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# Frequency Adaptation Modulates Spatial Integration of Sensory Responses in the Rat Whisker System

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**Higley MJ, Contreras D.** Frequency adaptation modulates spatial integration of sensory responses in the rat whisker system. *J Neurophysiol* 97: 3819–3824, 2007. First published March 21, 2007; doi:10.1152/jn.00098.2007. The generation of perceptual experiences requires the integration of complex spatiotemporal patterns of sensory input. The rodent whisker system is a useful model for understanding the cellular mechanisms of sensory integration, which often include the operation of local circuits distributed throughout the brain. An example is cross-whisker suppression, where the neuronal response to whisker deflection is strongly reduced by preceding deflection of a neighboring whisker. Suppressive interactions between whisker-evoked responses have largely been studied using pairs of single whisker deflections. However, rats typically sweep their whiskers across surfaces at frequencies ranging from 5 to 25 Hz. Repetitive afferent activation induces frequency-dependent adaptation of neuronal responses and alters the synaptic dynamics of circuits that play a role in suppression, suggesting that adaptation could modulate the spatial integration of whisker evoked responses. We tested this hypothesis by comparing the cross-whisker suppression of principal whisker (PW)-evoked cortical and thalamic responses when preceded by either a single deflection of an adjacent whisker (AW) or a train of AW deflections at frequencies covering the normal whisking range. We found that periodic deflection of the preceding AW significantly reduced the magnitude of cross-whisker suppression. Surprisingly, although higher frequencies resulted in greater adaptation of the AW-evoked response, the effect on suppression was independent of frequency. We suggest that these results follow from known local circuit operations at multiple levels within the afferent path. Our findings support the view that repetitive whisking subserves a transformation of the integrative and functional properties of the whisker system.

## INTRODUCTION

Rats use their whiskers to guide complex behaviors including texture discrimination and spatial localization (Brecht et al. 1997; Carvell and Simons 1990; Krupa et al. 2001). These actions require the neural integration of afferent inputs with varied and dynamic spatial and temporal properties. At the neuronal level, spatiotemporal integration is mediated by the interplay of cellular and synaptic mechanisms at multiple levels of the afferent pathway.

One well-studied form of sensory integration is cross-whisker suppression, where the neuronal response to whisker deflection is strongly reduced by preceding deflection of neighboring whiskers (Higley and Contreras 2005, 2007; Kida et al. 2005; Kyriazi et al. 1996; Simons and Carvell 1989). The magnitude of the reduction is dependent on the spatiotemporal features of the stimuli, including the interdeflection interval

and spatial arrangement of the paired whiskers (Higley and Contreras 2003, 2005; Kida et al. 2005; Simons and Carvell 1989). Similar forms of tactile surround suppression were previously described in both humans and nonhuman primates (Gardner and Costanzo 1980; Laskin and Spencer 1979a,b) and may serve to enhance discrimination and sensitivity to complex patterns of natural stimuli.

Although most studies of suppression used single deflections of neighboring whiskers, rats exploring their environment repeatedly sweep their whiskers across objects and surfaces at frequencies ranging from 5 to 25 Hz (Carvell and Simons 1990; Fee et al. 1997; Welker 1964). Moreover, neurons in the thalamus and cortex exhibit frequency-dependent adaptation of the synaptic and suprathreshold responses evoked by periodic whisker deflections (Ahissar et al. 2000; Castro-Alamancos 2002a; Chung et al. 2002; Garabedian et al. 2003; Higley and Contreras 2006; Khatri et al. 2004; Webber and Stanley 2006). Adaptation results in smaller cortical receptive fields (Katz et al. 2006) and more spatially limited cortical activation (Sheth et al. 1998) compared to responses evoked by single whisker deflections, suggesting that repetitive whisker deflection may influence spatial integration. Supporting this hypothesis, a recent extracellular study found that the suprathreshold cortical response to paired whisker deflection could be facilitated when the stimuli were applied as a train of two-whisker deflections (Ego-Stengel et al. 2005). Furthermore, intrathalamic inhibition, recently demonstrated to play a key role in cross-whisker suppression (Higley and Contreras 2007), is reduced by repetitive whisker deflection (Castro-Alamancos 2002a). In light of these findings, the present study was designed to further explore the interaction of adaptation and suppression.

We combined extracellular and intracellular recordings in the cortex and thalamus to test whether frequency adaptation within the normal whisking range modulates cross-whisker suppression. Our results demonstrate that repetitive deflection of the preceding whisker significantly reduces the magnitude of suppression, although this effect is independent of frequency. This finding is most likely explained by the interaction of multiple local circuit mechanisms within the afferent sensory path.

## METHODS

Methods for surgical procedures and electrophysiology were similar to those of previous studies (Higley and Contreras 2005, 2007). Briefly, adult male Sprague-Dawley rats ( $n = 15$ ) were anesthetized with isoflurane (0.5–1.0%), paralyzed, and ventilated. Heart rate,

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temperature, and expired CO<sub>2</sub> were monitored continuously. Intracellular recordings were made from barrel cortex neurons using glass micropipettes filled with 3 M potassium acetate (60–80 MΩ). Extracellular recordings were obtained using glass-insulated tungsten electrodes (1.5 MΩ at 1 kHz; Alpha-Omega, Alpharetta, GA). Single units in the medial ventroposterior thalamic nucleus (VPM) with constant amplitude, spike shape, and signal-to-noise ratios of >4:1 were extracted by a threshold algorithm. Cortical multiunit activity (MUA) consisted of two to four units of varying amplitude that could not be reliably separated by a simple threshold. Data were digitized at 20 kHz (intracellular) or 50 kHz (extracellular) using Spike2 (CED, Cambridge, UK). For each recording, the principal whisker (PW) and the immediately caudal adjacent whisker (AW) were mechanically deflected in the caudal direction using a piezoelectric stimulator (Piezo Systems, Cambridge, MA). All results are presented as means ± SE.

## RESULTS

To explore the interaction of frequency adaptation and spatial summation, we measured the magnitude of cortical and thalamic PW-evoked responses alone or when preceded by AW deflection. We compared the effect of either a single AW deflection or a train of four AW deflections at 5, 10, or 20 Hz. In all cases, the interval between the final AW deflection and PW deflection was 20 ms.

We first assessed the impact of adaptation on spatial summation in cortical layer 4 (L4, depth of 500–850 μm). In addition to micrometer depth, the short latency of whisker-evoked responses (<8 ms) confirmed that the electrode was in L4. Results from an example MUA recording are illustrated by the peristimulus time histograms (PSTHs, bin size = 1 ms) of Fig. 1A. The *bottom row* of PSTHs (single) shows the cortical response to PW deflection alone (filled arrowhead) and PW deflection preceded 20 ms by a single AW deflection (open arrowhead). Both PW and AW deflections evoked suprathreshold responses. The preceding AW deflection strongly reduced the magnitude of the PW-evoked response from 3.0 spikes/stimulus to 0.2 spike/stimulus. This cross-whisker suppression was quantified using a response ratio, calculated as the magnitude of the PW-evoked response after AW deflection divided by the response to PW deflection alone. For this example, the single preceding AW deflection yielded a response ratio of 0.07.

Next, we tested whether adaptation of the preceding AW-evoked response altered the magnitude of cross-whisker suppression. The *top rows* of PSTHs in Fig. 1A illustrate the responses to PW deflection either alone or 20 ms after the fourth AW deflection in a train at 5, 10, or 20 Hz. Repetitive deflection resulted in adaptation of the magnitude of the AW-evoked response that was greater for higher frequencies. As with the single-AW deflection, the preceding train of AW deflections resulted in a suppression of the PW-evoked response relative to PW deflection alone. However, response ratios were greater than those observed for single-AW deflection: 0.50, 0.47, and 0.59 for 5, 10, and 20 Hz, respectively.

We quantified the magnitude of AW-evoked response adaptation for the population of L4 MUA recordings ( $n = 11$ , Fig. 1B, *left*). Adaptation ratios were calculated as the magnitude of each response in a train divided by the magnitude of the first response. For all frequencies, the largest reduction in magni-

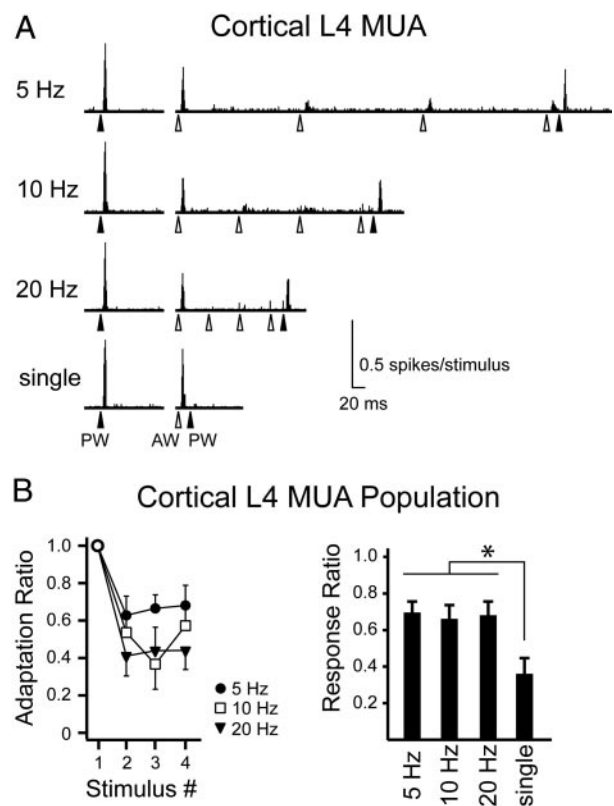


FIG. 1. Cross-whisker suppression of cortical spike output is reduced by repetitive deflection of the preceding whisker. *A*: example extracellular multiunit activity (MUA) recording (2–4 units) from L4 of barrel cortex. *Bottom PSTHs* (peristimulus time histograms; single) illustrate response to principal whisker (PW) deflection (filled arrowhead) alone or after deflection of a single adjacent whisker (AW, open arrowhead) by 20 ms. Preceding AW deflection strongly suppressed the PW-evoked response. *Top PSTHs* illustrate response to PW deflection alone or preceded by a train of 4 AW deflections at 5, 10, or 20 Hz. AW–PW interval was 20 ms in all cases. For all frequencies, cross-whisker suppression was reduced in comparison to the single AW deflection. *B*: population data for cortical L4 MUA data ( $n = 11$ ). *Left*: average adaptation ratios ( $\pm$ SE) for the AW-evoked response at different frequencies. *Right*: mean response ratios ( $\pm$ SE) for cross-whisker suppression under the different conditions. Values for 5, 10, and 20 Hz were significantly greater than those for single AW deflection.

tude occurred between the first and second deflections. For the fourth deflection, adaptation ratios were  $0.68 \pm 0.10$  (5 Hz, filled circles),  $0.57 \pm 0.10$  (10 Hz, open squares), and  $0.44 \pm 0.12$  (20 Hz, filled triangles). All adaptation ratios were significantly <1.0 (Student's *t*-test,  $P < 0.01$  for all). Furthermore, adaptation at 5 Hz was significantly less than that at 20 Hz (one-way ANOVA, Tukey's posttest,  $P < 0.05$ ). However, there were no differences between 5 and 10 Hz or 10 and 20 Hz ( $P > 0.05$ ).

We also quantified the magnitude of cross-whisker suppression for the population (Fig. 1B, *right*). Suppression by a single-AW deflection yielded a response ratio of  $0.36 \pm 0.09$  (significantly <1.0, Student's *t*-test,  $P < 0.0001$ ). Suppression was significantly reduced by adaptation of the preceding AW-evoked response, yielding response ratios of  $0.69 \pm 0.06$ ,  $0.67 \pm 0.07$ , and  $0.68 \pm 0.07$  for 5, 10, and 20 Hz, respectively (all values significantly <1.0, Student's *t*-test,  $P < 0.01$ , and significantly greater than the response ratio for single AW deflection, one-way ANOVA, Tukey's posttest,  $P < 0.001$  for all). There were no significant

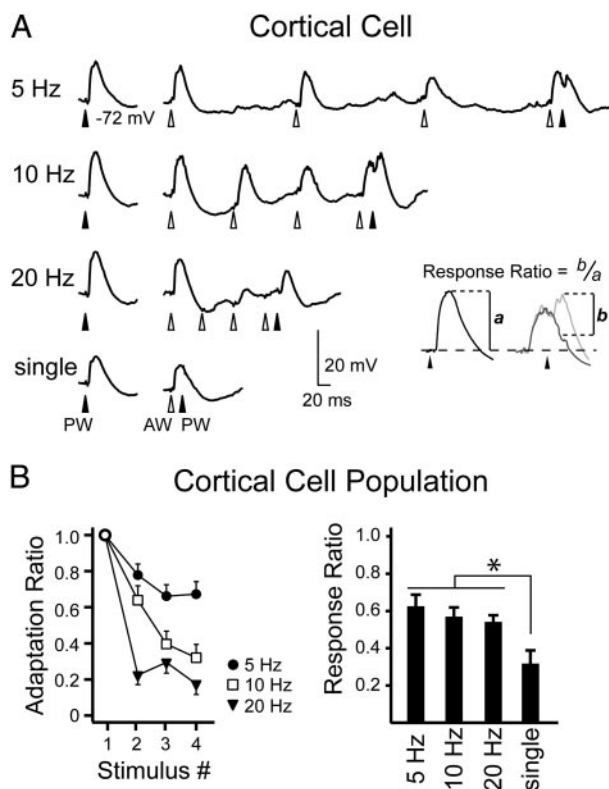


FIG. 2. Cross-whisker suppression of cortical synaptic responses is also reduced by repetitive deflection of the preceding whisker. *A*: example intracellular recording from an L4 cortical neuron. Resting membrane potential ( $V_m$ ) was  $-72$  mV. *Bottom traces* (single) illustrate response to PW deflection alone or after single deflection of AW by 20 ms. Paired deflection resulted in almost complete elimination of the PW-evoked response. *Top traces* illustrate response to PW deflection alone or preceded by a train of 4 AW deflections at 5, 10, or 20 Hz. AW–PW interval was 20 ms in all cases. For all frequencies, cross-whisker suppression was reduced in comparison to single AW deflection. *B*: population data for cortical intracellular recordings ( $n = 17$ ). *Left*: mean adaptation ratios ( $\pm$  SE) for repetitive AW deflections at different frequencies. *Right*: mean response ratios ( $\pm$  SE) for the different conditions. For intracellular data, response ratios were calculated as the amplitude of the PW-evoked postsynaptic potential (PSP) after subtracting the contribution from the temporally overlapping AW-evoked PSP divided by the amplitude of the PSP evoked by PW deflection alone (see Fig. 2*A*, *inset*). Values for 5, 10, and 20 Hz were significantly greater than those for single AW deflection.

differences between response ratios at the different adaptation frequencies ( $P > 0.05$ ).

To better understand the synaptic events underlying the observed modulation of cross-whisker suppression, we made intracellular recordings of cortical neurons. Preliminary analyses revealed no significant differences in results across cortical layers and thus we combined data from all intracellular recordings. Figure 2*A* shows an example cell from L4 (514  $\mu$ m depth). Both PW and AW deflection evoked a postsynaptic potential (PSP) consisting of an initial depolarization from the resting membrane potential ( $V_m$ ,  $-72$  mV) followed by a longer-lasting hyperpolarization. Synaptic responses to AW deflection were typically smaller in amplitude and had a slightly longer onset latency compared to PW-evoked responses. When PW deflection was preceded by a single-AW deflection, the peak amplitude measured from resting  $V_m$  of the PW-evoked PSP was reduced from 9.9 to 3.8 mV (Fig. 2*A*, *bottom traces*, single). To account for the temporal overlap of

the PSPs evoked by paired deflections, we measured the PW-evoked PSP amplitude after subtracting the contribution of the AW-evoked response. Response ratios for the intracellular data were calculated using this adjusted value (see Fig. 2*A*, *inset*). For the example cell, the response ratio for the single preceding AW deflection was 0.02 [(3.8 mV  $-$  3.6 mV)/9.9 mV].

As with the MUA data, repetitive AW deflection resulted in a frequency-dependent reduction in PSP amplitude over the course of the train, with an almost complete elimination of the synaptic response at 20 Hz. Notably, the whisker-evoked hyperpolarization also strongly adapted during repetitive deflection, indicating a simultaneous reduction of both excitation and inhibition, consistent with previous reports (Higley and Contreras 2006). Nevertheless, the preceding AW deflection still resulted in a decreased PW-evoked PSP, yielding response ratios of 0.44, 0.62, and 0.52, for 5, 10, and 20 Hz, respectively. We quantified the adaptation of the AW-evoked PSP for each cell in the population ( $n = 17$ ) using an adaptation ratio, calculated as the amplitude of each PSP in the train divided by the amplitude of the first PSP (Fig. 2*B*, *left*). As with the spike responses, the largest reduction in response magnitude occurred between the first and second deflections. Adaptation ratios for the fourth deflection were  $0.67 \pm 0.07$ ,  $0.32 \pm 0.07$ , and  $0.18 \pm 0.06$  for 5, 10, and 20 Hz, respectively. These values were all significantly  $< 1.0$  ( $P < 0.001$  for all). Furthermore, the adaptation ratio for 5 Hz was significantly greater than the value for 10 Hz ( $P < 0.01$ ) and 20 Hz ( $P < 0.001$ ), although the values for 10 and 20 Hz were not significantly different.

We also calculated the magnitude of cross-whisker suppression for the population (Fig. 2*B*, *right*). The mean response ratio for single preceding AW deflection was  $0.31 \pm 0.07$  (significantly  $< 1.0$ ,  $P < 0.0001$ ). This value was increased to  $0.61 \pm 0.06$ ,  $0.56 \pm 0.04$ , and  $0.53 \pm 0.03$  for 5, 10, and 20 Hz, respectively (all values significantly  $< 1.0$ ,  $P < 0.0001$ , and significantly greater than that for the single AW deflection,  $P < 0.05$  for all). As with the MUA data, there were no significant differences between response ratios at different frequencies.

Finally, to determine whether the adaptation-mediated reduction of cross-whisker suppression observed in the cortex is inherited from subcortical afferents, we made single-unit recordings of VPM neurons. Results from an example recording are shown in Fig. 3*A*. As with the cortical data, both PW and AW deflections evoked suprathreshold responses. The magnitude of the PW-evoked response was strongly reduced by a single preceding AW deflection from 2.0 spikes/stimulus to 0 spike/stimulus, yielding a corresponding response ratio of 0. Repetitive AW deflection resulted in a frequency-dependent reduction in the thalamic response. Moreover, as with the cortical data, preceding adaptation of the AW-evoked response resulted in less cross-whisker suppression, yielding response ratios of 0.42, 0.57, and 0.52 for 5, 10, and 20 Hz, respectively.

We quantified the magnitude of frequency adaptation for the population of thalamic units ( $n = 13$ , Fig. 3*B*, *left*). Again, the largest reduction in magnitude occurred between the first and second deflections. Adaptation ratios for the fourth deflection were  $0.81 \pm 0.10$ ,  $0.49 \pm 0.08$ , and  $0.43 \pm 0.08$  for 5, 10, and 20 Hz, respectively. The values for 10



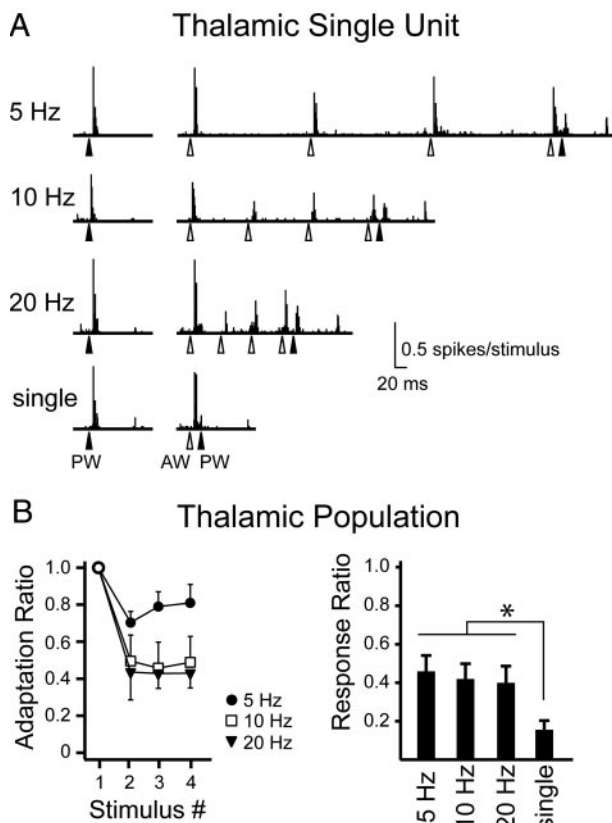


FIG. 3. Cross-whisker suppression of thalamic spike output is similarly reduced by repetitive deflection of the preceding AW. *A*: example single-unit recording of a thalamic neuron in medial ventroposterior thalamic nucleus (VPM). *Bottom PSTHs*: response to PW deflection alone or after AW deflection by 20 ms. Preceding AW deflection strongly suppressed the PW-evoked spike response. *Top PSTHs*: response to PW deflection alone or preceded by a train of 4 AW deflections at 5, 10, or 20 Hz. AW–PW interval was 20 ms in all cases. For all frequencies, cross-whisker suppression was reduced in comparison to single AW deflection. *B*: population data for thalamic single-unit recordings ( $n = 13$ ). *Left*: mean adaptation ratios ( $\pm$ SE) for repetitive AW deflections at different frequencies. *Right*: mean response ratios ( $\pm$ SE) for the different conditions. Values for 5, 10, and 20 Hz were significantly greater than those for single AW deflection.

and 20 Hz were both significantly  $< 1.0$  ( $P < 0.0001$ ). Furthermore, the mean adaptation ratio for 5 Hz was significantly larger than that obtained for 10 Hz ( $P < 0.05$ ) and 20 Hz ( $P < 0.01$ ), although the values for 10 and 20 Hz were not significantly different.

We also quantified the magnitude of cross-whisker suppression for the population (Fig. 3*B*, *right*). Preceding deflection of a single AW strongly suppressed the PW-evoked response, yielding a response ratio of  $0.16 \pm 0.05$  (significantly  $< 1.0$ ,  $P < 0.0001$ ). Adaptation of the preceding AW-evoked response yielded larger response ratios of  $0.45 \pm 0.07$ ,  $0.41 \pm 0.08$ , and  $0.40 \pm 0.08$  for 5, 10, and 20 Hz, respectively (all values significantly  $< 1.0$ ,  $P < 0.0001$ , and significantly greater than the response ratio for a single preceding AW deflection,  $P < 0.001$ ). As for the cortical data, there were no differences in response ratios across frequencies. Moreover, the average response ratios for the thalamic population were smaller than those observed for the cortical synaptic response, suggesting that cross-whisker suppression in the thalamus could account for the cortical suppression.

## DISCUSSION

In the present report, we demonstrated that cross-whisker suppression in both the thalamus and the cortex is significantly reduced by adaptation of the preceding whisker-evoked response. This result was observed for adaptation at frequencies spanning the entire range of natural whisking. Furthermore, although adaptation of the preceding AW-evoked response was greater for higher frequencies, the effect on suppression was independent of frequency. Although our present study used only caudal whisker deflections, recent work suggested that direction may be an important factor influencing cross-whisker suppression (Kida et al. 2005), although perhaps not frequency adaptation (Khatri and Simons 2007). Additionally, studies are necessary to further characterize the interaction of these phenomena.

The lack of correlation between reduced cross-whisker suppression and frequency was initially surprising. However, this result likely reflects the interaction of several local circuits that contribute to whisker-evoked responses. PW-related signals arise from primary afferents that project to the principal trigeminal nucleus (Hayashi 1980; Veinante and Deschenes 1999). Trigeminal neurons subsequently project to cells in VPM (Veinante and Deschenes 1999) that send axons to L4 of the barrel cortex (Arnold et al. 2001; Chmielowska et al. 1989). The cellular mechanisms underlying cross-whisker suppression include intrathalamic postsynaptic inhibition mediated by the reticular nucleus (Higley and Contreras 2007; Varga et al. 2002) as well as amplification by spike threshold in both thalamus and cortex (Higley and Contreras 2007). Previous studies showed that whisker-evoked responses in the reticular nucleus exhibit frequency-dependent adaptation over the normal whisking range (Hartings et al. 2003). Furthermore, intracellular recordings of VPM neurons revealed that whisker-evoked reticulothalamic inhibitory PSPs also exhibit adaptation (Castro-Alamancos 2002a). Thus repetitive deflection of the preceding AW should result in a frequency-dependent *increase* in the subsequent PW-evoked response magnitude (i.e., a reduction in suppression) as a result of the decreased intrathalamic inhibition.

Although this model does not describe why the reduction in suppression is independent of adaptation frequency, one explanation may arise from the finding that multiwhisker receptive fields in the thalamus and cortex are largely generated in the brain stem by projections from the spinal to principal trigeminal nucleus (Jacquin et al. 1990; Kwegyir-Afful et al. 2005; Timofeeva et al. 2004). Thus PW and AW deflections potentially activate a largely overlapping set of synapses in the thalamus and cortex. Both trigeminothalamic and thalamocortical synapses are known to depress after activation at whisking frequencies, a chief mechanism underlying adaptation (Castro-Alamancos 2002b; Castro-Alamancos and Oldford 2002; Chung et al. 2002; Gil et al. 1999). Thus repetitive deflection of the preceding AW should lead to cross-adaptation of the PW-evoked response. From this perspective, repetitive deflection of the preceding AW should result in a frequency-dependent *decrease* in the magnitude of the subsequent PW-evoked response (i.e., an enhancement of suppression) arising from cross-whisker adaptation. A contrasting view was recently provided by Katz et al. (2006) who showed an absence of cross-whisker

adaptation in cortical neurons. However, those authors also observed exclusively single-whisker receptive fields in the thalamus, which is suggestive of an increased depth of anesthesia reducing subcortical contributions to AW-evoked responses (Friedberg et al. 1999). In sum, under our conditions of light isoflurane anesthesia where multiwhisker receptive fields are observed in the thalamus and cortex, we suggest that the two competing frequency-dependent mechanisms of reduced intrathalamic inhibition and cross-whisker adaptation explain the observed independence of suppression reduction on adaptation frequency.

Our findings highlight the fact that spatial integration of sensory responses is critically influenced by the temporal context of stimulus presentation. Previous authors suggested that the whisker system optimizes its responsiveness for detection or discrimination of events (Fanselow and Nicolelis 1999; Moore 2004). In support of this hypothesis, whisker-evoked responses that occur within trains of deflections exhibit reduced response magnitudes (Ahissar et al. 2000; Castro-Alamancos 2002a; Chung et al. 2002; Garabedian et al. 2003; Higley and Contreras 2006; Khatri et al. 2004; Webber and Stanley 2006), smaller receptive fields (Katz et al. 2006), sharper directional tuning (Khatri and Simons 2007), and more limited regions of cortical activation (Sheth et al. 1998) compared to responses evoked by a single-whisker deflection. These findings suggest that adaptation gives rise to a different mode of sensory processing that facilitates discrimination of complex patterns of input (Moore 2004). In contrast, the larger, less spatially and directionally tuned responses to single deflections may serve as a more general alert that contact has occurred. Consistent with this hypothesis, the strong suppression that occurs with a single-whisker deflection temporarily blocks responses to all other nearby whiskers, producing a definitive, well-isolated impulse but also limiting the possibilities for coding by integration of responses. In contrast, reduced suppression during adaptation allows greater potential for summation of responses to neighboring whiskers to generate spike output. Indeed, one recent study showed that suppressive cross-whisker interactions can become facilitating at short intervals (<5 ms) when the paired deflections are repeated at frequencies in the whisking range (Ego-Stengel et al. 2005). Finally, our results suggest that the actual whisking frequency may be less important than previously considered as a coding parameter.

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