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Somatosensory Corticothalamic Projections: Distinguishing Drivers From Modulators

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Reichova, Iva and S. Murray Sherman. Somatosensory corticothalamic projections: distinguishing drivers from modulators. *J Neurophysiol* 92: 2185–2197, 2004. First published May 12, 2004; 10.1152/jn.00322.2004. We used a juvenile mouse thalamocortical slice preparation with whole cell recording to investigate synaptic properties of corticothalamic inputs from somatosensory cortex to the ventral posterior medial and posterior medial nuclei (98 cells). We compared these data to those obtained from activating retinal and cortical inputs to the lateral geniculate nucleus (8 cells), the former representing a prototypical driver input and the latter, a typical modulator. Retinogeniculate activation evoked large, all-or-none excitatory postsynaptic potentials (EPSPs) that showed paired-pulse depression antagonized by *N*-methyl-D-aspartate (NMDA) and AMPA receptor blockers but with no sign of a metabotropic glutamate receptor (mGluR) component. Corticogeniculate activation evoked small, graded EPSPs showing paired-pulse facilitation, and the EPSPs showed both NMDA and AMPA receptor component plus an mGluR1 component. In the somatosensory thalamic relays, cortical stimulation elicited glutamatergic EPSPs in all thalamic cells, and these EPSPs fell into two groups. One, elicited from cortical layer 6 to cells of both nuclei, involved small, graded EPSPs with paired-pulse facilitation, and most also showed an mGluR1 component. The other, elicited from layer 5 to cells only of the posterior medial nucleus, involved large, all-or-none EPSPs with paired-pulse depression, and none showed an mGluR component. By analogy with results from the lateral geniculate nucleus, we conclude that the input from layer 6 to both nuclei acts as a modulator but that the layer 5 input to the posterior medial nucleus serves as a driver. Our data extend a common organizing principle from first-order nuclei to higher-order thalamic relays and further implicate the latter in corticocortical communication.

INTRODUCTION

Guillery and Sherman have recently proposed that thalamic relays can be divided into two types: *first order* and *higher order* (Guillery and Sherman 2002; Sherman and Guillery 2001, 2002). First-order relays represent the first transmission to cortex of particular type of information from the periphery, and higher-order relays serve to transmit information between cortical areas via a cortico-thalamo-cortical route. Examples of the former are the lateral geniculate nucleus for vision (relaying retinal input) and the ventral posterior nucleus for somesthesis (relaying medial lemniscal input); examples of the latter are most or all of pulvinar for vision and the posterior medial nucleus for somesthesis.

A key to this hypothesis is identifying the information actually relayed through thalamus. To do so, Guillery and Sherman have divided inputs to relay cells into *drivers*, which bring the information to be relayed, and *modulators*, which serve to modulate thalamic transmission of the driver input (Sherman and Guillery 1998, 2001). Examples of the former are the retinal and medial lemniscal input to the lateral geniculate nucleus and ventral posterior nucleus, respectively. Examples of the latter are brain stem cholinergic inputs from the parabrachial region and feedback projections from layer 6 of cortex. At issue is the nature of the driver input to higher-order relays. A paramount aspect of the hypothesis of first- and higher-order relays is that the driver input to the latter derives from layer 5 of cortex. Thus all thalamic relays receive a modulatory input from layer 6 of cortex, but only higher-order relays receive, in addition, a driver input from layer 5. The layer 6 modulatory input is mainly feedback, whereas the layer 5 driver input is feedforward (Van Horn and Sherman 2004).

Evidence that the layer 5 input to proposed higher-order relays such as pulvinar and the posterior medial nucleus serves as a driver has been largely limited to morphology (reviewed in Guillery 1995; Sherman and Guillery 1996). That is, layer 5 input terminates in flowery, rich arbors with large boutons forming synapses on proximal dendrites of thalamic relay cells, and these axons do not appear to innervate cells of the thalamic reticular nucleus en route to thalamus. This is in stark contrast to the layer 6 axons, which terminate in sparser arbors with small boutons forming synapses on distal dendrites of thalamic relay cells, and these axons do form collaterals that innervate reticular cells. Morphologically, then, layer 5 corticothalamic axons closely resemble those from retina that innervate the lateral geniculate nucleus and those from the medial lemniscus that innervate the ventral posterior nucleus, and this was the main reason to argue that these layer 5 axons serve as drivers.

Recent support for this scheme come from the study of Li et al. (2003), who demonstrated in the in vitro preparation of the rat's thalamus that inputs to the lateral posterior nucleus (a higher-order thalamic relay) could be divided into two groups based on synaptic properties, one showing synaptic depression and the other, synaptic facilitation. They suggested that these inputs were cortical in origin and that one arose from layer 5, whereas the other arose from layer 6. However, the nature of their preparation did not allow them to identify the source of these inputs, and thus the laminar and even cortical source of the different synaptic patterns remains to be determined.

The purpose of the present study was to use techniques of in vitro physiology and pharmacology to test this hypothesis further. Specifically, we used the mouse thalamocortical slice preparation (Agmon and Connors 1991), which enabled us to activate corticothalamic axons from layer 5 or 6 and record the

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evoked synaptic responses in the ventral posterior nucleus (the model first-order relay) and the posterior medial nucleus (the model higher-order relay). We found significant differences in synaptic responses between the axons from layers 5 and 6, and these data further support the hypothesis that the layer 5 input to the posterior medial nucleus acts as a driver.

METHODS

BALB/c mice aged 14–19 days postnatal were used in this study. All animal procedures followed the State University of New York animal-care guidelines. The mice were anesthetized using a few drops of isoflurane (AErrane, Baxter Pharmaceuticals, Deerfield, IL) and decapitated. The brain was removed and placed in chilled (0°C) artificial cerebrospinal fluid (ACSF). After blocking the brain, thalamocortical slices (400–450 μm thick) were cut using the sectioning plane described in Agmon and Connors (1991). For recordings from the lateral geniculate nucleus, coronal slices (400 μm thick) were cut. Before recording, slices were held in a chamber with ACSF for ~2 h at room temperature. At all times, they were oxygenated with carbogen (5% CO_2-95% O_2). For recording, slices were transferred to the submergent recording chamber and continually perfused with oxygenated ACSF at 32°C. The ACSF composition was as follows (in mM): 125 NaCl, 25 $NaHCO_3$, 3 KCl, 1.25 NaH_2PO_4, 1 $MgCl_2$, 2 $CaCl_2$, and 25 glucose.

Whole cell recordings were made with electrodes pulled from borosilicate glass (Garner Glass, Claremont, CA) with input resistances of 4–10 MΩ after filling with the following intracellular solution (in mM): 135 KGluconate, 7 NaCl, 10 HEPES, 2 Na_2ATP, 0.3 Na_3GTP, 2 $MgCl_2$, and 0.5% biocytin. All chemicals were purchased from Sigma (St. Louis, MO). All recordings were made on a visualized rig with DIC enhancement (Axioskop, Carl Zeiss) using an Axoclamp 2A amplifier and pClamp software (Axon Instruments, Union City, CA). The barrel field of layer 4 in S1 as well as layers 5 and 6 could be routinely visualized in the living slice by using a low-magnification objective. The medial and lateral divisions of the ventral posterior nucleus were identified based on the presence of numerous fiber bundles crossing them and by their darker appearance. The posterior medial nucleus, which does not have clear boundaries, was located as a nuclear mass lying medially to the ventral posterior nucleus and extending further medially for ~200–300 μm (see also following text and Fig. 1). Whole cell recordings were made from visually identified neurons in the ventral posterior or posterior medial nuclei. Electrodes used for electrical stimulation of thalamic afferents were either low-resistance glass pipettes (the same as used for recording but with a broken tip) filled with ACSF or bipolar concentric electrodes (Frederick Haer, Bowdoinham, ME). Such electrodes were placed in layer 5 (which was identified based on its position just underneath the lighter band of layer 4 containing the barrels and also including a higher density of large pyramidal cells) or layer 6 (lying just above the white matter) of the barrel field and/or in subcortical sites along the corticothalamic pathway, including the striatum and internal and external capsules; we saw no differences in responses among these different subcortical sites (except for the latency) and have grouped them together below. Stimulation consisted of pulses lasting either for 100 or 200 μs at intensity levels as indicated in the figures.

Recordings from geniculate cells were performed under visual control, and the recording and stimulation parameters were identical to those described in the preceding text for the ventral posterior and posterior medial nuclei. Electrical stimulation was performed in the optic tract, which lies ventral to the lateral geniculate nucleus, and in the optic radiations, which lie dorsal.

Antagonists (all purchased from Tocris Cookson, Ellisville, MO) were dissolved in ACSF and applied continuously during the experiment. Antagonists and the receptors affected were: SR95531 (20 μM) for $GABA_A$; CGP46381 (40 μM) for $GABA_B$; 6,7-dinitroquinoxaline-2, 3-dione (DNQX, 50 μM) for AMPA; MK-801 (50 μM) for NMDA; LY367385 (20–50 μM) for the mGluR1 subtype of Group1 metabotropic glutamate receptors (mGluRs); and MPEP (30–60 μM) for the mGluR5 subtype of Group1 mGluRs.

During recording, the cells were routinely filled with 0.5% biocytin. After fixing the slices in 4% paraformaldehyde overnight, the tissue was reacted with 1:100 avidin/biotin complex (ABC reaction, Vectastain Elite ABC Kit, Vector Laboratories, Burlingame, CA) and then reacted with diaminobenzidine (DAB). The location of cells in the target nuclei was confirmed and their morphology examined. To assess morphologically the presence of intact corticothalamic axons in a subset of the recorded slices, biocytin (0.5% in ACSF) was iontophoresed into the barrel cortex using low-resistance patch electrodes (0.1–1.0 MΩ, 40 μA positive current at 1-Hz frequency, 1 s on/1 s off, for 10–20 min). The slices were kept overnight in the holding chamber at room temperature and oxygenated with carbogen and were then fixed in 4% paraformaldehyde, and the biocytin revealed as noted in the preceding text.

RESULTS

Figure 1 illustrates the basic recording and stimulation arrangements in the preparation. The barrel field in the somatosensory cortex can be seen clearly in Fig. 1*B*. Data were based on recordings from 104 thalamic neurons in various nuclei as described in the following text. We evoked synaptic responses in these cells by electrical activation of various cortical and subcortical loci as specified below. To isolate excitatory postsynaptic potentials (EPSPs) in all recordings, we used

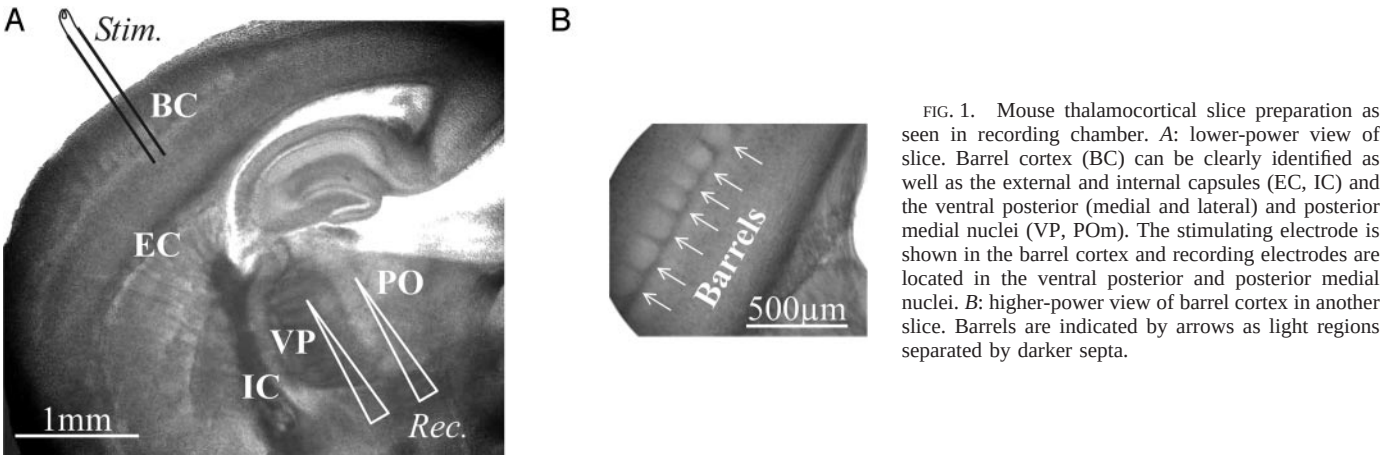

FIG. 1. Mouse thalamocortical slice preparation as seen in recording chamber. *A*: lower-power view of slice. Barrel cortex (BC) can be clearly identified as well as the external and internal capsules (EC, IC) and the ventral posterior (medial and lateral) and posterior medial nuclei (VP, POm). The stimulating electrode is shown in the barrel cortex and recording electrodes are located in the ventral posterior and posterior medial nuclei. *B*: higher-power view of barrel cortex in another slice. Barrels are indicated by arrows as light regions separated by darker septa.

GABA receptor antagonists (see METHODS). The bulk of the quantitative analysis was based on recordings from 98 cells of the ventral posterior medial and posterior medial nuclei (see Table 1).

Synaptic inputs to cells of the lateral geniculate nucleus

To help establish synaptic properties of drivers and contrast them with layer 6 modulator properties with our techniques, we first recorded from the lateral geniculate nucleus. The retinal input to geniculate relay cells is the prototypical driver, and the corticogeniculate input from layer 6 is a typical modulator. Prior studies of the lateral geniculate nucleus have established these differences in synaptic properties for these inputs in rodents and cats (rat: Granseth and Lindström 2003; Turner and Salt 1998; mouse: Chen and Regehr 2000; Chen et al. 2002; guinea pig: McCormick and Von Krosigk 1992; cat: Lindström and Wróbel 1990; also our own unpublished observations). We thought it important to demonstrate these differences with our mouse preparation. We thus electrically stimulated the optic tract and radiations while recording from geniculate relay cells. We recorded from eight cells with resting membrane potentials of -63.8 ± 7.6 mV (here and below, this refers to std. dev.) ($n = 8$) and input resistances of 244.1 ± 108.5 MΩ ($n = 6$). The results are summarized in Fig. 2.

Optic tract stimulation evoked large-amplitude, all-or-none EPSPs in these cells ($n = 5$), and these EPSPs showed paired-pulse depression (Fig. 2, *Ai* and *Bi*). The response latencies were very short because the stimulation site was located immediately adjacent to the lateral geniculate nucleus. These EPSPs were abolished by application of antagonists to ionotropic glutamate receptors (iGluRs: AMPA and NMDA receptors; Fig. 2*Ci*). To search for evidence of an mGluR component, we used high-frequency stimulation (≥100 Hz), which is often required to reveal such responses (e.g., McCormick and Von Krosigk 1992). With this approach, we found no evidence of mGluR participation in the postsynaptic response, even with high-frequency and -intensity stimulation (110 Hz; Fig. 2*Di*).

TABLE 1. *Properties of EPSPs recorded in the ventral posterior medial and posterior medial nuclei*

	mGluR+	mGluR−	Total
VPM			
PPF/graded	9	3	12
PPD/all-or-none	0	0	0
POm/L5			
PPF/graded	0	0	0
PPD/all-or-none	0	15	15
POm/L6			
PPF/graded	7	4	11
PPD/all-or-none	0	4	4
POm/SCx			
PPF/graded	29	22	51
PPD/all-or-none	0	5	5
Total			98

All showing paired-pulse facilitation (PPF) were graded, and all showing paired-pulse depression (PPD) were all-or-none, so these parameters were collapsed. Four 2 × 2 tables are shown for the various recording and stimulation conditions: the ventral posterior medial nucleus (VPM, which was subcortical), and the posterior medial nucleus POm from layer 6 (POm/L6), from layer 5 (POm/L5) and from subcortical sites (POm/SCx). The tables show the relationship between paired-pulse effects (and thus recruitment) and whether or not the excitatory postsynaptic potential (EPSP) had an mGluR component. Note that every response showing paired-pulse depression, and thus an all-or-none characteristic, was negative for mGluR.

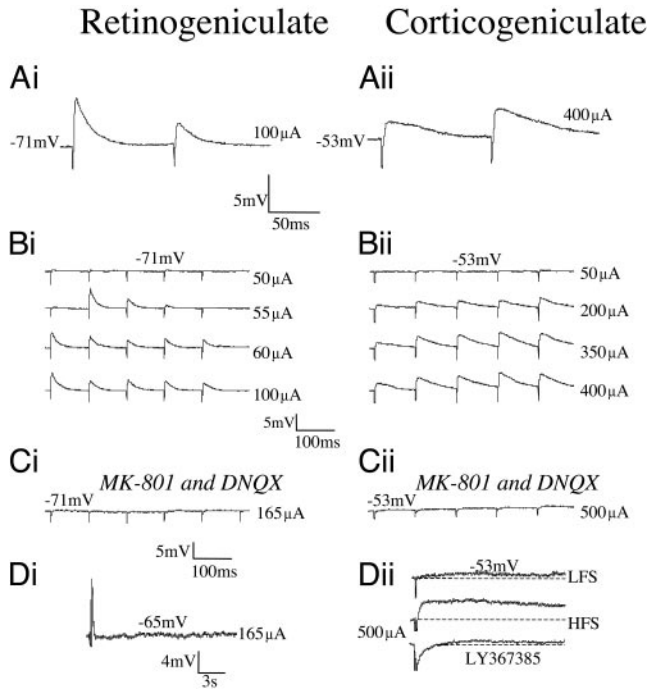

FIG. 2. Drivers and modulators in the mouse lateral geniculate nucleus showing excitatory postsynaptic potentials (EPSPs) evoked from stimulation of retinogeniculate afferents via the optic tract (*Ai–Di*) or corticogeniculate afferents via the optic radiation (*Aii–Dii*). In this and all subsequent figures showing evoked EPSPs, inhibition was blocked by application of SR95531 (a $GABA_A$ antagonist, 20 μM) and CGP46381 (a $GABA_B$ antagonist, 40 μM). *A*, *i* and *ii*: large EPSP showing paired-pulse depression evoked from retinogeniculate stimulation (*Ai*) contrasts with small EPSP showing paired-pulse facilitation evoked from corticogeniculate stimulation (*Aii*). *B*, *i* and *ii*: increasing stimulation intensity produces all-or-none response for retinogeniculate stimulation (*Bi*) and graded response for corticogeniculate stimulation (*Bii*). *C*, *i* and *ii*: EPSPs evoked by low-frequency stimulation (10 Hz) from both sites completely blocked by AMPA and *N*-methyl-D-aspartate (NMDA) receptor antagonists (DNQX, 50 μM, and MK-801, 50 μM, respectively). *D*, *i* and *ii*: high-frequency stimulation (HFS, 110 Hz) of retinogeniculate afferents evokes no further response with continued application of AMPA and NMDA antagonists (*Di*). Low-frequency stimulation (LFS, 10 Hz) of corticogeniculate afferents in the presence of continued AMPA and NMDA antagonists does not evoke any response (*Dii*, *top*), but high-frequency stimulation (HFS, 110Hz) evokes a sustained EPSP (*Dii*, *middle*) that is blocked by the mGluR1 antagonist, LY367385 (50 μM, 110Hz, *Dii*, *bottom*).

The responses to stimulation of the optic radiation were quite different ($n = 3$). Smaller-amplitude, graded EPSPs were evoked, and these showed paired-pulse facilitation (Fig. 2, *Aii* and *Bii*). Again, short latencies of evoked EPSPs were found because the stimulation was made just dorsal to the lateral geniculate nucleus. With low-frequency stimulation (10 Hz), these EPSPs were abolished with iGluR antagonists (Fig. 2*Cii*). Evidence from cats and guinea pigs indicates that layer 6 inputs to the lateral geniculate nucleus can activate Group 1, type1 mGluRs (mGluR1) (Godwin et al. 1996; McCormick and Von Krosigk 1992). As shown in Fig. 2*Dii*, we also found evidence for this in the mouse lateral geniculate nucleus, because, when we applied high-frequency stimulation (110 Hz) to corticothalamic axons, we evoked a long, depolarizing potential (30 s) of small amplitude (1–3 mV) with a slow onset and slow termination (60–90 s). This response was not affected by applying

an antagonist to mGluR5 but was abolished by applying LY367385, an mGluR1 antagonist (Fig. 2*Dii*). These data largely confirm those of Turner and Salt (2000) for layer 6 inputs to the lateral geniculate nucleus in the rat. The high-frequency stimulation (≥100 Hz) was performed at relatively depolarized membrane potentials to avoid activation of low-threshold Ca^{2+} currents that are prominent in thalamic neurons and not easily blocked by pharmacological means. Application of mGluR antagonists alone produced no detectable effect on the cell (not shown here but see Fig. 4*D* for another example).

Thus the retinal and cortical inputs to relay cells of the mouse lateral geniculate nucleus mimic those seen in the cat and rat. Furthermore, this suggests the driver/modulator distinction to be anticipated for the first- and higher-order somatosensory thalamic relays: the driver input should evoke large, all-or-none EPSPs showing paired-pulse depression and no evidence of an mGluR component; the modulator input from cortical layer 6 should evoke small, graded EPSPs showing paired-pulse facilitation and a clear mGluR1 component.

Synaptic inputs to cells of the ventral posterior medial and posterior medial nuclei

We moved to the somatosensory system of the mouse to make use of an intact corticothalamic pathway in vitro (e.g., Agmon and Connors 1991), something currently not possible for the visual pathways. We focused on two thalamic relays. One is the ventral posterior medial nucleus, which is a first-order relay, like the lateral geniculate nucleus, and thus receives only a layer 6 input from cortex. The other is the posterior medial nucleus, which is mostly a higher-order relay, like the pulvinar, and thus receives inputs from both layer 5 and layer 6 of cortex. Much of the corticothalamic projection to these nuclei derives from the primary somatosensory cortex (S1), including the barrel field (Bourassa et al. 1995; Chmielowska et al. 1989; Deschênes et al. 1998; Killackey and Sherman 2003; Veinante et al. 2000).

Overall, we recorded from 12 relay cells from the ventral posterior medial nucleus and 86 from the posterior medial nucleus. These cells had input resistances of 326.6 ± 273.9 MΩ ($n = 12$) and 130.9 ± 113.8 MΩ ($n = 83$) and resting membrane potentials of −62.2 ± 5.0 mV ($n = 12$) and −66.8 ± 4.0 mV ($n = 86$), respectively. The difference in neuronal input resistance between nuclei is statistically significant ($P < 0.001$ on a *t*-test), and we have no explanation for this difference. However, we noted no correlation between input resistance and any of the measures described in the following text, including paired-pulse effects and the presence of an mGluR component to the evoked EPSP. No corrections for junction potentials were made (under our conditions, liquid junction potentials were estimated to be ~10 mV). We kept the recorded cells at either depolarized potentials (−64 mV and more depolarized after correction for junction potentials) or hyperpolarized potentials (−78 mV and more hyperpolarized) to avoid activation of the low-threshold Ca^{2+} current that is present in all thalamic neurons.

CORTICOTHALAMIC CONNECTIONS IN THE SLICE. To confirm that our slice preparation preserved connections between barrel cortex and the thalamic relays of interest, we iontophoresed biocytin (0.5%) into barrel cortex in several slice preparations to label corticothalamic axons. Figure 3 shows the result from one such experiment. The injection sites in barrel cortex are clearly visible and cover both layers 5 and 6 (Fig. 3*A*, arrow). Labeling of terminal arbors in the ventral posterior medial and posterior medial nuclei is also clearly visible, demonstrating that at least some of these corticothalamic axons to both nuclei are intact in our slice preparations.

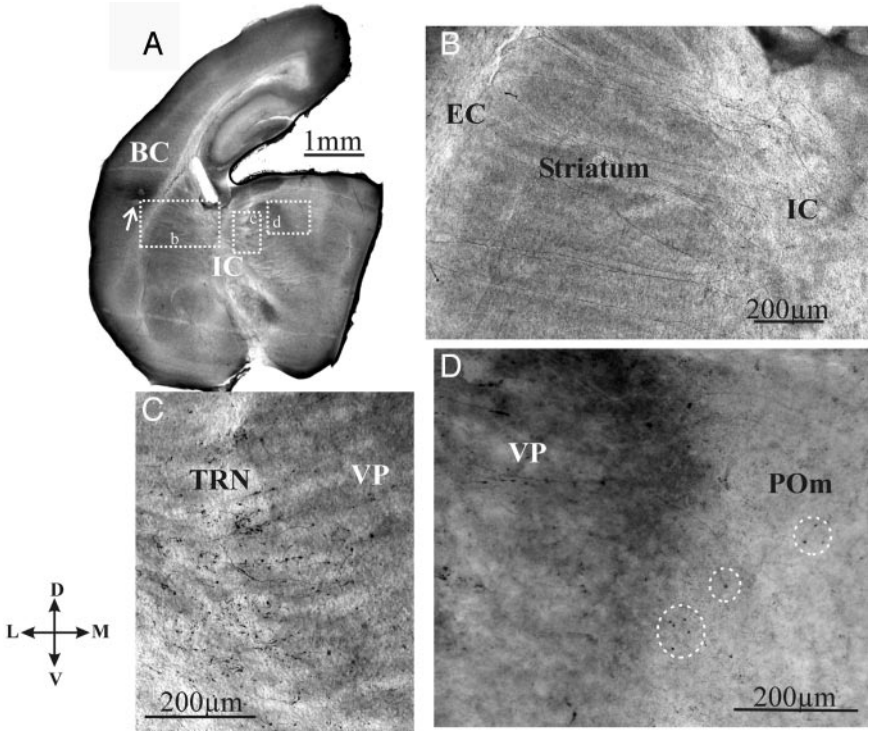

FIG. 3. Integrity of the corticothalamic pathway. Corticothalamic axons from layers 5 and 6 are orthogradely labeled by biocytin iontophoresis into the barrel cortex. *A*: injection site (*arrow*) in BC. Also visible is the IC. The lettered boxes refer to the higher power views in *B–D*. *B*: labeled axons running between external and internal capsules. *C*: terminal boutons of cortical fibers in thalamic reticular nucleus (TRN) and VP. Many axons ramify in the thalamic reticular and ventral posterior nuclei and terminate there, but a few continue further to the posterior medial nucleus. *D*: terminal boutons of cortical axons in the ventral posterior medial nucleus and POm. Several of the larger boutons in the posterior medial nucleus are circled.

Corticothalamic axons cross the external capsule, striatum, and internal capsule (Fig. 3*B*) and enter the ventral posterior medial nucleus, where most of them terminate (Fig. 3*C*). Some of the axons then enter the posterior medial nucleus and terminate there (Fig. 3*D*, circled areas). There are several possible reasons why the termination in the posterior medial nucleus seems smaller than that in the ventral posterior medial nucleus: the layer 6 projection from barrel cortex is probably denser in the ventral posterior medial nucleus; the extra layer 5 projection to the posterior medial nucleus likely involves relatively few axons because only a minority of layer 5 pyramidal cells give off collaterals that innervate thalamus; and the pathway to the posterior medial nucleus is longer and thus more axons will be interrupted during slicing.

SYNAPTIC PROPERTIES OF LAYER 6 INPUTS TO THE VENTRAL POSTERIOR MEDIAL NUCLEUS. Because the ventral posterior medial nucleus receives only layer 6 input from barrel cortex, it provides an excellent internal control for characterizing the signature properties of layer 6 (modulator) input in our preparation. Also, because essentially only layer 6 inputs are possible from cortex to this thalamic relay, we could reliably conclude that afferents onto relay cells activated from subcortical sites (by "subcortical" referring to stimulation sites here and below, we mean the striatum and internal and external capsules) represented a layer 6 corticothalamic input.

Figure 4 shows examples of the EPSPs evoked by subcortical stimulation. The evoked EPSPs are small but show paired-pulse facilitation so that the second EPSP is clearly of a much larger amplitude than the first (Fig. 4*A*). The EPSPs are activated in a graded manner (Fig. 4*B*). Figure 4*C* shows that although the EPSP evoked by low-frequency stimulation was blocked completely by adding iGluR antagonists (*top*), when we applied high-frequency stimulation (125 Hz for 800 ms, *middle*) to corticothalamic axons, we evoked a prolonged, depolarizing potential with an amplitude of 2 mV. This response was abolished by applying LY367385, an mGluR1 antagonist (Fig. 4*C*, *bottom*). Figure 4*D* shows that LY367385 by itself evoked no detectable response in another cell ($n = 6$).

As summarized in Table 1, we evoked EPSPs from subcortical stimulation in 12 cells of the ventral posterior medial nucleus. All 12 showed small EPSPs that were graded and showed paired-pulse facilitation, and 9 in addition showed evidence of an mGluR1 component. We found no obvious correlation between any other tested physiological properties of these cells and whether or not they displayed an mGluR response component. Furthermore, analysis of labeled neurons showed no obvious correlation of morphology with the presence or absence of an mGluR component. Possible reasons for the lack of an mGluR response in some cells are discussed in the following text.

We conclude from these experiments that layer 6 corticothalamic input to the ventral posterior medial nucleus has characteristics consistent with the modulatory layer 6 projection to the lateral geniculate nucleus: paired-pulse facilitation, a graded response, and, for at least most cells, activation of mGluR1s with high-frequency (100 Hz) stimulation.

CORTICAL INPUTS TO THE POSTERIOR MEDIAL NUCLEUS. Next we recorded from relay cells of the posterior medial nucleus. Here we expected to see responses with characteristics similar to those of cells from the ventral posterior medial nucleus representing the layer 6 input, but we also expected to see an additional pattern reflecting the layer 5 input. Furthermore, our hypothesis was that this additional input should act like a driver (Guillery and Sherman 2002; Sherman and Guillery 1998, 2001, 2002) and thus mimic retinogeniculate responses (see Fig. 2).

We obtained responses evoked from layer 6 in 15 cells of the posterior medial nucleus (see Table 1). Of these, four responded as if they received a driver input (not shown): a large EPSP evoked in an all-or-none manner and showing paired-pulse depression and no evidence of an mGluR component. However, in the other 11 cells, the responses were more typical of a modulator input closely resembling equivalent responses seen in the lateral geniculate and ventral posterior medial nuclei. In a typical such cell, layer 6 stimulation evoked a small-amplitude response (Fig. 5*A*). The response was graded

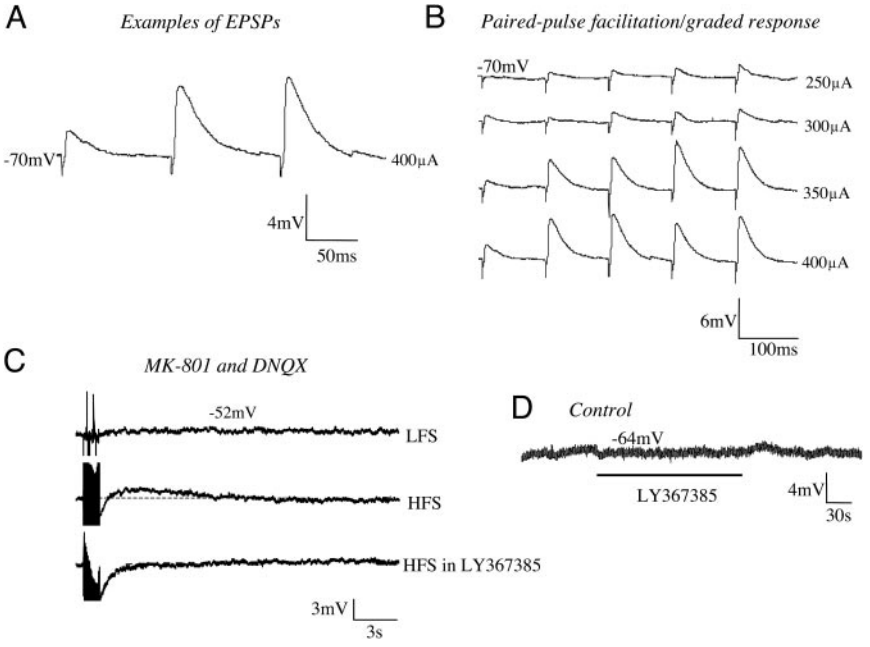

FIG. 4. Corticothalamic EPSPs evoked from subcortical stimulation in a cell in the ventral posterior medial nucleus. *A*: example of evoked EPSPs. *B*: paired-pulse facilitation and graded response of EPSPs. *C*: evidence of an mGluR1 component. The EPSPs evoked by low-frequency stimulation (LFS 400 μA, 14 Hz for 800 ms) are blocked with application of MK-801 and DNQX (*top*). With these antagonists present, high-frequency stimulation (HFS, 125 Hz for 800 ms) evoked a sustained EPSP (*middle*) that is blocked by the mGluR1 antagonist, LY367385 (50 μM, *bottom*). *D*: control. LY367385 (50 μM) applied to the cell does not show any effect on its membrane potential. The line below the trace marks the time of the drug application.

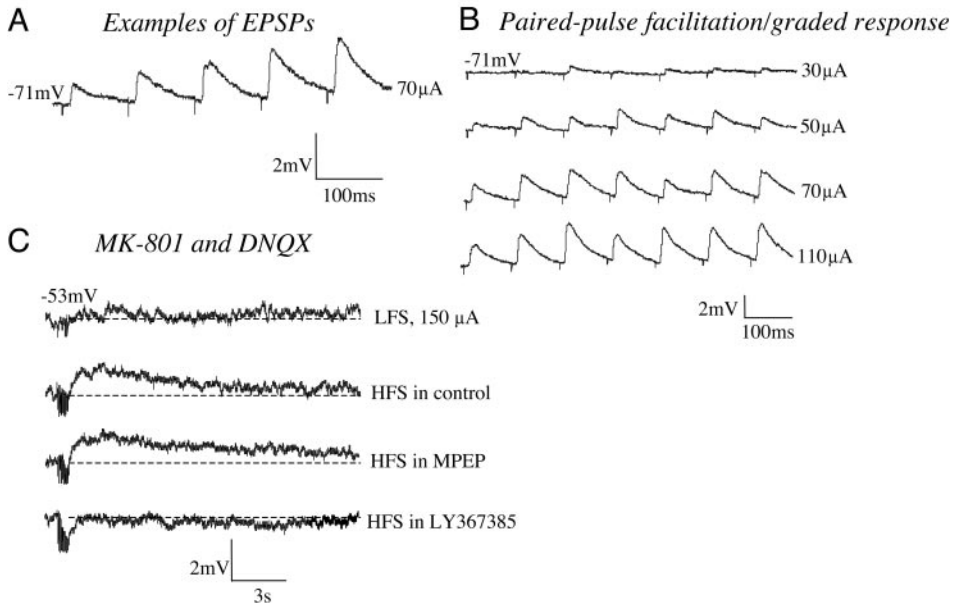

FIG. 5. Corticothalamic EPSPs evoked from stimulation of layer 6 of barrel cortex in a cell of the posterior medial nucleus. *A*: example of evoked EPSPs. *B*: paired-pulse facilitation and graded response of EPSPs. *C*: evidence of an mGluR1 component. The EPSPs evoked by LFS (13 Hz for 600 ms; for all traces, stimulation intensity was 150 μA) are blocked with application of MK-801 and DNQX (*top*). With these antagonists present, HFS (125 Hz for 600 ms) evoked a sustained EPSP (*2nd trace*) that is not blocked by MPEP, an mGluR5 antagonist (30 μM, *3rd trace*) but is blocked by LY367385, an mGluR1 antagonist (50 μM, *bottom*).

when the stimulation intensity was increased from threshold to >400% of threshold, and it showed paired-pulse facilitation (Fig. 5*B*). The EPSP evoked at low frequency (13 Hz for 600 ms) was blocked with antagonists to AMPA and NMDA receptors (Fig. 5*C*, *top*). However, subsequent high-frequency stimulation (125 Hz for 600 ms, Fig. 5*C*, *2nd trace*) evoked a sustained EPSP that was not blocked by a specific mGluR5 antagonist MPEP (Fig. 5*C*, *3rd trace*), but it was blocked by a specific mGluR1 antagonist LY367385 (Fig. 5*C*, *bottom*). All 11 cells showed small EPSPs with graded responses and paired-pulse facilitation, and 7 of the 11 cells showed evidence of an mGluR1 component.

Obtaining responses from cells of the posterior medial nucleus to layer 5 stimulation was more difficult, presumably because there are many fewer layer 5 inputs (see footnote 1 in the following text), but we nonetheless did so in 15 cells. Figure 6 shows the results from a typical example. The evoked EPSP was large (Fig. 6*A*) and showed pronounced depression (Fig. 6*B*). The EPSP was evoked in an all-or-none fashion, showing essentially no fractionation (Fig. 6*C*). That is, at a stimulation intensity of 50 μA there was no response to stimulation, and increasing the intensity to 60 μA evoked an EPSP that was as large as that evoked by the maximum current applied (300 μA). Finally, as shown in Fig. 6*D*, no evidence of an mGluR component to the EPSP could be detected, even with high-frequency stimulation at high stimulation intensities (>200 Hz and 400–500 μA). Every 1 of these 15 cells showed large EPSPs, an all-or-none activation, and paired-pulse depression (Table 1). Furthermore for each cell, the EPSPs evoked at low frequencies of stimulation were blocked by

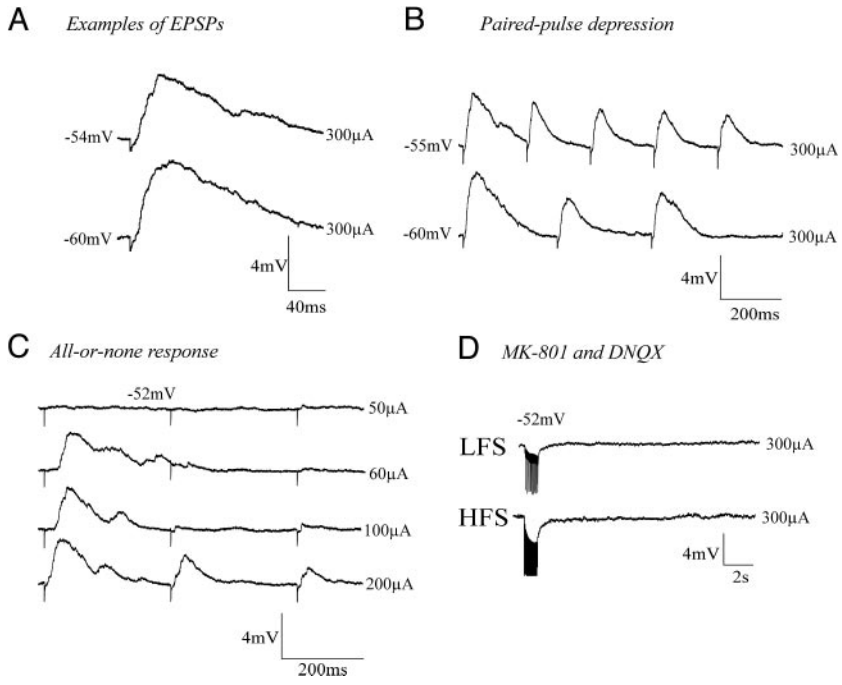

FIG. 6. Corticothalamic EPSPs evoked from stimulation of layer 5 of barrel cortex in a cell of the posterior medial nucleus. *A*: example of evoked EPSPs. *B*: paired-pulse depression. *C*: all-or-none response of EPSPs is apparent from responses to increasing stimulation intensities. *D*: lack of mGluR component. After blocking EPSPs with DNQX and MK-801, neither LFS (50 Hz for 855 ms, *top*) nor HFS (125 Hz for 855 ms, *bottom*) evoked an mGluR response.

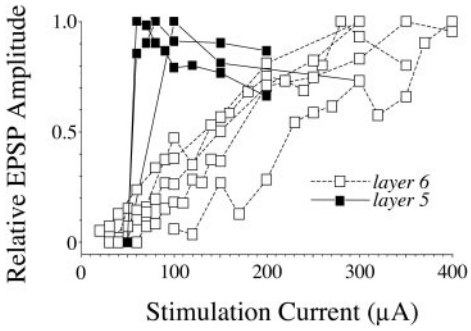

FIG. 7. Examples of graded and all-or-none EPSPs from cells of the posterior medial nucleus. The 3 examples of all-or-none responses (— and ■) reflect stimulation from layer 5, whereas the 5 examples of graded responses (- - - and □) reflect stimulation from layer 6.

antagonists to AMPA and NMDA receptors, but there was no evidence of any mGluR component, even at high frequencies of stimulation.

Figure 7 shows examples of graded versus all-or-none responses for representative cells of the posterior medial nucleus: the three cells showing an essentially all-or-none response were activated from layer 5, and the five showing a graded response were activated from layer 6.

Figure 8 represents a serendipitous experiment in which we were able to activate separately layer 5 and 6 inputs to a cell of the posterior medial nucleus, randomly switching the activation between stimulation sites, and this was repeated on another cell (not shown). Layer 5 was stimulated first, and after obtaining data from EPSPs activated there, we switched to the stimulating electrodes in layer 6 and repeated the paradigm. The layer 5 stimulation evoked a large-amplitude EPSP that showed clear paired-pulse depression (Fig. 8*Ai*) and all-or-none characteristics (Fig. 8*Bi*). These EPSPs were blocked by AMPA and NMDA receptor blockers (Fig. 8*Ci, top*) and layer 5 stimulation produced no evidence of an mGluR component to the EPSP, even after high-frequency stimulation (Fig. 8*Ci, bottom*). Layer 6 responses are shown in Fig. 8, *Aii–Cii.* The EPSP evoked from layer 6 was smaller in amplitude compared with the layer 5 response, and it showed clear facilitation with repeated stimulation (Fig. 8*Aii*). Also, the layer-6-evoked EPSP was graded in amplitude with increasing stimulus intensity (Fig. 8*Bii*). High-frequency stimulation in layer 6 evoked a slow, depolarizing potential (Fig. 8*Cii, middle*) that was due to mGluR1 activation as shown by its complete block by LY367385 (Fig. 8*Cii, bottom*). Thus the EPSPs evoked from layer 6 resembled those evoked from layer 6 in cells of the lateral geniculate and ventral posterior medial nuclei (Figs. 2 and 4), but the layer 5 responses were quite different, resembling EPSPs evoked from retina in geniculate cells (Fig. 2).

Figures 5–8 make it clear that the pattern of activation of cells of the posterior medial nucleus from layer 5 is very different from the pattern seen from stimulation of layer 6. The layer 5 pattern shows a large initial EPSP with paired-pulse depression, an all-or-none activation pattern, and no evidence of an mGluR component. In this regard, it is much like the pattern seen for retinogeniculate stimulation (e.g., Fig. 2). The layer 6 or subcortical pattern shows a small initial EPSP with paired-pulse facilitation, a graded activation pattern, and most cells show an mGluR component. This pattern is remarkably similar to that seen following cortical activation in the first-order relays of the lateral geniculate nucleus (Fig. 2) and the ventral posterior medial nucleus (Fig. 4), relays in which the corticothalamic input derives only from layer 6.

Likewise, as expected, we saw mixed responses in the population of 56 posterior medial nucleus cells to stimulation of subcortical sites. Figure 9 shows a typical example of the modulator pattern with a small EPSP showing paired-pulse facilitation (Fig. 9, *A* and *B*) and an mGluR1 component (Fig. 9*C*). Figure 10 shows an example of a cell that shows the driver pattern: a large EPSP with paired-pulse depression (Fig. 10, *A* and *B*) and no mGluR component (Fig. 10*C*). Overall in response to subcortical stimulation, the responses of 51 cells of the posterior medial nucleus showed mainly the modulator signature, with small EPSPs showing paired-pulse facilitation, but only 27 of these cells showed a clear mGluR1 component. Only five cells of the posterior medial nucleus showed the complete driver signature with large EPSPs, paired-pulse depression, and no mGluR component.[1]

We have indicated in the preceding text that the driver input evokes large EPSPs, and the modulator input, small ones. Figure 11, *A* and *B*, documents this. We measured the mean amplitude of the first EPSP evoked at 1.5 times threshold activation (because of paired-pulse effects, later EPSPs evoked by a stimulus train show less of an amplitude difference). We did this for all 12 cells in our sample from the ventral posterior medial nucleus, and of the sample from the posterior medial nucleus, we included all 36 showing the full modulator signature, including an mGluR1 component to the EPSP, and all 20 showing the driver signature (see Table 1). The amplitudes for these populations, respectively, are 1.51 ± 0.78, 1.65 ± 0.99, and 7.85 ± 3.44 mV. We found no significant difference between the values for the ventral posterior medial nucleus sample and that of the 36 cells of the posterior medial nucleus showing a modulator signature ($P > 0.4$ on a Mann-Whitney *U* test), but the amplitudes of the 20 cells of the posterior medial nucleus showing a driver signature are significantly larger than either those of the ventral posterior medial nucleus or of those of the posterior medial nucleus showing a modulator signature ($P < 0.001$ for either comparison on a Mann-Whitney *U* test).

Figure 11, *C* and *D*, also shows our analysis of paired-pulse effects for cells activated from cortex. We included the subset of such cells for which we obtained at least three repetitions of stimulation for averaging and used the ratio of the second to first EPSP amplitudes (A2/A1) as our measure of the effect. Cells of the ventral posterior medial nucleus showed only

[1] It seems reasonable to assume that the ratio of layer 5 and layer 6 inputs to a higher-order relay is similar to the ratio of retinal to layer 6 inputs to the lateral geniculate nucleus. In the cat, it has been estimated that there are ~5–10 times as many geniculate relay cells as there are retinal axons innervating them and that there are ~10–100 corticogeniculate axons for every geniculocortical axon (details of these numbers can be found in Sherman, 1985; Sherman and Koch, 1986). Extrapolated to a higher order relay, this would imply that there are about two to three orders of magnitude more axons from cortical layer 6 than from layer 5. Even this may be an underestimate of the difference because a recent analysis suggested that the ratio between layer 6 and layer 5 terminals in a higher-order relay (the pulvinar, which is analogous to the posterior medial nucleus) is higher than in a first-order relay (the lateral geniculate nucleus, which is analogous to the ventral posterior medial nucleus; Wang et al., 2002). Thus it is not surprising that the vast majority of responses in thalamic cells evoked from external capsule stimulation bear the signature of layer 6.

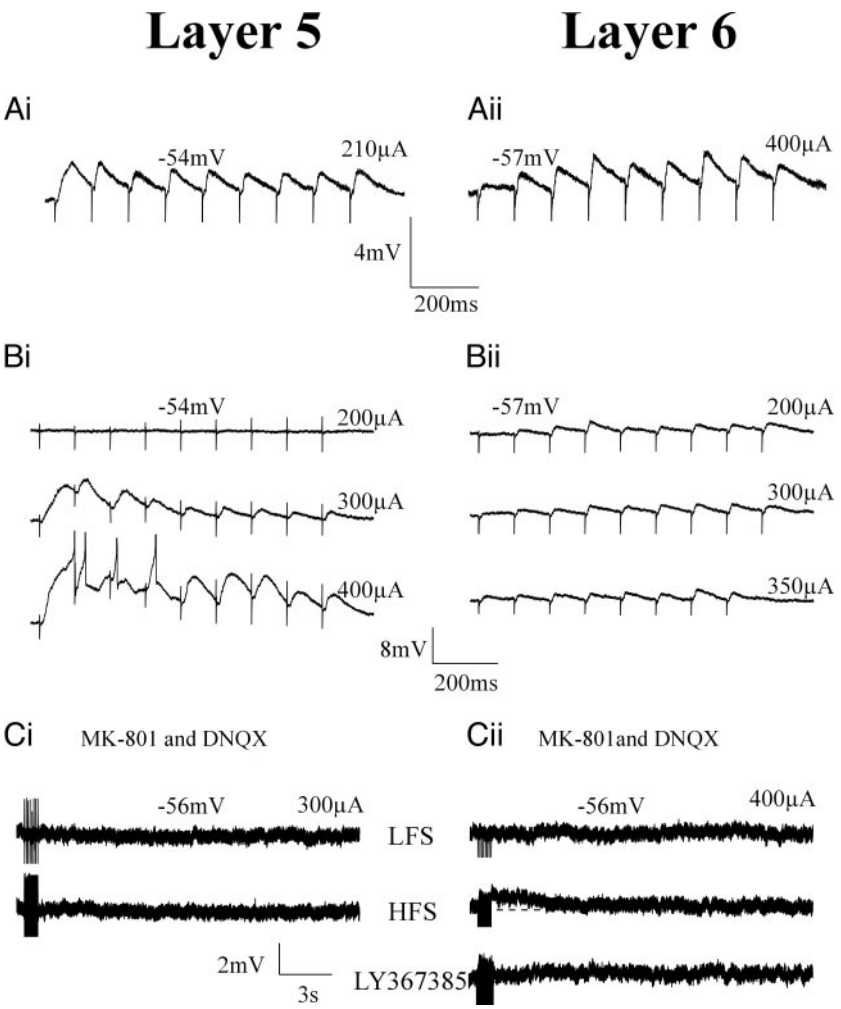

FIG. 8. Corticothalamic EPSPs evoked from separate stimulation of layers 5 and 6 of barrel cortex in the same cell of the posterior medial nucleus. *A*, *i* and *ii*: paired-pulse effects, showing depression for layer 5 stimulation (*Ai*) and facilitation for layer 6 stimulation (*Aii*). *B*, *i* and *ii*: recruitment properties, showing all-or-none response for layer 5 stimulation (*Bi*) and graded responses for layer 6 stimulation (*Bii*). The spikes were truncated. *C*, *i* and *ii*: contribution of mGluRs. Application of DNQX and MK-801 blocks EPSPs to LFS (9 Hz for 755 ms) both from layer 5 (*Ci*, *top*) and from layer 6 (*Cii*, *top*). HFS (125 Hz for 755 ms) evokes nothing further from layer 5 (*Ci*, *bottom*) but evokes a prolonged EPSP from layer 6 (*Cii*, *middle*), and this is blocked by LY367385 (125 Hz for 960 ms; *Cii*, *bottom*).

paired-pulse facilitation (Fig. 11*C*). In contrast, cells of the posterior medial nucleus showed both paired-pulse effects, and as a result, the distribution of A2/A1 values is clearly bimodal (Fig. 11*D*). All 11 of those activated from layer 5 showed depression. Of the 15 activated from layer 6, 11 showed facilitation and 4 showed depression.

DISCUSSION

We found that correlations among the synaptic properties of paired-pulse effects, recruitment of inputs, and presence of an mGluR component cleanly divided corticothalamic synapses for cells in the ventral posterior medial and posterior medial nuclei into two groups. One showed paired-pulse depression, an all-or-none response, and no evidence of an mGluR component, whereas the other tended to show paired-pulse facilitation, a graded response, and an mGluR component. For purposes of temporary exposition only, we shall refer to the former as a *category 1* synaptic response, and the latter, as *category 2*. Only a *category 1* response could be evoked from stimulation of layer 5 of somatosensory cortex, whereas layer 6 stimulation evoked both categories, but mostly *category 2*. Finally, recording in the ventral posterior medial nucleus revealed only *category 2* responses, whereas recording in the posterior medial nucleus revealed both categories.

Category 1 and 2 responses

The evidence for two distinct categories of response is fairly clear, especially when we look more closely at the relationships among the properties described in the preceding text (see Table 1). Every one of the 24 synaptic responses showing paired-pulse depression also showed evidence of an all-or-none response, whereas every one of the 74 synapses showing paired-pulse facilitation also showed evidence of a graded response. Furthermore, every one of the 45 synapses showing evidence of an mGluR component showed both paired-pulse facilitation and a graded response. The only exceptions were the 29 synaptic responses showing a graded response and paired-pulse facilitation but no evidence of an mGluR component. It is unclear if this is because of the likelihood of false negatives (i.e., it may not always be possible with our techniques to demonstrate mGluRs that are actually present) or because there is variability in this synaptic category (see also below). The robustness (amplitude and duration) of mGluR response clearly differs for corticothalamic input to the lateral geniculate nucleus (more robust; Fig. 2*Dii*) and corticothalamic input to the ventral posterior medial nucleus (less robust; Fig. 4*C*) and posterior medial nucleus (less robust; Fig. 5*C*). The reason might be that in case of lateral geniculate nucleus, stimulation was made adjacent to the nucleus and so the majority of corticothalamic fibers will be activated, whereas in

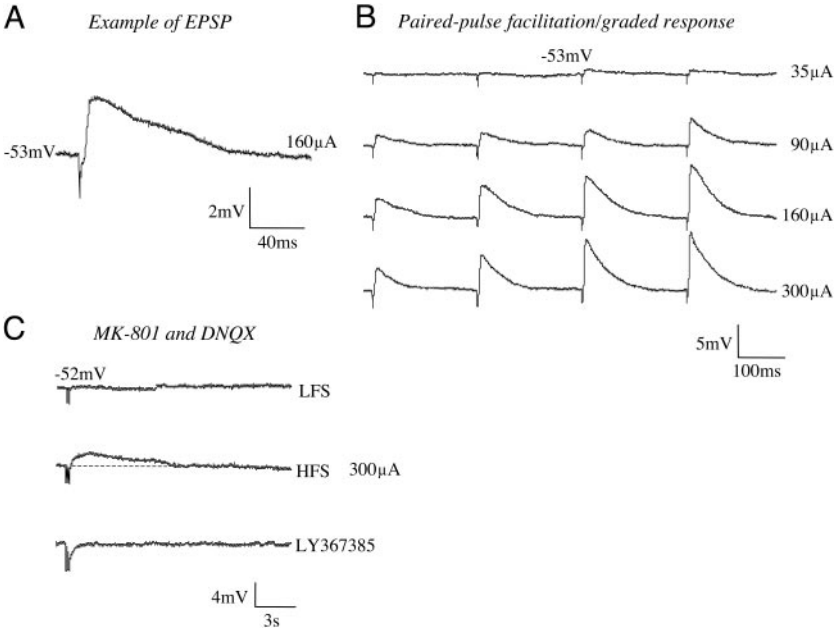

FIG. 9. Modulator response of a cell in posterior medial nucleus to subcortical stimulation. *A*: example of evoked EPSP. *B*: EPSPs show paired-pulse facilitation and are graded. *C*: presence of mGluR1 component. Application of DNQX and MK-801 blocks EPSPs in response to LFS (9 Hz for 220 ms), but HFS (90 Hz for 300 ms) evokes an mGluR response (*middle*) that is fully antagonized by LY367385 (110 Hz for 300 ms, *bottom*).

case of the ventral posterior medial and posterior medial nuclei, stimulation was made in cortex that is a long distance from thalamus and thus only a fraction of all fibers that converge on a recorded cell will be activated. It is plausible that a large fraction of mGluRs must be activated to detect a metabotropic component. In any case, there is considerable prior data that the (layer 6) cortical input to the ventral posterior nucleus is associated with mGluRs (Eaton and Salt 1996; Golshani et al. 1998; Liu et al. 1998; Martin et al. 1992).

It thus seems clear that all 45 synaptic responses showing evidence of an mGluR component are homogeneous with regard to the relationships among the properties tested and are *category 2*. The 24 responses that showed paired-pulse depression, an all-or-none response, and no evidence of an mGluR component are likewise clearly *category 1*. That leaves the 29 responses that showed no evidence for an mGluR component (a *category 1* property) but nonetheless display paired-pulse facilitation and a graded response (*category 2* properties). Either these represent a third category or are *category 2* synapses for which a present mGluR component remained unexposed. Parsimony suggests the latter explanation, and so we shall tentatively include these as part of the *category 2* population. This decision to "lump" rather than "split" has no serious implication for the major conclusions of the study.

Given this classification of synaptic categories, it is interesting that every one of the 12 cells recorded in the ventral posterior medial nucleus showed a *category 2* response, whereas those recorded in the posterior medial nucleus showed both responses (see also following text).

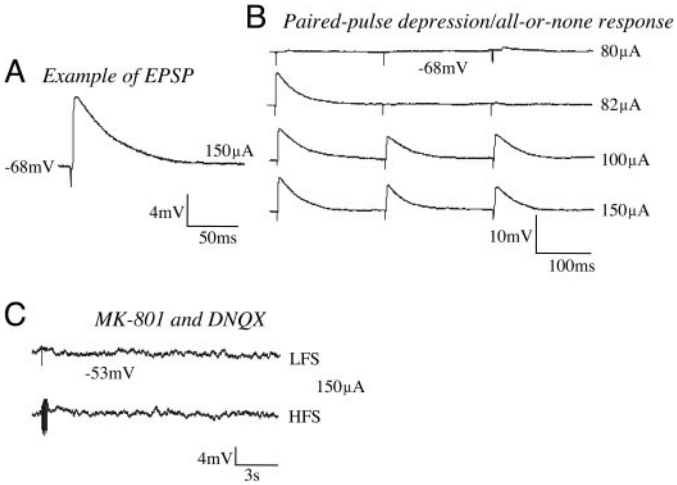

FIG. 10. Driver response of a cell in posterior medial nucleus to subcortical stimulation. *A*: example of evoked EPSP. *B*: EPSPs show paired-pulse depression and are all-or-none. *C*: absence of mGluR component. Application of DNQX and MK-801 blocks EPSPs in response to LFS and HFS (9 Hz for 150 ms and 100 Hz for 400 ms, respectively).

Evidence for laminar origin of response categories

The best evidence for the laminar origin of the different responses as described in the preceding text comes from experiments in which we directly stimulated in cortex. We were able to demonstrate using anatomical techniques that at least some of the corticothalamic projection was intact in our slices. The clearest results came from stimulation of layer 5 for which every single one of the 15 examples showed a *category 1* response. Layer 6 was less homogeneous: using the above-mentioned criteria for classifying responses based mostly on recruitment and paired-pulse effects, 4 synapses activated from layer 6 were *category 1* and 11 were *category 2* (see Table 1).

One possibility for this heterogeneity in layer 6 is that stimulation in layer 6, in addition to activating cells there, also activates some fibers of passage emanating from layer 5, and thus some or all of the *category 1* responses activated from layer 6 stimulation actually represent "ectopic" stimulation of layer 5 cells. One might also expect ectopic activation of layer 6 cells from layer 5 because these corticogeniculate cells in layer 6 have an axon collateral branch that ascends through layer 5 to layer 4. However, these layer 6 collaterals are quite thin and thus may be difficult to activate, whereas the corticogeniculate axons from layer 5 passing through layer 6 are quite thick and easy to activate. In line with this conclusion is the fact that we never saw a *category 1* response from stimulation

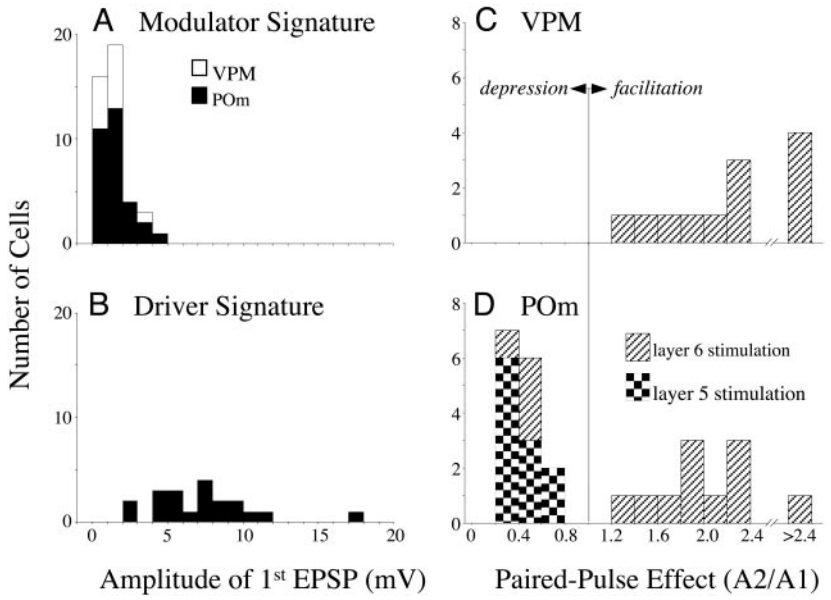

FIG. 11. Distributions of EPSP amplitudes and paired-pulse effects. *A* and *B*: distributions of amplitudes of 1st EPSPs evoked in a train of stimuli. (Data from the VPM and the POm are shown separately.) The distribution for EPSPs showing the modulator signature (paired-pulse facilitation, graded response, mGluR component) is shown in *A*, and that showing the driver signature (paired-pulse depression, all-or-none response, no mGluR component) is shown in *B*. *C* and *D*: distribution of paired-pulse effects, which is shown as the ratio of the amplitude of the 2nd EPSP (*A2*) in a train divided by the 1st (*A1*). In the VPM, all cells showed paired-pulse facilitation (*C*), whereas in the POm, both paired-pulse facilitation and depression are evident (*D*). However, layer 5 stimulation produces only depression in the posterior medial nucleus, whereas layer 6 stimulation produces mostly facilitation.

of layer 6 while recording in the ventral posterior medial nucleus, and these cells do not receive a layer 5 input, which means either that such responses seen for cells in the posterior medial nucleus are an artifact or that such a layer 6 input is seen in the posterior medial nucleus but not in the ventral posterior medial nucleus. It thus seems plausible that the apparent heterogeneity seen in responses activated from layer 6 is an epiphenomenon of our methodology, but we cannot rule out the possibility that synapses from layer 6 corticogeniculate axons include both *category 1* and *2* responses.

We thus conclude that corticogeniculate axons from layer 5 are strictly *category 1* in terms of their responses, whereas most and perhaps all of those from layer 6 are *category 2*, with the possibility that layer 6 might harbor some axons with *category 1* responses as well. This conclusion is consistent with and extends a recent study (Li et al. 2003).

Drivers versus modulators and first- versus higher-order thalamic relays

Sherman and Guillery (1998, 2001) have suggested that inputs to thalamic relay cells can be divided into *drivers* and *modulators*. The drivers are the inputs that deliver the information to be relayed to cortex, whereas the modulators are all other inputs the function of which is to modulate the thalamic relay of driver inputs. Examples of drivers are retinal inputs to the lateral geniculate nucleus and medial lemniscal inputs to the ventral posterior nucleus, and examples of modulators are the brain stem and layer 6 cortical inputs to these nuclei. A number of properties that distinguish drivers from modulators were listed by Sherman and Guillery (1998, 2001).

An extension of this hypothetical framework involved the suggestion that the drivers for many thalamic relays derived from layer 5 of cortex. This divided thalamic relays into two types: *first-order relays*[2] receive drivers from subcortical sources (e.g., the lateral geniculate nucleus and the ventral posterior nuclei, which receive drivers from retina and the medial lemniscus, respectively), and *higher-order relays* receive drivers from cortical layer 5. Thus all thalamic relays receive a modulatory input from layer 6 of cortex, which is mostly feedback, but some in addition receive a feedforward layer 5 driver input. The implication is that first order relays represent the first relay of a particular type of information to cortex (e.g., visual), whereas higher-order relays are part of a cortico-thalamo-cortical stream that represents functional corticocortical communication of information already in cortex, and this can be between a first-order cortical area (e.g., striate cortex) and a higher-order area (e.g., extrastriate cortex) or between higher-order areas (Guillery and Sherman 2002; Sherman and Guillery 2001, 2002).

The key to this concept that higher-order relays exist is that the layer 5 input is a driver. The main logic for this notion is that retinal input to the lateral geniculate nucleus or medial lemniscal input to the ventral posterior nucleus represent prototypical drivers and that these differ significantly from modulatory inputs, such as the layer 6 input. Evidence to date that layer 5 inputs to presumptive higher-order thalamic relays are similar in properties to retinal or medial lemniscal input has been mostly morphological (for details, see Guillery 1995; Sherman and Guillery 1996). Examples of similarities between retinal or medial lemniscal inputs and those from layer 5, when compared with layer 6 inputs, include the following.

- Layer 5 axons are very thick, whereas those of layer 6 are quite thin.
- Layer 5 inputs end in extremely large terminals that form multiple synaptic contacts onto proximal dendrites. Those from layer 6 end in small terminals forming single contacts onto distal dendrites.
- Layer 5 terminals often are involved in triadic synaptic arrangements, whereby the terminal contacts a dendritic terminal of a GABAergic interneuron, and both contact the same relay cell dendrite. Layer 6 terminals are not involved in triadic circuits.
- Layer 5 terminals often are found in complex synaptic zones

[2] We use "thalamic relays" rather than "thalamic nuclei," because some nuclei defined cytoarchitectonically seem to include both first and higher order relays (for details, see Sherman and Guillery 2001, 2002; Guillery and Sherman 2002).

known as glomeruli, whereas those from layer 6 rarely if ever are.

- Layer 5 inputs often branch to innervate extrathalamic subcortical targets but do not innervate the thalamic reticular nucleus. Layer 6 axons branch to innervate the thalamic reticular nucleus but do not innervate extrathalamic targets.
- Layer 5 inputs end in flowery terminal arbors with dense clusters of terminals (type 2 morphology of Guillery 1966), whereas those of layer 6 end in simpler arbors with single terminals attached to the preterminal branch by a short stalk (type 1 of Guillery 1966).
- Retinal and lemniscal inputs to the lateral geniculate and the ventral posterior nuclei do not activate mGluRs, whereas layer 6 inputs to these relays do. Morphological evidence based on immunocytochemistry suggests that layer 5 inputs from the visual cortex to the pulvinar region in rats are not associated with mGluRs, but that the layer 6 inputs to the lateral geniculate nucleus are.

We can now add functional evidence to this list. That is, like the synaptic properties of retinal or medial lemniscal inputs to the lateral geniculate or the ventral posterior nuclei, those of layer 5 inputs to the posterior medial nucleus show *category 1* responses: paired-pulse depression, an all-or-none response, and no evidence of an mGluR component. We thus conclude that the *category 1* responses are those of drivers. In contrast, those of most layer 6 inputs to either the ventral posterior or posterior medial nuclei show *category 2* responses: paired-pulse facilitation, a graded response, and evidence of an mGluR component. We thus conclude that the *category 2* responses are those of modulators. While it is true that some synapses onto cells of the posterior medial nucleus activated from layer 6 show some driver properties, we have argued in the preceding text that these may indeed represent the result of activating axons of passage emanating from layer 5.

The main point here, however, is that inputs to cells of the posterior medial nucleus arising from layer 5 clearly act like drivers based on the data we have obtained. When added to the aforementioned morphological evidence that layer 5 inputs to presumed higher order relays are drivers, this significantly strengthens the case for this assignment and thus strengthens the case for a division of thalamic relays into first and higher orders.

This notion is also consistent with previous studies observing the effects of cortical removal on response properties of the denervated thalamic neurons. In first-order relays that receive only layer 6 input, such as the lateral geniculate nucleus, removal of that input creates only subtle changes in receptive field properties of the thalamic relay cells (Baker and Malpeli 1977; Geisert et al. 1981; Kalil and Chase 1970; McClurkin and Marrocco 1984; McClurkin et al. 1994; Schmielau and Singer 1977). Likewise, removal of the layer 6 input to the ventral posterior nucleus, another first-order relay, creates only very subtle changes in the thalamic response properties (Diamond et al. 1992; Yuan et al. 1986). In contrast, removal of cortical inputs, including those from layer 5, to higher-order relays, has a much more devastating effect on thalamic cells, mostly silencing them. This occurs when cortical input is removed to the pulvinar (Bender 1983; Chalupa 1991) or to the posterior medial nucleus (Diamond et al. 1992).

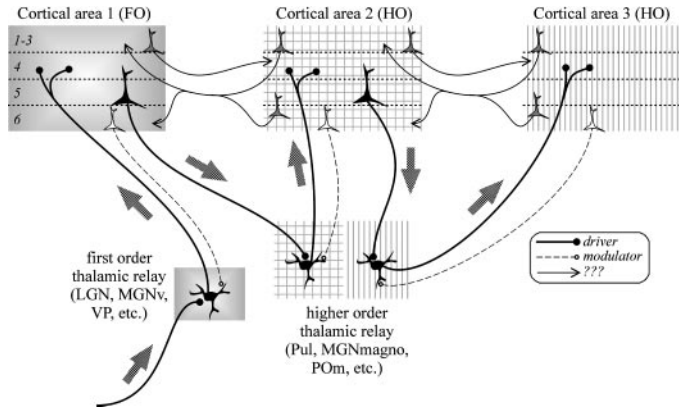

FIG. 12. Model of cortico-thalamo-cortical communication involving higher-order thalamic relays. This hypothesis suggests that information arrives initially at the cortical level after transmission through a 1rst-order (FO) thalamic relay such as the lateral geniculate nucleus, ventral division of the medial geniculate nucleus (MGNv), or medial or lateral VP. Further cortico-cortical communication in addition to or perhaps instead of direct pathways involves transmission via higher-order (HO) thalamic relays, such as the pulvinar (Pul), magnocellular division of the medial geniculate nucleus or the POm. A remaining issue is the identity of direct corticocortical pathways as driver or modulator [for details, see text and Sherman and Guillery (1998, 2001 2002) and Guillery and Sherman (2002)].

Conclusions

SIGNIFICANCE OF SYNAPTIC PROPERTIES. The differences between drivers and modulators in terms of synaptic responses seem consistent with their designation. As suggested previously (Sherman and Guillery 1998), a property of driver input is that it should have a relatively strong postsynaptic effect with relatively little convergence, and the large, all-or-none EPSPs are consistent with this. In contrast, the smaller, graded EPSPs of modulator input suggest that there is considerable convergence that underlies the many subtle modulatory effects that must be achieved.

The presence or absence of an mGluR component is also consistent, and this is related to the sustained EPSPs associated with them. Such EPSPs act like a low-pass temporal filter, which means that fast changes in patterns of input spike trains cannot be reproduced postsynaptically. It thus seems appropriate that a driver input, which is thought to be the route of information flow, should activate only faster EPSPs, thereby maximizing postsynaptic representation of information. However, the sustained EPSPs activated by modulators serve their function well. Not only does this serve to create sustained changes in excitability of the postsynaptic cell, but it also serves to control a number of voltage-gated properties that require such sustained changes in membrane potential; examples are the voltage-gated conductances underlying I_T and I_h (reviewed in Sherman and Guillery 1996, 2001).

The paired-pulse effects are more difficult to understand in this context. It is interesting that paired-pulse depression seems a property not only of driver input to thalamus, as suggested here, but also of thalamic input to cortex (Castro-Alamancos and Connors 1996; Castro-Alamancos and Oldford 2002; Chung et al. 2002). One recent suggestion is that paired-pulse depression plays an important role in information processing by helping the system to adapt to ongoing levels of activity (Chung et al. 2002), and if so, this would be a useful property of driver inputs. The significance of the paired-pulse facilita-

tion seen in the layer 6 modulatory inputs is less clear, and it appears that, for this input, postsynaptic effects are maximal when the modulator input is firing above a certain level. However, while several putative driver inputs (i.e., driver inputs to thalamus and corticothalamic inputs) show consistent paired-pulse depression, we need to determine the paired-pulse effects of more modulatory inputs before suggesting its significance.

IMPLICATIONS OF FINDINGS FOR CORTICOCORTICAL COMMUNICATION. The new data described here add credence to the scheme proposed by Guillery and Sherman for corticocortical processing. Namely, such processing largely and perhaps exclusively involves cortico-thalamo-cortical routes (Guillery 1995; Guillery and Sherman 2002; Sherman and Guillery 1996, 2001, 2002). Figure 12 schematically presents this proposal. This suggests that much and perhaps all of corticocortical processing involves a route via higher-order thalamic relays, such as the pulvinar or posterior medial nucleus, and also raises the question as to the identity of various direct corticocortical projections as driver or modulator. Such a scheme challenges the prevailing view that corticocortical processing is based on direct connections between cortical areas (e.g., DeYoe et al. 1994; Felleman and Van Essen 1991; Kaas 1978, 1987; Preuss et al. 1993; Van Essen 1985; Van Essen and Maunsell 1983; Van Essen et al. 1990, 1992; Zeki and Shipp 1988). For instance, the current view of the functional organization of visual cortical areas is based almost completely on the deduction of information flow via direct corticocortical pathways that establish hierarchical relationships among areas (e.g., Felleman and Van Essen 1991; Van Essen and Maunsell 1983; Van Essen et al. 1990), and part of the challenge we raise is that a consideration of cortico-thalamo-cortical pathways for information flow could radically alter these hierarchical relationships. Another implication of this notion that corticocortical processing relies heavily on cortico-thalamo-cortical pathways is that all information targeted for a cortical area, whether originating in the periphery (e.g., the retina) or another cortical area (e.g., layer 5) benefits from a thalamic relay. That is, just as retinal input is relayed through the lateral geniculate nucleus rather than directly innervating visual cortex, most or all information passed between cortical areas is relayed through the thalamus.

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GRANTS

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