Thalamocortical Specificity and the Synthesis of Sensory Cortical Receptive Fields

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Alonso, Jose-Manuel and Harvey A. Swadlow. Thalamocortical specificity and the synthesis of sensory cortical receptive fields. J Neurophysiol 94: 26–32, 2005, doi:10.1152/jn.01281.2004. A persistent and fundamental question in sensory cortical physiology concerns the manner in which receptive fields of layer-4 neurons are synthesized from their thalamic inputs. According to a hierarchical model proposed more than 40 years ago, simple receptive fields in layer 4 of primary visual cortex originate from the convergence of highly specific thalamocortical inputs (e.g., geniculate inputs with ON-center receptive fields overlap the ON subregions of layer 4 simple cells). Here, we summarize studies in the visual cortex that provide support for this high specificity of thalamic input to visual cortical simple cells. In addition, we review studies of GABAergic interneurons in the somatosensory “barrel” cortex with receptive fields that are generated from single whiskers (Swadlow 1989, 1995). Cytoarchitectonic “barrels” (Woolsey and Van der Loos 1970) are present in young animals of this species (Woolsey et al. 1975) and can be visualized in adults with appropriate staining methods (McMullen et al. 1994). Within the rabbit barrel cortex, thalamic afferents and most cortical neurons are highly selective for the direction of whisker displacement. Despite the directional selectivity of thalamic afferents, a population of layer-4 inhibitory interneurons (suspected inhibitory interneurons, SINs1) shows little or no direction selectivity. Interestingly, these SINs are extremely sensitive to small whisker displacements, much more so than are other cortical neurons (Swadlow 1989, 1995).

Thus, in somatosensory barrel cortex, putative inhibitory interneurons are much more sensitive to peripheral stimulation than are spiny neurons, but they are less selective for the direction of vibrissa displacement. Similarly, in cat visual cortex, inhibitory neurons are generally more sensitive than excitatory neurons to low-contrast stimuli, and some are much less selective to stimulus orientation and/or sign (light or dark). In this review, we argue that these differences in sensitivity/selectivity are the result of diverse, population-specific mechanisms of thalamocortical convergence.

INTRODUCTION

Primary sensory neocortex is characterized by a prominent layer 4, which constitutes the main entrance of sensory information from the thalamus. This layer is the first stage of cortical processing for sensory input and is thus at the center of many studies in perception. Thalamic afferents arborize extensively within layer 4 and make direct contact with both excitatory and inhibitory neurons (see reviews by Sherman and Guillery 2001; White 1989). Although combined morphological and physiological approaches have taught us a great deal about the response properties of excitatory populations, considerably less is known about the response properties of inhibitory interneurons.

In cat visual cortex, most layer-4 cells have simple receptive fields (Ferster and Lindstrom 1983; Gilbert and Wiesel 1979; Hirsch et al. 1998; Kelly and Van Essen 1974; Martin and Whitteridge 1984). In these cells, light and dark stimuli evoke excitatory responses in separate subregions of the receptive field and this spatial arrangement of subregions conveys the property of orientation selectivity (Ferster and Miller 2000; Lampl et al. 2001; Martinez et al. 2002). A smaller proportion of layer-4 cells have complex receptive fields, where light and dark stimuli evoke excitatory responses within the same region of the receptive field. Recently it has been shown that a population of layer-4 inhibitory neurons with such complex receptive fields shows little or no orientation selectivity (Hirsch et al. 2003). Moreover, some inhibitory neurons in cat visual cortex are more sensitive to low stimulus contrast than are excitatory neurons (Contreras and Palmer 2003). These recent findings share striking similarities with results from somatosensory cortex.

The vibrissa representation of rabbit somatosensory cortex is organized into functional columns that are dominated by input from single whiskers (Swadlow 1989, 1995). Cytoarchitectonic “barrels” (Woolsey and Van der Loos 1970) are present in young animals of this species (Woolsey et al. 1975) and can be visualized in adults with appropriate staining methods (McMullen et al. 1994). Within the rabbit barrel cortex, thalamic afferents and most cortical neurons are highly selective for the direction of whisker displacement. Despite the directional selectivity of thalamic afferents, a population of layer-4 inhibitory interneurons (suspected inhibitory interneurons, SINs1) shows little or no direction selectivity. Interestingly, these SINs are extremely sensitive to small whisker displacements, much more so than are other cortical neurons (Swadlow 1989, 1995).

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SPECIFICITY OF THALAMOCORTICAL CONVERGENCE ONTO LAYER-4 SIMPLE CELLS IN CAT VISUAL CORTEX

The exquisite discriminative capacities of mammalian sensory systems are consistent with a high degree of thalamocortical specificity. For example, humans can judge whether a line is located to the left or right of a point of reference with a precision of 5 s of arc—roughly one fifth the width of a single
cone (Westheimer and McKee 1977). This exceedingly high spatial resolution requires not only a large number of small and densely packed photoreceptors but also highly specific connections across the visual pathway—each connection, from the photoreceptor to the visual cortex, is wired with exquisite precision. Traces of this exquisite wiring can be found both at the anatomical and electrophysiological level. Most neurons in LGNd (dorsal lateral geniculate nucleus) receive input from just a few retinal afferents (Levick et al. 1972; Mastronarde 1987; Usrey et al. 1999) and, at the entrance of the visual cortex, each layer-4 neuron is estimated to receive input from just 30 geniculate afferents (Alonso et al. 2001). This is a very small number, given that 360–540 X afferents and 300–540 Y afferents are thought to coexist within a cylinder of cortex of 56-micron diameter (Peters and Payne 1993).

What determines which afferents will connect a given cortical neuron and which ones will not? A series of studies over the past years demonstrate that both the probability and strength of a geniculocortical connection are closely related to the quality of the match in the response properties of the geniculate input and cortical target (Alonso et al. 2001; Reid and Alonso 1995; Tanaka 1983). Figure 1A shows an example of a geniculate cell and a simple cell that were monosynaptically connected as estimated by cross-correlation analysis. The correlogram on the right shows a peak displaced from the zero with a fast rise time that is consistent with a monosynaptic connection from the geniculate cell to the simple cell. At the left, the geniculate receptive field (bottom) and the simple receptive field (top) are shown at 2 different time delays between stimulus and response (ON-responses in red, OFF-responses in blue). The geometry of the 2 receptive fields is clearly different—the geniculate receptive field is round, whereas the cortical receptive field has elongated and parallel subregions. In spite of this important difference, the 2 receptive fields share many features in common. The properties shared by the 2 receptive fields of Figure 1A illustrate the 5 main “rules of connectivity” (Alonso et al. 2001) that characterize most monosynaptic connections between geniculate cells and simple cells.

1) Receptive-field sign: The geniculate center overlaps a simple-cell subregion of the same sign (OFF-geniculate center superimposed with OFF-subregion).

2) Receptive-field position: The peak-to-peak distance between the geniculate center and the simple-cell subregion (in units of subregion width) is less than one along the length of the subregion and less than one half along the subregion width.

3) Time course of the response: The responses of the geniculate cell and the simple cell have similar time courses (e.g., they are strongest at the same 0–25 ms frame). This similarity in response time course is illustrated by the impulse responses shown at the bottom right of Fig. 1A (impulse responses show the response time course of the strongest pixel within each receptive field).

4) Subregion strength: The geniculate center overlaps the strongest subregion of the simple cell.

5) Receptive-field size: The geniculate center’s diameter is similar to the width of the overlapped simple-cell subregion.

These 5 rules of connectivity are listed in order of importance. Cell pairs that do not follow the first 2 rules are rarely connected. However, the last 2 rules give only a slight

FIG. 1. Rules of connectivity between dorsal lateral geniculate nucleus (LGNd) cells and layer-4 simple cells in cat visual cortex. A: example of 2 cells that were monosynaptically connected. Left: receptive fields (OFF-responses in blue, ON-responses in red). Top right: correlogram indicating a monosynaptic connection. Bottom right: response time courses. B: example of 2 cells that were not monosynaptically connected. C: summary of all geniculocortical cell pairs that were monosynaptically connected. Geniculate centers with the same sign as the strongest simple-cell subregion are shown in red and those with the same sign as the flanks in blue. Line thickness indicates connection strength. Data are taken from Reid and Alonso (1995) and Alonso et al. (2001).
increase in the probability of finding a monosynaptic connection. Figure 1B illustrates an example of a cell pair that failed to follow most of these rules. In this case, the geniculate center overlaps a simple-cell subregion of different sign (OFF- superimposed with ON-) that has also different response time course (e.g., the receptive field frame with the strongest response is 0–25 ms for the geniculate cell and 25–50 ms for the simple cell). As would be expected from such a poor match in response properties, the geniculocortical correlogram did not have a narrow peak indicative of a monosynaptic connection (Fig. 1B, top right).

Systematic recordings from cell pairs like those shown in Fig. 1, A and B indicate that the first 2 rules of connectivity are especially important in the wiring of geniculocortical connections (Alonso et al. 2001; Reid and Alonso 1995). Figure 1C illustrates this by showing the receptive fields from all the pairs of geniculate cells and simple cells that were monosynaptically connected. Red circles are the geniculate receptive fields that overlapped the strongest subregion of a simple cell and blue circles the geniculate receptive fields that overlapped a weaker subregion (the thickness of the circle represents the strength of the connection). The high specificity in the connections between geniculate cells and simple cells is very consistent with a hierarchical model of receptive-field generation. According to this model, simple receptive fields are generated by the convergent input of geniculate cells with receptive fields aligned in visual space—the convergence of ON-center geniculate cells generates ON-subregions and the convergence of OFF-center geniculate cells generates OFF-subregions (Hubel and Wiesel 1962).

**Nonspecific Thalamocortical Convergence Onto Layer-4 GABAergic Neurons of Rabbit Barrel Cortex**

SINs of rabbit S1 respond unselectively to the direction of vibrissa displacement, but they are exquisitely sensitive to low-amplitude stimulation, responding at much lower thresholds and higher stimulus frequencies than any other population studied in S1 (Swadlow 1989, 1995). Given the considerable directional specificity seen in most ventrobasal thalamic (VB) inputs to barrel cortex, it is reasonable to ask how the sensitive and broadly tuned receptive fields of inhibitory interneurons are synthesized. This section will review recent evidence indicating that the receptive fields of SINs are the result of a nonspecific convergent input from thalamocortical neurons with different receptive-field properties. This nonspecific thalamocortical connectivity contrasts dramatically with that described above for connections between geniculate cells and simple cells for cat visual cortex.

It is important to emphasize that this convergent thalamocortical connectivity does not imply a lack of topographical specificity. SINs of rabbit barrel cortex receive a functional input only from VB thalamocortical neurons that are in precise topographical alignment, and no functional connectivity is seen when recording sites are misaligned by even a single cortical barrel (Swadlow 1995; Swadlow and Gusev 2002). Moreover, thalamocortical connectivity is seen only for SINs in or very near to layer 4, and not for SINs located in superficial or deep layers. Thus the topography and depth distribution of thalamocortical connectivity onto SINs are highly precise. What is imprecise, and apparently unspecified, is the connectivity between neurons within a VB barreloid and SINs of the precisely aligned S1 barrel.

Evidence in support of a highly convergent/divergent thalamocortical connectivity to S1 SINs of rabbit S1 was initially provided by cross-correlation studies showing that a high proportion of topographically aligned thalamocortical–SIN pairs were functionally connected (Swadlow 1995). This result implies a similarly high degree of divergence and convergence in the functional connectivity of topographically aligned thalamocortical neurons and S1 SINs, and has also been recently confirmed for putative interneurons in rat barrel cortex (Bruno and Simons 2002). In the above studies, however, only single thalamocortical neurons were studied with single SINs. To examine this more directly, simultaneous recordings were obtained from multiple thalamocortical neurons of the same VB barreloid and from multiple SINs of the aligned barrel (Swadlow and Gusev 2002). To examine thalamocortical convergence, SINs were identified and studied simultaneously with 2–4 aligned thalamocortical neurons. Most of these SINs (24/29) received functional input from at least one half of the topographically aligned thalamocortical neurons that were studied (mean = 65% of the thalamocortical neurons tested). Figure 2A illustrates such convergent input, where one SIN was studied with 3 aligned thalamocortical neurons. All 3 thalamocortical neurons showed clear functional connectivity with the SIN, generating significant peaks in SIN spike frequency at intervals of 1.4–1.8 ms after thalamic spikes. This is an especially interesting case because each of the thalamocortical neurons showed strong directional selectivity, but these preferred directions differed over a range of 135°. The SIN responded equally to all directions of vibrissa displacement.

This strong convergence from thalamocortical neurons onto S1 SINs implies a high degree of divergence from single thalamic neurons to multiple SINs. To analyze this functional divergence, thalamocortical neurons were identified and studied simultaneously with 2–9 topographically aligned SINs (Swadlow and Gusev 2002). Nearly all of the thalamocortical neurons (26/28) showed functional connectivity with at least one half of the SINs studied in the topographically aligned S1 barrel. A remarkable instance of thalamocortical divergence is shown in Fig. 2B. Here, a single thalamocortical neuron (dubbed “Hercules” because of the potent connectivity) was studied with 9 different SINs over a 4-day period. Hercules had 2 “signature” features that ensured that the same neuron was under study on the successive recording days: 1) the spike train was unusually “bursty,” yielding autocorrelograms with unusual and distinctive sidebands that were stable over days, and 2) the receptive field was plotted several times each day, and this field was characteristic of only a small subset of thalamocortical neurons (transient response to only a single whisker,

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2 GABAergic interneurons display remarkable heterogeneity in their morphology, biochemistry, and membrane properties (Fairen et al. 1984; Gupta et al. 2000; Houser et al. 1983; Kawaguchi and Kubota 1997; Markram et al. 2004). In sensory neocortex about one half of GABAergic neurons express parvalbumen, and this proportion is even higher in layer 4 (Amitai et al. 2002; Ren et al. 1992). Within layer 4, these cells are usually fast-spiking (Amitai et al. 2002; Beierlein et al. 2003) and can be electrically coupled (Galarreta and Hestrin 1999; Gibson et al. 1999).
strongly directionally selective in a downward and back direction). Figure 2B illustrates the functional contacts made by Hercules with each of the SINs studied, and associated cross-correlograms are shown to the right. Each correlogram showed a significant peak in SIN spike discharge rate at intervals of 1.2–1.9 ms after the thalamic spike. The functional input provided by Hercules to SINs of the aligned S1 barrel was not only remarkably widespread (9/9 SINs studied) but was also extremely potent.

**A ROLE FOR POPULATION-RELATED DIVERSITY OF THALAMOCORTICAL SPECIFICITY**

In both visual and somatosensory systems, there is a considerable diversity in the response properties of layer-4 neurons. Here, we propose that some elements of this diversity result from differences in the specificity with which thalamocortical terminals make synaptic contacts onto neurons of layer 4. Moreover, we suggest that the degree of thalamocortical specificity is related to the selectivity, sensitivity, and reliability of the postsynaptic neuronal response.

A high degree of geniculocortical specificity onto layer-4 simple cells is an inherent feature of the hierarchical model of Hubel and Wiesel (1962). Although this model is still a focus of active debate (Ben-Yishai et al. 1995; Douglas et al. 1995; Monier et al. 2003; Shapley et al. 2003; Somers et al. 1995), it is clear that few LGNd afferents contact a layer-4 simple cell (Peters and Payne 1993; Reid and Alonso 1995; Tanaka 1983) and that these connections follow a set of very specific rules (Alonso et al. 2001; Reid and Alonso 1995; but see Ringach 2004 for an alternative view). Moreover, the receptive field geometry and orientation selectivity of a layer-4 simple cell can be explained in great part by the convergence of these few LGNd afferents (Chung and Ferster 1998; Ferster et al. 1996; Hirsch et al. 1998; Lampl et al. 2001; Martinez et al. 2002).

Evidence for specificity of thalamocortical connections onto layer-4 spiny neurons has also been obtained in rat barrel cortex. In this system, VB thalamocortical neurons are less likely to provide a functional input to layer-4 “regular spiking” neurons, than to “fast-spiking” neurons, but connected VB–regular-spiking pairs are better matched for directional preference (Bruno and Simons 2002). Moreover, Miller et al. (2001b) reported considerable specificity in the connectivity from auditory thalamic nuclei to primary auditory cortex. Although the recipient cell types were not specified in this latter system, it is likely that most were spiny neurons, given the predominance of excitatory neurons in neocortical tissue. Together, these results strongly support the proposal of a high degree of thalamocortical specificity onto spiny neurons of sensory cortical layer 4. In contrast to the above model, SINs receive highly convergent/divergent input from large numbers of thalamocortical afferents. Such connectivity is reminiscent
of an early neural network proposed by Griffith\(^3\) that he called a “complete transmission line” (Griffith 1963). In this scheme of serially connected layers, all elements of the first layer excite all elements of the second. Such networks are characterized by highly sensitive\(^4\) and reliable transmission, but they must sacrifice any differences in selectivity among the elements of the first layer (what Griffith called “complexity of task”). The “complete transmission line” of Griffith is very consistent with the properties of SINs. These neurons have very low thresholds, respond with great reliability to a wide range of stimulus frequencies, and have sacrificed “complexity of task” in that they lack directional selectivity, a property seen in most of their thalamocortical afferents.

It is noteworthy that populations of SINs with response properties similar to those found in barrel cortex have been documented in numerous regions of the rabbit neocortex. In both the second somatosensory cortex and in motor cortex, for example, SINs reliably follow much higher stimulus frequencies than do efferent populations (Swadlow 1994, 1991). In rabbit primary visual cortex, whereas most identified efferent (spiny) neurons show both orientation and directional selectivity (as in the cat), SINs respond to light and dark stimuli within the same region of the receptive field and lack orientation and direction selectivity (Swadlow 1988; Swadlow and Weyand 1987).

Until recently, it was not clear whether GABAergic interneurons with properties similar to SINs (highly sensitive and broadly tuned) existed in the cat visual cortex. Miller and colleagues (Lauritzen and Miller 2003) strongly argued that such neurons were necessary to explain many of the response properties of layer-4 simple cells. Recently, Hirsch et al. (2003) identified a class of layer-4 inhibitory neurons, which lack orientation selectivity and have complex receptive fields (i.e., light and dark stimuli evoke responses within the same region). Moreover, in another recent study of cat visual cortex, Contreras and Palmer (2003) demonstrated that inhibitory neurons are generally more sensitive to stimulus contrast than excitatory neurons. Taken together, these studies indicate that layer 4 of cat and rabbit sensory cortices share a type of inhibitory neuron that is highly sensitive and poorly selective (see also Bruno and Simons 2002 for similar results in rodents, a third mammalian order). We propose that such broadband feed-forward inhibitory interneurons are a common element in layer 4 of sensory neocortex. Figure 3 illustrates our view of how differences in the specificity of thalamocortical connections generate 2 types of cortical receptive fields in 2 types of neurons: highly sensitive, broadband inhibitory neurons and less-sensitive narrowband excitatory neurons. Broadband inhibitory neurons receive highly convergent thalamocortical input, whereas narrowband excitatory neurons receive highly specific thalamic inputs.\(^5\)

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\(^3\) In addition to his seminal theoretical work on the concept of protein self-replication (prions; Griffith 1967), Griffith made early contributions to neural network theory (for discussion see also Abeles 1991).

\(^4\) In a “complete transmission line,” high sensitivity results because each output neuron can be driven by the most sensitive of the many converging input neurons. Alternative mechanisms for generating sensitivity are, of course, possible (e.g., powerful input from even a single, ultrasensitive, input neuron).

\(^5\) It is important to note that our argument does not imply that all inhibitory interneurons are of the broadband variety. Indeed in cat visual cortex many layer-4 inhibitory neurons have simple receptive fields and sharp orientation tuning. A considerable body of theoretical work suggests that a highly sensitive, broadband, feed-forward inhibitory population could serve to enhance the discriminative abilities of these excitatory neurons, both in spatial and temporal domains. For example, Miller and colleagues (Lauritzen and Miller 2003; see also Miller 2003; Miller et al. 2001a) proposed that a broadly tuned feed-forward inhibition could, in V1 simple cells, maintain orientation tuning over a wide range of orientation tuning (Azouz et al. 1997; Hirsch et al. 2003). These “selective” inhibitory neurons are likely to be important in the generation of subregion antagonism in the layer-4 simple receptive field (Ferster 1986; Hirsch et al. 1998; Tolhurst and Dean 1987). Conversely, we cannot exclude the possibility that some classes of excitatory neurons receive convergent nonspecific thalamocortical input, although there is little experimental evidence supporting this.
of stimulus contrasts. Similarly, in the somatosensory cortex of rabbits and rodents, fast and potent feed-forward inhibition is thought to sharpen the responses of recipient spiny cells in both spatial and temporal domains (Pinto et al. 2003; Swadlow 2003). In summary, we propose that different modes of connectional specificity in the thalamocortical pathway are associated with separate populations of excitatory and inhibitory neurons that differ in their selectivity and sensitivity to sensory stimuli. The presence of corresponding fast-spike GABAergic populations within both the somatosensory and visual cortex suggests that these connectional strategies may reflect a general feature of sensory neocortex.

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References


