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Extraretinal Inputs and Feedback Mechanisms to the Lateral Geniculate Nucleus (LGN)

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7.1 Introduction

Walker argued that the thalamus holds 'the secret of much that goes on in the cerebral cortex' (Walker, 1938). The thalamus is the first point at which most sensory signals arriving from the periphery can be modified by the rest of the brain. Therefore, the essence of what thalamic sensory relays do lies not so much in the quality of the sensory signals that they receive from the periphery but in how those signals are modified on their way to cortex and how these signals contribute to the survival of the organism. Given this perspective, it is surprising how little we actually know about the functional roles of the many modulatory signals that regulate the flow of sensory inputs to cortex. There may be several reasons why the role or roles of thalamic sensory relay nuclei remain unclear. One reason simply could be that most studies of thalamic cell properties have been performed in anesthetized preparations where modulatory inputs are likely not operating or are actively being blocked by the anesthetic. A second reason may be conceptual, namely, the idea that sensory thalamic cells must faithfully represent the periphery in order for percepts to be built up in cortex via a strictly feedforward pathway. The latter view tightly constrains possible roles for modulatory pathways and argues against the value of looking actively for the modifications of sensory signals that may occur at the level of the thalamus as a result of inputs that come via routes other than directly from the periphery especially via feedback from cortex. Finally, the assumption that basic sensory messages sent by thalamic cells can be decoded simply by examining

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the average firing rate of one cell at a time may have turned attention away from evidence that modulatory pathways can impact the temporal structure of firing of many cells that send convergent and divergent signals to cortex: signals that likely also carry important messages about the significance of sensory information.

In this chapter we focus on the best known of sensory 'relay' nucleus in the thalamus, the lateral geniculate nucleus (LGN). The aim is to review what is known about non-retinal inputs to the LGN in an effort to link these inputs to the function or functions of this nucleus. The goal is not to provide a global overview of LGN structure and function since this has been covered in detail in a number of older as well as recent reviews (Casagrande and Norton, 1991; Sherman and Guillery, 1996, 2001; Hendry and Reid, 2000; Casagrande and Xu, 2004) in addition to contributions to this book (Chapter 6). Instead, the goal is to briefly cover the essential features of LGN structure and circuitry. The bulk of the chapter explores what is known about extraretinal inputs to the LGN and what questions remain about the modulation of visual signals at this level. Given that species differ in the organization of their visual pathways and their LGN organization in particular, this chapter stresses the primate LGN. Since much more research has been done on the LGN of carnivores (especially cats) than on primates, information on other species is also covered where unavailable in primates.

In the past, it has been common to emphasize the feedforward nature of sensory signals. In this model, information goes from retina through the LGN to higher and higher levels of cortex to construct percepts which are then utilized for 'action'. Instead, in this chapter we emphasize the dynamic nature of the system and the importance of feedback pathways. Although the LGN can be considered an early component in the feedforward visual hierarchy, it also can be considered to be at the highest level of the feedback hierarchy. Clearly in awake animals vision is an active process. The visual system is never a one-way street. Each view of the world is the result of a purposeful decision to move the head and eyes to a location to acquire new information. This decision presumably occurs through a combination of pathways including higher cortical areas involved with memory, planning, and decision making, as well as limbic circuits that add emotional tone and motivation. To be efficient for survival the system must acquire essential information quickly and screen out irrelevant material. If an animal is searching for food, then it would make sense to pay attention to the locations where the food is normally found, its size, shape, and other characteristics such as whether it is moving or stationary. If an animal is simultaneously avoiding predators, it is essential that relevant characteristics of such predators also remain available and that information from different sensory modalities be organized to either enhance or inhibit each other depending upon the circumstances such as looking in the direction of the sounds made by prey or predator. Flooding the system with irrelevant sensory detail is wasteful and potentially dangerous in terms of the animal's survival. In this chapter, we argue that the LGN is actively involved in the selection process and receives constant feedback input from cortex directly or indirectly through the midbrain and brainstem, feedback that regulates which retinal signals reach cortex and which are enhanced or suppressed. We further argue that as early as the LGN the visual system is biased and that these biases are never fixed but are dynamically updated moment to moment.

This review is divided into five sections including the introduction. In section 7.2 we provide an overview of LGN cell types and introduce the basic circuitry. It is

important to appreciate the basic circuitry to understand the ways extraretinal inputs can modify signals. In section 7.3 we consider the spatial and temporal response properties of individual LGN cells. The purpose here is not to provide a detailed review (Chapter 6) but to introduce the framework against which any modulatory pathway to the LGN must act to have an impact at the next stage of processing in cortex. In section 7.4 we review the circuitry, organization, and possible functions of non-retinal inputs. In the final section we provide a brief summary of key points reviewed in this chapter and list some unanswered questions.

7.2 Cell types and basic circuitry of the LGN

In primates the LGN consists of two principal cell types, relay cells which contain glutamate and send axons mainly to primary visual cortex (V1), and interneurons which contain gamma-aminobutyric acid (GABA) and communicate with other cells in the LGN itself (Casagrande and Ichida, 2002a). Eighty percent of cells in the LGN are relay cells and these cells consist of several classes which are organized into layers (Chapter 6; Conley *et al.*, 1985).

Unlike relay cells, the interneurons of the LGN are scattered relatively evenly throughout the nucleus. These neurons also are morphologically distinct having very thin dendrites which are purported to extend long distances in macaque monkey LGN (Wilson and Hendrickson, 1988). Whether one or several types of LGN interneurons exist in primates remains unclear, but all contain GABA. Given that there exists evidence for two types of LGN interneurons in cat LGN (Bickford *et al.*, 1999) and that there are many classes of interneurons in visual cortex (Hendry *et al.*, 1994) and other areas of the brain, it is likely that LGN interneurons in primates will also eventually be divided into subtypes. The LGN interneurons mainly communicate via dendro-dendritic synapses with relay cells (see also below). The size and extent of the thin branching dendrites of LGN interneurons and the fact that they are presynaptic have led to the proposal that the dendritic compartments may form circuits that are independent of the soma/axonal communication network of the cell (Bloomfield and Sherman, 1989; Erisir *et al.*, 1998). Since there is some evidence in cats (Bloomfield and Sherman, 1989; Erisir *et al.*, 1998) that LGN interneurons also communicate with relay cells via their axons (no axons were identified in reconstructed interneurons in monkeys; Wilson, 1986), this means that one interneuron could communicate different messages to different relay cells simultaneously via different dendrites and via their axons.

LGN relay cells and interneurons receive many inputs as described below. Before considering the complexities of all of these connections, it is worth initially laying out the basic circuitry. Both LGN relay cells and interneurons respond primarily on the basis of the information they receive from the retina. Sherman and Guillery (2001) have made the distinction between *drivers* and *modulators*, with drivers being essential to the response of a cell measured primarily via extracellular single unit recording of action potentials. Basically they argue that 'drivers are the information bearing input . . . to cortex' (Sherman and Guillery, 2001, p. 572). According to this distinction, retinal inputs are the main drivers for most LGN relay cells and interneurons. Given the long latency to respond to chiasm stimulation on the part of some koniocellular (KC) LGN relay

cells (maybe also their associated interneurons), it has been speculated that some KC cells could receive their main 'drive' indirectly from the retina via the superior colliculus (Norton and Casagrande, 1982; Casagrande, 1994). This hypothesis remains to be tested empirically. Regardless, if the retina provides the main drive to the vast majority of LGN cells, then all other inputs to the LGN are, by definition, modulators. The problem with this definition in terms of information processing in the LGN, however, is that it assumes that the other pathways are not carrying essential information. LGN cells are never silent, so if a modulatory input causes changes in the spontaneous spike production of LGN cells in the absence of direct retinal input, does this modulator then act as a 'driver' if it is carrying information relative to another modality or when the LGN is active while subjects imagine a visual scene? For example, we know that LGN cells of all classes can be modulated by auditory and somatosensory input and by eye movements in the absence of visual input (Irvin *et al.*, 1986; Royal *et al.*, 2005). Regardless, it is obvious in the case of the LGN that visual receptive fields (both relay cells and interneurons) in awake animals derive their signature receptive field structure (defined by extracellular recording) from their retinal inputs (Chapter 6). Retinogeniculate axons end as large terminals that make multiple synapses on the proximal dendrites of relay cells and on the cell body as well as proximal and distal dendrites of interneurons (Pasik *et al.*, 1986; Wilson, 1986). In addition, relay cells receive *feedforward inhibition* from interneurons via dendro-dendritic synapses that often occur in 'triadic' assemblies where a retinal terminal contacts both an LGN relay cell and a presynaptic dendrite of an interneuron that, in turn, synapses on the same relay cell dendrite (Sherman and Guillery, 2001). In macaque monkeys triads appear to be common in the magnocellular (MC) layers and much rarer in the parvocellular (PC) layers (Wilson, 1993), suggesting a difference in the impact of inhibitory interneurons between these cell classes in primates. Relay cells also project a collateral axon to the thalamic reticular nucleus (TRN) whose cells provide *feedback inhibition* to all LGN cell classes (see following sections for details).

7.3 Response properties: A brief overview

Since the seminal work of Wiesel and Hubel (1966) we have known that LGN cells have visual receptive field properties that are similar to their retinal ganglion cell inputs. It is not the purpose of this section to review, in detail, the spatial and temporal structure of LGN receptive fields (for review, see Casagrande and Norton, 1991; Chapter 6). Instead, we simply summarize information that is basic to understanding the potential impact of extraretinal signals in an effort to unravel their functional messages. LGN cells are never silent even when animals are placed in a dark room or are asleep. These cells are spontaneously active, so even without a visual message these cells will have a differential effect on cortical cells by resetting levels of depolarization in V1 and thereby changing the thresholds of V1 cells. The relative state of LGN cells also affects the visual message sent to cortex since burst and tonic, non-rhythmic and various rhythmic modes can transmit information differently (see below). Different cell classes also respond to stimuli with very different latencies (Irvin *et al.*, 1986; Schmolesky *et al.*, 1998; Royal *et al.*, 2004) and different levels of transience. The timing of these messages to cortex will, of course, be critical in determining which V1 cortical cells reach threshold, which messages are

combined, and when and what messages are sent to the next level, or how messages are combined with feedback from higher visual areas in a dynamic network. Within this context the relevant properties of LGN cells are described in the following sections.

7.3.1 Spatial properties

In anesthetized and paralyzed primates the majority of MC, PC, and KC LGN cells have been shown to have center/surround organizations that can be modeled by a Difference of Gaussians (DoG) model (Norton *et al.*, 1988; Irvin *et al.*, 1993; Xu *et al.*, 2002; Chapter 6). Using this model, one can compare also the receptive field structure of ganglion cells that provide input to the receptive field structure of LGN cells. Comparison suggests that either the surround of LGN cells is stronger or the center response weaker presumably because of the addition of feedforward and feedback inhibition in the LGN. The net result also is that the proportion of spikes produced by an LGN cell is generally less than that produced by the ganglion cell input to that cell (i.e. the transfer ratio is less than 1.0) (Casagrande and Norton, 1991). Examining the transfer ratio and modeling the spatial receptive field of LGN cells is useful in understanding the impact of other inputs to these cells (Uhlrich *et al.*, 1995). Viewed from the perspective of the DoG model, extraretinal inputs can impact the structure of the receptive field by either changing the gain or space constant of the inhibitory surround mechanism or changing the gain or space constant of the excitatory center mechanism. Of course, the output of many LGN cells is combined to drive cortical cells and these LGN cells are, in turn, dynamically linked to each other through feedback from cortex and input from other areas. This means that stimuli presented elsewhere in space outside of the classical single LGN receptive field can potentially impact the spatial structure of the receptive field and/or the transfer ratio of signals from retina. The fact that LGN ensembles, not single cells, encode information utilized by cortex is attested to by results showing that natural scenes with recognizable moving objects could be reconstructed from six to eight pairs of ON- and OFF- center LGN cells per point in space using a simple decoding algorithm applied to the population (Stanley *et al.*, 1999).

7.3.2 Temporal properties

It is clear that what is communicated to cortex by the LGN will depend on the postsynaptic impact of spikes produced by these cells in relationship to the state of the recipient cortical cell. Many LGN cells also communicate with each individual V1 cell; therefore, how the spikes are packaged across time within each LGN cell and how these spikes are synchronized across LGN cells will define the postsynaptic response in V1 and beyond. Both LGN relay cells and interneurons have many voltage-dependent channels that control various currents including both high and low threshold Ca^{2+} conductances, K^+ conductances, and Na^+ conductances (Hernandez-Cruz and Pape, 1989). Depending upon the circumstances, relay cells tend to adopt two basic modes of firing referred to as burst and tonic. During tonic firing, action potentials of relay cells are triggered to more faithfully reflect the temporal sequence of retinal inputs. During burst firing, activation of Ca^{2+} spikes in response to retinal input can trigger several action potentials, and the ratio is no longer one-to-one (Sherman and Guillery, 1996, 1998, 2002 [Fig. 3]). These two modes of firing are controlled by a transient (T) type calcium current (I_T). When relay cells are hyperpolarized

below −70 mV for approximately 100 ms, I_T is slowly de-inactivated. The following suprathreshold depolarization or excitatory post-synaptic potential (EPSP) above −70 mV then activates I_T which produces an all-or-none Ca^{2+} spike called a 'low threshold Ca^{2+} spike' (Ramcharan *et al.*, 2000). The amplitude of the Ca^{2+} spike depends on the magnitude and the length of the preceding hyper-polarization. Depolarization (inactivation of I_T) and hyperpolarization (de-inactivation of I_T) are the key processes for switching the firing of LGN cells between tonic and burst modes (Hillenbrand and van Hemmen, 2001; Guillery and Sherman, 2002). Inactivation or de-inactivation of I_T depends on the duration of the sustained membrane potentials. Sustained membrane potentials require slow-responding receptors. In the LGN, neurotransmitters act on either ionotropic or metabotropic receptors at postsynaptic terminals. Ionotropic receptors include glutamate-responsive AMPA and NMDA receptors, $GABA_A$ receptors, and nicotinic receptors (see also below). Metabotropic receptors include glutamine receptors (mGLURs 1–8), $GABA_B$ receptors, and acetylcholine M1 and M2 receptors. Ionotropic receptors respond with a fast postsynaptic potential, but the metabotropic receptors act through second messengers and so are much slower (Coutinho and Knopfel, 2002; Salt, 2002). The slow and sustained actions of the metabotropic receptors are necessary for inactivation or de-inactivation of I_T. Interestingly, whereas all retinal inputs to LGN relay cells act on ionotropic receptors, other inputs activate both ionotropic and metabotropic receptors, suggesting that extraretinal inputs play a role in switching between burst and tonic modes of firing. Since burst firing is more effective in causing cortical spikes than tonic firing (Swadlow and Gusev, 2001) and tonic firing more faithfully represents the retinal input message, Sherman has suggested that burst mode in the LGN of awake animals acts as a 'wake-up call' for detection of novel stimuli whereas tonic mode transmits information about stimulus quality. The difficulty with this hypothesis is that bursts occur very rarely in behaving primates that are engaged in routine visual tasks (Royal *et al.*, 2003). On the other hand, bursts are common in sleeping animals and it has been argued that their main function is to disconnect thalamus from cortex when animals are asleep (McCormick and Prince, 1986; Steriade and Llinás, 1988). The timing of oscillatory bursts of activity or the general synchronization of activity between LGN and cortex may also be involved in coordinating the effectiveness of messages within the visual network as suggested by various investigators (Sillito and Jones, 2002; Worgotter *et al.*, 2002).

Regardless, it is clear that different messages may be conveyed to cortex depending upon the temporal structure of the spike train (see also Dan *et al.*, 1998; Usrey and Reid, 1999). The same holds true whether or not LGN cells are conveying visual messages or other non-visual messages concerning the animal's state.

7.4 Organization of extraretinal inputs

The extraretinal inputs to the LGN far outnumber, in terms of synapses, the retinal input (Wilson and Forestner, 1995). From the standpoint of function, it is important to appreciate how these inputs are organized (Figure 7.1). Clearly, if an input is visuotopic and specific to certain layers or cell types, it will be a position to regulate those signals locally. A number of inputs fall within this category although their relative visuotopic specificity varies. These inputs include glutamatergic projections from visual cortical areas and

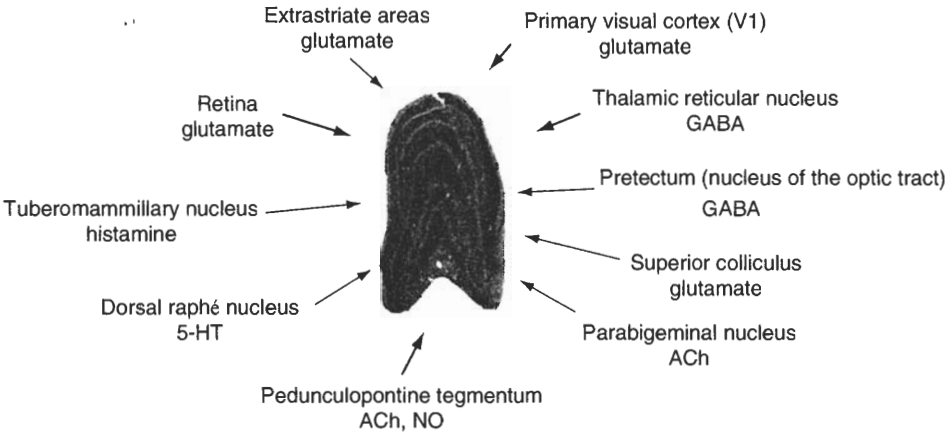

Figure 7.1 Organization of the LGN inputs in primates. The figure shows the known inputs to the LGN in primates. For simplicity, we did not show the input to relay cells and interneurons separately. Arrows indicate the relative weight of the inputs. Transmitters are shown with the name of the input. See text for details. GABA: gamma-aminobutyric acid; ACh: acetylcholine; 5-HT: serotonin; NO: nitric oxide

from the superior colliculus, GABAergic inputs from the pretectum (see also Chapter 8) and TRN, and possibly the cholinergic parabigeminal input. An input could also show a restricted distribution but relate to another type of mapping dimension other than vision. The cholinergic inputs from the pedunculopontine area appear to be of this type. Finally, extraretinal inputs can regulate LGN signals very globally via non-synaptic release of transmitter. The histaminergic and serotonergic inputs to the LGN from the hypothalamus and the brainstem, respectively, fall into this last category. In the following sections we consider the organization and possible functions of each of these inputs in more detail.

7.4.1 Visuotopically organized glutamatergic inputs

Visual cortex (V1 and other cortical areas)

Primary visual cortex (e.g. striate cortex, area 17 or V1) provides the major extraretinal input to the LGN in all species where this input has been examined (see for review Sherman and Guillery, 1996). As in other species, in primates the V1 input to LGN arises in cortical layer 6 (Lund *et al.*, 1975; Conley and Raczkowski, 1990; Fitzpatrick *et al.*, 1994; Casagrande and Ichida, 2002b). Unlike in cats, however, this input to the LGN appears to be more precise both in terms of its visuotopic relationship to the LGN and in terms of the regulation of individual cell classes and layers (Ichida and Casagrande, 2002). For example, in owl monkeys, bush babies, and macaque monkeys, anatomical studies indicate that V1 axons never innervate *both* PC and MC LGN cell layers and that cortical cells that give rise to these axons tend to be segregated to the upper and lower portions of layer VI, respectively (Lund *et al.*, 1975; Conley and Raczkowski, 1990; Fitzpatrick *et al.*, 1994; Ichida and Casagrande, 2002). The situation for KC cells appears different in that KC cells that lie near MC LGN cells receive input from the same cells that innervate MC cells via collateral axons, while KC cells that lie near PC LGN cells

share cortical input with neighboring LGN PC cells (Ichida and Casagrande, 2002). Axon reconstructions also suggest that some axons innervate only single eye-specific LGN layers, at least in owl monkeys (Ichida and Casagrande, 2002). At the level of the LGN electron microscopic (EM) immunocytochemical studies indicate that cortico-geniculate axons (which themselves contain glutamate) innervate primarily glutamatergic relay cells and not GABAergic interneurons, suggesting that their primary initial effect is excitatory (Ichida *et al.*, 2004). Taken together, these patterns of cortico-geniculate projections in primates suggest that V1 can modulate activity in the LGN in both a functionally and a retinotopically specific manner in relationship to other input pathways (see also below). It is noteworthy, however, that since V1 receives feedback from a number of higher-order visual cortical areas and sends axons to a number of other subcortical sites that, in turn, send input to the LGN, the functional impact of V1 on LGN activity likely is complex and context-dependent.

Studies in other species, particularly rats, cats, and ferrets, indicate that signals provided to the LGN from visual cortex can be regulated in complex ways depending upon the types of receptors that are activated. When cortico-geniculate projections are active, both fast and slow EPSPs have been identified in the LGN. In cats, slow EPSPs are reduced when glutamate metabotropic receptor (mGluR) antagonists are applied, suggesting that cortical inputs to the LGN activate metabotropic glutamate receptors which, in turn, act more slowly since, as mentioned earlier, second messengers are involved (von Krosigk *et al.*, 1999). Fast EPSPs in cat LGN are mediated by the actions of the ionotropic glutamate receptors (iGluRs) in addition to NMDA and non-NMDA receptors (Godwin *et al.*, 1996a).

Two types of mGluRs have been identified in LGNs of non-primates: mGluR1s that are located in the cortical recipient zone of relay cell distal dendrites and mGluR5s that are found in association with interneuronal dendrites and on proximal dendrites where retinal inputs can terminate (Godwin *et al.*, 1996a). Also, mGluR1s in the LGN are activated in response to cortical inputs (Turner and Salt, 2000) and cortical inputs have been reported to be the sole activators of mGluR1 in cat LGN (Godwin *et al.*, 1996b). Since both cortical and retinal inputs are glutamatergic, unique localization of mGluR1and mGluR5 on dendrites may allow relay cells to respond only to the specific source of inputs (Godwin *et al.*, 1996a). One function of this arrangement may be to regulate the temporal properties of LGN cells. Recently Eyding *et al.* (2003) selectively eliminated cortico-geniculate neurons in cats in order to test the hypothesis that this pathway was important in synchronizing LGN and cortical signals. The neurons in the LGN fire in burst mode when animals exhibit a synchronized electro encephalographic (EEG) state. When the EEG state changes to a desynchronized state indicative of wakefulness, the same LGN neurons respond in tonic mode. Upon elimination of the cortico-geniculate projections, LGN neurons no longer switch to tonic mode to match the change in EEG state. Furthermore, the synchronized EEG state no longer induces higher incidents of burst firing (Eyding *et al.*, 2003). Cooling of the cortex also has been shown to cause LGN relay cells to remain in tonic firing mode (Worgotter *et al.*, 2002). In another experiment, an mGluR1 antagonist was applied to LGN relay cells. As a result low-threshold Ca^{2+} spikes were abolished, and the response mode was shifted from burst to tonic (Godwin *et al.*, 1996b). These findings indicate that cortical inputs influence the firing mode of LGN relay cells. When mGluRs are activated, the potassium leak

channels close, leading to depolarization and a shift in firing mode from burst to tonic. On the other hand, when $GABA_B$ receptors are activated, the potassium leak channels open generating hyperpolarization (Hillenbrand and van Hemmen, 2001). It still remains to be demonstrated whether the effects seen in the cat can be translated directly to the primate LGN.

In addition to inputs from V1, it is known that other primate visual areas, including the second (V2), middle temporal (MT), and dorsal-lateral (DL) visual areas (also called V4 and V5), provide a minor input to the LGN as demonstrated in several primate species (Symonds and Kaas, 1978; Graham *et al.*, 1979; Benevento and Yoshida, 1981). Interestingly, the latter appear to target specifically the LGN KC layers for reasons that remain unclear.

Feedback from cortex to the LGN has been suggested to play a variety of roles. In the spatial domain it has been proposed that feedback enhances the contrast gain of PC and MC cells (Przybyszewski *et al.*, 2000), is involved in both global integration (binding) of visual features and segmentation (Sillito and Jones, 2002), and is critical to binocular integration for stereo vision (McIlwain, 1995). In the temporal domain it has been argued that feedback synchronizes the firing of relay cells (Sillito *et al.*, 1994) as well as changing firing from burst to tonic mode (see above). It is clear that given the topographic specificity of V1 to LGN projections this pathway also may be involved in independently regulating different classes of LGN cells as well.

Superior colliculus

The superficial grey layer of superior colliculus sends topographically restricted axons to the LGN in all species that have been studied (Harting *et al.*, 1991a; Feig and Harting, 1994). This collicular input can be found within all KC layers in macaques and bush babies (Harting, 1977; Harting *et al.*, 1991a; Lachica and Casagrande, 1993; Feig and Harting, 1994). In strepsirrhine primates (bush babies) axon reconstruction studies provide evidence for two classes of axons that project from the colliculus to the LGN KC layers. Although both types of collicular axons terminate within restricted zones, the spread of colliculogeniculate arbors is somewhat broader than retinal input to KC cells. At the ultra-structural level, both collicular and retinal inputs to LGN KC cells terminate as asymmetric synapses very close together on distal dendrites, suggesting that visual drive to some KC LGN cells may arise indirectly from the colliculus or that visual drive to these cells requires a combination of retinal and collicular inputs to reach threshold (Feig and Harting, 1994). In cats, data indicate that colliculogeniculate axons contain glutamate which is consistent with ultra-structural evidence in both cats and primates (Feig and Harting, 1994). Since the superior colliculus also is connected reciprocally with the parabigeminal nucleus and both the colliculus and the parabigeminal nucleus favor the KC LGN layers as targets in all species studied, it could be that these inputs provide information about eye movements (Sherk, 1979; see also below and Chapter 8). Additionally, since the superficial layers of the superior colliculus have been implicated as important in visual attention (Wurtz *et al.*, 1982; Newsome, 1996), it also has been suggested that information about attentional shifts might be carried to cortex from the colliculus via LGN KC cells (Casagrande, 1994). Recent evidence, however, indicates that MC, PC, and KC LGN cells can all be modulated by attention in awake behaving macaque monkeys (Royal *et al.*, 2004).

7.4.2 Visuotopically organized gabaergic inputs

Pretectum (nucleus of the optic tract)

In macaque monkeys and bush babies, pretectal input to the LGN arises from the nucleus of the optic tract (NOT; Chapter 8). In cats, pretectal input is GABAergic and terminates primarily in the A layers (e.g. on X- and Y-cells) of the LGN (Cucchiaro *et al.*, 1991; Wahle *et al.*, 1994). In bush babies and likely other primates, this input is also GABAergic (Feig and Harting, 1994). At present, it is unclear whether pretectal input in primates ends preferentially in specific layers although the input appears to show some retinotopic specificity (Bickford *et al.*, 2000). In bush babies, more pretectal input was identified in the PC layers than in the other LGN layers (Harting *et al.*, 1986), whereas in the macaque monkeys some reports have suggested there is more pretectal input to the MC layers (Büttner-Ennever *et al.*, 1996). Bickford *et al.* (2000), however, found that some pretectal cells send input to both MC and PC layers. In bush babies, this input has been found to target principally relay cells where it terminates on distal dendrites (Feig and Harting, 1994). The latter result suggests that in primates pretectogeniculate input may directly inhibit relay cells. Interestingly, the opposite appears in cats where pretectogeniculate input ends primarily on the dendrites of interneurons, indicating that this projection would disinhibit cat relay cells (Schmidt, 1996; Wang *et al.*, 2002). Regardless, it is possible that the pretectal input to the LGN is made up of several pathways to the LGN that have different roles.

In functional terms the NOT can be considered a visuo-motor nucleus. In macaque monkey there is evidence the NOT encodes position, velocity, and acceleration components of retinal error that may be used by the targets of NOT for synthesis of smooth-pursuit eye movements and for image stabilization (Das *et al.*, 2001; see also Chapters 8 and 10). In awake cats and in wallabies, it has also been reported that cells in NOT respond to saccades and to eye blinks. These results could account for the suppression of activity seen in the LGN during saccades and/or the enhancement seen after saccades that we and others have reported in the LGN of awake behaving macaque monkeys (Zuber and Stark, 1966; Montero and Robles, 1971; Riggs *et al.*, 1974; Ross *et al.*, 1996; Zhu and Lo, 1996; Lee and Malpeli, 1998; Ramcharan *et al.*, 2001; Royal *et al.*, 2004, submitted; Thilo *et al.*, 2004). In fact, studies using antidromic activation in cats have demonstrated that pretectogeniculate cells are selectively sensitive to saccadic eye movements (Schmidt, 1996). Taken together with other results that have reported eye movement effects in LGN, it seems likely that the role of the NOT is to inform the LGN about particular aspects of planned ocular movements.

Thalamic reticular nucleus

Perhaps the most important key to understanding how visual information and sensory information, in general, are altered in the thalamus lies in an understanding of the role of the TRN. This interesting nucleus, which forms a shell around the thalamus and contains GABAergic neurons, is subdivided into zones which project to individual thalamic nuclei (Jones, 2002). The portion of this nucleus that sends and receives input from the LGN has been examined most thoroughly. Among primates the relationship between the TRN and the LGN has been best studied in the bush baby where it has been shown that reciprocal connections between all layers of the LGN and the TRN are topographic and specific (Harting *et al.*, 1991a). Similar evidence of a high degree of retinotopic specificity in

connections between the TRN and the LGN have been reported also in the macaque monkey (Bickford *et al.*, 2000; Wang *et al.*, 2001). In cats, it has been suggested that cells in the visual portion of the TRN, referred to as the perigeniculate nucleus, project primarily to LGN Y-cells (Fitzgibbon, 2002). This preference for one pathway has not been reported in primates; instead the TRN appears to project to all LGN cell classes in primates (Harting *et al.*, 1991b). The portion of the TRN that projects to the LGN is also innervated by the collateral branches of axons that arise from cells in layer VI of V1 (see preceding text). At present, it is unclear if all corticogeniculate axons provide such collaterals to the TRN or only a subset (Ichida and Casagrande, 2002), but in cats all reconstructed axons from visual cortex were found to send a collateral branch to the perigeniculate nucleus (Murphy and Sillito, 1987). The TRN also receives input from collateral axons of LGN relay cells and sends its output back to these relay cells as well as to LGN interneurons. These circuits allow the TRN not only to provide feedback inhibition to the LGN, but also to regulate LGN cell output in complex ways depending upon other inputs that the TRN receives from both extrastriate visual areas and the brainstem (Sherman and Guillery, 1996; Guillery *et al.*, 1998 for review; Jones, 2002). For example, inhibitory reticular inputs have been shown to affect the temporal correlation between LGN input and output, pushing the neural circuit toward synchronized oscillation (Le Masson *et al.*, 2002). This process could increase the efficiency of signal transmission between LGN and V1 (Sillito and Jones, 2002). Simulation studies of the LGN–V1–TRN pathway show that the TRN activity suppresses the background and improves the signal-to-noise ratio (Bickle *et al.*, 1999). Cortical inputs presumably regulate oscillations in LGN in the following way. When a long enough period of hyperpolarization has occurred, relay cells fire in burst mode when I_T is de-inactivated while the cells recover from an inhibition provided by the TRN. This burst firing excites the TRN cells. The activated TRN cells re-inhibit relay cells, and relay cells fire again in burst mode as they recover from the inhibition produced by the TRN. These events occur repeatedly, generating a low-frequency oscillation. Therefore, the TRN not only induces the burst mode of firing in relay cells, but also generates oscillation by repeatedly inducing the burst firing (Jones, 2002). Activation of the TRN, however, does not always lead to the result one might predict by such a model. Glutamate, which is generally an excitatory neurotransmitter, can also directly inhibit TRN cells. This inhibition occurs when glutamate activates group II mGluRs and the potassium conductance is increased. Activation of group I mGluRs has the opposite effect leading to depolarization; this suggests that the glutamatergic inputs to the TRN can be either excitatory or inhibitory, depending on the group of receptors that is activated (Cox *et al.*, 1998; Cox and Sherman, 1999). Additionally, evidence exists in mice for GABA to act directly on retinal axons via presynaptic $GABA_B$ receptors (Chen and Regehr, 2003). Whether this involves input from interneurons or the TRN remains unclear. Regardless, this sort of receptor-dependent excitation and inhibition may add great flexibility to the modulatory roles of the TRN but also predicts that understanding the role of the TRN requires appreciation of the complexity of the circuit and the fact that the system is dynamic. Although the TRN has been proposed to play specific roles in sleep, arousal, and attention (Crick and Koch, 1990), it seems likely that the TRN is not tied to a specific role relative to LGN activity but is utilized in a variety of ways. Nevertheless, unlike the more global modulatory inputs to the LGN, the visual TRN, like V1 to which it is intimately linked, is in a position to

modulate visual activity quite precisely given its retinotopically specific connections with the LGN.

7.4.3 Cholinergic inputs

The largest non-retinal brainstem input to the LGN in primates (as well as other species) is cholinergic (Bickford *et al.*, 2000). This input may account for as much as 25 percent of synapses in the LGN, at least in the cat (Erisir *et al.*, 1997). The cholinergic input comes from two sources, cells in pedunculopontine tegmentum (PPT) and from the parabigeminal nucleus of the midbrain. The PPT source (referred to also as CH5 by Mesulam, 1990) innervates all LGN layers in primates, but appears to show differences in innervation density that correlate with visual lifestyle. Thus, in the nocturnal simian owl monkey and nocturnal prosimian bush baby, acetylcholinesterase (the degradative enzyme for acetylcholine) is densest in the LGN PC layers, whereas it is densest in the MC layers of diurnal simian squirrel monkeys and macaque monkeys (Fitzpatrick and Diamond, 1980; Graybiel and Ragsdale, 1982; Wilson *et al.*, 1999). In contrast to the input from the PPT, the parabigeminal cholinergic input (CH8 of Mesulam, 1990) projects primarily to the LGN KC layers although its primary output is to the superior colliculus (Feig and Harting, 1994); KC layers also receive sparse cholinergic input from the PPT (Bickford *et al.*, 2000). Additionally, the axonal projections from the PPT provide the exclusive source of the neurotransmitter nitric oxide (NO) to the LGN (Bickford *et al.*, 2000) since no bNOS positive cell bodies have been found in primate LGN (Wiencken and Casagrande, 2000; see, however, Bickford *et al.*, 1999 for evidence of bNOS positive interneurons in the cat LGN). PPT projections make asymmetric synaptic contacts onto both proximal and distal relay cell dendrites as well as onto the dendrites of interneurons. Parabigeminal inputs also are found to synapse on both relay and interneuronal cell dendrites in bush babies (Feig and Harting, 1992). Both cholinergic inputs to primate LGN are bilateral, although the ipsilateral input to LGN dominates (Feig and Harting, 1992; Bickford *et al.*, 2000). The fact that projections are bilateral suggests that cholinergic brainstem pathways can potentially send signals that integrate across the two hemifields of visual space. Add to this complexity the fact that cholinergic inputs can act through at least three types of receptors (nicotinic and two muscarinic [M1 and M2] receptors) and it is clear that these cholinergic pathways can potentially influence LGN cell activity in complex ways depending upon the circumstances. Evidence exists that the net effect of activation of the PPT pathway in non-primates (primates have not been studied) is excitation of LGN relay cells. This is accomplished via nicotinic and M1 receptors on relay cells and via M2 receptors on presynaptic dendrites of interneurons (McCormick and Prince, 1986; McCormick and Pape, 1990). The depolarization of relay cells is further enhanced by the co-release of NO (Nucci *et al.*, 2003). Studies of anesthetized cat LGN neuronal responses to visual stimuli (drifting gratings) in the presence of electrical stimulation of the PPT pathway demonstrated that the most common effect of PPT activation was response enhancement. Interestingly, stimulation of the PPT pathway could induce robust responses to visual stimuli even in cases in which LGN cells did not respond at all to the same stimulus (Uhlrich *et al.*, 1995). PPT activation in the study by Uhlrich *et al.* (1995) mainly resulted in an increase in both the center and surround responses of LGN cells, suggesting that the main effect is an increase

of the transfer ratio of the retinal signal (see preceding text). They also found a more variable effect on the surround response as well as on the spontaneous activity of LGN cells, presumably because both are affected by the inhibitory circuitry within the LGN itself as well as by other inputs, not just input from the retina. Many functions have been attributed to the PPT. It is beyond the scope of this review to cover all the studies of the PPT but activity in this region has been implicated as important in a variety of behaviors including eye movements, attention, arousal, rapid eye movement, and sleep (Fitzpatrick *et al.*, 1989). Understanding the function of the PPT pathway, or pathways, to the LGN has been difficult given that in primates the cells of origin are scattered and not confined tightly to a nucleus.

So far, we have less information on the impact of the parabigeminal on LGN responses, although given its strong connections with the superior colliculus and given evidence that parabigeminal cells in awake behaving cats reflect retinal position error, it seems likely that this pathway would inform LGN cells about target location (Cui and Malpeli, 2003). It is interesting in this regard that the main cells in cats and primates that receive input from parabigeminal axons are cat LGN W-cells and primate LGN KC cells (Harting *et al.*, 1991c).

7.4.4 Diffuse modulatory inputs (histamine and serotonin)

All of the LGN layers of macaque monkey and squirrel monkey have been shown to receive diffuse input from brainstem and hypothalamic sources that appears capable of globally modulating LGN activity via mainly non-synaptic release of the transmitters serotonin and histamine, respectively (Morrison and Foote, 1986; Pasik *et al.*, 1986; Wilson and Hendrickson, 1988; Uhlrich *et al.*, 1995). There has been some debate about whether serotonergic input is more dense in the KC or MC layers than in the PC layers. Nevertheless, it is generally agreed that all LGN layers receive these modulatory inputs and that these inputs are non-topographic relative to the visual coordinates of the nucleus (Wilson and Hendrickson, 1988; Uhlrich *et al.*, 1995).

Serotonin

Although some reports have suggested that serotonergic input to the monkey LGN is moderately dense (Morrison and Foote, 1986; Pasik *et al.*, 1986; Wilson and Hendrickson, 1988), quantitative estimates suggest that serotonergic input makes up approximately 1 percent of the vesicle-filled profiles (Wilson and Hendrickson, 1988). All studies of the function of serotonin in the LGN have been done in non-primates, typically in slice preparations. In slice preparations of LGN, serotonin has been found to have a complex effect on LGN cell responses which appears to be either excitatory or inhibitory. Given that stimulation of the dorsal raphé or infusion of serotonin *in vivo* causes inhibition of LGN relay cells, suggest that serotonin could act indirectly by exciting GABAergic LGN cells (Funke and Eysel, 1995). In slice preparations of mouse LGN, evidence was found for presynaptic action on retinal axons within the LGN operating via 5HT1A receptors (Nucci *et al.*, 2003). Since no synapses have been reported on retinal axons from labeled serotonin fibers, this transmitter must diffuse hormone-like to reach these receptors. Regardless, the fact that serotonin could block or blunt retinal transmission presynaptically would make it ideal for regulating transmission during sleep, although

other pathways have been implicated (Steriade and Deschênes, 1984; Steriade and Llinás, 1988; McCormick and Pape, 1990).

Histamine

Receptor binding studies in LGN indicate that the impact of this pathway could be larger than suggested by the limited population of tuberomammillary hypothalamic cells labeled retrogradely from the LGN in macaque monkeys (Bickford *et al.*, 2000). A high density of dendritic histamine H1 and H2 receptors and presynaptic H3 receptors (Bouthenet *et al.*, 1988; Ruat *et al.*, 1990; Chazot *et al.*, 2001) have been identified in the LGN. Although no direct functional studies of the tuberomammillary to LGN pathway have ever been done in primates, in the thalamus the histaminergic system is thought to play a primary role in general arousal, with tuberomammillary neurons active during the waking state and relatively inactive during sleep (Vanni-Mercier *et al.*, 1984; Lin *et al.*, 1988, 1990; Monti, 1993). Receptors for histamine presumably exist only on LGN relay cells since there is no evidence that GABAergic LGN interneurons respond to this input (Uhlrich *et al.*, 1995). Application of histamine in slice preparations of non-primates changes the firing pattern of LGN neurons from the burst mode of firing to the tonic mode by decreasing K^+ conductance causing depolarization and inactivating I_T (McCormick and Williamson, 1991; McCormick, 1992), mimicking the change in general firing activity recorded in the thalamus as the brain transitions from sleep to waking (Steriade and Deschênes, 1984; Steriade and Llinás, 1988). Uhlrich *et al.* (1995) have shown that stimulation of the tuberomammillary nucleus causes release of histamine within the cat LGN, resulting in an increase in baseline activity as well as an increase in firing activity to a visual stimulus and thus an increase in the transfer ratio of information from the retina. This supports the idea that this pathway is part of a general arousal system.

Since there are several pathways that result in increased transmission through the LGN, it is likely that each pathway brings a different context to bear on the visual signal. Histamine release is often associated with negative stimuli. Thus, one might speculate that this pathway to the LGN functions to increase the transfer ratio of retinal signals in situations where potential danger exists or possibly be more globally tied to enhancing visual signals in relationship to reward and punishment or to general levels of motivation.

7.5 Concluding remarks and remaining questions

The LGN and primary visual cortex (V1) are part of a dynamically linked loop. Unlike in cats, the extrastriate output of LGN cells in primates is relatively small (Casagrande and Norton, 1991). Whether this extra-geniculostriate pathway can function in the absence of primary visual cortex is still hotly debated (Collins *et al.*, 2003) under the heading of 'blind sight'. Regardless, it is generally agreed that area V2 is silenced by the removal of V1 (Schiller and Malpeli, 1977; Merigan *et al.*, 1993); therefore, if the LGN is to communicate visual messages to the rest of the brain, it likely does so via V1 in primates. As we have seen earlier, however, LGN can receive messages that may not directly involve V1 and can arrive via a number of routes. Subcortical sites that send axons to LGN, of course, also receive from additional cortical and subcortical sources, so

LGN cells can be informed about sensory, motor, and limbic activities via these indirect sources. Because the system is dynamically linked, LGN relay cells can potentially carry messages that are non-retinal together with or before or after retinal messages arrive. These non-retinal inputs can be demonstrated by showing modulation of the level and the temporal structure of spontaneous LGN activity in the absence of retinal stimulation (Royal *et al.*, 2004, submitted). In fact, LGN activation has been detected using fMRI in subjects with eyes closed and no direct visual input while these subjects imagined visual scenes (Chen *et al.*, 1998). Given that LGN and V1 are connected dynamically, the latter result also indicates that both areas may be actively involved in processing signals during visual imagery. Furthermore, it has been demonstrated recently in imaging studies using voltage-sensitive dyes that even in the anesthetized state, and in the absence of visual stimulation, visual cortical activity is not random but seems to show intrinsic patterns of activity that evolve over time by switching among different states that resemble the architecture of activity produced in response to visual stimuli (Kenet *et al.*, 2003). This finding indicates that so-called spontaneous activity in visual cortex is not random. Since LGN and visual cortex are so intimately linked, it seems reasonable to propose also that the 'spontaneous' activity of LGN neurons is not random noise in the system but instead reflects different states.

Additionally, since inputs to the LGN act through both fast ionotopic and slow metabotropic receptors, this means that the impact of retinal or other signals to LGN cells could outlast a peripheral stimulus under some circumstances just as easily as they could be truncated by direct or indirect inhibitory inputs. Enhancement of relevant stimuli and suppression of irrelevant stimuli would make sense for species survival. This idea implies, for example, that under conditions where a very negative, potentially painful stimulus (dentist drill, large angry wasp, large knife coming at you) is seen, it may activate LGN cells via direct retinal pathways as well as cortical pathways associated with the learned meaning of the stimulus, pathways that attach emotional tone/arousal (histamine) or allow increased attention (acetylcholine). Temporal coordination of all of these inputs to LGN could lead to a temporary or permanent enhancement of specific types of visual or other signals through the LGN gateway to the cortex. In fact, a variety of functions (reviewed above) have been attributed to each of the non-retinal inputs to LGN in addition to those mentioned earlier. Key related questions for each input pathway to the LGN are as follows: (1) Are some non-retinal messages to the LGN used to communicate non-visual messages to V1 via changes in baseline firing or changes in the temporal structure of LGN cell firing? In other words, does the level or structure of spontaneous activity convey information independent of vision? (2) In addition to simply controlling the transfer ratio between the retina and the cortex (Sillito and Jones, 2002), does the LGN aid in the construction of visual images? Although much more information will be required, the data reviewed above suggest that the answer to both of these key questions is *yes*. Many other more specific questions remain about each of the non-retinal pathways to LGN reviewed above. Several examples follow which are not intended as an exhaustive list. (3) Do the inhibitory pathways from interneurons and the TRN relate differently to different classes of relay cells in primates as suggested for cat relay cells (Sherman and Guillery, 2001)? (4) How many classes of LGN interneurons exist in the LGN of primates? (5) Why are there two or more cholinergic inputs to the LGN? (6) How are LGN indirect retinal inputs (via superior colliculus, pretectum) coordinated

with direct retinal messages to the LGN? (7) Why do the superior colliculus, parabigeminal nuclei, and extrastriate visual areas send input primarily to the KC LGN layers? (8) Does the histaminergic input convey information about potential reward or punishment of visual stimuli?

Although we understand a great deal about the anatomy of the LGN, our understanding of the LGN's function, especially with respect to the LGN's extraretinal inputs, is largely a proverbial 'black box'. This is a direct consequence of the fact that for far too long the process of 'vision' has been considered strictly a cortical phenomenon. The bulk of this chapter along with the questions listed above, however, demonstrate that a complete understanding of visual information processing will remain beyond our reach until research shifts subcortically, to the array of non-retinal inputs that continually and selectively modulate the visual stream.

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