in yellow.

(C) There are at least two important parallel thalamocortical pathways for signaling whisker-related sensory information to the barrel cortex. Neurons in the ventral posterior medial (VPM) nucleus (labeled red, left) are glutamatergic and signal information relating primarily to deflections of a single whisker.

The axons of VPM neurons terminate predominantly in individual layer 4 barrels, with a minor innervation in upper layer 6 (right). Corticothalamic layer 6 neurons provide reciprocal feedback to the VPM (not shown). Neurons of the posterior medial (POM) thalamic nucleus (labeled green, left) have broader receptive fields and are tightly regulated by state-dependent control imposed by zona incerta and the cortex. The axons of POM neurons avoid the layer 4 barrels and target primarily layer 1 and 5A (right). Corticothalamic neurons in layer 5 provide a strong input to POM (not shown).

(D) Neurons in the barrel cortex are reciprocally connected to other cortical areas through long-range glutamatergic corticocortical synapses. The most important pathways connect the primary somatosensory (S1) barrel cortex with secondary somatosensory cortex (S2) and primary motor cortex (M1) on the same hemisphere. Callosal projections are also present but less prominent.

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target of VPM axons is layer 4, there is also a weaker innervation of upper layer 6 (Figure 1C). The clear anatomical maps segregating neighboring whisker representations in this “lemniscal” pathway strongly suggest a labeled-line single-whisker signaling pathway from the periphery to the barrel cortex. However, there are two striking differences in the whisker-related sensory processing comparing the periphery to the barrel cortex. First, whereas sensory information in the trigeminal ganglion at the periphery encodes whisker stimuli with remarkable reliability (Jones et al., 2004; Arabzadeh et al., 2005), the neocortex instead responds with enormous trial-to-trial variability to identical well-controlled stimuli (Petersen et al., 2003b; Sachdev et al., 2004; Arabzadeh et al., 2005). This variability is driven predominantly by interactions with ongoing spontaneous cortical activity (Petersen et al., 2003b; Sachdev et al., 2004). Second, the single-whisker receptive fields found in the trigeminal ganglion contrast with the broad receptive fields in the neocortex (Simons, 1978; Moore and Nelson, 1998; Zhu and Connors, 1999; Brecht et al., 2003; Higley and Contreras, 2003). These observations suggest that a primary function of the neocortex is to generate associations of different sensory inputs which are processed in a highly context-dependent manner.

The increasing complexity of sensory processing in higher brain areas is likely to be mediated, in part, through interactions of parallel ascending pathways for processing

whisker-related information. Although the lemniscal pathway is likely to be a major sensory pathway for whisker-related information, it is by no means the only one (Yu et al., 2006). In addition to the synapses formed in the principal trigeminal nucleus, the axons of the trigeminal sensory neurons also provide excitatory input to spinal trigeminal brainstem nuclei. The trigeminal spinal interpolaris nucleus is also somatotopically organized into barrelettes and responds well to whisker deflections. The interpolaris nucleus can be subdivided into two anatomically and functionally distinct regions (Furuta et al., 2006). The caudal part forms the recently discovered “extralemniscal” pathway signaling through a ventrolateral strip of the VPM to the secondary somatosensory cortex and the “septal” regions of S1 (Pierret et al., 2000). In the rat there can be large gaps, called “septa,” between individual layer four barrels, which have different microcircuits to the barrel columns (Kim and Ebner, 1999). Although these septal regions may play an important role in the rat whisker sensorimotor system, they are not obvious in the mouse, where neighboring barrels are tightly apposed to each other. For the sake of simplicity and presenting a unified view of the rat and mouse barrel cortex, the septal system will not be further discussed in this review. The rostral part of the interpolaris nucleus forms the beginning of the important “paralemniscal” pathway, projecting to the posterior medial (POM) nucleus of the thalamus, which in turn primarily innervates layer 1 and 5A of the primary

somatosensory cortex (Figure 1C), the secondary somatosensory cortex and the motor cortex. In anesthetized animals, this paralemniscal pathway is unlikely to contribute strongly to sensory processing since a rapid GABAergic inhibition from zona incerta silences the POM nucleus (Lalavée et al., 2005). However, this inhibition depends upon brain state (Trageser et al., 2006) and in addition POM receives strong cortical excitatory input (Diamond et al., 1992). The paralemniscal pathway may therefore play important roles during active exploration, perhaps contributing to sensorimotor coordination.

Following a whisker deflection, cortical sensory processing might be further distributed to other cortical areas through cortico-cortical synaptic connections from primary to secondary somatosensory cortex and from somatosensory to motor cortex (White and DeAmicis, 1977; Welker et al., 1988; Chakrabarti and Alloway, 2006; Figure 1D). Callosal connectivity between the barrel cortices on opposite hemispheres appears to be limited to the representation of the most medial A-row whiskers (Petreanu et al., 2007).

### Functional Mapping of the Barrel Cortex Visualizing the Cortical Representation of a Single Whisker

Classical methods of repeatedly introducing an extracellular electrode into the somatosensory cortex to record action potential firing have been used extensively to study the suprathreshold receptive fields of individual neurons (for example, Welker, 1971; Simons, 1978; Armstrong-James et al., 1992; de Kock et al., 2007). These measurements are time consuming since each electrode penetration provides information relating to a very small area of the cortex and the number of penetrations will therefore determine the accuracy of the resulting map. A number of techniques have therefore been developed in order to rapidly and reliably map the distribution of cortical sensory processing evoked by whisker deflections.

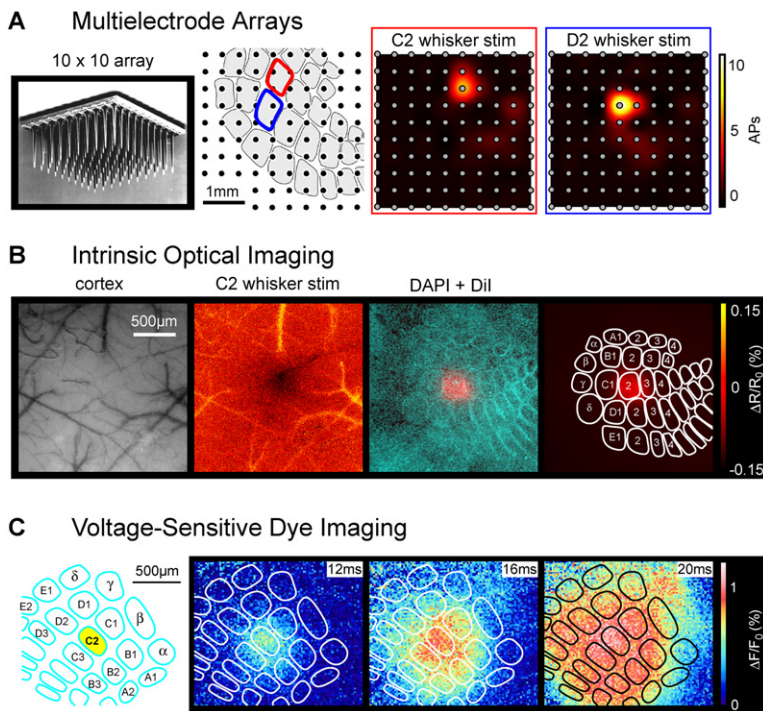
The simplest extension of the classical extracellular receptive field-mapping strategy is to record from many electrodes simultaneously. The most elegant solution is to use a spatially ordered array of electrodes, such as that shown in Figure 2A (Harris et al., 1999; Petersen et al., 2001). The number of action potentials recorded on each electrode can be color-coded and presented as an image mapping the distribution of sensory-evoked activity. Deflection of a single whisker evokes action potentials recorded on only a few neighboring electrodes, with a clear somatotopic shift in activity when different whiskers are stimulated (Figure 2A). However, the spatial resolution is of course limited by the number of electrodes in the matrix.

Optical imaging techniques are the most obvious approaches to obtaining higher spatial resolution. One of the simplest and least invasive mapping techniques is intrinsic optical imaging (Grinvald et al., 1986; Polley et al., 1999). In the mouse, highly localized intrinsic signals evoked by repetitive deflection of the C2 whisker can be imaged through the intact skull without thinning

(Figure 2B). The physical basis of the intrinsic signals are related to changes in blood flow and are therefore similar to those underlying the blood oxygenation level-dependent (BOLD) signal observed in functional magnetic resonance imaging (fMRI). Indeed, with the increasing availability of the necessary equipment and new technical developments, it should be possible to routinely map the brain areas (both cortical and subcortical) activated by a single-whisker stimulus in an entirely noninvasive manner through fMRI (Yang et al., 1996). Intrinsic optical imaging has the advantage of being cheap, rapid, and extremely reliable. That it is an almost noninvasive technique makes it ideal as a mapping tool before carrying out other experimental manipulations such as for targeting whole-cell recordings (Crochet and Petersen, 2006) or targeted viral manipulations (Aronoff and Petersen, 2006). However, intrinsic imaging inherently suffers from a poor time resolution, since its physical basis is only indirectly related to neuronal activity.

Direct mapping of the electrical activity of the cortex can be obtained at millisecond temporal resolution and subcolumnar spatial resolution by voltage-sensitive dye (VSD) imaging (recently reviewed by Grinvald and Hildesheim, 2004). Typically, the dye is applied directly to the cortical surface after making a craniotomy. The VSD diffuses into the superficial layers of the cortex and changes fluorescence rapidly and linearly with respect to membrane potential (Petersen et al., 2003a, 2003b; Ferezou et al., 2006; Berger et al., 2007). In particular, VSD imaging is very sensitive to subthreshold membrane potential changes, which under anesthesia and during some awake states dominates the electrical activity of cortical neurons. A single brief deflection of the C2 whisker evokes a sensory response with complex spatiotemporal dynamics measured with VSD (Figure 2C). The earliest response occurring ~10 ms after whisker deflection is highly localized to its corresponding C2 barrel column. However, in the following milliseconds the response increases in amplitude and propagates horizontally to cover a large fraction of the barrel cortex. The overall impression with VSD imaging is therefore that although cortical columns are functionally present, they only last a few milliseconds and then large areas of the cortex become depolarized. The results obtained by VSD imaging are in excellent agreement with the broad subthreshold receptive fields of supragranular neurons observed during whole-cell recordings (Moore and Nelson, 1998; Zhu and Connors, 1999; Brecht et al., 2003). The propagating VSD responses therefore indicate that large numbers of neurons across the cortical map are influenced by a single-whisker deflection. The dynamic distributed processing of information is likely to be important for integrating different sensory inputs in a context-dependent manner necessary for perception and associational learning.

However, the spreading sensory responses observed with VSD imaging contrast with the localized responses observed with extracellular measures of action potentials (Figure 2A) and intrinsic optical imaging (Figure 2B). The



**Figure 2. Functional Mapping of the Barrel Cortex**

(A) Cortical action potential activity can be mapped using well-ordered arrays of electrodes, for example the “Utah” array of  $10 \times 10$  electrodes with a grid spacing of  $400 \mu\text{m}$  (far left). The array can be inserted into the rat somatosensory barrel cortex (center left). Deflection of a single whisker evokes a localized increase in action potential activity under urethane anesthesia, which can be color-coded for each electrode to form an image of evoked electrical activity. Responses evoked by deflection of the C2 whisker (center right) is somatotopically separated from evoked action potentials resulting from D2 whisker deflection (far right).

(B) Intrinsic optical imaging can be used to noninvasively map sensory processing in the mouse neocortex through the intact unthinned skull. The cortical surface blood vessels can be imaged with green light (far left). Repetitive 10 Hz deflection of the C2 whisker under urethane anesthesia evokes a highly localized change in reflected red light resulting from the coupling of blood flow to neural activity (center left). A crystal of Dil was subsequently placed in the location of the functionally mapped C2 representation, by alignment of the blood vessels with the intrinsic optical image. After allowing time for Dil diffusion, the brain was sectioned horizontally and stained with DAPI to reveal the location of nuclei, which outline the layer 4 barrel

walls in the mouse somatosensory cortex. Red Dil fluorescence is located in the C2 barrel indicating a close match between functional mapping by intrinsic optical imaging and the anatomical barrel map (center and far right).

(C) The spatiotemporal dynamics of supragranular membrane potential changes can be imaged with millisecond temporal resolution and subcolumnar spatial resolution using voltage-sensitive dye imaging. The voltage-sensitive dye RH1691, here applied to the mouse barrel cortex under urethane anesthesia, increases fluorescence in response to depolarization. A brief deflection of the C2 whisker evokes an early localized depolarization limited to the C2 cortical barrel column (12 ms). However, over the next milliseconds, the depolarization spreads across the barrel field. These data indicate that even a single brief whisker deflection can inform a large area of the cortex.

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most important reasons for the different spatial extents of the sensory responses likely relates to the measurement of suprathreshold versus subthreshold membrane potential changes. Action potential activity correlates closely with the extent of the intrinsic signal (Polley et al., 1999, 2004), whereas subthreshold membrane potential changes dominate the VSD signal. Since action potentials are only evoked when membrane potential crosses a threshold, the more localized suprathreshold activity could simply reflect the “tip of the iceberg” visible above a large and distributed subthreshold depolarization (Berger et al., 2007). An additional factor regulating the cortical extent of the single-whisker response is the frequency of whisker stimulation, with higher frequency stimulation giving rise to more focused cortical activity (recently reviewed by Moore, 2004). The spreading VSD response (Figure 2C) was evoked by single-whisker deflections with long inter-stimulus intervals of many seconds, whereas the localized intrinsic signals (Figure 2B) were evoked by repetitive trains of 10 Hz stimuli each lasting 4 s.

These techniques for mapping the barrel cortex relate to different aspects of cortical function, each with its own advantages. Their common point is that they provide

strong functional evidence for somatotopic sensory processing precisely aligned to the anatomical barrel map. Information relating to deflections of an individual whisker will therefore be primarily, although not exclusively, processed in a well-defined cortical barrel column. During whisker-guided exploration of an object, different whiskers will contact different parts of the object at different times and this might lead to a dynamic pattern of activity evoked across the barrel map giving rise to something similar to an “imprint” of the object.

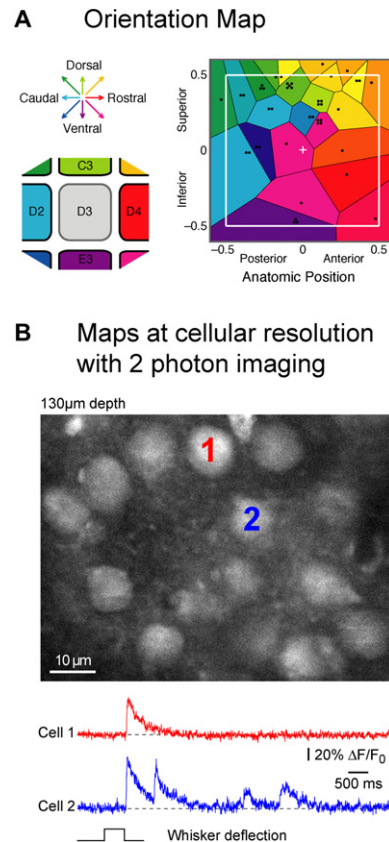
In addition to providing a spatial map, the different whiskers also exhibit different resonant frequencies (Hartmann et al., 2003; Neimark et al., 2003). During texture discrimination, the longer posterior whiskers might resonate to lower frequency textures than the short anterior whiskers, possibly leading to a “texture” map superimposed upon the somatotopic map (Andermann et al., 2004).

#### **Fine-Scale Mapping within a Barrel Column**

In analogy with the visual system, where there are several superimposed maps of different functional aspects relating to retinotopy, ocular dominance, and orientation selectivity, researchers have begun to search for further organizing principles within a barrel column. Within layer 4,

there is evidence for subdivisions within the larger rat barrels, but not in mouse barrels (Land and Erickson, 2005). These could relate to the observation of clusters of nearby layer 4 neurons, which preferentially respond to similar directions of whisker deflection (Bruno et al., 2003). Although in layer 4 direction tuning does not appear to be organized into an obvious map (Bruno et al., 2003; Andermann and Moore, 2006), tetrode recordings in layer 2/3 have provided evidence for a direction-preference map within the supragranular layers of a barrel column (Figure 3A). The proposed map places neurons responding to a given direction of a whisker deflection to be located closer to the neighboring barrel in the direction of the deflection. Thus, if the D3 whisker is deflected caudally (i.e., toward the D2 whisker), then more neurons in the half of the D3 barrel closer to the D2 barrel would respond than in the half of the barrel closer to the D4 whisker (Andermann and Moore, 2006). The proposed orientation map is attractive and it encodes an important feature of the whisker stimulus, which also has a clear mapping in the VPM thalamus (Timofeeva et al., 2003). However, as discussed earlier, it is difficult to derive maps from electrode penetrations, and clearly it would be of great interest to image the functional organization of the barrel cortex with cellular resolution.

Every action potential in a neuron is accompanied by calcium influx primarily mediated by voltage-gated calcium channels. Highly specific calcium-sensitive dyes have been developed, and of particular interest are membrane-permeable AM ester dyes, which are trapped intracellularly following hydrolysis (Tsien, 1981). These dyes can be applied extracellularly to brain slices (Peterlin et al., 2000; Cossart et al., 2003; Berger et al., 2007) or to intact brain (Stosiek et al., 2003; Kerr et al., 2005; Ohki et al., 2005; Berger et al., 2007; Sato et al., 2007) in order to image network activity reflected by intracellular calcium changes associated with action potential firing. In combination with two-photon microscopy (Denk et al., 1990), it has been possible to image cortical activity in the supragranular layers in vivo at cellular resolution (Stosiek et al., 2003; Kerr et al., 2005; Ohki et al., 2005; Sato et al., 2007). Neurons in layer 2/3 responding to whisker stimulation were already imaged in the first pioneering paper developing this technique for in vivo calcium imaging of network activity (Stosiek et al., 2003; Figure 3B). Further work has shown that cells responding to stimulation of different whiskers are somatotopically arranged, although neighboring neurons in layer 2/3 can respond preferentially to different whiskers (Sato et al., 2007). Application of this technique to the visual system has revealed that orientation selectivity in the cat primary visual cortex is exquisitely organized in maps on a scale of a few tens of microns, whereas the rat visual cortex contains no orientation map, but rather nearest neighbor cells can have opposite direction selectivity (Ohki et al., 2005). Future experiments using this technique in the rodent somatosensory cortex will undoubtedly shed further light on the functional architecture of individual barrel columns with cellular



**Figure 3. Fine Structure Mapping of a Barrel Column**

(A) A map of direction tuning of whisker deflections within layer 2/3 of a barrel column has been proposed based on multiple sequential tetrode recordings in the rat somatosensory cortex. According to this map, a caudal deflection of the D3 whisker toward the D2 whisker would preferentially evoke action potentials lying in the caudal part of the D3 barrel column adjacent to the D2 column.

(B) Using two-photon imaging of calcium-sensitive dye loaded into large populations of layer 2/3 neurons, it is possible to image the action potential activity of individual neurons within a network. This technique will likely provide detailed information relating to further functional maps at cellular resolution.

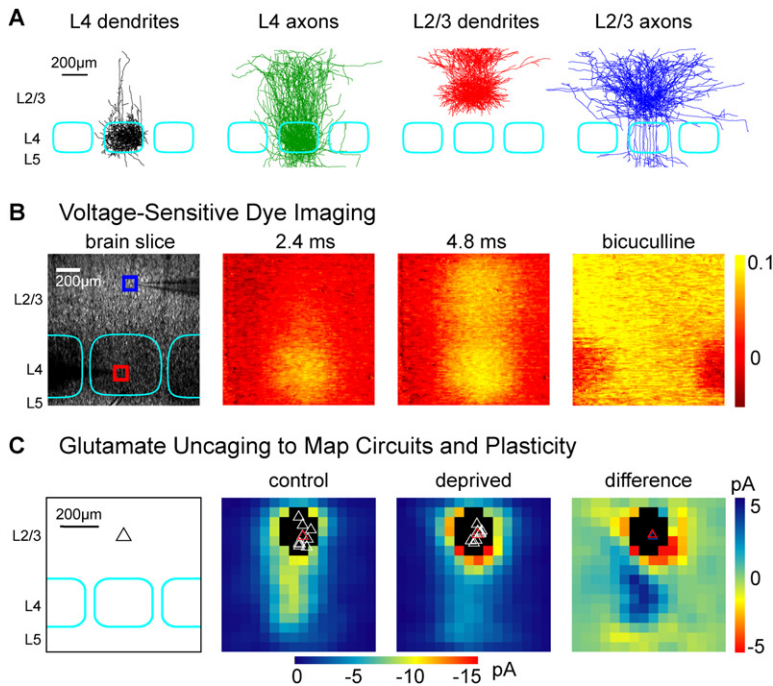
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resolution, allowing more detailed investigations of the putative direction map for whisker deflection and perhaps leading to the discovery of maps for other tactile features.

### Cortical Synaptic Circuits for Processing Simple Whisker-Related Sensory Information

The synaptic circuits in the barrel cortex that are likely to underlie the most prominent aspects of the sensory response to a simple stimulus in an anesthetized animal have begun to be examined in detail. Sensory information related to a single-whisker deflection arrives in the primary somatosensory neocortex mainly via the dense



**Figure 4. Synaptic Circuits Underlying Simple Sensory Responses in Layer 2/3**

(A) Superimposed reconstructions of dendrites and axons of many excitatory neurons in layer 4 and layer 2/3 of the barrel cortex. The dendrites (black) of the glutamatergic layer 4 spiny stellate and pyramidal neurons are largely confined to the home barrel. The axons (green) of the excitatory layer 4 neurons are laterally restricted to the width of the home barrel but project strongly to both layer 4 and layer 2/3. Therefore, the axons of layer 4 neurons anatomically define a cortical column. The dendrites (red) of layer 2/3 pyramidal neurons do not extend far outside the barrel column, but the layer 2/3 axons project long distances laterally (blue). Action potentials in layer 2/3 pyramidal neurons are therefore likely to contribute to the spreading sensory responses observed in vivo.

(B) Voltage-sensitive dye imaging of barrel cortex brain slices in vitro reveals functional evidence for columnar organization of synaptic circuits in the barrel cortex. An electrical stimulus delivered to the central layer 4 barrel (outlined in cyan, far left) evokes an early depolarization in the barrel (2.4 ms poststimulus, center left) which subsequently propagates into layer 2/3 defining a functional cortical column (4.8 ms poststimulus, center right). Under control conditions the response does not propagate further due to lack of evoked action po-

tential activity in layer 2/3. However, if GABAergic inhibition is blocked, then the evoked activity spreads laterally across both supragranular and infragranular cortex (far right).

(C) An alternative approach to map the structure of synaptic connectivity in the barrel cortex is to record the membrane potential from a single postsynaptic neuron and search for presynaptic partners by locally uncaging glutamate to evoke action potentials in neurons in different layers. Synaptic input to barrel-related layer 2/3 pyramidal neurons in normal control rats was found to originate in a columnar fashion with strong input from layer 4 (center left). However, following whisker deprivation, input from layer 4 to layer 2/3 was reduced (center and far right). Sensory-experience therefore plays an important role in determining the functional connectivity of the barrel cortex microcircuit.

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glutamatergic thalamocortical innervation of the neurons located in the VPM. The axon of a VPM neuron primarily innervates a single somatotopically aligned layer 4 barrel (Jensen and Killackey, 1987). Strong GABAergic feedback from the reticular nucleus to the thalamus prevents prolonged depolarization of the VPM neurons and sharpens the timing of sensory input to the cortex (Brecht and Sakmann, 2002; Bruno and Sakmann, 2006). As a first-order approximation, a single deflection of the C2 whisker therefore evokes a volley of near-synchronous thalamic input to arrive within layer 4 of the C2 barrel column. Thalamic axons make synapses on a diversity of dendrites in the layer 4 barrel. The most important dendritic elements are provided by the excitatory and inhibitory layer 4 neurons, with an additional fraction coming from infragranular neurons (e.g., the apical dendrites of some layer 5 neurons and the apical tuft of some corticothalamic layer 6 neurons). The excitatory layer 4 barrel neurons have dendritic and axonal arbors laterally confined to a single layer 4 barrel (Figure 4A; Feldmeyer et al., 1999; Petersen and Sakmann, 2000, 2001; Schubert et al., 2003), and the thalamic input arriving in a single layer 4 barrel therefore largely remains confined to that barrel for the initial step of cortical processing. The excitatory layer 4 axons prominently in-

nervate layer 2/3 in the immediately overlying area, therefore structurally defining a cortical column delimited laterally by the width of the layer 4 barrel. Functionally, the columnar propagation of activity from layer 4 to layer 2/3 has been examined by voltage-sensitive dye imaging in vitro (Figure 4B; Petersen and Sakmann, 2001; Laaris and Keller, 2002). A stimulus delivered to a layer 4 barrel first causes depolarization within the layer 4 barrel, which then in the subsequent milliseconds spreads to depolarize neurons in layer 2/3 in a strictly columnar fashion. In the converse experiment, the location of presynaptic neurons synapsing onto a single layer 2/3 pyramidal neuron mapped through glutamate uncaging reveals a strictly columnar input from layer 4 (Figure 4C; Shepherd et al., 2003). Both anatomically and functionally there is therefore strong evidence for cortical columns defined by the horizontal extent of the layer 4 barrels.

The single-whisker deflection-evoked early sensory response, which in VSD imaging is localized to a single cortical column, is therefore likely to reflect the columnar input from neurons in the layer 4 barrel to layer 2/3 neurons. However, as noted above, the sensory response subsequently propagates across the barrel map over the next milliseconds. The axonal arborization of the layer 2/3

pyramidal neurons extends well beyond the boundaries of a barrel column, and since single-whisker deflections can drive action potential firing in layer 2/3 pyramidal neurons, the glutamatergic output of these neurons will depolarize neurons widely distributed across the barrel cortex, likely underlying the spreading VSD signal. In addition to contacting other layer 2/3 neurons, the axons of the layer 2/3 pyramidal neurons also form a prominent input to layer 5 (Reyes and Sakmann, 1999). Synaptic integration in layer 5 neurons is complex since they can also receive substantial direct thalamic input (Bureau et al., 2006) along with excitatory input both from layer 4 (Feldmeyer et al., 2005; Schubert et al., 2006) and from other pyramidal neurons in the infragranular layers (Markram et al., 1997).

In contrast to the propagating sensory responses observed following single-whisker deflection *in vivo*, the VSD response *in vitro* remains columnar throughout the duration of the evoked response under control conditions, but when GABAergic inhibition is blocked by applying bicuculline, the signal propagates extensively in both supragranular and infragranular layers (Figure 4B). The neocortex *in vivo* might therefore be more excitable than that observed *in vitro* under most experimental conditions, which might also be reflected in the prominent spontaneous activity recorded *in vivo*.

In addition to the canonical excitatory synaptic circuit from VPM to layer 4 barrel to layer 2/3 to layer 5 (recently reviewed by Lübke and Feldmeyer, 2007), there are a number of other important synaptic connections that are likely to play prominent roles during information processing in awake animals. Perhaps most important are the long-range corticocortical inputs from secondary somatosensory cortex and motor cortex and the likely influence of POM thalamic input during certain behaviors. POM input arrives predominantly in layer 1 and 5A, defining the starting point of a paralemniscal cortical processing pathway. Layer 5A in turn projects to layer 2 (Shepherd and Svoboda, 2005; Bureau et al., 2006). It will be of great interest to determine the functional interactions between these different synaptic networks *in vivo* and how they contribute to different aspects of whisker-related sensory perception.

### **Development and Plasticity of the Barrel Cortex Patterning of the Neocortex and Early Postnatal Development**

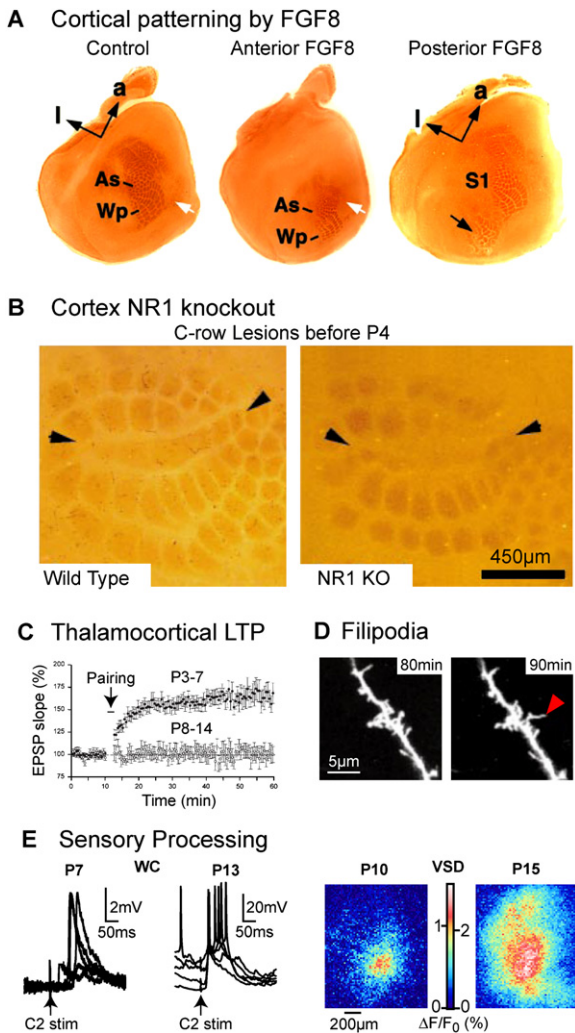
In common with the general patterning of the neocortex (Molnar et al., 2002), the somatotopic organization of the barrel cortex appears to be primarily determined by genetic programs. For example, gradients of secreted FGF8 during embryonic development can determine both the position and dimensions of the barrel field in the neocortex (Fukuchi-Shimogori and Grove, 2001; Figure 5A). Intriguingly, ectopic posterior expression of FGF8 can also induce formation of a secondary barrel field (Fukuchi-Shimogori and Grove, 2001; Figure 5A).

Refinement of the somatotopic map, including the differentiation of the layer 4 barrel structure is likely to be

guided by activity-dependent mechanisms. Barrels are less clearly defined or absent in mice with genetic knockout of several genes relating to neuronal activity and synaptic transmission: cortical NMDA receptors (Iwasato et al., 2000), phospholipase C beta 1/metabotropic glutamate receptors (Hannan et al., 2001), adenylyl cyclase 1/“barrelless” (Welker et al., 1996; Abdel-Majid et al., 1998), and monoamine oxidase A (Cases et al., 1996).

The barrel map develops early being clearly visible within a few days of birth. Lesioning of whisker follicles within the first days after birth prevents formation of the corresponding barrels (Van der Loos and Woolsey, 1973; Wong-Riley and Welt, 1980; Iwasato et al., 2000; Figure 5B). Interestingly, forebrain specific knockout of NMDA receptor function in the neocortex, does not affect this lesion-induced plasticity (Figure 5B). Clearly, NMDA receptor-mediated synaptic plasticity cannot play a major role in this early sensitivity of the barrel map to sensory deprivation. The ability to change the large-scale anatomical organization of the barrel field only lasts a few days after birth, and by postnatal day 4 this is no longer possible. There is therefore an early critical period for anatomical map formation, but a great deal of plasticity remains in the barrel cortex throughout life on a finer structural and functional scale. The next critical period that has been defined relates to NMDA receptor-dependent plasticity at the thalamocortical synapse. Long-term potentiation (LTP) can only be induced during the first postnatal week in thalamocortical slices (Crair and Malenka, 1995; Figure 5C) and the ability to induce long-term depression (LTD) at thalamocortical synapses disappears within the next days (Feldman et al., 1998). These reductions in plasticity during development are accompanied by a dramatic decrease in the relative importance of NMDA receptors compared to AMPA receptors in thalamocortical synaptic transmission (Crair and Malenka, 1995). During the first two weeks of postnatal cortical development there is also a dramatic increase in axon and dendrite complexity accompanied by large increases in synapse number. Presumably related to this massive synapse formation, filopodia, and spine growth (and retraction) are prevalent in the young neocortex (Lendvai et al., 2000; Figure 5D). Filopodia/spine motility decreases during development (Holtmaat et al., 2005; Zuo et al., 2005), likely reflecting the reduced plasticity of the adult barrel cortex.

These synaptic and structural changes are also reflected by profound changes in sensory processing during the first postnatal weeks. There is little spontaneous activity and cortical sensory responses are weak and slow in young animals (Bureau et al., 2004; Borgdorff et al., 2007; Figure 5E). Interestingly, the sensory responses evoked by single-whisker deflection and imaged with voltage-sensitive dye are localized to individual cortical columns in young mice in contrast to the spreading sensory responses in the mature barrel cortex (Borgdorff et al., 2007; Figure 5E). This likely reflects the reduced synaptic connectivity and weak action-potential firing of pyramidal neurons in young animals, which in the mature barrel cortex are thought to



**Figure 5. Early Development of the Barrel Cortex**

(A) Cytochrome oxidase stained flattened cortices show the location of the barrel field in control mice (left; “a” anterior, “l” lateral, “As” anterior snout, “Wp” whisker pad). Enhancement of the normal FGF8 gradient (high anteriorly) in the cortex shifts the barrel field posteriorly and reduces the total extent of the barrel field (middle). An ectopic posterior source of FGF8 can induce formation of a secondary barrel field (arrow, right).

(B) Forebrain specific knockout of NMDA receptor function results in a less clearly defined barrel field. Lesion of the C-row whiskers between P0-3 causes disruption of the C-row in the barrel cortex equally in wild-type and NR1 knockout mice.

(C) Thalamocortical NMDA receptor-dependent LTP can be induced by pairing synaptic stimulation and postsynaptic depolarization during the first postnatal week, but not after P8.

(D) During early postnatal development filipodia and spines are highly motile, here shown by two photon imaging of GFP expressing layer 2/3 pyramidal neurons at postnatal day 11. In the 10 min separating the two images, a long filipodia appeared (red arrowhead).

(E) Sensory processing changes dramatically over the first postnatal weeks. Whole-cell (WC) recordings (left) indicate that sensory responses become larger and more rapid in older mice (for each age there are five overlaid traces from consecutive sweeps; note difference in scale comparing P7 and P13 recordings). Voltage-sensitive dye (VSD) imaging indicates that the extent of the sensory response evoked by C2 whisker deflection increases strongly during development (right).

mediate the lateral spread of sensory information in layer 2/3. These data suggest that barrel cortex neurons receive information relating to their principal whisker early in development and later become more broadly tuned perhaps reflecting the later development of more complex receptive field properties relating to more diverse sensory experiences and top-down influences.

**Experience-Dependent Map Plasticity in Mature Rodents**

Although the anatomical barrel map is fixed early in development, the physiological response properties of neurons can be changed in an experience-dependent manner even into adulthood. One of the first plastic events in the barrel cortex driven by sensory deprivation is depression of evoked responses to deflection of the trimmed whiskers (Glazewski and Fox, 1996). There is strong evidence that this depression of sensory processing in layer 2/3 neurons is primarily caused by a reduction in the efficacy of the excitatory synaptic connection between layer 4 to layer 2/3 (Allen et al., 2003; Shepherd et al., 2003). Quantitative mapping of synaptic connectivity using glutamate uncaging, shows that layer 2/3 pyramidal neurons no longer receive a strong input from layer 4 following whisker trimming (Figure 4C). Investigation of the molecular mechanisms of this depression has revealed that it involves pre-synaptic reduction in neurotransmitter release probability (Bender et al., 2006). The observed depression is entirely consistent with a Hebbian spike-timing-dependent plasticity (Allen et al., 2003) since whisker trimming appears to reverse the relative timing of action-potential firing from the normal reinforcing sequence of L4 followed by L2/3 (postsynaptic spike in L2/3 following presynaptic L4 spike) to the depressing sequence of L2/3 followed by L4 (postsynaptic L2/3 spike preceding presynaptic L4 spike). Together with similar observations in the primary visual cortex (Heynen et al., 2003), these form the first synaptic explanations for experience-dependent plasticity in the neocortex.

Although depression of responses evoked by sensory deprivation is one of the most robust observations, it is not the only type of plasticity in the rodent barrel cortex (recently reviewed by Feldman and Brecht, 2005). Perhaps, of greater importance than the reduction of responses to the trimmed whiskers, is what happens to sensory processing of the remaining intact whiskers. Extracellular recordings of action potential activity have shown that

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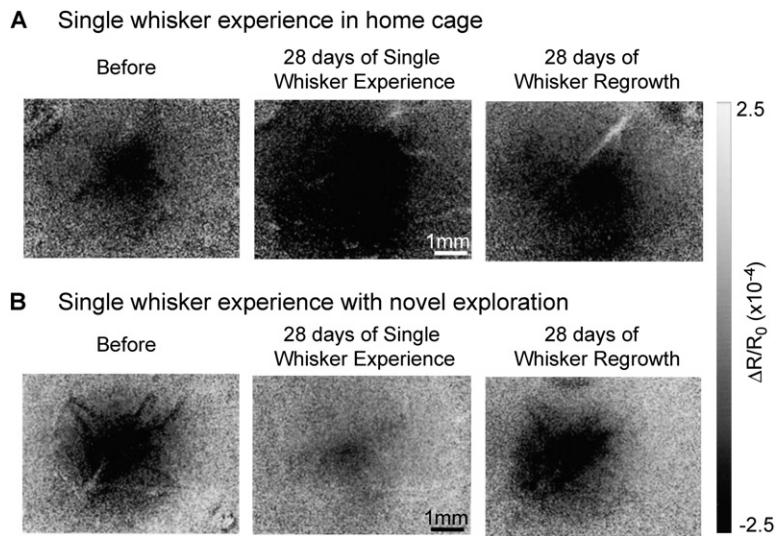
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**Figure 6. Experience-Dependent Map Plasticity**

(A) Intrinsic optical imaging was carried out repeatedly in the same animal allowing a direct comparison of the response to single whisker stimulation under control conditions, following 28 days of single-whisker experience in the home cage and after a further 28 days during which the whiskers were allowed to regrow. Single-whisker experience induced a profound and reversible expansion of the spared whisker representation.

(B) The same experiment was carried out in another group of animals, with the only difference being that during the 28 days of single-whisker experience, the rats were put in a novel environment for 2 min every 3–4 days to encourage active whisker guided exploration. Surprisingly, this leads to a striking and reversible contraction of the spared whisker representation. (A) and (B) are modified and reproduced from Neuron, Polley et al. (1999), Copyright (1999), with kind permission from Cell Press, Elsevier.

neurons in the barrel cortex become more responsive to deflection of spared whiskers (Fox, 1992; Diamond et al., 1994). Some of the most elegant and convincing results come from repeated intrinsic optical imaging of the same animals during whisker deprivation paradigms where only a single whisker is left intact (Figure 6; Polley et al., 1999). The cortical area responding to stimulation of the spared C2 whisker was much larger following 28 days of single whisker experience in the home cage (Figure 6A). Allowing all the whiskers to regrow reversed the plasticity. This result is in good agreement with the expectations from many other plasticity experiments, including the results from monocular visual deprivation where the remaining open eye “takes over” the cortical territory normally occupied by the deprived eye. However, the results from different animals were quite variable, which could have resulted from different whisker use during the deprivation period. Polley et al. (1999) therefore began to monitor whisker behavior by placing the single-whisker animals in a novel environment every 3–4 days and measuring the time spent in single whisker-guided exploration. Surprisingly, these brief periods of exploration caused a complete inversion of the plasticity. Single-whisker animals subjected to exploration of novel environments had smaller cortical representations of the spared whisker (Figure 6B), which was also reversible upon whisker regrowth. Clearly, map plasticity is complex and is strongly regulated by the behavior of the animal. Experience-dependent plasticity is an adaptive process, which is not uniquely driven by manipulation of the periphery, but also strongly influenced by spontaneous activity (Erchova and Diamond, 2004) and internal top-down processes, likely to be of great importance for goal-directed learning. In order to examine map plasticity and determinants of experience-dependent reorganization of cortical synaptic circuits in greater detail, it will therefore be important to record in awake behaving animals investigating brain function during alterations in sensory experience and learning.

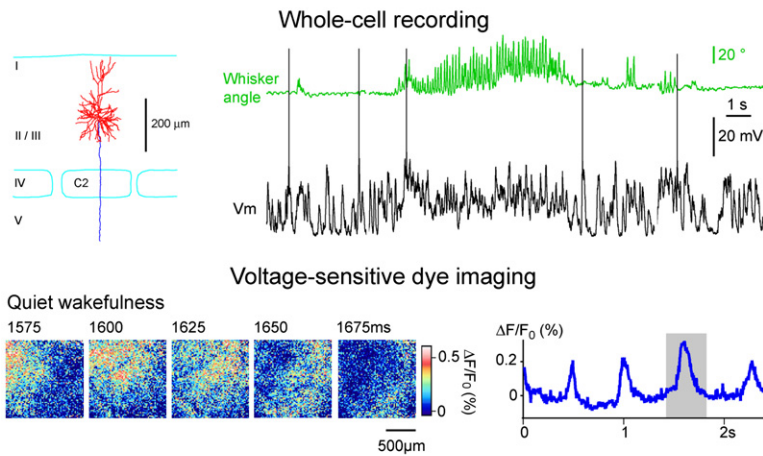
### Cortical Correlates of Whisker Perception in Awake Behaving Rodents

#### State-Dependent Processing of Sensory Information

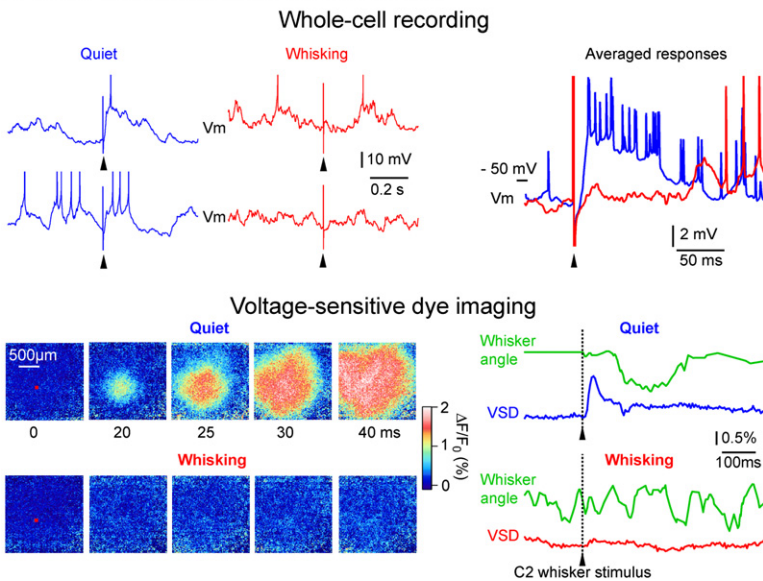
Considerable technical progress has been made over the last years with respect to recording cortical activity in awake behaving animals. Although extracellular recordings have been carried out extensively in behaving monkeys for several decades, much less is known about the electrical activity of the rodent neocortex during quantified behavior. With the growing realization of the power and specificity of mouse genetics, this situation is changing, and a great deal of attention is now being drawn to recording and manipulating the mouse brain during trained behaviors. A variety of recording techniques, e.g., extracellular unit recordings (Krupa et al., 2004; Leiser and Moxon, 2007), whole-cell recordings (Crochet and Petersen, 2006; Lee et al., 2006), voltage-sensitive dye imaging (Ferezou et al., 2006), and two-photon microscopy (Helmchen et al., 2001; Dombeck et al., 2007) have recently been adapted for awake recordings in rodents.

Whole-cell recordings of layer 2/3 barrel cortex pyramidal neurons show prominent changes in membrane-potential dynamics during different whisker-related behaviors. During quiet wakefulness, when the whiskers are not moving, there are slow large-amplitude membrane potential changes (Crochet and Petersen, 2006), which can be imaged with voltage-sensitive dye as propagating waves of activity (Ferezou et al., 2006; Figure 7A). During active whisking, the slow oscillation disappears, the membrane-potential variance becomes smaller, and neurons on average depolarize by a few millivolts (Crochet and Petersen, 2006). These striking correlations of membrane potential dynamics in cortical layer 2/3 with behavior are, however, not obvious at the level of action potential firing, which on average across cells is around 1 Hz during both quiet wakefulness and active whisking (Crochet and Petersen, 2006).

**A Neuronal Correlates of Spontaneous Whisker-related Behaviour**



**B State-dependent Sensory Processing**



**Figure 7. State-Dependent Processing of Sensory Information**

(A) Whole-cell recordings from awake mice during quantified spontaneous whisker-related behavior reveal striking state-dependent changes in membrane potential dynamics (upper panels). A layer 2/3 pyramidal neuron located in the C2 barrel column (left) shows slow large-amplitude membrane potential changes (black trace, membrane potential,  $V_m$ ) when the C2 whisker is not moving (green trace, whisker angle). During active whisking the membrane potential depolarizes, and the slow oscillations are replaced by higher-frequency fluctuations. Voltage-sensitive dye imaging of mouse barrel cortex during quiet wakefulness reveals that the spontaneous slow oscillations occur as propagating waves of depolarization spreading across the neocortex (lower panels). The images (left) show a wave spreading from upper-left to lower-right in the field of view, and the time-course of fluorescence changes are quantified across a small central region of interest (right, gray shading indicates the time of the images).

(B) Passively applied brief deflections of the C2 whisker evoke different cortical sensory responses during different spontaneous whisker-related behaviors. Whole-cell recordings (upper panels, action potentials are truncated to allow an expanded y axis) show that the depolarizing sensory response is strongly reduced during active whisking (red) compared to during quiet wakefulness (blue). This state-dependent reduction in sensory processing is not limited to individual neurons but is a network property, which can also be imaged with voltage-sensitive dye (lower panels). Passively evoked sensory responses during quiet wakefulness have large amplitude and spread across large cortical areas, whereas the response is smaller and more localized during whisking. The red square on the images at 0 ms indicates the region of interest centered on the C2 barrel column from which voltage-sensitive dye fluorescence changes are quantified in the adjacent traces (lower right).

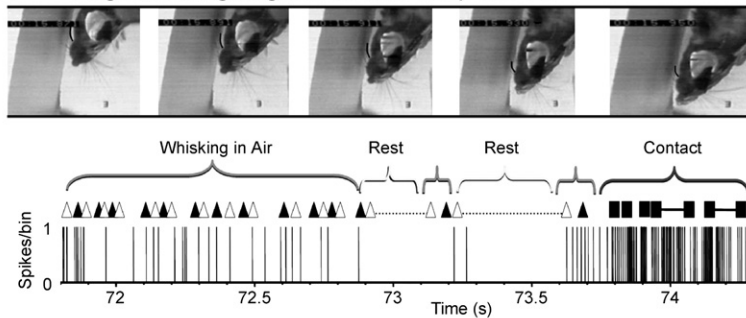
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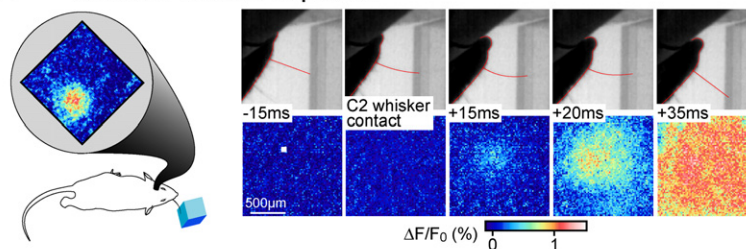
Processing of sensory information in the barrel cortex also differs strongly between quiet wakefulness and active whisking (Figure 7B). Controlled deflection of a whisker by the experimenter (a passive whisker deflection for the animal) results in a strong cortical sensory response during quiet wakefulness, but only a weak response during active whisking as measured with extracellular recordings (Hentschke et al., 2006), whole-cell recordings (Crochet and Petersen, 2006), or voltage-sensitive dye imaging (Ferezou et al., 2006). The large-amplitude sensory responses observed during quiet wakefulness evoked propagating waves of activity that spread across the barrel cortex (Figure 7B). Thus, the spreading sensory responses

observed under anesthesia (Figure 2C) are not an artifact of the anesthetized brain but are of physiological relevance and may be an important integrative property of cortical function. The behavioral modulation of cortical sensory processing appears to be downstream of the mechanosensitive receptors in the whisker follicle, since similar effects are observed in the barrel cortex following electrical stimulation of the trigeminal nerve (Fanselow and Nicolelis, 1999; Castro-Alamancos, 2004). Further experiments are needed to investigate the different contributions of thalamus and neocortex in governing the state-dependent control of sensory processing. It is already clear, however, that thalamic responses can be altered by behavioral state

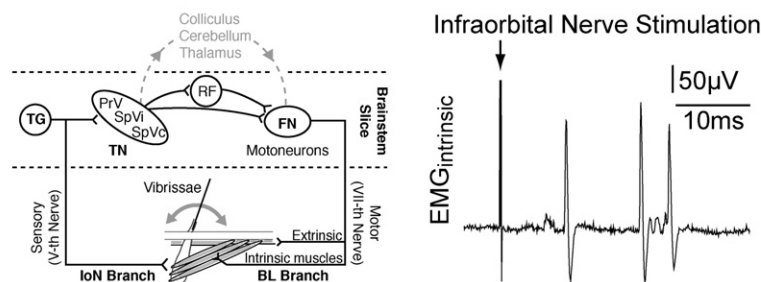
**A** Trigeminal ganglion touch responses



**B** Cortical touch response



**C** Brainstem sensorimotor loop



(Fanselow and Nicolelis, 1999; Castro-Alamancos and Oldford, 2002) and that synaptic depression at thalamo-cortical synapses could contribute significantly (Chung et al., 2002; Castro-Alamancos and Oldford, 2002) along with more direct state-dependent effects of activity and neuromodulators on the neocortical network.

**Actively Acquired Sensory Information**

Mice and rats actively move their whiskers during exploration, and the weak sensory responses evoked by passive stimuli during whisking are therefore surprising since this is when one might expect whisker-related sensory processing to be most important for the animal. The passively applied stimuli are of course quite different from natural sensory input during whisking, which would primarily be expected to occur during whisker contact with real objects.

Recordings from the first-order sensory neurons in the trigeminal ganglion of awake rodents have revealed three important facts (Leiser and Moxon, 2007; Figure 8A). First, in the absence of whisker movement, there is no spontaneous action potential firing in the trigeminal ganglion. Second, during whisking without object contact, also

**Figure 8. Actively Acquired Sensory Information**

(A) The primary sensory trigeminal ganglion neurons do not fire action potentials during periods of quiet wakefulness when the whiskers are not moving (labeled as “rest”). They fire at low rates during free whisking (labeled as “whisking in air”). The sensory neurons fire at high rates during active touch when the whiskers contact an object (labeled as “Contact”). (B) Fiber-optic imaging using voltage-sensitive dye in freely moving mice (schematic left) shows that large-amplitude spreading sensory responses can be evoked in the barrel cortex in response to whisker-object contact. The upper image sequence shows the C2 whisker (highlighted in red) making contact with a Plexiglas object and the lower image sequence shows the simultaneously recorded voltage-sensitive dye response.

(C) Sensory neurons of the infraorbital branch (ION) of the trigeminal (TG) nerve excite neurons in the trigeminal nuclei (TN) of the brainstem (principal, PrV; spinal interpolar, SpVi; spinal caudal, SpVc). These brain stem neurons in turn project centrally, but some also make excitatory synapses onto motoneurons of the facial nucleus (FN), driving the whiskers forward causing further deflection of the whisker contacting an object. Stimulation of the sensory infraorbital nerve (right) rapidly evokes electrical activity in the intrinsic muscles of the whisker pad measured by the electromyogram (EMG). Sensory responses to whisker-object contacts may therefore be amplified by positive feedback in this brain sensorimotor loop. (A) is modified and reproduced from *Neuron*, Leiser and Moxon (2007), Copyright (2007), with kind permission from Cell Press, Elsevier. (B) is modified and reproduced from *Neuron*, Ferezou et al. (2006), Copyright (2006), with kind permission from Cell Press, Elsevier. (C) is modified and reproduced from *Neuron*, Nguyen and Kleinfeld (2005), Copyright (2005), with kind permission from Cell Press, Elsevier.

called “whisking in air,” there is only a low level of spiking activity in the sensory neurons. This free-whisking activity can be phase-locked to the whisking cycle (Szwed et al., 2003) and similar phase-locked signals have also been found in the somatosensory cortex (Fee et al., 1997; Crochet and Petersen, 2006). Such phase-locked signals could form the basis of a map of positional information (Kleinfeld et al., 2006). Third and most importantly, many action potentials in the sensory neurons were evoked when the whiskers contacted objects (Leiser and Moxon, 2007). Whisker-related trigeminal ganglion neurons are therefore sensitive object detectors, showing much less activity at other times.

This activity at the periphery is robustly transmitted to the cortex, since whisker-object contact evokes strong sensory responses in the barrel cortex during active touch (Crochet and Petersen, 2006; Ferezou et al., 2006; Figure 8B). Voltage-sensitive dye imaging demonstrates that single-whisker active touch responses can also propagate across the barrel map, similar to the passively evoked responses during quiet wakefulness, but unlike

the responses to passive stimulation during whisking. It is currently unclear what underlies this difference in sensory processing during whisking. One possibility is that the passive stimulus during whisking is weak and the evoked response might then be obscured by the increased background action-potential firing at the periphery and by the different cortical state during whisking. Real whisker-object contacts, but not remotely applied passive stimuli, might be specifically amplified by a rapid low-level sensorimotor loop (Figure 8C; Nguyen and Kleinfeld, 2005). Axons of the sensory neurons in the trigeminal nerve make direct monosynaptic excitatory input onto the facial nucleus motoneurons responsible for generating whisker movement. The net result is that sensory input evokes a whisker protraction. If the whisker contacts a real object, the whisker will be accelerated into the object, resulting in a positive-feedback loop generating a strong contact response. This brainstem sensorimotor loop is the first point of interaction between sensory input and motor output, but there are several higher-order sensorimotor loops including anatomical evidence for cortical connectivity between barrel cortex and primary motor cortex (White and DeAmicis, 1977; Welker et al., 1988; Chakrabarti and Alloway, 2006). Sensory processing in motor cortex is likely to be of profound importance in active sensation. In the same way that we change our finger movements when we touch objects to explore their shape and texture, it is likely that rodents will change their whisker movements to enhance the extraction of sensory information. Further exploration of the control of whisker movements (Carvell et al., 1996; Hattox et al., 2003; Brecht et al., 2004; Haiss and Schwarz, 2005; Cramer et al., 2007) and sensorimotor integration (Kleinfeld et al., 2002) will be crucial in our understanding of active sensory processing.

### **Sensory Information Processing during Learned Behaviors**

The state-dependent active processing and acquisition of sensory information observed during different spontaneous behaviors (Figures 7 and 8) leads naturally to curiosity regarding learned whisker-dependent behaviors. In the primate visual system, there is clear evidence that the activity of individual neurons evoked by the same visual stimulus can be strongly regulated in a task-specific manner (Gilbert and Sigman, 2007). Active selection of relevant sensory input might therefore also occur during processing of whisker-related information in rodents. Indeed, one might already argue that the differential sensory processing observed during quiet wakefulness and active whisking perform a useful role. When the animal is quiet and the whiskers are not moving, then only passive whisker deflections can occur, and these evoke large cortical responses. On the other hand, during active whisking, when the animal is actively exploring its environment, it is indeed highly sensitive to touch of real objects. It is likely that there are many more subtle context- and experience-dependent alterations in cortical processing of whisker-related information. For example, rewarding large-amplitude whisking causes enhanced phase-locking of cortex to the whisker

cycle (Ganguly and Kleinfeld, 2004), and the association of whisker deflection with reward leads to enhanced deoxyglucose uptake in the stimulated barrels (Siucinska and Kossut, 2004).

An important further reason to investigate sensory processing in animals performing well-defined tasks is to gain insight into the perceptual basis of decisions. Ultimately, sensory information serves to guide behavior and sensory processing can therefore be viewed as a starting point for motor control and the planning of future actions. In the laboratory, rodents can learn to use their whiskers to perform various behavioral tasks, which can be roughly divided into two broad categories: the detection of edge locations and the discrimination of textures (Figure 9A).

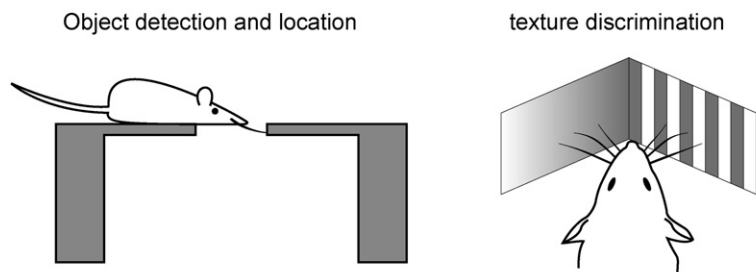
The landmark study of Hutson and Masterton (1986) showed that a rodent perched on one elevated platform can reach across with its whiskers to touch and locate another platform to where it jumps in order to receive a reward (see Movie S1 in the Supplemental Data available with this article online). Importantly, for the experimentalist, this behavior can be performed with a single whisker (Movie S2) and depends upon an intact somatosensory barrel cortex (Hutson and Masterton, 1986). Some of the sensory learning underlying the gap-crossing task may take place in the local sensory maps of the barrel cortex (Harris et al., 1999).

In a simpler behavior, it has also been shown that rodents with a single whisker can be trained to discriminate the position of a vertical bar, with one position rewarded and another not (Knutsen et al., 2006; Mehta et al., 2007). These results suggest that even a single whisker provides sufficient information not just for detection of a deflection evoked by whisker-object contact during active whisking, but also that the position of the whisker-object contact is encoded. Action-potential firing and membrane-potential oscillations in the barrel cortex phase locked to the whisking cycle could contribute to encoding the position of whisker object touch (Fee et al., 1997; Szwed et al., 2003; Crochet and Petersen, 2006; Kleinfeld et al., 2006).

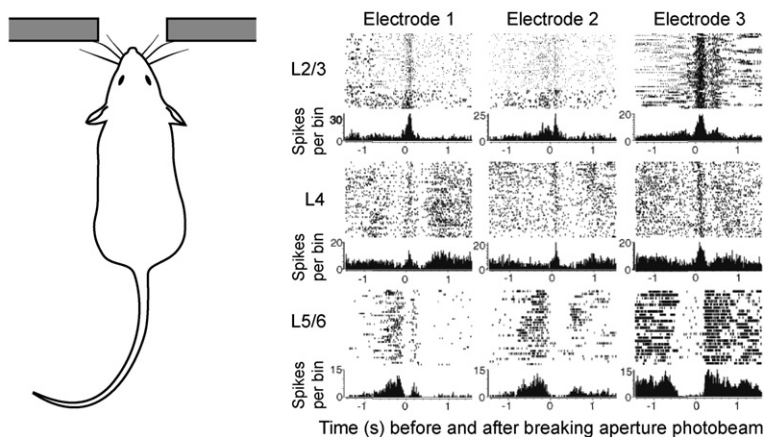
In order to explore the psychophysical properties of whisker detection, Stuttgen et al. (2006) trained head-fixed rats to respond by licking upon detection of precisely controlled single-whisker stimuli. Interestingly, they found evidence for two separate psychophysical channels, one specialized for small-amplitude high-velocity whisker deflections and another for low-velocity large-amplitude deflections. These psychophysical channels correlated well with the response properties of rapidly adapting (low amplitude threshold) and slowly adapting (low velocity threshold) trigeminal sensory neurons (Stuttgen et al., 2006). The ability to train head-fixed rodents to respond to sensory input originating from a single whisker may turn out to be of considerable importance for investigating the synaptic basis of learned whisker-dependent behaviors.

The first extracellular recordings of cortical activity during trained whisker-dependent behaviors were carried out in freely moving rats and generated interesting results (Figure 9B; Krupa et al., 2004). The behavioral paradigm

## A Learned whisker-dependent behaviours



## B Aperture discrimination



involved the detection of two edges forming an aperture (Krupa et al., 2001). The rat was trained to poke into the aperture with its nose, and depending upon the width of the aperture, it would receive a reward to the left or to the right. Such aperture discrimination is interesting since it involves bilateral sensory integration and is likely of ethological importance since rodents live in tunnels and need to know if a hole is of a suitable size to enter. Recordings from trained animals entering the aperture showed different action-potential activities in different cortical layers. One of the most striking observations is that many infragranular neurons fired action potentials before the rat entered the aperture, suggesting a prominent top-down input. Further study of this behavior with quantitative analysis of whisker deflections and more detailed characterization of the location of recording electrodes would be of great interest.

In addition to the detection of pulsatile whisker deflections encountered during such edge detection tasks, the rodent whisker system has been shown to be able to discriminate between different textures. Indeed, Carvell and Simons (1990) showed that rats can discriminate textural differences using their whiskers to a comparable degree of accuracy as humans using their finger tips. Whisker deflections similar to the vibrations evoked by sweeping a whisker across a rough surface result in robust sequences of action-potential firing in sensory neurons of the trigem-

## Figure 9. Learned Whisker-Dependent Behaviors

(A) The rodent whisker sensorimotor system performs two classes of behavioral tasks: location of edges and discrimination of textures. Edge detection and location forms the basis of the gap-crossing task (left) where the rodent must reach across a gap with its whiskers to locate a target platform where a reward is placed. Rodents are also able to discriminate textures using their whiskers (right), and quantitative behavioral measurements suggest that texture discrimination by the whiskers equals the performance of the human finger tip.

(B) The first recordings of neuronal activity during learned whisker-dependent behaviors have provided interesting results. Rats were trained to perform a bilateral edge-location task, where the animal must determine the width of an aperture to receive a reward (left). Recording of cortical action potential activity during execution of this learned behavior showed that action potential firing rates changed during different phases of the task. Most surprisingly, infragranular neurons often showed elevated firing rates before the rat entered the aperture, suggesting interesting top-down input to somatosensory cortex.

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inal ganglion (Jones et al., 2004; Arabzadeh et al., 2005). The faithful encoding of sensory input at the periphery likely leads to different percepts and behavioral choices, which could result from differential cortical activity as demonstrated in the monkey somatosensory system (de Lafuente and Romo, 2006).

## Future Perspectives

The rodent whisker-related sensorimotor system offers unique opportunities for studying sensory processing in well-defined synaptic pathways. Recent studies directly correlating neuronal activity with whisker-related behavior shed light on active versus passive sensory processing, sensorimotor integration, and the differential sensory processing during different brain states. The growing body of work relating to trained whisker-dependent behaviors is likely to allow an in-depth analysis of the mechanisms underlying associative learning of sensory perception with the execution of a specific motor program. In combination with the increasing sophistication of molecular biology and genetics, it seems likely that significant progress can be expected in the next years providing a quantitative analysis of sensory processing within the anatomically defined somatotopic barrel maps.

## Supplemental Data

The Supplemental Data for this article can be found online at <http://www.neuron.org/cgi/content/full/56/2/339/DC1/>.

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## REFERENCES

- Abdel-Majid, R.M., Leong, W.L., Schalkwyk, L.C., Smallman, D.S., Wong, S.T., Storm, D.R., Fine, A., Dobson, M.J., Guernsey, D.L., and Neumann, P.E. (1998). Loss of adenylyl cyclase I activity disrupts patterning of mouse somatosensory cortex. *Nat. Genet.* **19**, 289–291.
- Allen, C.B., Celikel, T., and Feldman, D.E. (2003). Long-term depression induced by sensory deprivation during cortical map plasticity in vivo. *Nat. Neurosci.* **6**, 291–299.
- Andermann, M.L., and Moore, C.I. (2006). A somatotopic map of vibrissa motion direction within a barrel column. *Nat. Neurosci.* **9**, 543–551.
- Andermann, M.L., Ritt, J., Neimark, M.A., and Moore, C.I. (2004). Neural correlates of vibrissa resonance; band-pass and somatotopic representation of high-frequency stimuli. *Neuron* **42**, 451–463.
- Arabzadeh, E., Zorzin, E., and Diamond, M.E. (2005). Neuronal encoding of texture in the whisker sensory pathway. *PLoS Biol.* **3**, e17. 10.1371/journal.pbio.0030017.
- Armstrong-James, M., Fox, K., and Das-Gupta, A. (1992). Flow of excitation within rat barrel cortex on striking a single vibrissa. *J. Neurophysiol.* **68**, 1345–1358.
- Aronoff, R., and Petersen, C.C.H. (2006). Controlled and localized genetic manipulation in the brain. *J. Cell. Mol. Med.* **10**, 333–352.
- Bender, K.J., Allen, C.B., Bender, V.A., and Feldman, D.E. (2006). Synaptic basis for whisker deprivation-induced synaptic depression in rat somatosensory cortex. *J. Neurosci.* **26**, 4155–4165.
- Berger, T., Borgdorff, A.J., Crochet, S., Neubauer, F.B., Lefort, S., Fauvet, B., Ferezou, I., Carleton, A., Luscher, H.R., and Petersen, C.C.H. (2007). Combined voltage and calcium epifluorescence imaging in vitro and in vivo reveals subthreshold and suprathreshold dynamics of mouse barrel cortex. *J. Neurophysiol.* **97**, 3751–3762.
- Borgdorff, A.J., Poulet, J.F.A., and Petersen, C.C.H. (2007). Facilitating sensory responses in developing mouse somatosensory barrel cortex. *J. Neurophysiol.* **97**, 2992–3003.
- Brecht, M., and Sakmann, B. (2002). Whisker maps of neuronal subclasses of the rat ventral posterior medial thalamus, identified by whole-cell voltage recording and morphological reconstruction. *J. Physiol.* **538**, 495–515.
- Brecht, M., Roth, A., and Sakmann, B. (2003). Dynamic receptive fields of reconstructed pyramidal cells in layers 3 and 2 of rat somatosensory barrel cortex. *J. Physiol.* **553**, 243–265.
- Brecht, M., Schneider, M., Sakmann, B., and Margrie, T.W. (2004). Whisker movements evoked by stimulation of single pyramidal cells in rat motor cortex. *Nature* **427**, 704–710.
- Bruno, R.M., and Sakmann, B. (2006). Cortex is driven by weak but synchronously active thalamocortical synapses. *Science* **312**, 1622–1627.
- Bruno, R.M., Khatri, V., Land, P.W., and Simons, D.J. (2003). Thalamocortical angular tuning domains within individual barrels of rat somatosensory cortex. *J. Neurosci.* **23**, 9565–9574.
- Bureau, I., Shepherd, G.M., and Svoboda, K. (2004). Precise development of functional and anatomical columns in the neocortex. *Neuron* **42**, 789–801.
- Bureau, I., von Saint Paul, F., and Svoboda, K. (2006). Interdigitated paralemniscal and lemniscal pathways in the mouse barrel cortex. *PLoS Biol.* **4**, e382. 10.1371/journal.pbio.0040382.
- Carvell, G.E., and Simons, D.J. (1990). Biometric analyses of vibrissal tactile discrimination in the rat. *J. Neurosci.* **10**, 2638–2648.
- Carvell, G.E., Miller, S.A., and Simons, D.J. (1996). The relationship of vibrissal motor cortex unit activity to whisking in the awake rat. *Somatosens. Mot. Res.* **13**, 115–127.
- Cases, O., Vitalis, T., Seif, I., De Maeyer, E., Sotelo, C., and Gaspar, P. (1996). Lack of barrels in the somatosensory cortex of monoamine oxidase A-deficient mice: Role of a serotonin excess during the critical period. *Neuron* **16**, 297–307.
- Castro-Alamancos, M.A. (2004). Absence of rapid sensory adaptation in neocortex during information processing states. *Neuron* **41**, 455–464.
- Castro-Alamancos, M.A., and Oldford, E. (2002). Cortical sensory suppression during arousal is due to the activity-dependent depression of thalamocortical synapses. *J. Physiol.* **541**, 319–331.
- Chakrabarti, S., and Alloway, K.D. (2006). Differential origin of projections from SI barrel cortex to the whisker representations in SII and MII. *J. Comp. Neurol.* **498**, 624–636.
- Chung, S., Li, X., and Nelson, S.B. (2002). Short-term depression at thalamocortical synapses contributes to rapid adaptation of cortical sensory responses in vivo. *Neuron* **34**, 437–446.
- Cossart, R., Aronov, D., and Yuste, R. (2003). Attractor dynamics of network UP states in the neocortex. *Nature* **423**, 283–288.
- Crair, M.C., and Malenka, R.C. (1995). A critical period for long-term potentiation at thalamocortical synapses. *Nature* **375**, 325–328.
- Cramer, N.P., Li, Y., and Keller, A. (2007). The whisking rhythm generator: a novel mammalian network for the generation of movement. *J. Neurophysiol.* **97**, 2148–2158.
- Crochet, S., and Petersen, C.C.H. (2006). Correlating whisker behavior with membrane potential in barrel cortex of awake mice. *Nat. Neurosci.* **9**, 608–610.
- de Kock, C.P., Bruno, R.M., Spors, H., and Sakmann, B. (2007). Layer- and cell-type-specific suprathreshold stimulus representation in rat primary somatosensory cortex. *J. Physiol.* **587**, 139–154.
- Denk, W., Strickler, J.H., and Webb, W.W. (1990). Two-photon laser scanning fluorescence microscopy. *Science* **248**, 73–76.
- Diamond, M.E., Armstrong-James, M., Budway, M.J., and Ebner, F.F. (1992). Somatic sensory responses in the rostral sector of the posterior group (POm) and in the ventral posterior medial nucleus (VPM) of the rat thalamus: dependence on the barrel field cortex. *J. Comp. Neurol.* **319**, 66–84.
- Diamond, M.E., Huang, W., and Ebner, F.F. (1994). Laminar comparison of somatosensory cortical plasticity. *Science* **265**, 1885–1888.
- Dombeck, D.A., Khabbaz, A.N., Collman, F., Adelman, T.L., and Tank, D.W. (2007). Imaging large scale neural activity with cellular resolution in awake mobile mice. *Neuron* **56**, 43–57.
- Ebara, S., Kumamoto, K., Matsuura, T., Mazurkiewicz, J.E., and Rice, F.L. (2002). Similarities and differences in the innervation of mystacial vibrissal follicle-sinus complexes in the rat and cat: a confocal microscopic study. *J. Comp. Neurol.* **449**, 103–119.
- Erchova, I.A., and Diamond, M.E. (2004). Rapid fluctuations in rat barrel cortex plasticity. *J. Neurosci.* **24**, 5931–5941.
- Fanselow, E.E., and Nicolelis, M.A.L. (1999). Behavioral modulation of tactile responses in the rat somatosensory system. *J. Neurosci.* **19**, 7603–7616.
- Fee, M.S., Mitra, P.P., and Kleinfeld, D. (1997). Central versus peripheral determinants of patterned spike activity in rat vibrissa cortex during whisking. *J. Neurophysiol.* **78**, 1144–1149.
- Feldman, D.E., and Brecht, M. (2005). Map plasticity in the somatosensory cortex. *Science* **310**, 810–815.

- Feldman, D.E., Nicoll, R.A., Malenka, R.C., and Isaac, J.T. (1998). Long-term depression at thalamocortical synapses in developing rat somatosensory cortex. *Neuron* 21, 347–357.
- Feldmeyer, D., Egger, V., Lubke, J., and Sakmann, B. (1999). Reliable synaptic connections between pairs of excitatory layer 4 neurons within a single ‘barrel’ of developing rat somatosensory cortex. *J. Physiol.* 521, 169–190.
- Feldmeyer, D., Roth, A., and Sakmann, B. (2005). Monosynaptic connections between pairs of spiny stellate cells in layer 4 and pyramidal cells in layer 5A indicate that lemniscal and paralemniscal afferent pathways converge in the infragranular somatosensory cortex. *J. Neurosci.* 25, 3423–3431.
- Ferezou, I., Bolea, S., and Petersen, C.C.H. (2006). Visualizing the cortical representation of whisker touch: voltage-sensitive dye imaging in freely moving mice. *Neuron* 50, 617–629.
- Finnerty, G.T., Roberts, L.S., and Connors, B.W. (1999). Sensory experience modifies the short-term dynamics of neocortical synapses. *Nature* 400, 367–371.
- Fox, K.D. (1992). A critical period for experience-dependent synaptic plasticity in rat barrel cortex. *J. Neurosci.* 12, 1826–1838.
- Friedberg, M.H., Lee, S.M., and Ebner, F.F. (1999). Modulation of receptive field properties of thalamic somatosensory neurons by the depth of anesthesia. *J. Neurophysiol.* 81, 2243–2252.
- Fukuchi-Shimogori, T., and Grove, E.A. (2001). Neocortex patterning by the secreted signaling molecule FGF8. *Science* 294, 1071–1074.
- Furuta, T., Nakamura, K., and Deschenes, M. (2006). Angular tuning bias of vibrissa-responsive cells in the paralemniscal pathway. *J. Neurosci.* 26, 10548–10557.
- Ganguly, K., and Kleinfeld, D. (2004). Goal-directed whisking increases phase-locking between vibrissa movement and electrical activity in primary sensory cortex in rat. *Proc. Natl. Acad. Sci. USA* 101, 12348–12353.
- Gilbert, C.D., and Sigman, M. (2007). Brain states: Top-down influences in sensory processing. *Neuron* 54, 677–696.
- Glazewski, S., and Fox, K. (1996). Time course of experience-dependent synaptic potentiation and depression in barrel cortex of adolescent rats. *J. Neurophysiol.* 75, 1714–1729.
- Grinvald, A., and Hildesheim, R. (2004). VSDI: a new era in functional imaging of cortical dynamics. *Nat. Rev. Neurosci.* 5, 874–885.
- Grinvald, A., Lieke, E., Frostig, R.D., Gilbert, C.D., and Wiesel, T.N. (1986). Functional architecture of cortex revealed by optical imaging of intrinsic signals. *Nature* 324, 361–364.
- Haiss, F., and Schwarz, C. (2005). Spatial segregation of different modes of movement control in the whisker representation of rat primary motor cortex. *J. Neurosci.* 25, 1579–1587.
- Hannan, A.J., Blakemore, C., Katsnelson, A., Vitalis, T., Huber, K.M., Bear, M., Roder, J., Kim, D., Shin, H.S., and Kind, P.C. (2001). PLC- $\beta$ 1, activated via mGluRs, mediates activity-dependent differentiation in cerebral cortex. *Nat. Neurosci.* 4, 282–288.
- Harris, J.A., Petersen, R.S., and Diamond, M.E. (1999). Distribution of tactile learning and its neural basis. *Proc. Natl. Acad. Sci. USA* 96, 7587–7591.
- Hartmann, M.J., Johnson, N.J., Towal, R.B., and Assad, C. (2003). Mechanical characteristics of rat vibrissae: resonant frequencies and damping in isolated whiskers and in the awake behaving animal. *J. Neurosci.* 23, 6510–6519.
- Hattox, A., Li, Y., and Keller, A. (2003). Serotonin regulates rhythmic whisking. *Neuron* 39, 343–352.
- Helmchen, F., Fee, M.S., Tank, D.W., and Denk, W. (2001). A miniature head-mounted two-photon microscope: High-resolution brain imaging in freely moving animals. *Neuron* 31, 903–912.
- Hentschke, H., Haiss, F., and Schwarz, C. (2006). Central signals rapidly switch tactile processing in rat barrel cortex during whisker movements. *Cereb. Cortex* 16, 1142–1156.
- Heynen, A.J., Yoon, B.J., Liu, C.H., Chung, H.J., Hugarin, R.L., and Bear, M.F. (2003). Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nat. Neurosci.* 6, 854–862.
- Higley, M.J., and Contreras, D. (2003). Nonlinear integration of sensory responses in the rat barrel cortex: an intracellular study in vivo. *J. Neurosci.* 23, 10190–10200.
- Holtmaat, A.J., Trachtenberg, J.T., Wilbrecht, L., Shepherd, G.M., Zhang, X., Knott, G.W., and Svoboda, K. (2005). Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* 45, 279–291.
- Hutson, K.A., and Masterton, R.B. (1986). The sensory contribution of a single vibrissa’s cortical barrel. *J. Neurophysiol.* 56, 1196–1223.
- Iwasato, T., Datwani, A., Wolf, A.M., Nishiyama, H., Taguchi, Y., Tonegawa, S., Knopfel, T., Erzurumlu, R.S., and Itoharu, S. (2000). Cortex-restricted disruption of NMDAR1 impairs neuronal patterns in the barrel cortex. *Nature* 406, 726–731.
- Jensen, K.F., and Killackey, H.P. (1987). Terminal arbors of axons projecting to the somatosensory cortex of the adult rat. I. The normal morphology of specific thalamocortical afferents. *J. Neurosci.* 7, 3529–3543.
- Jones, L.M., Depireux, D.A., Simons, D.J., and Keller, A. (2004). Robust temporal coding in the trigeminal system. *Science* 304, 1986–1999.
- Kerr, J.N., Greenberg, D., and Helmchen, F. (2005). Imaging input and output of neocortical networks in vivo. *Proc. Natl. Acad. Sci. USA* 102, 14063–14068.
- Kim, U., and Ebner, F.F. (1999). Barrels and septa: separate circuits in rat barrels field cortex. *J. Comp. Neurol.* 408, 489–505.
- Kleinfeld, D., Sachdev, R.N.S., Merchant, L.M., Jarvis, M.R., and Ebner, F.F. (2002). Adaptive filtering of vibrissa input in motor cortex of rat. *Neuron* 34, 1021–1034.
- Kleinfeld, D., Ahissar, E., and Diamond, M.E. (2006). Active sensation: insights from the rodent vibrissa sensorimotor system. *Curr. Opin. Neurobiol.* 16, 435–444.
- Knott, G.W., Quairiaux, C., Genoud, C., and Welker, E. (2002). Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. *Neuron* 34, 265–273.
- Knutsen, P.M., Pietr, M., and Ahissar, E. (2006). Haptic object localization in the vibrissal system: behavior and performance. *J. Neurosci.* 26, 8451–8464.
- Krupa, D.J., Matell, M.S., Brisben, A.J., Oliveira, L.M., and Nicolelis, M.A. (2001). Behavioral properties of the trigeminal somatosensory system in rats performing whisker-dependent tactile discriminations. *J. Neurosci.* 21, 5752–5763.
- Krupa, D.J., Wiest, M.C., Shuler, M.G., Laubach, M., and Nicolelis, M.A. (2004). Layer-specific somatosensory cortical activation during active tactile discrimination. *Science* 304, 1989–1992.
- de Lafuente, V., and Romo, R. (2006). Neural correlate of subjective sensory experience gradually builds up across cortical areas. *Proc. Natl. Acad. Sci. USA* 103, 14266–14271.
- Land, P.W., and Erickson, S.L. (2005). Subbarrel domains in rat somatosensory (S1) cortex. *J. Comp. Neurol.* 490, 414–426.
- Laaris, N., and Keller, A. (2002). Functional independence of layer IV barrels. *J. Neurophysiol.* 87, 1028–1034.
- Lavallee, P., Urbain, N., Dufresne, C., Bokor, H., Acsady, L., and Deschenes, M. (2005). Feedforward inhibitory control of sensory information in higher-order thalamic nuclei. *J. Neurosci.* 25, 7489–7498.
- Lee, A.K., Manns, I.D., Sakmann, B., and Brecht, M. (2006). Whole-cell recordings in freely moving rats. *Neuron* 51, 399–407.

- Leiser, S.C., and Moxon, K.A. (2007). Responses of trigeminal ganglion neurons during natural whisking behaviors in the awake rat. *Neuron* 53, 117–133.
- Lendvai, B., Stern, E.A., Chen, B., and Svoboda, K. (2000). Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. *Nature* 404, 876–881.
- Lübke, J., and Feldmeyer, D. (2007). Excitatory signal flow and connectivity in a cortical column: focus on barrel cortex. *Brain Struct. Funct.* 212, 3–17.
- Markram, H., Lübke, J., Frotscher, M., Roth, A., and Sakmann, B. (1997). Physiology and anatomy of synaptic connections between thick tufted pyramidal neurones in the developing rat neocortex. *J. Physiol.* 500, 409–440.
- Mehta, S.B., Whitner, D., Figueroa, R., Williams, B.A., and Kleinfeld, D. (2007). Active spatial perception in the vibrissa scanning sensorimotor system. *PLoS Biol.* 5, e15. 10.1371/journal.pbio.0050015.
- Molnar, Z., Lopez-Bendito, G., Small, J., Partridge, L.D., Blakemore, C., and Wilson, M.C. (2002). Normal development of embryonic thalamocortical connectivity in the absence of evoked synaptic activity. *J. Neurosci.* 22, 10313–10323.
- Moore, C.I. (2004). Frequency-dependent processing in the vibrissa sensory system. *J. Neurophysiol.* 91, 2390–2399.
- Moore, C.I., and Nelson, S.B. (1998). Spatio-temporal subthreshold receptive fields in the vibrissa representation of rat primary somatosensory cortex. *J. Neurophysiol.* 80, 2882–2892.
- Neimark, M.A., Andermann, M.L., Hopfield, J.J., and Moore, C.I. (2003). Vibrissa resonance as a transduction mechanism for tactile encoding. *J. Neurosci.* 23, 6499–6509.
- Nguyen, Q.T., and Kleinfeld, D. (2005). Positive feedback in a brainstem tactile sensorimotor loop. *Neuron* 45, 447–457.
- Ohki, K., Chung, S., Ch'ng, Y.H., Kara, P., and Reid, R.C. (2005). Functional imaging with cellular resolution reveals precise micro-architecture in visual cortex. *Nature* 433, 597–603.
- Peterlin, Z.A., Kozloski, J., Mao, B.Q., Tsiola, A., and Yuste, R. (2000). Optical probing of neuronal circuits with calcium indicators. *Proc. Natl. Acad. Sci. USA* 97, 3619–3624.
- Petersen, C.C.H., and Sakmann, B. (2000). The excitatory neuronal network of rat layer 4 barrel cortex. *J. Neurosci.* 20, 7579–7586.
- Petersen, C.C.H., and Sakmann, B. (2001). Functionally independent columns of rat somatosensory barrel cortex revealed with voltage-sensitive dye imaging. *J. Neurosci.* 21, 8435–8446.
- Petersen, R.S., Panzeri, S., and Diamond, M.E. (2001). Population coding of stimulus location in rat somatosensory cortex. *Neuron* 32, 503–514.
- Petersen, C.C.H., Grinvald, A., and Sakmann, B. (2003a). Spatiotemporal dynamics of sensory responses in layer 2/3 of rat barrel cortex measured in vivo by voltage-sensitive dye imaging combined with whole-cell voltage recordings and anatomical reconstructions. *J. Neurosci.* 23, 1298–1309.
- Petersen, C.C.H., Hahn, T.T.G., Mehta, M., Grinvald, A., and Sakmann, B. (2003b). Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex. *Proc. Natl. Acad. Sci. USA* 100, 13638–13643.
- Petreaun, L., Huber, D., Sobczyk, A., and Svoboda, K. (2007). Channelrhodopsin-2-assisted circuit mapping of long-range callosal projections. *Nat. Neurosci.* 10, 663–668.
- Pierret, T., Lavalée, P., and Deschenes, M. (2000). Parallel streams for the relay of vibrissal information through thalamic barreloids. *J. Neurosci.* 20, 7455–7462.
- Polley, D.B., Chen-Bee, C.H., and Frostig, R.D. (1999). Two directions of plasticity in the sensory-deprived adult cortex. *Neuron* 24, 623–637.
- Polley, D.B., Kvasnak, E., and Frostig, R.D. (2004). Naturalistic experience transforms sensory maps in the adult cortex of caged animals. *Nature* 429, 67–71.
- Reyes, A., and Sakmann, B. (1999). Developmental switch in the short-term modification of unitary EPSPs evoked in layer 2/3 and layer 5 pyramidal neurons of rat neocortex. *J. Neurosci.* 19, 3827–3835.
- Sachdev, R.N., Ebner, F.F., and Wilson, C.J. (2004). Effect of sub-threshold up and down states on the whisker-evoked response in somatosensory cortex. *J. Neurophysiol.* 92, 3511–3521.
- Sato, T.R., Gray, N.W., Mainen, Z.F., and Svoboda, K. (2007). The functional microarchitecture of the mouse barrel cortex. *PLoS Biol.* 5, e189. 10.1371/journal.pbio.0050189.
- Schubert, D., Kotter, R., Zilles, K., Luhmann, H.J., and Staiger, J.F. (2003). Cell type-specific circuits of cortical layer IV spiny neurons. *J. Neurosci.* 23, 2961–2970.
- Schubert, D., Kotter, R., Luhmann, H.J., and Staiger, J.F. (2006). Morphology, electrophysiology and functional input connectivity of pyramidal neurons characterizes a genuine layer Va in the primary somatosensory cortex. *Cereb. Cortex* 16, 223–236.
- Shepherd, G.M., and Svoboda, K. (2005). Laminar and columnar organization of ascending excitatory projections to layer 2/3 pyramidal neurons in rat barrel cortex. *J. Neurosci.* 25, 5670–5679.
- Shepherd, G.M., Pologruto, T.A., and Svoboda, K. (2003). Circuit analysis of experience-dependent plasticity in the developing rat barrel cortex. *Neuron* 38, 277–289.
- Simons, D.J. (1978). Response properties of vibrissa units in rat SI somatosensory neocortex. *J. Neurophysiol.* 41, 798–820.
- Simons, D.J., and Carvell, G.E. (1989). Thalamocortical response transformation in the rat vibrissa/barrel system. *J. Neurophysiol.* 61, 311–330.
- Siucinska, E., and Kossut, M. (2004). Experience-dependent changes in cortical whisker representation in the adult mouse: a 2-deoxyglucose study. *Neuroscience* 127, 961–971.
- Stosiek, C., Garaschuk, O., Holthoff, K., and Konnerth, A. (2003). In vivo two-photon calcium imaging of neuronal networks. *Proc. Natl. Acad. Sci. USA* 100, 7319–7324.
- Stuttgen, M.C., Ruter, J., and Schwarz, C. (2006). Two psychophysical channels of whisker deflection in rats align with two neuronal classes of primary afferents. *J. Neurosci.* 26, 7933–7941.
- Szwd, M., Bagdasarian, K., and Ahissar, E. (2003). Encoding of vibrissal active touch. *Neuron* 40, 621–630.
- Timofeeva, E., Merette, C., Emond, C., Lavalée, P., and Deschenes, M. (2003). A map of angular preference in thalamic barreloids. *J. Neurosci.* 23, 10717–10723.
- Trageser, J.C., Burke, K.A., Masri, R., Li, Y., Sellers, L., and Keller, A. (2006). State-dependent gating of sensory inputs by zona incerta. *J. Neurophysiol.* 96, 1456–1463.
- Tsien, R.Y. (1981). A non-disruptive technique for loading calcium buffers and indicators into cells. *Nature* 290, 527–528.
- Van der Loos, H., and Woolsey, T.A. (1973). Somatosensory cortex: structural alterations following early injury to sense organs. *Science* 179, 395–398.
- Veinante, P., and Deschenes, M. (1999). Single- and multi-whisker channels in the ascending projections from the principal trigeminal nucleus in the rat. *J. Neurosci.* 19, 5085–5095.
- Welker, C. (1971). Microelectrode delineation of fine grain somatotopic organization of (Sml) cerebral neocortex in albino rat. *Brain Res.* 26, 259–275.
- Welker, E., Hoogland, P.V., and Van der Loos, H. (1988). Organization of feedback and feedforward projections of the barrel cortex: a PHA-L study in the mouse. *Exp. Brain Res.* 73, 411–435.



Welker, E., Armstrong-James, M., Bronchti, G., Ourednik, W., Gheorghita-Baechler, F., Dubois, R., Guernsey, D.L., Van der Loos, H., and Neumann, P.E. (1996). Altered sensory processing in the somatosensory cortex of the mouse mutant barrelless. *Science* 271, 1864–1867.

White, E.L., and DeAmicis, R.A. (1977). Afferent and efferent projections of the region of mouse Sml cortex which contains the posteromedial barrel subfield. *J. Comp. Neurol.* 175, 455–482.

Wong-Riley, M.T., and Welt, C. (1980). Histochemical changes in cytochrome oxidase of cortical barrels after vibrissal removal in neonatal and adult mice. *Proc. Natl. Acad. Sci. USA* 77, 2333–2337.

Woolsey, T.A., and Van der Loos, H. (1970). The structural organisation of layer IV in the somatosensory region (SI) of the mouse cerebral cortex: the description of a cortical field composed of discrete cytoarchitectonic units. *Brain Res.* 17, 205–242.

Yang, X., Hyder, F., and Shulman, R.G. (1996). Activation of single whisker barrel in rat brain localized by functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* 93, 475–478.

Yu, C., Derdikman, D., Haidarliu, S., and Ahissar, E. (2006). Parallel thalamic pathways for whisking and touch signals in the rat. *PLoS Biol.* 4, e124. 10.1371/journal.pbio.0040124.

Zhu, J.J., and Connors, B.W. (1999). Intrinsic firing patterns and whiskers-evoked synaptic responses of neurons in the rat barrel cortex. *J. Neurophysiol.* 81, 1171–1183.

Zuo, Y., Lin, A., Chang, P., and Gan, W.B. (2005). Development of long-term dendritic spine stability in diverse regions of cerebral cortex. *Neuron* 46, 181–189.