Heterogeneous Integration of Bilateral Whisker Signals by Neurons in Primary Somatosensory Cortex of Awake Rats

Michael C. Wiest, Nick Bentley, and Miguel A. L. Nicolelis. Heterogeneous integration of bilateral whisker signals by neurons in primary somatosensory cortex of awake rats. *J Neurophysiol* 93: 2966–2973, 2005. First published November 24, 2004; doi:10.1152/jn.00556.2004. Bilateral single-unit recordings in primary somatosensory cortex (S1) of anesthetized rats have revealed substantial cross talk between cortical hemispheres, suggesting the possibility that behaviorally relevant bilateral integration could occur in S1. To determine the extent of bilateral neural responses in awake animals, we recorded S1 multi- and single-unit activity in head-immobilized rats while stimulating groups of 4 whiskers from the same column on both sides of the head. Results from these experiments confirm the widespread presence of single units responding to tactile stimuli on either side of the face in S1 of awake animals. Quantification of bilateral integration by multunits revealed both facilitative and suppressive integration of bilateral inputs. Varying the interval between left and right whisker stimuli between 0 and 120 ms showed the temporal integration of bilateral stimuli to be dominated on average by suppression at intervals around 30 ms, in agreement with comparable recordings in anesthetized animals. Contrary to the anesthetized data, in the awake animals we observed a high level of heterogeneity of bilateral responses and a strong interaction between synchronous bilateral stimuli. The results challenge the traditional conception of highly segregated hemispheric processing channels in the rat S1 cortex, and support the hypothesis that callosal cross-projections between the two hemispheres mediate rats’ known ability to integrate bilateral whisker signals.

INTRODUCTION

One approach to understand the coding of whisker stimuli in the rat primary somatosensory cortex (S1) focuses on a one-to-one relationship between anatomically discrete cortical “barrels” in layer IV and a single principal whisker on the contralateral whisker pad (Armstrong-James 1995; Brumberg et al. 1996; Petersen et al. 2002). Because of the relative scarcity of connections between layer IV excitatory cells in different barrels, and because these cells tend to respond to principal whisker stimulation with the shortest latency, the layer IV barrel field can be interpreted as an array of dedicated detectors for deflections of each contralateral whisker. The fact that whiskers other than the principal whisker do modulate responses in a barrel can be explained in a number of ways. Brumberg et al. (1996) proposed that inhibitory circuitry within barrels functions to “increase the ‘principal whiskerness’ of the cortical column” by suppressing weaker responses so that “only . . . the initial perturbation of the principal whiskers will overcome the . . . cortical inhibition” (Brumberg et al. 1996). For Armstrong-James (1995), a “transient insularity” between barrels includes the whole cortical column centered over a barrel. That is, for some time after each stimulus the barrel columns can encode the activity of single whiskers. Similarly, Petersen et al. (2002) recently noted that the earliest evoked spike after an isolated punctate single-whisker stimulus contains most of the information about which the single whisker was stimulated. From this they concluded that later activity, reflecting interactions between different barrels, was largely redundant for neural coding of stimulus identity.

In the supra- and infragranular layers intercolumnar connections are more common, and receptive fields in those layers are correspondingly larger (Armstrong-James et al. 1992; Ghazanfar et al. 2000; Schubert et al. 2001). Moreover, these multi-whisker receptive fields are dynamic over poststimulus time (Ghazanfar and Nicolelis 1999, 2001a). It is more difficult to interpret the responses of cells in these layers primarily in terms of the stimulation of individual whiskers. A complementary view emphasizes the integrative function of S1. Thus although Simons (1985) considered that “each barrel is the morphological correlate in layer IV of a functional cortical column that extends throughout the thickness of cortex,” he also concluded “that an important function of the S1 cortex is to integrate information from different, individual vibrissae on the contralateral face.” He suggested intercolumnar integration functioned to make SI neurons sensitive to spatiotemporal patterns of whisker activity characterizing the movement of particular objects across the contralateral whisker pad (Simons 1985), as have others (Ghazanfar and Nicolelis 1997; Shimegi et al. 2000). Even for coding single-whisker stimuli, Ghazanfar et al. (2000) showed that the relative contribution of temporal interactions between neurons increases with the number of whiskers to be discriminated. Inhibitory intercolumnar interactions have also been suggested to maintain a dynamic range and prevent response saturation (Mirabella et al. 2001).

It is important to note that the different approaches to inter-columnar interactions sketched above need not be exclusive, but could reflect different processing strategies appropriate to different behavioral contexts. This idea has arisen in the whisker sensory-motor literature, in terms of different S1 neuronal response properties in the quiet waking state as...
compared with the whisking state (Castro-Alamancos 2004; Fanselow and Nicolelis 1999; Moore 2004; Moore et al. 1999; Nicolelis and Fanselow 2002). These authors proposed that greater response magnitudes during the quiet state could perform a gross “detection” function, whereas relatively less spike adaptation during the whisking state would allow for finer “discrimination” of spatiotemporal patterns of stimulation. Based on the finding that the horizontal extent of cortex activated by stimulation of a vibrissa is relatively smaller during whisking than during an isolated passive contact, some authors (Castro-Alamancos 2004; Moore 2004; Moore et al. 1999) have further speculated that a more spatially “focused” sensory representation during whisking could improve tactile discrimination.

All the coding studies mentioned above have in common that the whisker cortex is interpreted as a topographic map of whisker deflections on the contralateral whisker pad, in line with the cortical homunculus as a map of somatosensory activity in general. A topographic organization does not prohibit lateral interactions, but implies that they should be relatively local. In particular, SI cortex is understood to encode stimulation of the contralateral whisker pad. Such a view is apparently supported by behavioral experiments demonstrating that certain unilateral tactile detection tasks do not require ipsilateral S1 (Hutson and Masterton 1986).

This picture is overly restrictive. It has long been known that callosal cross-projections integrate the two S1 hemispheres (Cauller et al. 1998; Koralek et al. 1990; Olavarria et al. 1984; White and DeAmicis 1977). Interhemispheric connections are concentrated in the homologous portions of the barrel field, innervating primarily but not exclusively the supra- and infragranular layers (Hayama and Ogawa 1997). Those callosal connections that do innervate layer 4 are concentrated in the septal regions outside the barrel centers (Hayama and Ogawa 1997; Olavarria et al. 1984), as are unilateral interbarrel connections in layer IV (Kim and Ebner 1999). In the present study we focus on the bilateral integration of whisker sensory signals in S1 through these interhemispheric connections, which offers an advantageous window on the larger issue of the dynamic integration of distributed sensory representations because the peripheral signals to be integrated are clearly segregated in space and may be independently manipulated up to the level of the S1 cortex.

Pidoux and Verley (1979) recorded S1 local field potential (LFP) responses to ipsilateral whisker stimulation in anesthetized rats, the first electrophysiological evidence of cross talk between the S1 hemispheres. Shuler et al. (2001) demonstrated that whisker stimulation on either side of the face of an anesthetized rat could evoke responses in the same layer V S1 neuron. This result has been recently confirmed by intracellular recordings (Manns et al. 2004). Other studies have shown that the responses of individual neurons in S1 are suppressed in the absence of activity in the contralateral hemisphere (Shin et al. 1997). Rema and Ebner (2003) found similar response suppression as well as changes in whisker-pairing plasticity in all layers arising from contralateral lesions.

One potentially relevant function of the commissural interhemispheric connections is to transfer learned associations from one hemisphere to the other (Calford and Tweedle 1990; Ebner and Myers 1962). Such transfer of plasticity on relatively long timescales might be imagined to preserve the unambiguous representation of the contralateral whisker pad in each S1 hemisphere implied by the traditional models mentioned above. However, if bilateral receptive fields (Manns et al. 2004; Shuler et al. 2001) observed in anesthetized preparations remain functional in the behaving animal, the conception of the S1 barrel cortex as an encoder for exclusively contralateral whisker activity will need to be refined or replaced.

Previous behavioral experiments in our laboratory have demonstrated that rats can integrate whisker signals from both sides of the face in a tactile discrimination task (Krupa et al. 2001b; Shuler et al. 2002). In fact, the rat integrated bilateral whisker signals even in an aperture width discrimination task that does not force rats to use a bilateral strategy (Krupa and Nicolelis 2004a; Oliveira et al. 2003), suggesting that bilateral integration is a natural function of the rat whisker system. S1 is the first place where bilateral whisker sensory afferents converge (Erzurumlu and Kilacky 1980; Smith 1973; Waite 1969). Accordingly, Shuler et al. (2002) found that intact S1 cortex in both hemispheres was required for successful performance of a bilateral tactile discrimination task.

If S1 is an actual site of integration, rather than merely a conduit for sensory information that is integrated at higher processing stages, then the influence of ipsilateral as well as contralateral stimuli should be measurable in S1. It remains unknown whether the bilateral connections between the S1 hemispheres are fully functional on millisecond timescales in awake, behaving animals. Our experiments addressed this question using bilateral multielectrode recordings in S1 of head-immobilized awake rats during controlled bilateral stimulation of columns of whiskers. Following Shuler et al. (2001) we looked for evidence of bilateral integration in layer V, which contains the main output neurons of S1.

**Methods**

**Head-immobilized awake electrophysiology experiments**

A sample of 5 female Long–Evans rats was used in the present experiments. Details of surgery and recording procedures may be found elsewhere (Nicolelis 1997; Nicolelis and Chapin 1994). Briefly, surgery was performed under pentobarbital anesthesia to implant rats with pairs of 16 electrode arrays (2 × 8) bilaterally in S1. The arrays were positioned stereotactically and by means of tactile stimulation during surgery to record in cortical layer V (~3 mm caudal from bregma, 5.5 mm mediolateral, and about 1.3 mm depth from brain surface). During the same surgery a brass head post (1/4-in. width; Small Parts, Miami Lakes, FL) was fixed to the dental-cement head cap for head-immobilized awake recordings. Rats were given ≥7 days after surgery to recover.

Control of whisker stimulus delivery was achieved by combining head-immobilization with a computer-controlled multiple individual-whisker stimulator (Krupa et al. 2001a) adapted for use on an awake animal. For all experiments in this study the stimulator nozzle was attached to the bottom 4 large whiskers in a single arc (B–E) (Fig. 1A). Animals were partially acclimated before surgery to restraint in a Plexiglas restraint tube with mild food deprivation and calorie-dense liquid reward during sessions in the restraint tube, and wearing light drawing “jackets” to minimize traction against the Plexiglas tube and prevent the subject from using her forepaws to remove the stimulator arms.

The whisker stimulator was used to apply controlled 5-ms rostral deflections of the bottom 4 whiskers in a single column on each side of the subject’s face. To lasso 4 whiskers, the nozzle was first opened wide, then fine forceps were used to pull through the whiskers one at
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a time before tightening the noose. Two basic protocols were run. In both experiments, stimuli were presented in random order at random intertrial intervals of between 2 and 4 s. In **expt. 1** the stimulus set consisted of a left-column deflection, a right-column deflection, and simultaneous bilateral deflections. In **expt. 2** the stimulus set consisted of a left-then right-column deflection at interstimulus intervals (ISIs) of 0, 30, 60, 90, and 120 ms. TEMPO software (Reflective Computing, St. Louis, MO) controlled the stimulus administration and sent time-stamped stimulus events with millisecond accuracy to the file of neural recordings described below. The Duke University Institutional Animal Use Committee approved all surgical and behavioral methods.

Histology of coronal slices of the experimental animals’ brains confirmed the localization of the electrode arrays in each animal to the infragranular layers of S1. A Nissl-stained slice from one animal, containing the track of an electrode, is shown in Fig. 1B.

**Data analysis**

Significant firing rate responses of SUs were identified from post-stimulus time histograms (PSTHs) for each session using the standard statistical function built-in to the Nex data analysis software package (Nex Technologies, Littleton, MA; Abeles 1982), which assumes Poisson spike count statistics to derive confidence intervals on the spike counts in each PSTH bin. To identify significant SU responses we used a bin width of 10 ms and set the confidence level to 99%.

To achieve greater precision in response latencies and magnitudes we constructed the MU PSTHs using 1-ms bins. However, despite the greater numbers of spikes generally in the MU PSTHs, bin counts could fluctuate above and below the 99% confidence limits, adding uncertainty to a latency calculation. To circumvent this problem but avoid smoothing the histograms, which would introduce complexities into the determination of confidence intervals, we applied a method based on the statistical distribution of cumulative-summed spike counts (e.g., Ghazanfar et al. 2001b; Ushiba et al. 2002). This approach takes into account the statistics of all the spiking activity up to a given moment, as opposed to considering each bin independently. Additionally, the method requires no assumption of a particular parametric form of the spiking statistics.

To find the onsets of significant deviations from prestimulus activity, we calculated the deviation **Dn** of the poststimulus cumulative summed spike count from the expected cumulative sum, based on the average prestimulus firing rate **λ**, at each poststimulus bin **n**

\[ D_n = \sum_{i=1}^{n} \text{Post}_i - n \lambda \]

Here **λ** is the expected number of spikes per bin calculated from the baseline, and **Post** is the observed spike count in poststimulus bin **i**.

To assess the significance of deviations from the expected cumulative sum, an empirical distribution of the cumulative-summed spike count at each time bin before the stimulus was constructed from 1,000 bootstrapped samples (with replacement) of the prestimulus spike histogram. The prestimulus cumulative sums were counted starting from 200 ms before stimulus onset. This empirical distribution of prestimulus firing was then used to find the poststimulus bin (if any) at which the cumulative-summed **poststimulus** spike count exceeded or was <99% of the cumulative spike counts from the baseline distribution (Martinez and Martinez 2002). This bin was recorded as the onset of an excitatory or inhibitory response.

The response offset was identified as the first zero crossing of the derivative of the cumulative deviation from the baseline spike count, meaning that the cumulative sum was no longer deviating from its expected growth with time. This procedure identified the time at which the PSTH returned to a baseline firing rate. The magnitude of the response was quantified as the number of excess spikes between onset and offset, compared with the baseline expected number, divided by the number of trials. This procedure gives the average number of spikes per trial, over and above the baseline number expected, fired by an MU in response to a particular whisker column stimulation.

**RESULTS**

**Bilateral integration by single units in S1**

We isolated 361 layer V SUs recorded over 38 sessions in 5 animals. Of the 361 SUs, 198 (55%) showed significant responses to stimulation, on at least one side of the face, and 96 (27%) responded to both ipsilateral and contralateral stimulation. That is, 49% of those responding to contralateral stimulation also responded to ipsilateral stimulation. Several examples of SU responses to ipsilateral and contralateral stimulation are shown in Fig. 2. These results strongly suggest that the firing rates of individual neurons in S1 of awake rats are driven by both ipsilateral and contralateral stimuli.

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**FIG. 1.** **A:** close-up of a whisker-stimulator noose around 4 whiskers from an arc. **B:** a Nissl-stained slice from one animal showing an electrode track down to layer V (indicated by the arrow).
Most SU responses were initially excitatory, occasionally followed by a period of significantly reduced firing (e.g., the SU in row 2 of Fig. 2). However, “direct” inhibitory responses were observed occasionally, such as the SU on the bottom row of Fig. 2. The firing of 11 SUs was suppressed by stimulation on either side of the face, whereas 19 other SUs reduced their firing in response to one unilateral stimulus but not the other. Such inhibitory responses thus accounted for 30 (15%) of the significant SU responses. Sachdev et al. (2000) reported direct inhibitory responses in S1 of awake rats in response to stimulation of single whiskers. In that study most neurons exhibiting direct inhibition were found to be located over the septal regions outside the central barrel region of the cortex, in layers II, III, IV, and V. They also noted that repetitive stimulation faster than 6 Hz tended to turn the inhibitory responses into excitation. Swadlow (2003) described the electrophysiology of layer IV inhibitory interneurons in rabbits, believed to relay feedforward inhibition to excitatory cortical cells. Interestingly, in freely moving rats engaged in an active whisker-dependent discrimination task, 54% of infragranular S1 neurons responded to multiwhisker deflections with purely inhibitory or inhibitory followed by excitatory responses, indicating a greater role for inhibitory coding in the discriminating animals compared with the passively stimulated animals (Krupa et al. 2004b).

**Multiunit responses in S1 to ipsi- and contralateral stimuli**

In the same experiments we recorded 1,103 multiunit channels (MUs) that showed significant modulation in response to bilateral stimulation of 4 whiskers in a single column on each side of the rat’s face. Overall, 984 MUs significantly modulated their firing rates in response to contralateral stimulation, and 585 responded to ipsilateral stimulation. Of those that responded to contralateral stimulation, 50% (491 MUs) responded to ipsilateral stimulation as well, in agreement with the results observed for SUs (49%). Figure 3 shows several examples of MU responses to ipsilateral and contralateral whisker stimulation.

**FIG. 3.** Multiunits (MUs) respond to contralateral and ipsilateral whisker stimuli. Each row shows poststimulus time histograms (PSTHs) of one layer V single unit in response to contralateral (left column) and ipsilateral (right column) whisker column stimuli delivered at $t = 0$. Spike counts are based on 10-ms bins. Dashed lines show the 99% confidence limit for the spike counts, based on the prestimulus baseline firing rate. Bottom row: example of an SU whose firing was suppressed by whisker stimulation, a relatively rare type of response.

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Figure 4A shows the distribution of response latencies corresponding to contralateral, ipsilateral, and synchronous bilateral stimulation. The average response latencies for contralateral, ipsilateral, and bilateral stimuli were 14.67 ± 0.02, 23.78 ± 0.04, and 15.07 ± 0.02 ms (SDs: 19, 24, and 17 ms, respectively). For comparison, response latencies in S1 SUs in pentobarbital-anesthetized rats, for contralateral and ipsilateral whisker stimuli similar to those used in the present study, were 11 ± 3.4 and 23 ± 4.7 ms, respectively (Shuler et al. 2001), consistent with the present study.

One potential confound in interpreting the bilaterally evoked responses we observed is the possibility that a startle reaction arising from an ipsilateral stimulus might lead to a movement of contralateral whiskers against the (stationary) stimulator noose, leading to a response resulting from contralateral self-stimulation. Such a response could be misinterpreted as an evoked ipsilateral response. This scenario can be ruled out as follows: First, sessions with the stimulator attached on only one side of the face continue to show ipsilateral responses. Four examples are shown in Fig. 5. This rules out the possibility that false ipsilateral responses resulted from contralateral self-stimulation against the stimulator noose. That leaves the possibility that a contralateral movement “in air” could generate a false ipsilateral response in S1.

This is possible in principle because Fee et al. (1997) found that whisking movements modulate spiking activity in S1. However, they found that the whiskers’ movement signal proceeded to S1 by “direct sensory activation,” implying that a signal arising from a motor reaction would take at least the time of the motor reaction plus the time of the sensory relay to reach S1. The timing of ipsilateral responses is inconsistent with what we know about the latency of a startle movement, the fastest possible motor response the rats could make. Using the same type of head restraint in a separate series of experiments (Wiest and Nicolelis 2003), we were able to record occasional startle responses in anesthetized animals, where whisker movements did not occur.

Figure 4B shows the distribution of response magnitudes for the 3 stimulation conditions, quantified in terms of excess spikes per trial. The average response magnitudes were 0.82 ± 0.02, 0.64 ± 0.04, and 0.83 ± 0.03 spikes above background per trial, in response to contralateral, ipsilateral, and bilateral stimulation, respectively (SDs: 0.76, 0.84, and 0.84 spikes per trial).

Direct inhibitory responses were rare, accounting for only 32 of 984 (3%) responses to contralateral stimulation, 30 of 585 (5%) responses to ipsilateral stimulation, and 35 of 1,103 (3%) responses to simultaneous bilateral stimulation. The lower incidence of inhibitory MU responses (3–5%) as compared with SU responses (15%) suggests that excitatory responding
from other neurons in the same MU sometimes masks inhibitory modulation within an MU.

Integration of synchronous bilateral stimuli in S1

The observation that single and multiunits respond to ipsilateral whisker stimulation clearly indicates that bilateral stimuli are integrated in rat S1. However, the average neuronal response to synchronous bilateral stimulation (0.83 ± 0.03 spikes per trial) is not significantly different from the response elicited by contralateral stimulation alone (0.82 ± 0.02 spikes per trial).

To go beyond such average measures, Fig. 6A shows a histogram of the ratios of bilateral response magnitude to contralateral response magnitude for each MU for all rats. The distribution of ratios is peaked near one, but many are less than or greater than one, indicating that ipsilateral stimulation can result in either inhibitory (<1) or excitatory (>1) modulation of the contralateral response. To assess whether bilateral stimuli are integrated sub- or supralinearly, a ratio >1 indicates supralinear summation of the 2 whisker column stimuli. Most MUs showed supralinear summation of bilateral stimuli, but almost as many were supralinear.

Temporal integration of asynchronous bilateral stimuli in S1

The above results demonstrate that simultaneous ipsilateral and contralateral whisker signals interact in each S1 hemisphere. To characterize the modulation of these bilateral interactions by the ISI between the left and right stimuli, we recorded S1 responses at varying ISIs. The net excitatory neuronal responses at each ISI are shown in Fig. 7. The significant dip at 30 ms shows that response suppression dominates at ISIs around 30 ms. This is another confirmation that ipsilateral stimulation can modulate the spiking activity in S1 on behaviorally relevant timescales.

DISCUSSION

The main result of the present study is that neurons in S1 of awake rats integrate bilateral inputs over >100 ms. This result suggests the potential importance of bilateral integration in S1 for whisker-guided behavior. Moreover, this finding further challenges the traditional conception of the organization of rat somatosensory cortex into independent representational “modules” in each hemisphere.

In awake, immobilized rats, neural responses in S1 to punctate whisker stimuli were similar in terms of response latencies...
to those recorded in anesthetized animals (Shuler et al. 2001). In terms of bilateral integration, 49% of SUs responding to contralateral whisker column stimulation also responded to ipsilateral stimulation, compared with 62% in the anesthetized study [M. Shuler, personal communication; the published report (Shuler et al. 2001) contains the percentage that responded to either of 2 whisker columns (73%)]. In these terms, the degree of bilateral integration is similar in the anesthetized and waking S1 (but see following text).

**Principles of spatiotemporal integration of multiple unilateral stimuli**

Previous studies of spatiotemporal integration of multiwhisker inputs in the rat whisker sensory system have found evidence of both inhibitory and excitatory interactions. Extracellular and intracellular studies of S1 responses to combinations of unilateral stimuli found inhibitory interactions dominating between pairs of neighboring whiskers (Brumberg et al. 1996; Higley and Contreras 2003; Simons 1985) at ISIs around 10–20 ms. [Moore (2004) recently suggested that these relatively slow temporal interactions are supplemented by resonances at higher frequencies that could account for rats’ texture discrimination ability.] Pairs of synchronous stimuli were found to sum linearly (Mirabella et al. 2001; Simons and Carvell 1989), whereas Mirabella et al. (2001) reported that synchronous stimulation of 4 whisks usually resulted in sublinear summation. These studies focused on responses of neurons in middle and supragranular layers of S1 in immobilized or anesthetized rats. Brumberg et al. (1996) suggested that surround inhibition could function for contrast enhancement in layer IV and to “effectively increase the ‘principal whiskerness’ of the cortical column,” in line with a model of barrel columns as “single-whisker processing units.” Mirabella et al. (2001) suggested that inhibitory interactions could serve to avoid response saturation and maintain a dynamic response range under naturalistic multiwhisker inputs. Recent recordings in freely moving rats engaged in an active whisker-dependent discrimination task have suggested (Krupa et al. 2004b) that inhibitory response modes in all layers are significantly more common in the discriminating animals as compared with passively stimulated animals.

In undrugged rats, similar temporal integration of multiple unilateral inputs in S1 layer V was reported in Fanselow and Nicolelis (1999). SU responses to the second of a pair of unilateral electrical stimulations of the facial afferent infrarostral nerve in awake rats were suppressed most strongly at ISIs around 25–50 ms. This suppression was most pronounced during rats’ awake quiet behavioral state as compared with the whisking and active exploring states.

However, not all unilateral interactions are inhibitory: synchronous multiple-whisker deflections have also been reported to sum supralinearly. Shimegi et al. (2000) reported supralinear summation of neighboring single-whisker stimuli in 37% of S1 neurons, primarily by cells in supragranular layers. They noted that enhanced responses were often selective for specific combinations of stimulus features such as whisker position, angle of deflection, and relative timing of multiwhisker stimuli, supporting the idea that S1 cells code for spatiotemporal patterns of whisker stimulation. Ghazanfar and Nicolelis (1997) found that 81% of SUs in S1 layer V showed supralinear responses to simultaneous stimulation of triplets of whisksers as compared with single-whisker stimulations. They reported a bias toward supralinear summation of within-column triplets as compared with within-row triplets. They pointed out that their findings were consistent with the reports of sublinear summation of unilateral stimuli because sublinear spatial summation was reported in studies of responses in granular and supragranular layers to pairs of neighboring whiskers, as opposed to the layer V responses to stimulation of triplets of relatively distant whiskers in their study. Together these findings imply dynamic excitatory as well as inhibitory nonlinear interactions among multiple whisker stimuli, which could function to encode spatiotemporal patterns of unilateral whisker stimulations.

**Principles of spatiotemporal integration of bilateral stimuli**

Shuler et al. (2001) found primarily inhibitory interactions between pairs of bilateral whisker column stimuli in S1 layer V of anesthetized rats, with greatest suppression occurring at ISIs of 30–90 ms. The responses in the anesthetized animals increased monotonically on average from ISIs of 60 to ≤180 ms. In our study, the net excitatory responses increased from ISIs of 30 ms to ISIs of 60 or 90 ms, but were relatively smaller for ISIs of 120 ms (Fig. 7). Thus bilateral integration appears somewhat more dynamic in the waking animals.

Furthermore, the anesthetized study found only a marginal difference between the responses to synchronous bilateral stimuli as compared with contralateral stimulation alone. This was expected because contralateral stimuli universally suppressed the responses to ipsilateral stimuli. Because the latency for the contralateral response is shorter, the ipsilateral excitatory response is suppressed before it occurs. We also found no significant difference between the average response to contralateral and bilateral stimulation. However, in the awake rats many individual units showed significant supralinear spatial summation (Fig. 5B) as well as sublinear summation of synchronous bilateral inputs. This difference suggests that the profile of excitatory and inhibitory contributions to ongoing S1 responses to bilateral stimuli is substantially altered in the anesthetized animal. The heterogeneity of responses we observed in the awake animals could function to enhance discrimination of patterns of whisker stimulation (Maas et al. 2002).

We conclude that individual neurons in the cortical whisker representation in the awake rat are influenced by nonlinear combinations of inputs from multiple whiskers on both sides of the face, over time spans up to and greater than a hundred milliseconds. Moreover, the spatiotemporal integration of these inputs can depend strongly on the animal’s behavioral state (Castro-Alamancos 2004; Fanselow and Nicolelis 1999; Krupa et al. 2004b; Moore 2004; Moore et al. 1999; Nicolelis and Fanselow 2002). The fact that rats can perform a variety of unilateral and bilateral whisker tasks points to the possibility that the degree of tactile bilateral integration through the corpus callosum can be modulated according to the animal’s current behavioral context. This would amount to using different sensory codes for different behavioral contexts. If this is the case, mechanisms for adaptive control of bilateral connectivity revealed in the whisker system may provide insight into dynamical mechanisms for adjusting the functional connectivity within and among other brain areas as well.


