

Reducing the Uncertainty: Gating of Peripheral Inputs by Zona Incerta

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Sensory inputs are relayed to the neocortex by “first-order” thalamic nuclei, the responses of which are determined by ascending inputs from peripheral receptors. In contrast, “higher-order” thalamic nuclei respond poorly to peripheral inputs, and their responses are thought to be determined by descending cortical inputs. We tested this hypothesis by recording from neurons in the higher-order somatosensory posterior medial (POm) nucleus of narcotized rats. As reported previously, POm neurons responded to whisker stimuli with long-latency (median, 27 msec) and low-magnitude responses, consistent with cortically driven responses. However, when we suppressed inhibitory inputs from the subthalamic nucleus zona incerta (ZI), POm responses were of significantly higher magnitude and shorter latency, with many POm neurons responding at latencies consistent with ascending driving inputs from trigeminal nuclei. Our data suggest that POm comprises two neuronal populations: one population is driven by both peripheral and cortical inputs, and the second population responds only to cortical inputs. These findings demonstrate that ZI gates peripheral inputs to POm, enabling it to function both as a first-order and higher-order nucleus. Because ZI innervates all higher-order nuclei, this gating mechanism may exert similar regulation of thalamic processing in other sensory systems.

Key words: posterior medial nucleus; thalamus; first-order nucleus; higher-order nucleus; thalamocortical; corticothalamic

Introduction

Sensory inputs are relayed to the neocortex by thalamic nuclei termed “first-order” relays [e.g., the lateral geniculate nucleus in the visual system and the ventral posterior medial (VPM) nucleus in the somatosensory system] (Jones, 1985). In addition, a number of thalamic nuclei, such as the pulvinar of the visual system, are hypothesized to be involved in relaying information from one cortical area to another and have been termed “higher-order” relays (Sherman and Guillery, 2001).

First-order nuclei contain neurons with receptive field properties that are determined by ascending inputs (e.g., from the retina or brainstem) that drive these cells to firing threshold. Higher-order nuclei contain neurons with drivers that are descending cortical inputs and receptive fields that are determined by these descending projections. Morphologically, driver afferents, whether cortical or subcortical, are characterized by thick and highly branched (type II) axons with large terminals (Guillery, 1966; Jones, 1983).

In the somatosensory system, the posterior medial thalamic nucleus (POm) is thought to function as a higher-order relay that is driven by descending cortical inputs. POm receives dense innervation from corticothalamic axons, the morphological criteria of which suggest that they are driver afferents (Hoogland et al.,

1991; Deschênes et al., 1994). Indeed, Diamond et al. (1992a) showed that POm neurons respond to whisker stimuli at latencies that are significantly longer than those of VPM cells (mean, 19 vs 7 msec) and that these POm responses are abolished after cortical inactivation (Diamond et al., 1992b). These and other findings (Killackey and Sherman, 2003) support the designation of POm as a higher-order nucleus.

However, there are anatomical and physiological data suggesting that POm receives driving brainstem inputs. Anatomically, POm receives inputs from brainstem afferents that fulfill the morphological criteria of driver inputs (Veinante et al., 2000). Physiologically, Chiaia et al. (1991) showed that electrically stimulating the trigeminal nucleus principalis or the subnucleus interpolaris in the brainstem generates action potentials with similar onset latencies in the VPM and POm, suggesting that both nuclei respond in a similar manner to brainstem inputs. Furthermore, Ahissar et al. (2000) reported that some POm neurons respond to whisker deflections at short latencies (7–8 msec). Together, these data indicate that POm can be driven by brainstem inputs and may therefore also function as a first-order nucleus.

Why do subcortical inputs rarely result in short-latency whisker-evoked responses in POm neurons? Here, we tested the hypothesis that the subthalamic nucleus zona incerta (ZI) suppresses subcortical inputs to POm. [We are indebted to Prof. M. Deschênes (Laval University, Quebec City, Canada) for fostering this idea.] The ZI provides dense GABAergic inputs to POm neurons (Power et al., 1999; Bartho et al., 2002), suggesting that it exerts potent inhibition on POm neurons preventing it from reliably responding to subcortical activation.

We show that suppressing ZI-mediated inhibition reveals robust short-latency whisker-evoked responses in POm neurons.

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Our findings suggest that POM functions both as a first-order relay (driven by brain-stem inputs) and a higher-order relay (driven by cortical inputs). We propose a model in which ZI (Greek for “zone of uncertainty”) selectively gates these inputs, depending on the behavioral state of the animal.

Materials and Methods

Surgical procedures. Nineteen female Sprague Dawley rats weighing 250–350 gm were used in this study. All procedures strictly adhered to institutional and federal guidelines. Under halothane anesthesia (3%) and infusion of local anesthetics at surgical sites, a craniotomy was performed over the right POM thalamus and ZI. The dura was removed, and agarose (1.4% in buffered saline) was poured over the craniotomy to prevent drying. A venous catheter was inserted in the jugular vein for drug delivery, and a second catheter was placed in the femoral artery for monitoring blood pressure and heart rate. After the surgical procedures, administration of halothane was discontinued, and the rats were infused intravenously with fentanyl (10 μ g/kg/hr) for the rest of the experiment. The rats were then immobilized with pancuronium bromide (1.5 mg/kg/hr) and artificially respired with a positive pressure respirator at 90 breaths/min. Blood pressure, heart rate, and electroencephalographs were monitored throughout the experiment to ensure that the animal was in no pain or distress. Body temperature was maintained at 37°C with a servo-controlled heating blanket.

Recording. Extracellular unit recordings were obtained with quartz-insulated platinum electrodes (2–4 M Ω). Electrodes were advanced to the POM thalamus in the right hemisphere based on stereotaxic coordinates [anteroposterior (AP), 3.2; mediolateral (ML), 2.6]. Animals were maintained within the stereotaxic frame throughout the recordings. Whiskers on the contralateral face were stimulated continually during electrode penetrations to detect units with low or no spontaneous activity. Waveforms recorded from well isolated units were digitized through a data acquisition system (Plexon, Dallas, TX) at 40 kHz. Units were isolated off-line with Offline Sorter (Plexon), and auto-correlograms were generated with Neuroexplorer (Littleton, MA) software to confirm that recordings were obtained from single units.

At the end of the experiment, recording sites were marked with electrolytic lesions (5 μ A for 10 sec). The animals were then deeply anesthetized with sodium pentobarbital (60 mg/kg) and perfused transcardially with buffered saline, followed by 4% buffered paraformaldehyde. Tissue sections were Nissl stained, and recording sites were identified in coronal sections.

ZI inactivation and histology. In six of the 19 rats, before recording POM neurons, we identified the whisker representation in the ZI by advancing a recording electrode into the nucleus following stereotaxic coordinates (AP, 3.5; ML, 2.8). We continuously stimulated the contralateral whiskers until well isolated units responding to the stimulation were identified. We then replaced the recording electrode with a blunt tungsten metal electrode (0.5 M Ω ; 200 μ m tip diameter) and created an electrolytic lesion by passing 2.5 mA of negative current for 4 sec. Verification of lesion sites was performed as described above. Only animals with clear lesions within the ZI were included in the analyses. POM recordings were obtained within 30 min of creating lesions in the ZI, and the recording session lasted up to 6 hr. No significant differences were observed in any of the parameters over the course of an experiment.

Whisker stimulation. After isolation of whisker-sensitive neurons in POM, whiskers were stimulated by air puffs delivered through a tube (0.5 mm diameter) by a computer-controlled Picospritzer. Air puffs were

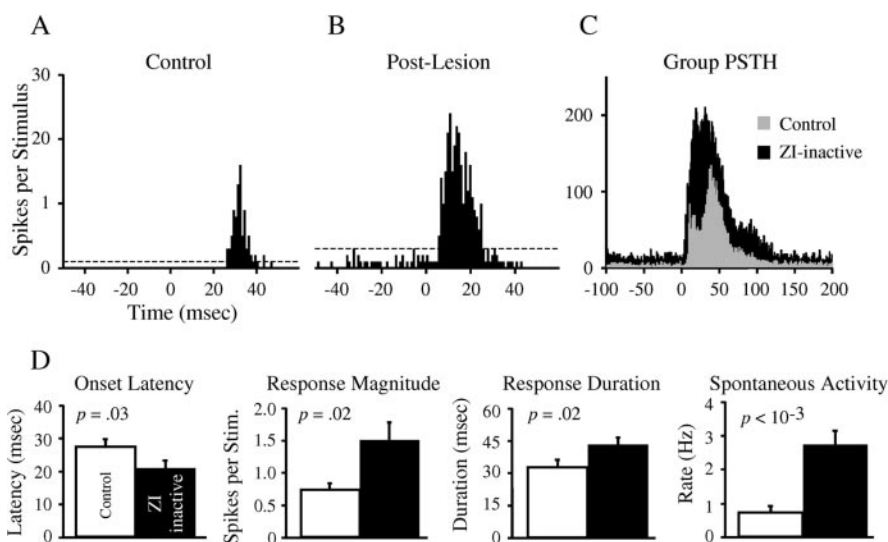


Figure 1. Effects of ZI inactivation on POM response properties. *A, B*, PSTHs constructed from responses of POM neurons to a 50 msec air puff delivered to the whiskers at time $t = 0$. *A*, Control POM neuron. *B*, POM neuron recorded after ZI inactivation. In these and subsequent PSTHs, the horizontal broken lines depict response magnitude levels exceeding (99% confidence interval) spontaneous activity levels (computed from a 200 msec period preceding stimulus onset). *C*, Group PSTHs constructed from pooled data of 40 control neurons and 42 neurons recorded after ZI inactivation. *D*, Response onset latency, response magnitude, response duration, and spontaneous activity rates were all significantly affected by ZI inactivation. Bar graphs depict mean \pm SEM. *p* values were computed with Mann–Whitney *U* test.

delivered at 1 Hz with a pressure of 60 psi, resulting in whisker deflections of $\sim 30^\circ$. Whiskers were deflected in their preferred direction (i.e., the direction that elicited the shortest latency, highest magnitude response). At least four whiskers were deflected simultaneously to evoke responses in POM neurons.

Data analysis. Time stamps of well isolated units and of stimulus triggers were exported to Matlab (MathWorks, Natick, MA) for analyses using custom-written algorithms. Peristimulus time histograms (PSTHs; 1 msec bins) were constructed from these time stamps. Significant stimulus-evoked responses were defined as PSTH bins with a response magnitude that significantly exceeded (99% confidence interval) spontaneous activity levels, computed from a 200 msec period preceding the stimuli.

We defined response onset as the first two consecutive bins (post-stimulus) displaying significant responses (defined as above), and response offset was defined as two consecutive bins in which response magnitude fell below the 99% confidence interval. We defined response magnitude as the total number of spikes per stimulus occurring between response onset and offset.

Statistical analyses were performed in SPSS (SPSS, Chicago, IL). Between-group statistical comparisons were assessed with the nonparametric Mann–Whitney *U* test. Data are presented as means \pm SEM.

Results

POM responses to whisker stimuli

In fentanyl-narcotized rats, we characterized responses of well isolated POM neurons to whisker stimuli, evoked by deflecting whiskers with air puffs (see Materials and Methods). Typical response properties of a representative POM neuron are depicted in the PSTH in Figure 1*A*. POM neurons responded poorly to whisker stimuli, requiring large amplitude deflections of multiple whiskers to evoke spikes. Response magnitudes were variable [coefficient of variation (CV), 0.82] and low (median, 0.65 spikes/stimulus; mean \pm SEM, 0.74 ± 0.096 spikes/stimulus) (Fig. 1*D*). Also variable (CV, ≥ 0.51) were response duration (median, 28.0 msec; 32.8 ± 3.2 msec) and spontaneous firing rates (median, 0.2 Hz; 0.7 ± 0.19 Hz). As a group (Fig. 1*D*), POM

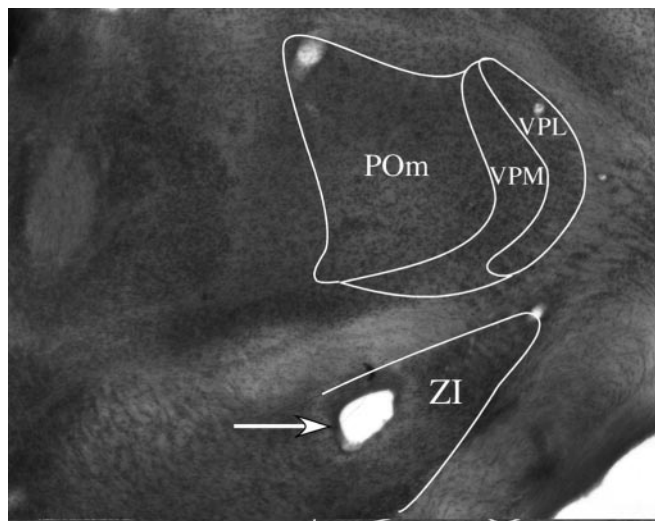


Figure 2. Coronal section through the thalamus illustrating the anatomical relationship between the thalamic nuclei POm, VPM, ventral posterior lateral (VPL), and the subthalamic nucleus ZI; note the lesion (arrowhead) localized to the dorsal/ventral subregion of the ZI.

neurons responded at variable latencies, ranging from 6 to 66 msec (median, 27.0 msec; 27.4 ± 2.2 msec).

These results are consistent with previous reports on POm neurons recorded under urethane (Chiaia et al., 1991; Diamond et al., 1992a; Sosnik et al., 2001), demonstrating that under anesthesia, as well as under fentanyl analgesia (present study), these neurons respond poorly and inconsistently to whisker stimuli.

ZI regulates POm responses

The weak and labile responses of POm neurons are surprising in light of the fact that POm receives direct, short-latency inputs from trigeminal nuclei (see Introduction). We reasoned, therefore, that POm responses might be suppressed by GABAergic inhibition. The source of GABAergic inhibition to POm is likely to arise from extrinsic sources, because POm in the rat is reported to contain few, if any, GABAergic neurons (Barbaresi et al., 1986; Harris and Hendrickson, 1987). These extrinsic GABAergic sources include the thalamic reticular nucleus (TRN) (Pinault and Deschênes, 1998), pretectal and mesencephalic nuclei, and the ZI (Power et al., 1999; Acsady et al., 2003). We chose to focus on the role of GABAergic inputs from the ZI for the following reasons. Unlike the other nuclei, ZI neurons respond at short latency (4 msec) to whisker stimuli (Nicolelis et al., 1992; our unpublished observations), suggesting that they may mediate feed-forward inhibition of POm neurons. Furthermore, unlike TRN axons, which terminate on distal dendrites of thalamocortical projection neurons (Peschanski et al., 1983; Wang et al., 2001), ZI axons synapse on the perisomatic regions of these cells (Bartho et al., 2002), suggesting that they exert potent tonic inhibition of POm neurons.

To test the role of the ZI in regulating POm responses, we inactivated ZI by placing electrolytic lesions in the physiologically identified whisker representation of the ZI (Fig. 2) (see Materials and Methods). The lesions were 300–500 μ m in diameter and included the dorsal/ventral subregions of the ZI, which contain somatotopic representations of the whiskers (Nicolelis et al., 1992). We compared data obtained from neurons recorded from the control group (rats with intact ZI) with data from neurons recorded from the ZI inactivated group (rats receiving ZI lesions before POm recordings). Figure 1 depicts representative PSTHs

recorded from two different neurons. The control neuron (Fig. 1A) had no spontaneous activity and responded to whisker stimuli at a latency of 26 msec. In contrast, the cell recorded after the ZI lesion (Fig. 1B) fired spontaneously at 9 Hz and responded to whisker deflections at 6 msec. Similar results were obtained from 80 additional neurons (39 control and 41 postlesion) (Fig. 1D). POm neurons from rats having lesions responded significantly ($p = 0.03$; Mann–Whitney U test) earlier (median, 16.0 msec; 21.2 ± 2.4 msec) than did neurons recorded from controls (median, 27.0 msec; 27.4 ± 2.2 msec). Inactivating ZI also affected the kinetics of POm responses, as depicted in the group PSTHs (Fig. 1C), constructed by pooling data from 40 control neurons and 42 neurons recorded from the ZI inactivated group. Both response magnitude (median, 0.84 vs 0.65 spikes/stimulus) and duration (40.0 vs 28.0 msec) were significantly ($p = 0.02$) increased, and spontaneous firing rates were significantly ($p < 10^{-3}$) higher after ZI inactivation (median, 1.7 Hz) compared with control (median, 0.2 Hz) (Fig. 1D). These findings demonstrate that inactivation of the ZI reveals in POm neurons robust, short-latency responses to whisker deflections.

POm contains two neuronal populations

The PSTH constructed by pooling data from control neurons (Fig. 1C) has a bimodal distribution, suggesting that some control neurons respond to whisker deflections at relatively short latencies. (This bimodal distribution in the group data does not represent biphasic response kinetics in individual neurons because PSTHs computed for individual neurons were always monophasic.) To quantify the distribution of onset latencies in both control and postlesion neurons, we constructed cumulative probability plots (Fig. 3A): these demonstrate a leftward shift in the distribution of latencies ≤ 30 msec and an overlapping distribution of latencies > 30 msec. This suggests either that we failed to suppress ZI inputs to some POm neurons or that a subset of these neurons fails to respond to whisker inputs at short latency, even when the ZI is suppressed.

To distinguish between these possibilities, we compared the response kinetics of control ($n = 10$) and postlesion ($n = 13$) neurons that responded at latencies > 30 msec (Fig. 3B). In this group, ZI lesions had no significant effect on onset latency ($p = 0.28$) or response magnitude ($p = 0.38$) and duration ($p = 0.61$). However, spontaneous activity rates were significantly ($p = 0.002$) higher (median, 2.4 Hz; 2.5 ± 0.38 Hz) after ZI lesions compared with control (median, 0.1 Hz; 0.6 ± 0.47 Hz). The increase in spontaneous activity suggests that ZI lesions were effective in relieving tonic inhibition from this group of POm neurons. Thus, the fact that ZI lesions did not affect response latency or kinetics in this group is not likely attributable to incomplete suppression of their ZI inputs. Rather, this group of POm neurons may represent a distinct population of cells that receive no direct trigeminal inputs.

In contrast, ZI lesions had significant effects on the group of POm neurons that respond at ≤ 30 msec ($n = 30$ control; $n = 29$ postlesion). The lesions resulted in a leftward shift in onset latency, demonstrating that ZI lesions significantly ($p < 10^{-3}$) increased the proportion of neurons responding to whisker stimuli at short latency (median, 12.0 msec; 12.3 ± 1.3 msec vs median, 24.0 msec; 21.0 ± 1.5 msec). In this group of neurons, ZI lesions resulted also in significant increases in spontaneous activity ($p = 0.01$; median, 1.4 Hz; 2.6 ± 0.54 Hz vs median, 0.4 Hz; 0.7 ± 0.20 Hz), response magnitude ($p = 0.008$; median, 1.2 spikes/stimulus; 1.9 ± 0.36 spikes/stimulus vs median, 0.79 spikes/stimulus; 0.85 ± 0.11 spikes/stimulus), and response duration ($p = 0.02$;

median, 40.0 msec; 42.0 ± 3.9 msec vs median, 24.0 msec; 30.0 ± 3.2 msec) (Fig. 3C).

Discussion

Methodological considerations

We chose to inactivate ZI by producing electrolytic lesions because this structure is large and wraps around the ventral aspect of the dorsal thalamus, rendering it difficult to inactivate pharmacologically. Although electrolytic lesions may inadvertently affect axons of passage, this is not likely to be a concern because there are no known GABAergic axons coursing through the ZI on their way to POM.

The majority (>90%) of incerto-thalamic afferents are GABAergic (Bartho et al., 2002). Although there are reports that some ZI efferents are glutamatergic (Kolmac and Mitrofanis, 1998), others have argued that this result may represent a labeling artifact (Bartho et al., 2002). Our finding that ZI lesions reveal short-latency POM responses is inconsistent with a dominant glutamatergic incerto-thalamic pathway (or excitatory fibers-of-passage coursing through the ZI). If such glutamatergic pathways existed, we would expect ZI lesions to suppress whisker-evoked responses rather than reveal the short-latency responses we observed. We therefore conclude that our lesions of the ZI selectively inactivated incerto-thalamic GABAergic inputs.

ZI regulates POM responses

Our findings demonstrate that inactivating the ZI has a profound effect on POM responses. Median spontaneous activity rates were eightfold higher in neurons recorded after lesions compared with controls, suggesting that the ZI exerts tonic inhibition on POM neurons. This conclusion is supported by the fact that GABAergic afferents from ZI synapse on perisomatic regions of POM neurons (Bartho et al., 2002), where they are likely to exert potent postsynaptic inhibition, and by the fact that ZI neurons fire spontaneously (Eaton and Moss, 1989; Koyama et al., 2003).

Inactivating the ZI also affected the responses of POM neurons to whisker stimuli. Response latencies in rats with lesions were significantly shorter than in controls, and both the magnitude and duration of the responses were significantly increased. Indeed, after ZI lesions, response latencies of many POM neurons were similar to those of VPM cells (8 msec) (Ito, 1988; Hartings and Simons, 1998; Ahissar et al., 2000; Sosnik et al., 2001). Whereas in the control group, only 12% of POM neurons responded to whisker stimuli at these latencies, in the ZI inactivated group, 33% responded at ≤ 8 msec (Fig. 3A). These findings are consistent with the hypothesis that POM receives driving inputs from ascending trigeminal afferents and that the efficacy of these inputs is regulated by inhibitory inputs from the ZI.

Not all POM neurons were equally affected by inactivating the ZI: in $\sim 30\%$ of the cells recorded from the ZI inactivated group, the lesions did not affect the latency or kinetics of whisker-evoked responses (Fig. 3). The fact that inactivating the ZI increased the spontaneous firing in this subpopulation of neurons suggests that the lesions were effective in suppressing ZI inputs to these neurons. Together, these findings suggest that POM contains two neuronal populations, one that receives driving brainstem inputs

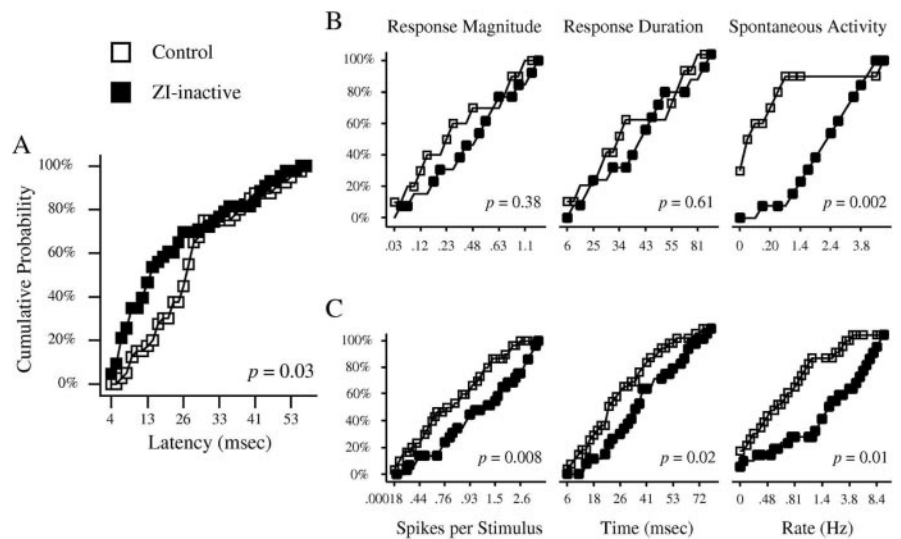


Figure 3. POM comprises two neuronal populations. *A*, Cumulative probability plots showing the distribution of response onset latencies of POM neurons recorded from control rats versus neurons recorded after ZI inactivation. ZI inactivation results in a significant leftward shift in the distribution of response latencies. Note that the distribution of neurons responding at >30 msec is unaffected by ZI inactivation. *B*, Cumulative probability plots constructed for the group of POM neurons that responded at >30 msec. In this group, ZI inactivation resulted in significant increases in spontaneous firing rates but had no effect on response magnitude or duration. *C*, Cumulative probability plots constructed for the group of POM neurons that responded at ≤ 30 msec. All metrics were significantly affected by ZI inactivation in this group.

that are modulated by inhibitory inputs from the ZI and one that receives few or weak inputs from brainstem afferents and is primarily driven by descending cortical inputs.

POM as both a first- and higher-order nucleus

Our findings suggest that the dichotomy between first-order thalamic nuclei (driven by ascending sensory afferents) and higher-order nuclei (driven by descending cortical inputs) may not apply to the POM. Although POM has been conclusively shown to function as a higher-order nucleus (see Introduction), our findings demonstrate that it functions also as a first-order nucleus with response properties that are shaped by ascending trigeminal inputs.

To our knowledge, our findings provide the first support for the conjecture originally proposed by Sherman et al. (2001) that “it is possible that several thalamic nuclei may represent a mixture of the two types of circuit, having some afferents from lower centers contributing to first-order circuits and others coming from the cortex and contributing to higher-order circuits . . . The possibility that two such pathways might interact in the thalamus remains completely unexplored.”

ZI affects all higher-order thalamic nuclei

GABAergic incerto-thalamic afferents target all higher-order thalamic nuclei (but do not project to first-order nuclei) (Power et al., 1999; Bartho et al., 2002). It is therefore likely that the regulation of POM responses by these afferents applies also to higher-order thalamic nuclei of other sensory systems. For example, the pulvinar is classified as a higher-order thalamic nucleus of the visual system (Sherman and Guillery, 2001). However, retinal axons innervate the pulvinar (Grieve et al., 2000), suggesting that ascending inputs may drive these neurons. Furthermore, retinal axons innervate the ZI, which in turn projects to the pulvinar (Power et al., 1999, 2001). This anatomical connectivity is analogous to the one in the somatosensory system (see Introduction). It is therefore possible that the pulvinar, like POM, may function

both as a first-order and a higher-order nucleus and that these functions are regulated by inhibitory inputs from the ZI. Thus, the dichotomy between first-order and higher-order nuclei of all sensory systems may need to be revised to include the dual functions of thalamic nuclei.

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