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CHAPTER 2

On the impact of attention and motor planning on the lateral geniculate nucleus

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Abstract: Although the lateral geniculate nucleus (LGN) is one of the most thoroughly characterized thalamic nuclei, its functional role remains controversial. Traditionally, the LGN in primates has been viewed as the lowest level of a set of feedforward parallel visual pathways to cortex. These feedforward pathways are pictured as connected hierarchies of areas designed to construct the visual image gradually — adding more complex features as one marches through successive levels of the hierarchy. In terms of synapse number and circuitry, the anatomy suggests that the LGN can be viewed also as the ultimate terminus in a series of feedback pathways that originate at the highest cortical levels. Since the visual system is dynamic, a more accurate picture of image construction might be one in which information flows bidirectionally, through both the feedforward and feedback pathways constantly and simultaneously. Based upon evidence from anatomy, physiology, and imaging, we argue that the LGN is more than a simple gate for retinal information. Here, we review evidence that suggests that one function of the LGN is to enhance relevant visual signals through circuits related to both motor planning and attention. Specifically, we argue that major extraretinal inputs to the LGN may provide: (1) eye movement information to enhance and bind visual signals related to new saccade targets and (2) top-down and bottom-up information about target relevance to selectively enhance visual signals through spatial attention.

1 Introduction

In this chapter we defend the position that the LGN is involved in the selection of environmental signals by both updating the cortex about anticipated visual and motor events and by highlighting regions of space where relevant visual information is anticipated. The LGN is in an ideal position to carry out these functions because the LGN lies at the interface between the periphery (retina) and the cortex and is potentially informed about levels of arousal, mood, motivation, and intention via a number of non-retinal inputs (Sherman and Guillery, 1996, 2002; Casagrande et al., 2005). Here we focus specifically on the impact of saccadic eye movements and on spatial attention both because more information is available and because evidence suggests that the circuitry involved in attentional selection and target selection for planned eye movements may be shared (Hahnloser et al., 1999; Horwitz and Newsome, 2001).

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This chapter is divided into five parts, in addition to this introduction. In Section 2, we introduce the circuitry of the LGN, emphasizing the key elements that constrain the way eye movements and visual attention might impact retinal information passing through the LGN to primary visual cortex (V1). In the next section, we provide a general overview of nonvisual inputs to the LGN and the circuitry of those inputs that are most likely to carry signals related to eye movements and attention. In the fourth section, we discuss evidence that the LGN carries information about motor planning and the circuits that could carry this information. We argue that several nonvisual inputs to the LGN carry oculomotor messages. In the fifth section, we define ways in which visual attention could impact LGN cell responses and the circuits that are most likely to carry this information. The final section provides a summary and outlines the questions that remain to be answered.

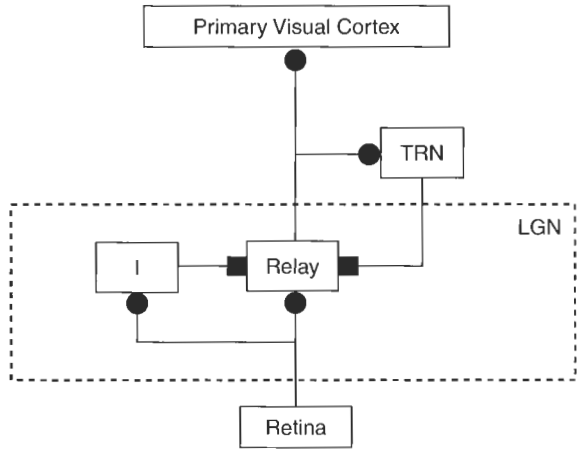

Fig. 1. Diagram of feedforward and feedback inhibitory pathways that influence LGN relay cells. Excitatory inputs are indicated by filled circles. Inhibitory inputs are indicated by filled squares. Abbreviations: TRN: thalamic reticular nucleus, LGN: lateral geniculate nucleus, I: LGN interneuron. See text for details.

2 Basic properties and circuitry of the LGN

To understand how LGN cells are modified by motor planning or attention, it is necessary to review the LGN's organization and circuitry. Rather than reviewing all details of the functional properties and circuitry of the LGN (Casagrande and Norton, 1991; Casagrande, 1994; Sherman and Guillery, 1996, 1998; Hendry and Reid, 2000; Sherman and Guillery, 2002), our goal is to present only a brief review of the ways information flow can be constrained by the LGN's design. Since there is considerable species variation in LGN structure (Kaas et al., 1972), we focus here on the primate LGN. All primate LGNs are layered. Each layer receives input from one hemiretina of one eye and mainly from one of three classes of ganglion cells, koniocellular (K), magnocellular (M), and parvocellular (P). Retinal axons project to only a small number of LGN cells. Therefore, each monocularly innervated LGN layer has a precise map of the opposite hemifield representing either the contralateral nasal retina or the ipsilateral temporal retina. These monocular laminar maps lie in precise retinotopic register. Two cell types are resident within each layer, glutamatergic relay cells (~75–80% of the cells) that send axons to cortex and GABAergic interneurons (~20–25% of the cells) that maintain connections only within the LGN. LGN relay cells and interneurons relate to each other and to the GABAergic cells of the thalamic reticular nucleus (TRN) in unique feedforward and feedback inhibitory circuits as shown in Fig. 1 (Casagrande and Norton, 1991). Feedforward inhibition is produced by retinal axons and collaterals that synapse simultaneously on both relay cells and nearby interneurons; these interneurons in turn inhibit the same relay cells via dendrodendritic synapses. The LGN relay cells send axons to cortex and collaterals to the TRN, which in turn, feed back inhibition to the relay cells. Since LGN relay cells, interneurons, and TRN cells have many different receptors on their dendrites, including both fast acting ionotropic receptors and slow acting metabotropic receptors, the way signals can be regulated within these LGN circuits via both retinal and nonretinal inputs can be quite complex (Sherman and Guillery, 2001).

The primate LGN receives 30–40% of its synaptic input from the retina (Wilson and Forestner, 1995). Therefore, the majority of synapses in the LGN are from nonretinal sources. In spite of this fact, it has been difficult to identify the functions of the many nonretinal inputs to the LGN primarily because the

responses of LGN cells to visual stimuli appear so similar to those of their retinal inputs, at least as defined by average spikes/second over tens of milliseconds (i.e., a standard rate code) in anesthetized preparations (Casagrande and Norton, 1991). The latter definition becomes important because the temporal relationship between spikes can vary between the retina and the LGN. We shall return to this issue shortly. First, it is useful to review the visual receptive field properties defined classically in LGN cells. From the first time responses of primate LGN single units were measured (Wiesel and Hubel, 1966; De Valois et al., 1977; Rodieck and Dreher, 1979), the majority of LGN visual receptive fields were described as organized (same as their retinal ganglion cell inputs) into opposed centers and surrounds (ON center/OFF surround and vice versa). This center/surround organization has been modeled using a difference of Gaussians (DOG) in primate LGN (Irvin et al., 1993; Croner and Kaplan, 1995; White et al., 2001; Xu et al., 2002) and accounts well for the differences in contrast sensitivity between cell classes. This organization, of course, is present already in retinal bipolar cells (Rodieck and Stone, 1965). If the receptive field structure of bipolar cells, retinal ganglion cells, and LGN cells are all so similar, why lengthen the transmission time of visual signals by routing visual information through an intermediary "relay station" like the LGN? It has been argued that center/surround relationships are sharpened in the LGN, reflecting a change in the center/surround relationship. It has also been argued that receptive field surrounds at the level of the LGN are not merely a product of the retina but reflect other contributions from circuits in the LGN itself or other inputs to the LGN given that they do not disappear (as in the retina) under scotopic conditions (for discussion, see Casagrande and Norton, 1991). The latter fact, of course, refutes the idea that the LGN acts as a simple gate to retinal information that passes through it relatively unaltered.

The description above generally assumes a rather static one-way feedforward relationship between inputs and outputs of the visual system. Since the vast majority of information on receptive fields of visual cells has been gathered in anesthetized paralyzed preparations or in slice preparations with a very limited stimulus set, it is natural to build models of this type. The LGN, however, most certainly does not work in isolation from the rest of the brain. In a highly dynamic system retinal signals will always become mixed temporally with signals coming back from cortex and from subcortical sources. Thus, a retinal signal may arrive at an LGN cell at the same time as other signals concerning planned eye movements or the animal's motivational or attentional state. The feedforward LGN signals are also being sent to visual cortical cells at different times given that K, M and P LGN cells respond to the same stimulus with onset latencies that can differ by more than 30 ms (Schmolesky et al., 1998; Ichida et al., 2003, see Fig. 2). The impact of the LGN's message depends ultimately upon how cells in primary visual cortex respond to this input. The fact that each cortical cell in the primary visual cortex receives input from several hundred LGN cells (Davis and Sterling, 1979; Alonso, 2002, for review), not to mention the thousands of local synapses and synapses from many other extrageniculate sources, argues again for the importance of temporal factors in understanding the influence of LGN messages.

Beyond these issues, it is important to appreciate that most LGN cells exhibit spontaneous activity in the absence of visual stimuli that can be modulated by a variety of factors including eye movements and potentially attention (see Section 3). Additionally, the temporal structure of LGN cell firing can adopt modes that do not reflect directly the pattern of their retinal inputs, thus influencing the transfer of visual signals. Sherman and colleagues, as well as others (Guido and Weyand, 1995; Sherman and Guillery, 1996, 1998, 2002; Ramcharan et al., 2000), have shown that LGN and other thalamic relay cells can adopt two basic modes of firing referred to as "burst" and "tonic". During tonic firing, action potentials of LGN relay cells reflect more faithfully the temporal sequence of retinal ganglion cell action potentials. During burst mode, retinal ganglion cell input can trigger a burst of Ca^{2+} spikes after a sufficient period of hyperpolarization. Since burst firing in the thalamus is more effective in causing cortical spikes than tonic firing (Swadlow and Gusev, 2001; Izhikevich et al., 2003) and tonic firing more faithfully represents the retinal input message, Sherman (2001) has suggested that bursts in the

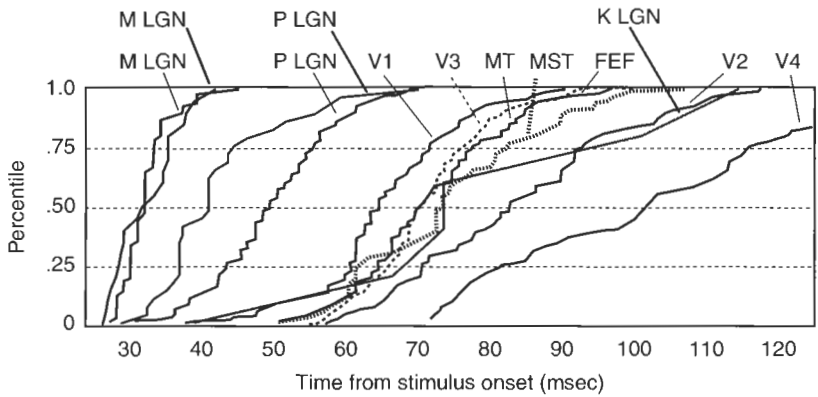

Fig. 2. Cumulative distributions of visually evoked onset response latencies in the LGN, striate and extrastriate visual areas as labeled. Percentile of cells that have begun to respond is plotted as a function of time from stimulus presentation. The V4 curve is truncated to increase resolution of the other curves; the V4 range extends to 159 msec. Abbreviations: M LGN: magnocellular LGN cells, P LGN: parvocellular LGN cells, K LGN: koniocellular LGN cells, V1: primary visual cortex, V2: visual cortical area 2, V3: visual cortical area 3, V4: visual cortical area 4, MT: middle temporal cortical area, MST: medial superior temporal cortical area, FEF: frontal eye field. Modified from Schmolesky et al. (1998) with permission. M LGN (red), P LGN (green), and K LGN (blue) data from Ichida et al. (2003).

LGN of awake animals function as a "wake-up call" for the detection of novel stimuli whereas tonic activity transmits information about stimulus quality (see also below). The timing of bursts and the general synchronization of activity between LGN and cortex may play important roles in coordinating the effectiveness of messages in the visual network (Sillito and Jones, 2002; Wörgötter et al., 2002). Taken together, these facts indicate that both the spatial structure and temporal structure of LGN receptive fields can be modified in a variety of ways depending upon the message. Messages are most likely modified by a combination of extraretinal inputs to the LGN, which are described in the next section.

3 Extraretinal inputs to LGN

Figure 3 shows all of the known connections to the primate LGN with the major connections indicated with bold arrows. A glance at the list can remind the reader of the huge diversity of inputs that can modulate retinogeniculocortical transmission. These sources of input can be classified in various ways. One proposal is to classify these inputs based upon their effect, specific or global (Casagrande and Norton, 1991). Extraretinal inputs from visual sources generally maintain retinotopic fidelity. In other words, regions representing a common point in visual space are connected. Extraretinal visually related input to the LGN has been documented from the following areas in primates (transmitter type in parentheses): primary visual cortex, V1 (glutamate), some extrastriate areas (possibly glutamate), superior colliculus (glutamate), nucleus of the optic tract, NOT (GABA), parabigeminal nucleus (acetylcholine or ACh), and the visual sector of the thalamic reticular nucleus (GABA) (for review, see Bickford et al., 2000). In primates the majority of the latter inputs to the LGN project to all three LGN cell classes (K, M, and P) but some inputs show a degree of specificity for a particular cell class/layer. Thus, the superior colliculus and extrastriate areas project almost exclusively to K LGN cells, parabigeminal inputs show a preference for K LGN cells, and the input from NOT shows a preference for P LGN cells (Casagrande et al., 2004). Of the latter sources only two, the superior colliculus and NOT, receive direct retinal input. The largest of the visually related sources of input to the LGN comes from V1 and TRN. In addition to these more specific inputs, there are three other main inputs to the LGN. The largest of these is the cholinergic input from the pedunculopontine tegmentum (PPT). This input has been studied in some detail in both cats and monkeys and is known to

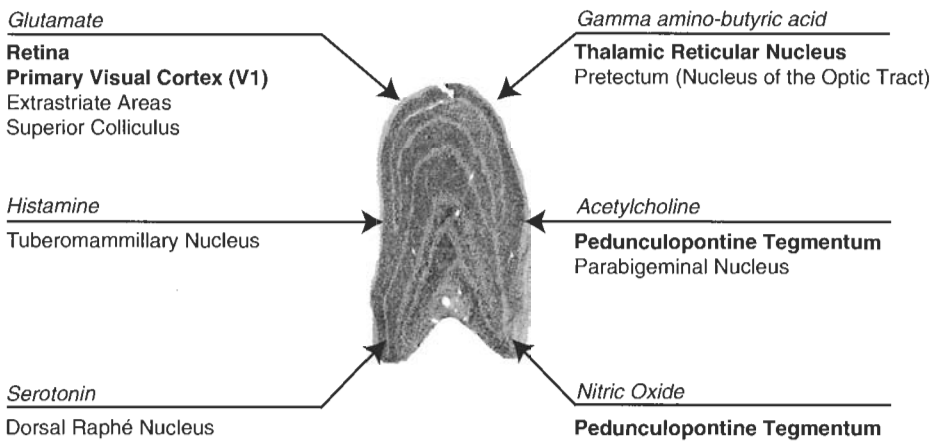

Fig. 3. Diagram demonstrating the brain areas connected directly with the LGN and their chemical messages. Bold text indicates areas that provide the heaviest input to the LGN in terms of synapse number. Abbreviations: 5-HT: serotonin, GABA: gamma amino-butyric acid, NO: nitric oxide, ACh: acetylcholine. Modified from Casagrande et al. (2005) with permission.

show some evidence of synaptic specificity (Cucchiaro et al., 1988). In addition to ACh, the latter pathway also uses nitric oxide as a transmitter (Bickford et al., 1999). Finally, there are two additional inputs to the LGN that provide for global regulation of information mainly via non-synaptic release of transmitter. These inputs are the histaminergic input from the hypothalamic tuberomammillary nucleus, which appears to increase activity in the LGN (Hobson and Pace-Schott, 2002; Uhlrich et al., 2002) and the serotonergic input from the dorsal raphé nucleus, which appears to reduce LGN activity in vivo. Here, we consider three examples of major inputs to the LGN that could regulate information concerned with motor planning or spatial attention, although additionally they may contribute to the visual stream by providing information relevant to general states of arousal or motivation (Casagrande et al., 2004 for details).

V1 feedback

V1 provides the largest input in terms of synapse number to the LGN. Almost all of the extraretinal inputs to the LGN could also be sources of signals related to motor planning or attention. V1, for example, receives input not only from the LGN but also from other thalamic nuclei such as the central lateral (CL) intralaminar nucleus which has been shown to contain cells that respond to various aspects of saccadic eye movements and motor planning (Wyder et al., 2004) and which projects broadly to layer 1 and layer 6 of V1 (Deschenes et al., 1996; Ichinohe et al., 2001). CL also receives input from V1. Additionally, V1 receives a major feedback projection from the middle temporal area (MT, also called V5). MT also has a minor projection directly to the LGN (and also receives direct input from the LGN) but this input appears to involve primarily LGN K cells (Lin and Kaas, 1977; Casagrande and Kaas, 1994; Sincich et al., 2004). Studies by Sillito and Jones (2002) have shown that enhancing the activity of MT feedback cells with a GABAb antagonist and using a moving texture patch to stimulate cells visually changed the activity of topographically matched LGN cells (Jones et al., 2002). Their data show that feedback from MT via V1 can rapidly impact LGN cells which will then dynamically modify the feedforward signal. Given the separation in time of responses of different LGN cell classes (see Fig. 2), this means that the M pathway to MT via V1 (or a direct projection to MT from K cells) and back to the LGN could occur prior to, or simultaneously with, the feedforward inputs from the LGN P and K pathways that travel via V1. The V1 layer 6 cells that project to LGN also receive feedback from many other higher order visual areas including V2, V3, V3a/DM, V4/DL and parts of the temporal cortex. The layer 6 to LGN projection in

primates also shows laminar specificity. In other words, axons from V1 terminate within either the M or P layers but never in both sets of layers, although axons to the K LGN cells always appear to be collaterals of axons projecting to a neighboring P or M layer (Ichida and Casagrande, 2002). The fact that V1 projects to a variety of other areas including the claustrum, pulvinar, TRN, pregeniculate, the superficial layers of the superior colliculus, pretectum, and motor nuclei in the pons (Casagrande and Kaas, 1994) also implies that motor planning could be influenced via V1 through a number of direct and indirect circuits to the LGN.

V1 could also influence spatial attention in LGN through many of the top-down and bottom-up circuits outlined above. In a recent study, Przybyszewski et al. (2000) showed that V1 feedback can enhance the contrast gain of both macaque monkey P and M LGN cells significantly. This finding indicates that V1 could be responsible for enhancing its own input. Other studies have provided evidence that feedback to LGN is important for both global integration (or binding) of visual features as well as segmentation (Sillito and Jones, 2002). In the temporal domain, it also 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 section 2).

Regulation by the TRN

TRN has been implicated as an important player in several models of visual attention (Crick, 1984; Guillery et al., 1998). All cells in the TRN contain GABA; however, the pattern and time course of GABA release depends upon which combination of ionotrophic or metabotropic receptors are activated (Sherman and Guillery, 1996, 2002). The major inputs to the TRN are retinotopic connections from the visual cortex and the LGN. Since TRN cells have ON/OFF receptive field centers that are larger than those of their LGN counterparts, they must combine input from more than one LGN cell (Hale et al., 1982). Among primates, the anatomical relationship between the TRN and LGN has been studied most thoroughly 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 LGN have been reported also in the macaque monkey (Bickford et al., 2000). Additionally, 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. This visual portion of the TRN additionally receives input from a number of other sources including global noradrenergic input from the locus coeruleus, serotonergic input from the dorsal raphé, and histaminergic input from the tuberomammillary nucleus as well as very strong cholinergic projections arriving from the PPT and, to a lesser extent, from the basal forebrain (Hobson and Pace-Schott, 2002; Uhlrich et al., 2002). Furthermore, the midbrain reticular formation and several intralaminar thalamic nuclei, including CL, provide input to the TRN.

These circuits allow the TRN to provide not only 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 from the brainstem (Sherman and Guillery, 1996; Guillery et al., 1998, for review; Jones, 2002). For example, inhibitory reticular inputs can modulate the retinogeniculate transfer ratio selectively, 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, 2002). Simulations of the LGN-V1-TRN pathway also show that the TRN activity suppresses the background and improves the signal-to-noise ratio (Bickle et al., 1999).

Although seemingly straightforward, the circuitry connecting the TRN and LGN belies the dynamic nature of TRN activation. For example, glutamate, generally considered excitatory, can both excite and inhibit the TRN depending on which group of glutamate receptors is activated (mGluRI and mGluRII respectively) (Cox et al., 1998; Cox and Sherman, 1999). Viewed holistically, this sort of receptor-dependent excitation and inhibition in the TRN allows for greater flexibility in LGN modulation and suggests that the role of the TRN may be quite dynamic depending on the demands of the visual system. Although 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 linked intimately, is in a position to modulate visual activity quite precisely given its retinotopically specific connections with the LGN.

Circuits involving the PPT

It is estimated that as much as 25% of the synapses in the LGN are cholinergic (at least in the cat (Erisir et al., 1997)). Less is known about primate thalamus, however, data show that cholinergic input to the LGN from the midbrain and brainstem forms one of the largest non-retinal brainstem inputs to the primate LGN as well (Bickford et al., 2000). Cholinergic input originates from two sources, the pedunculopontine tegmentum (PPT) and the parabigeminal nucleus of the midbrain. Although some differences have been observed in the density of cholinergic input to different LGN layers in different primate species (Fitzpatrick and Diamond, 1980; Graybiel and Ragsdale, 1982; Wilson et al., 1999) this input is found in all LGN layers with the PPT primarily innervating the M and P LGN layers and the parabigeminal nucleus primarily the K LGN layers (Bickford et al., 2000). In addition to acetylcholine, the PPT pathway to the LGN contains the neurotransmitter nitric oxide and so can regulate activity in a number of ways given that: (1) at least three types of cholinergic receptors are found in the LGN, (2) cholinergic axons project to both interneurons and relay cells, and (3) the PPT provides heavy input to the TRN (Feig and Harting, 1992; Bickford et al., 2000). Added to this complexity is the fact that projections from both the PPT and the parabigeminal nucleus receive input from other sources and project bilaterally to the LGN. In spite of this complexity, the net effect of activation of the PPT pathway in nonprimates has been reported to be excitation of LGN relay cells. Uhlrich et al. (1995) studied the effect of activation of this pathway in cats in some detail and concluded that the main result was response enhancement to visual stimuli but other changes were also seen including an increase in spontaneous activity as well as more complex effects on the receptive field structure of LGN cells. In primates the PPT pathway to the LGN has been difficult to study in isolation given that the PPT cells that innervate the LGN are scattered among cells that project elsewhere. Nevertheless, many functions have been attributed to this pathway based upon both physiological and clinical data including involvement in rapid eye movement sleep, saccadic eye movements, attention, and arousal (see below and Fitzpatrick et al., 1989 for review).

In contrast to the PPT the parabigeminal nucleus appears to have much more limited connections; primarily with the superior colliculus. Functionally it has not been studied in primates, but in cats data suggest that one likely role of the parabigeminal nucleus is to inform the LGN about target location (Cui and Malpeli, 2003). Why this information would primarily target the LGN K layers in primates remains an open question (Harting et al., 1991b).

4 The LGN and motor planning

In all primates there is a strong specialization for central vision. The visual system is designed to track visual targets closely, recentering the eyes on objects of interest either by smooth pursuit movements, or via ballistic movements, called saccades. Saccades are very rapid and can reach speeds of over 100 degrees per second. These eye movements recenter the eye on objects of interest several times a second reflecting decisions to shift attention. For example, while reading this page you have made thousands of saccades. What is particularly interesting about saccadic eye movements is that saccades sweep the visual field across the retina at remarkable speeds and yet, we are completely unaware of the 'visual blur' that should occur while our eyes are in flight. Furthermore, neither are we aware that we are getting small discrete snapshots of a bigger visual picture instead of a seamless view. The fact that we see a unified picture suggests that visual perception is coordinated with saccadic eye movements at early levels of the system. In fact, as we will see, there is evidence that the LGN is modulated by eye movements and that the circuits that could provide such modulation to the LGN

could also receive information relevant to decisions to shift visual attention.

Although there is considerable evidence in both cats and monkeys that LGN cells respond to saccadic eye movements, results have been conflicting. In earlier studies, the focus was on linking the perceptual experience of saccadic suppression with activity in the LGN. In these early studies, the percentages of cells found to exhibit suppression in the LGN varied from almost none (Michael and Ichinose, 1970) to over 50% (Jeannerod and Putkonen, 1971). Some investigators found evidence of saccade related suppression of LGN activity only while animals made saccades to a visual target (Fischer et al., 1998), only a few have reported suppression also associated with spontaneous saccades in total darkness (Buttner and Fuchs, 1973; Bartlett et al., 1976). Presumably, changes in activity in total darkness were simply not detected for technical reasons since it had been shown more than a decade before that rapid eye movement sleep modulates LGN activity (Bizzi, 1966). Also, pulling on the eye muscles of rabbits and cats was shown to modulate LGN activity significantly even when these animals were anesthetized (Molotchnikoff and Casanova, 1985; Lal and Friedlander, 1990a, b). More recently, investigators have focused on not only active suppression of LGN cell responses before or during eye movements, but also upon changes that occur directly after eye movements, changes which might aid in linking relevant images across eye movements by a postsaccadic facilitation mechanism (Lee and Malpeli, 1998). In fact, Lee and Malpeli (1998) reported that although a percentage of X and Y LGN cells in cats show a modest suppression before and during eye movements, the largest effect was a postsaccadic enhancement of activity. Our results in awake behaving macaque monkeys are in good agreement with those of Lee and Malpeli (1998) in showing that LGN cells of all three classes (K, M and P) exhibit a modest suppression which starts well before saccades are initiated and transitions into a strong post-saccadic enhancement where LGN activity nearly doubles (Royal et al., 2005 (submitted); see also Fig. 4.). Since all of our measurements were performed without direct visual stimulation of receptive fields, it cannot be argued that saccade-related modulations are confounded by transient changes seen when receptive fields sweep visual stimuli during gaze shifts. Although not all studies have found modulation of LGN cell activity with saccades in monkeys (Maunsell et al., 1999), at least two other studies in awake behaving macaque monkeys report that the strongest effect of saccades on visually driven LGN activity is a postsaccadic enhancement (Ramcharan et al., 2001; Reppas et al., 2002).

Most of the above findings were the result of comparing average firing rates during saccades with periods where the animal was fixating. Interestingly, however, Ramcharan et al. (2001) found that both M and P LGN cells in awake behaving macaque monkeys (K cells were not examined) show a

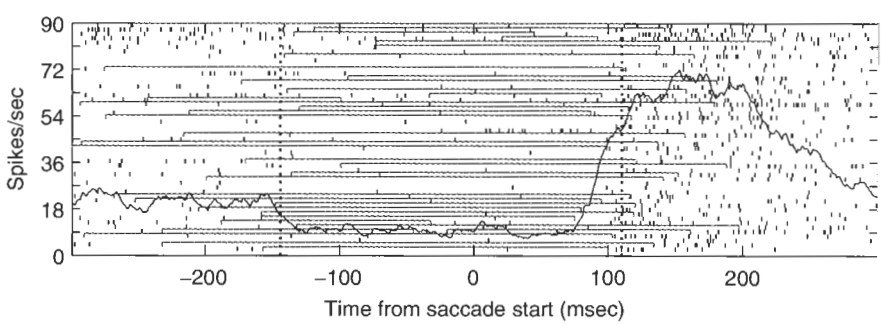

Fig. 4. Effect of spontaneous saccades on LGN cell activity. A peristimulus time histogram for an LGN cell recorded while the monkey produced 53 spontaneous saccades in a completely darkened room. Saccade start was determined by examining eye velocity and segments of the spike train were aligned on saccade start (0 m). The small tick marks represent spikes and the horizontal brackets represent significant increases in interspike interval as determined by a Poisson analysis. The vertical dashed lines represent the modal onset (−144 m) and offset (110 m) of the periods of significant modulation relative to saccade start.

significant suppression of burst firing during saccades, suggesting that the temporal structure of the LGN message is changed during saccades, perhaps increasing the visual threshold in this manner. Our examination of the prevalence of bursts during fixations and saccades in awake behaving monkeys supports the results of Ramcharan et al. (2001), showing that bursts are reduced during saccades (Royal et al., 2003). However, since, on average, less than 6% of spikes met the criteria for being classified as a burst and considering that saccades are generally very short (lasting on average 40 msec), it is not clear if such changes in burst number are behaviorally meaningful (Royal et al., 2003).

Recently, Thilo et al. (2004) addressed the issue of saccade related modulation of the LGN in humans. Although their experimental design prevented them from addressing the issue of postsaccadic enhancement, their data argue that LGN activity is suppressed during saccades. Using a combination of direct retinal stimulation and transcranial visual cortical stimulation to produce phosphenes, they showed that subjects experienced a significant reduction in contrast sensitivity during saccades only when the phosphenes were induced retinally, not cortically, suggesting that the site of saccadic suppression must be the LGN.

Additionally, there are reports suggesting that cells both in the LGN and V1 are sensitive to changes in eye position (Weyand and Malpeli, 1993) and microsaccadic eye movements — local eye movments of less than 2° that presumably refresh the image on the retina (Martinez-Conde et al., 2000). In fact, cells in many extrastriate cortical areas have been reported to be sensitive to changes in eye position (Anderson and Mountcastle, 1983; Andersen et al., 1985; Galletti and Battaglini, 1989). In anesthetized, paralyzed cats, Lal and Friedlander (1989, 1990) demonstrated that modulation of visual responses were eliminated with a retrobulbar block, suggesting that information from eye muscles reaches the LGN. Weyand and Malpeli (1993) reported a monotonic relationship between eye position and excitability in visual cortical cells in cats. It may be then that in addition to providing information about the saccade target of the eye, the LGN extracts information about the absolute external coordinates of visual targets and this information is combined with visual information before reaching V1.

The obvious question then is where do the signals come from that orchestrate the saccade-related and eye position-related changes we see in the LGN. These signals result in changes in gain that are linked in time directly to the saccade. These saccadic modulatory changes in the LGN cannot be driven by motivation since they occur spontaneously in the dark. The timing of saccade related suppression begins so far in advance of the saccade in both cats and monkeys that the signals that arrive at the LGN likely relate more to the decision to shift gaze (i.e., motor planning) than to the actual motor command underlying the gaze shift. The PPT has been implicated both in attentional orienting to a target and to the production of saccades and so may provide both types of information although this input is generally thought to enhance, not suppress, LGN activity (Uhlrich et al., 1995). Nevertheless, the complex circuitry of the PPT and its links to the intermediate layers of the superior colliculus and many other areas suggest that the PPT could function to control the biphasic change in activity seen in the LGN during saccades. It is also possible that several inputs working together provide the signals that modulate LGN activity during eye movements. The simplest explanation for LGN suppression is that the input signals either are directly inhibitory or activate the inhibitory circuits through GABAergic LGN interneurons or GABAergic TRN neurons. One possible source of this inhibitory information is the pretectogeniculate pathway specifically from the NOT (Schmidt, 1996; Schmidt et al., 1996). NOT cells are GABAergic and are excited during saccades (Schmidt, 1996). Schmidt and colleagues (Schmidt, 1996; Schmidt et al., 1996) have argued that NOT cells that project to LGN inhibit LGN interneurons in cats, thus causing excitation of LGN relay cells. The latter circuit again would be more appropriate to explain postsaccadic enhancement than perisaccadic suppression given its effect on relay cells in cats and given that the activation starts after saccades begin. In primates this pathway could contribute to saccade related suppression and enhancement since this pathway projects to both interneurons and relay cells (Feig and Harting, 1994), although it tends to project mainly to P LGN layers. The superior colliculus also is a good candidate to contribute to saccade related modulation given that cells in the intermediate layers show the

appropriately timed modulation in relation to saccades (Mohler and Wurtz, 1976). However, the intermediate collicular layers do not project directly to the LGN and the superficial collicular layers that project to the LGN project only to the K layers (Harting et al., 1991a; Lachica and Casagrande, 1993). The colliculus has been proposed to provide saccade related signals indirectly to the LGN in the rabbit (Zhu and Lo, 1996). This circuit involves a projection from the intermediate layers of the superior colliculus to the TRN via the central lateral thalamic nucleus. The central lateral nucleus belongs to the intralaminar nuclear group which has been shown in several studies to contain cells that respond in relationship to saccadic eye movements, motor planning, and shifts in attention (Schlag and Schlag-Rey, 1984, 1985; Wyder et al., 2004). As mentioned earlier, CL projects not only to the basal ganglia but widely to layer I of visual cortex. The beauty of the latter indirect circuit is that the overall time course of activation in the colliculus and suppression in the LGN fit with the time course of saccadic suppression, beginning well before saccade initiation and ending just prior to saccade end.

5 Visual attention in the thalamus and LGN

Attention is defined as the ability to actively select or give priority to relevant internal or external stimuli, cognitive processes, or motor activities (Machinskaia, 2003). As such, attention can refer to a number of processes (Sieb, 1990). Attention should be distinguished from general arousal or the overall sensitivity of a system to events. We know, for example, that LGN activity can be modulated globally by different stages of sleep and arousal (McCormick and Prince, 1986; McCormick and Pape, 1990; Steriade, 1996). Attention is selective. Evidence demonstrates that there are different forms of attention. Selective attention can occur in the form of orienting to stimuli in such a way as to give them priority. Such orienting can either be covert (no movement required) or overt anticipating the necessity for action. Some have argued that orienting may not require higher level processing but be part of a "bottom up" attentional system (Julesz, 1990; Graboi and Lisman, 2003). Other forms of attention clearly require volitional control involving memory and are generally regarded as part of a "top down" attentional system (Montero, 2000; Freeman et al., 2003; Graboi and Lisman, 2003; Sussman et al., 2003). Posner and Dehaene (1994) proposed that there are three neural networks of attention, a posterior system involved in orienting, an anterior system concerned with directing attention and providing awareness, and a third neural system connecting the two others concerned with vigilance. Vigilance is generally defined as the process of maintaining a particular focus of attention over time. The question we pose here is whether or not the LGN participates in any of these processes defined as attention. The common belief, however, is that the LGN is a low level sensory relay in a feedforward pathway to cortex; attentional effects are thought to mainly involve networks in higher cortical areas especially the frontal and parietal lobes (Corbetta, 1998). Nevertheless, some investigators have argued that shifting attention is the reason the thalamus exists since thalamic nuclei form the major gateway to cortex for all sensory information except olfaction (Crick, 1984; Jones, 2002). In fact, Crick (1984) proposed twenty years ago that the main function of the TRN was to direct the "searchlight" of attention. Given that the TRN lacks a direct connection with cortex, the TRN can communicate with cortex only through an intermediate thalamic nucleus such as the LGN.

Now that the concept of attention is introduced, let us consider whether LGN responses are influenced by attention. In the literature, the pulvinar is most often cited as the thalamic nucleus or nuclei concerned with shifts in visual attention. The extensive connections of the pulvinar with cortex, the fact that the pulvinar receives its main visual drive from V1 in primates and gets input from the superficial superior colliculus (also implicated in visual attention), and is linked to visual attentional deficits following inactivation (Bender and Youakim, 2001) all have argued in favor of the pulvinar as the main thalamic nucleus concerned with visual attention (Petersen et al., 1987). Additionally, several past studies of visual attention at the cortical level did not find evidence that attention impacts responses of V1 cells as would be expected if the LGN paid attention (Wurtz and Mohler, 1976; Robinson et al., 1980); changes with attention were identified in these same studies in

higher cortical visual areas. More recent studies, however, have documented significant effects of attention in V1 although not necessarily in the LGN (Bender and Youakim, 2001). For example, Motter (1993) showed that 30% of the cells in V1, V2, and V4 exhibit enhanced responses in an orientation discrimination task where stimuli were presented either inside or outside the receptive fields of neurons. These effects were just as strong in V1 as in the other visual areas examined. Similarly Haenny and Schiller (1988) found that the responses of V1 neurons were enhanced by attention but the magnitude of this effect was much greater for cells in V4 in the latter study. Roelfsema and Spekreijse (2001) also reported that macaque V1 responses show evidence of attention when monkeys must decide whether a line passing across the receptive field is connected to the fixation point or disconnected from it. In both of the latter tasks the neuron's receptive field received identical stimulation but neural responses differed and reflected the monkey's interpretation of the relevance of the stimulus in relation to a planned saccade to receive a reward.

In all the above examples where attention was found to influence V1 cell responses, the effect of attention served to enhance the response to the attended stimulus. In some cases, however, suppression of unattended stimuli has been found. Vanduffel et al. (1997) used a double-labeling 2-deoxyglucose (2-DG) technique in an orientation discrimination task in macaque monkeys to demonstrate that unattended stimuli in V1 produced lower than baseline labeling suggesting that activity in these unattended areas was suppressed. Relevant to this chapter is the fact that they also saw suppression of labeling magnitude in unattended retinotopic zones in the LGN. Interestingly, the effects in LGN and V1 were confined to the M LGN layers (and possibly the surrounding K layers) and the M dominated cortical layers in V1. Until very recently the latter was the only study that demonstrated clear attentional effects in the LGN. Recently, strong attentional effects were reported using fMRI in human LGN under covert orienting conditions where subjects attended or ignored flickering checkerboard stimuli of variable contrast presented in both hemifields (O'Connor et al., 2002). In the latter experiment eye movements were ruled out based upon control experiments conducted outside of the scanner. The effects of attention within V1 and several other visual cortical areas were also compared (Fig. 5). In both LGN and V1, O'Connor et al. (2002) reported that neural responses were enhanced to attended stimuli and attenuated to ignored stimuli. Furthermore, and perhaps most interestingly, activity in LGN increased on the attended side in the absence of any visual stimulation. Surprisingly, the magnitude of attentional effects were much larger in LGN than in V1 (Fig. 5), suggesting that the attentional modulation in LGN comes not from V1 but from other sources of input to the LGN or from a combination of sources given the magnitude of these effects (see later in the chapter). Given the low spatial resolution of fMRI, it could be argued that the authors were actually seeing attentional effects in the pulvinar rather than the LGN especially since the pulvinar is larger and lies directly adjacent to the LGN. In a second study (Kastner et al., 2004), the authors attempted to rule out this possibility by showing that attention related activation of pulvinar is distinct from that observed in the LGN, suggesting that each nucleus may contribute to a different form of attention; Perhaps the LGN-V1 circuit contributes where precise spatial attention is required and the pulvinar-cortical circuits contribute mainly to nonspatial forms of attention.

Recently, we examined if the effect of attention could be demonstrated at the single cell level in the LGN of awake behaving macaque monkeys (Royal et al., 2004, 2005). In these preliminary studies, the receptive field was stimulated with a flashing square using stimuli optimized for each cell. Monkeys were trained to perform several tasks but in all conditions the LGN receptive fields were stimulated identically under attended and ignored conditions, eye movements were controlled, and any changes in activity were measured prior to the initiation of saccadic eye movements. The monkeys were required to saccade to one of the two stimuli and, if it was rewarded, the monkey could expect to be rewarded at the same location for the next 20–30 trials. An error indicated to the monkeys that the other stimulus was now correct for the next block of trials. Under these conditions while baseline activity generally did not change, some cells demonstrated a significant enhancement of the response when the receptive field target was correct and thus located in the

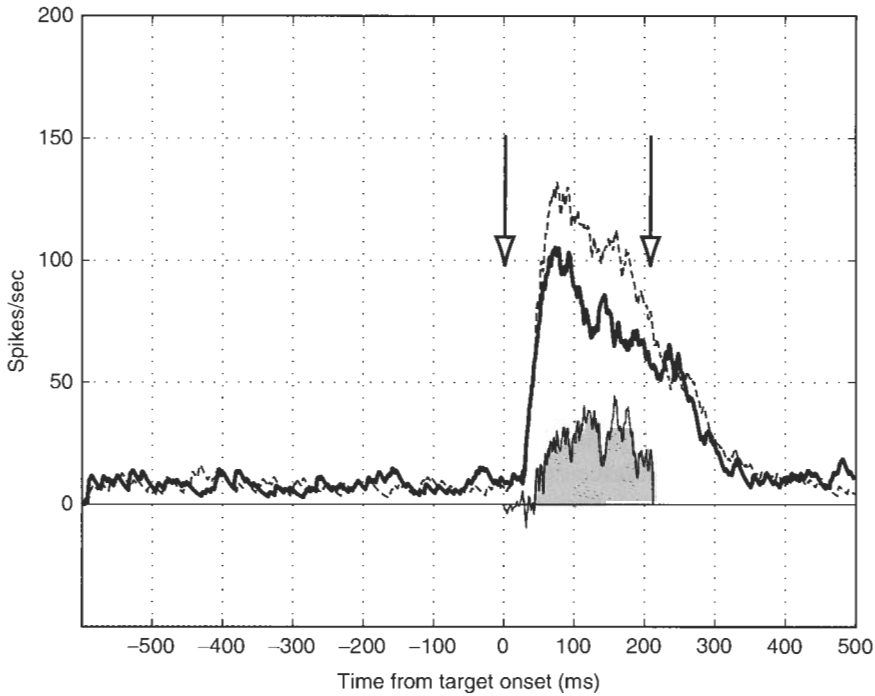

Fig. 5. Attentional modulation of LGN cells in macaque monkey. Peristimulus time histogram showing average firing rates of one LGN unit over 20 trials per condition during a task where the monkey was presented with two stimuli simultaneously. One stimulus was always in the receptive field (RF) of the neuron, the other was placed symmetrically, at the same eccentricity, outside of the RF (nonRF stimulus). The location of the rewarded stimulus alternated in blocks of 20 trials. Arrows indicate target onset and mean latency of the saccades. Dashed curve shows cellular activity in the condition when the rewarded target was in the RF of the neuron, bold line shows the mean response level when the animal had to make a saccade to the nonRF stimulus. Grey area shows the difference of the areas under the curves. The responses differed significantly, i.e., the same pair of stimuli elicited larger responses when the animal had to make a saccade to the RF compared to the condition, when the target of the saccade was the nonRF stimulus. From Royal et al. (2004). (See text for details.)

presumed attended field relative to the response when the non-receptive field target was correct (Fig. 6.). We used the same paradigm to test whether an attentional effect could be demonstrated when both targets were placed in the upper and lower quadrants of the same hemifield. The result was the same, i.e., when the correct target was in the receptive field the response differed from the response when this target was incorrect. The results from the task where targets were presented in the same hemifield suggest that attentional regulation of responses may be spatially quite restricted. These preliminary results support the idea that attention may regulate LGN responses but given that each block of trials was not presented more than once, more comprehensive experiments will be required to confirm these results. This form of restricted spatial attention has also been reported in V1 but has not been reported for the dorsomedial pulvinar where more global spatial attentional shifts are reported and where the receptive fields of cells are very large (Petersen et al., 1987). Taken together with imaging results in humans, these results support the view that the LGN can pay attention. However, again, further analysis and tests will be required to rule out other explanations.

Given that very few studies have been done to examine the responses of LGN cells in awake primates (see also Sherman and Guillery, 1996, 1998), many questions still remain about the types of attention that can be demonstrated at the level of the LGN and the circuitry involved in these LGN attentional effects. The results summarized above support the idea that LGN and V1 responses to restricted attended targets can be enhanced much as

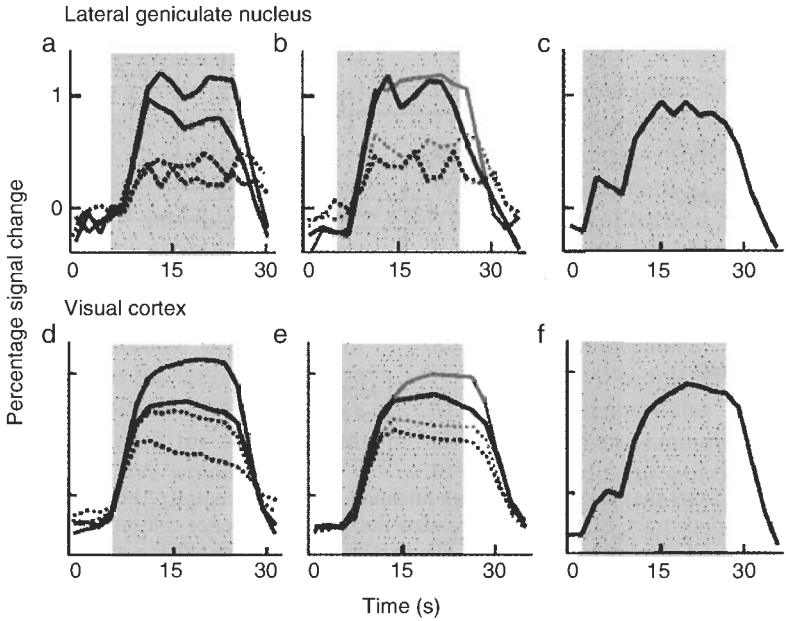

Fig. 6. Time series of fMRI signals in the LGN (a–c) and visual cortex (d–f). Group analysis ($n=4$). Data from the LGN and visual cortex were combined across left and right hemispheres. Activity in visual cortex was pooled across areas V1, V2, V3/VP, V4, TEO, V3A and MT/MST. (a,d) Attentional enhancement. During directed attention to the stimuli (red curves), responses to both the high-contrast stimulus (100%, solid curves) and low-contrast stimulus (5%, dashed curves) were enhanced relative to an unattended condition (black curves). (b, e) Attentional suppression. During an attentionally demanding fixation task (black curves), responses evoked by both the high-contrast stimulus (10%, dashed curves) were attenuated relative to an easier attention task at fixation (green curves). (c, f) Baseline increases. Baseline activity was elevated during directed attention to the periphery of the visual hemifield in expectation of the stimulus onset (blue). Gray shades indicate periods of checkerboard presentation. From O'Connor et al. (2002) with permission.

would be predicted by Crick's hypothesized "searchlight" of attention. That imaging results show a smaller attentional effect in V1 than in LGN argues against feedback from V1 as the searchlight source, although it is, however, possible that the impact of V1 feedback is enhanced via collateral branches within the TRN (see above), particularly if the TRN also is responsible for suppressing activity in regions that are not retinotopically aligned with the target stimulus.

The superior colliculus is unlikely to provide this input directly to LGN even though very similar attentional effects have been reported in the superficial layers of the colliculus (Goldberg and Wurtz, 1972; Wurtz and Goldberg, 1972; Ignashchenkova et al., 2004). This is because colliculo-geniculate input primarily targets the K LGN layers. As with visual cortex, however, collicular input could impact LGN responses via the TRN given that collicular projections are retinotopic and the TRN sends a topographically specific projection back to all LGN layers. Since attentional effects in one LGN can be compared between the two hemifields and each LGN only represents one hemifield, this presumably means that relevant information must pass either cortically or subcortically between hemispheres. Visual cortical, TRN, and collicular inputs to LGN remain ipsilateral but cholinergic input to the LGN from the PPT is bilateral. The wide connections of this pontine region with the rest of the brain (Fig. 7) and the fact that stimulation within this region results in enhanced responses in the LGN emphasize that connections from PPT may contribute although they cannot alone account for retinotopic specificity of the spatial attentional effects reported by many. Other inputs to the LGN described above seem less likely to contribute to attentional shifts. Serotonergic input from the dorsal raphé and histaminergic input from

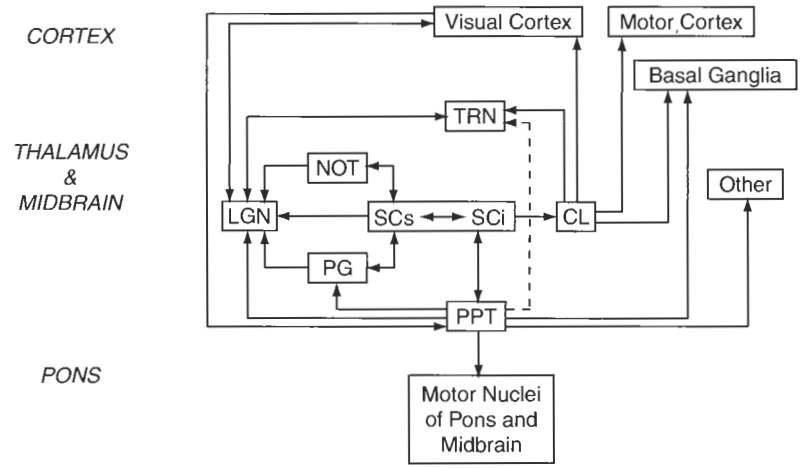

Fig. 7. Circuits involving the LGN that are related to both attention and motor control. Abbreviations: TRN: thalamic reticular nucleus, NOT: nucleus of the optic tract, LGN: lateral geniculate nucleus, SCs: superior colliculus (superficial layers), SCi: superior colliculus (intermediate layers), CL: central lateral nucleus, PG: parabigeminal nucleus, PPT: pedunculopontine tegmentum. See text for details.

the tuberomammillary nucleus have been proposed to provide for either global suppression or global enhancement, respectively, of activity in the LGN without much topographic specificity and so would need to work together with other inputs to contribute to any spatial attention seen in LGN. GABAergic input from the NOT and cholinergic input from the parabigeminal nucleus (Fig. 3) could also contribute when motor planning is involved, but attentional effects have not been described for either of the areas. It seems likely given the dynamic nature of the system that the signals from many of these areas contribute to the final output of each LGN cell.

Experiments of Davidson et al. (1999) support the idea that the cholinergic input from the PPT could contribute to the spatial attentional effects seen in the LGN. Davidson and colleagues (1999) observed a dose-dependent increase in reaction time and decrease in accuracy of eye movements in a task where the target was preceded by a visual cue when the cholinergic muscarinic antagonist scopolamine was administered. The slowing was most prominent when the animal received valid cues in either visual field. Slowing, however did not occur in those trials whose cues lacked spatial information, or in tasks in which attention was directed to events at the fixation point. These results provide additional support for the hypothesis that ACh plays a key role in reflexive attentional shifting to peripheral visual targets and supports the idea that the PPT pathway to the LGN may contribute to this role.

Conclusions and remaining questions

As we have described above, the LGN receives many non-retinal sources of input that together outnumber the retinal input to the LGN. Given the diversity of connections that each of these input sources has with the rest of the brain, it is clear that LGN cells are probably modulated by many different sensory, motor, and cognitive messages. Closer inspection of the types of circuits that impact the LGN suggest that signals leaving this nucleus are mainly influenced by three types of information. First, LGN cells are clearly influenced by the global state of the animal. Many investigations have documented the differences in LGN responses that occur when animals are awake or asleep (McCormick and Prince, 1986; McCormick and Pape, 1990; Steriade, 1996). Second, many inputs to the LGN appear to be concerned with motor planning — conveying signals concerning saccade targets, eye position, as well as eye movements themselves. Finally, evidence indicates that several inputs to the LGN carry signals that are designed to enhance activity to particular visual targets or to

visual stimuli within particular spatial locations via prominent inputs from both brainstem and cortex via shifts in attention. The fact that some of these inputs to the LGN, like the cholinergic input from the PPT, also carry signals concerned with saccadic eye movements supports previous models which have suggested that spatial attention is intimately linked to planned saccadic eye movements (Fig. 7; Hahnloser et al., 1999; Horwitz and Newsome, 2001). Some have argued that this relationship is obligatory, namely, that one cannot make a saccadic eye movement without switching attention to the target of that eye movement (Deubel and Schneider, 1996; Ditterich et al., 2000). Others have argued for very separate circuits (Murthy et al., 2001). We would argue for a partial relationship since some inputs to the LGN do appear to carry eye movement or eye position related signals that have not been directly linked to attention such as the NOT and the parabigeminal nucleus. The latter connections suggest that modulation of LGN by eye movements may not always be linked to attentional modulation in an obligatory way.

Since very few studies have directly examined the impact of motor planning and attention on LGN activity in awake behaving animals, many questions still remain to be answered. Some of these questions are listed below. Improvements in the resolution of imaging techniques and the ability to record from multiple brain sites simultaneously in awake behaving animals open new doors that will allow us to answer some of these questions in future studies.

- Why do collicular, parabigeminal, and extrastriate inputs project mainly to LGN K layers?
- Why does the input from NOT target mainly the P layers?
- Does the PPT contribute to eye movement related modulation of LGN activity?
- Does the visual TRN in primates show saccade or attention related modulation?
- Is cholinergic input from the PPT the essential circuit for the attentional effects seen in LGN?
- Are the attention related effects in V1 and LGN really independent as fMRI data suggest?
- Which high-level processes influence LGN activity and under what conditions is modulation most evident/favorable?

Abbreviations

LGN	lateral geniculate nucleus
TRN	thalamic reticular nucleus
V1	primary visual cortex
V2	visual cortical area 2
V3	visual cortical area 3
V3a	visual cortical area 3a
V4	visual cortical area 4
V5	visual cortical area 5
K	koniocellular
P	parvocellular
M	magnocellular
GABA	gamma-aminobutyric acid
PPT	pedunculopontine tegmentum
fMRI	functional magnetic resonance imaging
2-DG	2-deoxyglucose
NOT	nucleus of the optic tract
DOG	difference of Gaussians
ACh	acetylcholine
CL	central lateral nucleus
MT	middle temporal cortical area
DM	dorsomedial cortical area
DL	dorsolateral cortical area
mGluRI	metabotropic glutamate receptor, type I
mGluRII	metabotropic glutamate receptor, type II

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