Visual Functions of the Thalamus

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Abstract

The thalamus is the heavily interconnected partner of the neocortex. All areas of the neocortex receive afferent input from and send efferent projections to specific thalamic nuclei. Through these connections, the thalamus serves to provide the cortex with sensory input, and to facilitate interareal cortical communication and motor and cognitive functions. In the visual system, the lateral geniculate nucleus (LGN) of the dorsal thalamus is the gateway through which visual information reaches the cerebral cortex. Visual processing in the LGN includes spatial and temporal influences on visual signals that serve to adjust response gain, transform the temporal structure of retinal activity patterns, and increase the signal-to-noise ratio of the retinal signal while preserving its basic content. This review examines recent advances in our understanding of LGN function and circuit organization and places these findings in a historical context.

Keywords

retina; LGN; vision; primate; cat; mouse

INTRODUCTION

With the exception of the olfactory system, sensory information from the periphery is first processed in the thalamus before reaching the cerebral cortex. Although precortical thalamic processing is a fundamental feature of sensory systems, its role in sensory processing is often underappreciated. In the visual system, retinal ganglion cells (RGCs) project directly to the lateral geniculate nucleus (LGN) of the dorsal thalamus, which in turn projects to the primary visual cortex (V1). The LGN is considered a first-order thalamic nucleus on the basis of its close relationship with the retina. In contrast, the pulvinar nucleus—another thalamic nucleus involved in vision—is considered a second-order nucleus, as it primarily receives afferent input from the cortex. Although both thalamic nuclei play fundamental roles in visual processing, this review focuses on the LGN.

Historically, studies comparing visual responses in the retina and LGN have emphasized the high degree of similarity between the receptive fields of cells in these two structures. This

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similarity, along with the strong driving force that the retina has on the LGN, has led to a general view that the LGN does little in terms of processing or refining visual signals en route to cortex. Although the spatial organization of neuronal receptive fields in the retina and LGN are indeed quite similar, a closer examination of the activity patterns of RGCs and LGN neurons reveals major differences in the temporal structure of neuronal spike trains. These differences arise via a variety of mechanisms and serve to decrease noise in the signals transmitted to cortex and to adjust the efficacy of geniculocortical communication under different behavioral and cognitive states. In this review, we examine recent and past work on the organization of inputs to the LGN, the powerful influence of retinal inputs on evoking LGN responses, how retinal activity is transformed temporally within the LGN, and how nonretinal inputs influence these transformations. We also consider the powerful influence of behavioral state and network oscillations on the transmission of retinal information to V1. Taken together, these results extend our understanding of visual circuits in the thalamus, underscore the prevalence of dynamic processing of visual signals en route from retina to cortex, and emphasize the central role of the LGN in visual processing.

ANATOMICAL OVERVIEW

Convergence and divergence are present in the pathway from the retina to the LGN. Individual LGN neurons are estimated to receive synaptic input from one to five RGCs, and individual retinal axons provide synaptic input to multiple LGN neurons (Cleland 1986, Hamos et al. 1987, Reid & Usrey 2004). Although this convergence and divergence has functional implications for the activity profiles of LGN neurons (described in more detail below in the subsection titled "Remapping the Retinal Mosaic Increases the Efficacy and Resolution of the Visual Signal") the tight retinotopic specificity of RGC–LGN connections ensures that presynaptic and postsynaptic receptive fields have similar sizes and shapes (Hubel & Wiesel 1961; Cleland et al. 1971a,b; Kaplan et al. 1987; Mastronarde 1987; Usrey et al. 1998, 1999; Levine & Cleland 2001; Rowe & Fischer 2001; Sincich et al. 2007, 2009; Weyand 2007; Rathbun et al. 2010). The position of the LGN between the retina and V1 is conserved across species, but its structural arrangement, including the number of layers and the organization of parallel processing streams with respect to these layers, can vary tremendously (Figure 1).

In Old World monkeys and in humans, the LGN is composed of two magnocellular layers, four parvocellular layers, and six koniocellular layers. As we discuss below (see the section titled "Cell Classes and Visual Physiology"), neurons in magnocellular, parvocellular, and koniocellular layers differ dramatically in terms of their visual physiology, a distinction evident in the responses of their afferent input. These layers also differ in their projections to V1: Magnocellular neurons project to layer 4Cα, parvocellular neurons project to layer 4Cβ, and koniocellular neurons project to layer 2/3.

Lamination in the feline LGN follows a different plan. The feline LGN has two principal layers, A and A1, which receive input from the contralateral and ipsilateral eyes, respectively. Both of these layers contain X- and Y-type neurons, and project axons to layer 4 of V1 (reviewed in Jones 2006). In addition to these layers, the feline LGN contains four C

layers (Hickey & Guillery 1974) that contain Y- and/or W-type neurons: the Y-cells project to layer 4 of the cortex, and the W-cells project to the superficial layers.

Lamination is less evident in rodents; input from the contralateral eye extends across the entire LGN, and ipsilateral eye input overlaps within the binocular zone (Godement et al. 1984, Reese 1988; see also Howarth et al. 2014). Interest in rodent vision has increased rapidly over the past decade, and recent studies have identified a structural organization and segregation of cell types that is more complex than originally thought. For instance, RGCs that respond well to stimulus motion in the anterior and posterior directions provide input to a thin region along the edge of the rodent LGN, which contains neurons that provide input to direction-selective neurons in cortex (Huberman et al. 2009, Marshel et al. 2012, Piscopo et al. 2013, Cruz-Martín et al. 2014).

Independent of species and laminar classification, LGN neurons belong to one of two major classes, thalamocortical relay neurons and inhibitory interneurons, both of which receive monosynaptic excitation from the retina. Thalamocortical relay neurons are excitatory and provide glutamatergic excitation to target neurons in V1. Although historically thought to make no direct contribution to local processing, recent work in the cat has identified a sparse collateral projection from thalamocortical relay axons that provides synaptic input to other neurons in the LGN (Bickford et al. 2008). In contrast, LGN inhibitory interneurons provide only local, GABAergic inhibition within the LGN; they do not project to the primary visual cortex.

GENERAL PROPERTIES OF LATERAL GENICULATE NUCLEUS RECEPTIVE FIELDS

The prototypical, classical receptive fields of RGCs and LGN neurons have a circularly symmetric, spatially antagonistic, center–surround organization. On-center LGN neurons have a center subunit that is excited by luminance increments and suppressed by luminance decrements. In contrast, the surround subunit of on-center cells is excited by luminance decrements and suppressed by luminance increments. Off-center cells have the opposite polarity; the center is excited by dark and suppressed by light, and the surround is excited by light and suppressed by dark. This receptive field structure makes neurons selective for spatial position and phase, as well as for spatial frequency. In general, LGN neurons and their presynaptic retinal partners are not selective for stimulus orientation or direction of motion. As we discuss below (see the section titled "Cell Classes and Visual Physiology"), however, certain classes of LGN neurons in the rodent are selective for both orientation and direction of motion.

The center–surround organization of visual receptive fields was recognized more than 50 years ago (Kuffler 1952, 1953; Barlow et al. 1954). Regarding his recordings from cat RGCs, Steven Kuffler noted (1953; page 62), "In all fields there exists a central region giving a discharge pattern which is the opposite from that obtained in the periphery. The center may be predominately 'off', the surround 'on' or vice versa. In view of the fixed nature of the of the center discharge, it may be convenient to classify receptive fields into 'on' center and 'off' center." The center–surround filter of early receptive fields appears to

be fundamental for visual processing, as this receptive field organization has been observed in a wide range of species, including frogs (Barlow 1953), monkeys (De Monasterio & Gouras 1975), tree shrews (Conway & Schiller 1983), and mice (Stone & Pinto 1993). The center–surround receptive field can be modeled accurately using a difference of Gaussians (DOG) equation (Rodieck 1965, Rodieck & Stone 1965). In this model, receptive fields comprise two antagonistic linear subregions: The center and surround subunits (Gaussians) are spatially overlapping, and the center subunit is smaller in spatial extent but higher in peak amplitude than the surround subunit. Importantly, the surround subunit is not an annulus around the center subunit; instead, its presence in the center of the receptive field is overwhelmed by the strength of center subunit.

NONLINEAR RECEPTIVE FIELD PROPERTIES

Although the receptive fields of RGCs and LGN neurons can be approximated as linear filters and are indeed highly linear relative to those of cortical neurons, important nonlinear response properties, such as gain control (described in the following subsection), were identified early on from subcortical recordings. These nonlinearities are now recognized as standard features found in the retina, LGN, and visual cortex. Since their identification, the nonlinear features of the early visual system have been described in much greater detail (Bonin et al. 2005, Mante et al. 2008, Carandini & Heeger 2011).

Gain Control

The linear receptive field organization described by the DOG model provides specific predictions about the behavior of neurons that can be compared with measured responses. First, the linear DOG model predicts that the gain of a linear neuron should be constant, regardless of the strength of the visual stimulus. However, many RGCs and LGN neurons have markedly nonlinear contrast response functions that saturate at high contrasts (Enroth-Cugell & Robson 1966, Kaplan & Shapley 1986, Benardete et al. 1992, Usrey & Reid 2000, Alitto et al. 2011). The gains of these neurons are high at low contrast and low at high contrast. Second, the linear DOG model predicts that the temporal response properties of these neurons, such as response latency and duration, should be invariant as stimulus strength changes. Instead, the temporal response properties of RGCs and LGN neurons change dramatically as stimulus luminance and contrast increase (Shapley & Victor 1980, Benardete et al. 1992, Usrey & Reid 2000, Alitto & Usrey 2004, Mante et al. 2008). Responses to high-contrast stimuli have shorter latencies and durations relative to responses to low-contrast stimuli. Functionally, this difference makes visual neurons more sensitive to high temporal frequencies at high contrast and more sensitive to low temporal frequencies at low contrast.

Extraclassical Surround

Beyond the region of space defined as the classical receptive field is the extraclassical receptive field. In contrast to the classical receptive field, in which a stimulus of the preferred polarity excites the neuron (e.g., a black stimulus in the classical surround of an on-center receptive field excites an on-center neuron), in the extraclassical surround, visual stimulation of either polarity suppresses the activity of the neuron. Functionally, this

behavior leads to a phenomenon known as extraclassical suppression that can be demonstrated by the area summation response function of a neuron (Jones et al. 2000, Solomon et al. 2002, Bonin et al. 2005, Alitto & Usrey 2008, Mante et al. 2008). An area summation function reveals the response of a neuron to visual stimuli of varying spatial diameters. If the visual stimulus is selected carefully, the magnitude and spatial extent of the extraclassical receptive field can be estimated from the area summation function. If the wrong stimulus is chosen, disambiguating suppression from the classical surround versus that from the extraclassical surround is difficult (Bonin et al. 2005, Alitto & Usrey 2008).

CELL CLASSES AND VISUAL PHYSIOLOGY

Primates

The primate LGN contains three types of layers—magnocellular, parvocellular, and koniocellular—that represent distinct parallel streams for visual processing. Years of investigation have demonstrated that the visual physiology, sources of retinal input, and synaptic targets within V1 differ among neurons in these layers (reviewed in Schiller & Logothetis 1990, Merigan & Maunsell 1993, Casagrande 1994, Casagrande & Kaas 1994, Lee 1996, Hendry & Reid 2000, Nassi & Callaway 2009). Briefly, magnocellular neurons respond faster, more transiently, and with greater response gain than parvocellular neurons do, whereas parvocellular neurons respond better to stimuli with high spatial frequencies and to stimuli with chromatic structure than do magnocellular neurons. These differences in the visual physiology of magnocellular and parvocellular neurons are established in the retina and are evident in the visual physiology of the RGCs that innervate them. The segregation of signals through the LGN is maintained in projections to V1; magnocellular and parvocellular neurons provide nonoverlapping input to cortical layers 4Cα and 4Cβ, respectively.

Beneath each magnocellular and parvocellular layer is a koniocellular layer containing neurons whose projections bypass cortical layers 4Cα and 4Cβ and terminate directly on neurons in the superficial layers of V1 (Fitzpatrick et al. 1983). Neurons in the koniocellular layers also differ from those in the magnocellular and parvocellular layers in many other respects. Most notably, in contrast to neurons in the magnocellular and parvocellular layers, which receive selective input from only one type of RGC (parasol or midget, respectively), the koniocellular layers receive input from a diverse array of RGCs, including the small and large bistratified cells, the recursive monostratified and bistratified cells, the narrow and broad thorny cells, and the smooth and sparse inner cells (reviewed in Dacey & Packer 2003; Wässle 2004; Masland 2011, 2012; Crook et al. 2014). Moreover, in contrast to neurons in the magnocellular and parvocellular layers, which have monocular responses, some neurons in the koniocellular layers have binocular responses (Cheong et al. 2013), suggesting that individual koniocellular neurons combine retinal inputs either directly or through polysynaptic circuits. Finally, as evidence of the diversity of circuits that establish koniocellular responses, recent results have identified the full circuitry of a retinal pathway that supplies target neurons in the koniocellular layers with orientation and directional information, similar to that found in the mouse LGN (Cheong et al. 2013, Percival et al. 2014).

Felines

The feline LGN contains X cells, Y cells, and W cells. X cells are the most common cell type in the feline LGN and have highly linear center–surround receptive fields that are nonselective for either stimulus orientation or direction of motion (Enroth-Cugell & Robson 1966, Scholl et al. 2013). Although X cells are likely the first to have been fit to the linear DOG model, these cells are not completely linear: They often display a degree of contrast gain control and extraclassical suppression (Jones et al. 2000; see also Alitto & Usrey 2004). By comparison, Y cells exhibit stronger nonlinear responses, greater contrast gain control, and more robust extraclassical suppression. Perhaps the single greatest defining feature of Y cells is that they have high-frequency nonlinear receptive-field subunits that are made evident with a so-called null test. In contrast to X cells, which have a phase-dependent null point in their responses to counterphasing sinusoidal stimuli (as predicted for cells with linear responses), the responses of Y cells display a phase-dependent frequency doubling. This response property, first observed by Enroth-Cugell & Robson (1966), is believed to result from nonlinear subunits (Hochstein & Shapley 1976, Derrington et al. 1979) contributed by rectifying amacrine cells and bipolar cells (Stafford & Dacey 1997, Demb et al. 2001). Several other key aspects of the response dynamics of Y cells also differ from those of X cells. In particular, Y cells have shorter visual response latencies, respond more transiently to visual stimuli, and can follow stimuli at higher temporal frequencies in comparison with X cells (Cleland et al. 1971a,b; Fukada 1971; Ikeda & Wright 1972; Usrey et al. 1999).

Rodents

Research on the mouse visual system has experienced tremendous growth in recent years, largely owing to the advent of molecular tools for identifying cell types, dissecting neural circuits, and manipulating activity. Although mice generally are not considered to be highly visual when compared with more traditional animal models used in vision research, dismissing results obtained from the mouse would be a mistake. Indeed, recent results from studies in mice, including those conducted in the retina and LGN, have provided valuable information that would be difficult or impossible to obtain in other model systems.

Importantly, electrophysiological and optical recordings from the mouse LGN have revealed greater diversity among cell types and response properties than has been reported for either cats or primates. This diversity includes cells that have receptive field properties generally considered more typical of V1 neurons in monkeys and cats, such as orientation selectivity and direction selectivity, and cells that have response properties not commonly found in the retinogeniculocortical pathway in more traditional animal models, such as neurons that encode the absence of contrast (Huberman et al. 2009, Marshel et al. 2012, Piscopo et al. 2013, Scholl et al. 2013, Cruz-Martín et al. 2014; see also Barlow et al. 1964). Although cells that have these more complex receptive field properties that are absent or rare in the principal layers of the LGN (those that project to cortical layer 4 in V1) in cats (A layers) and monkeys (magnocellular and parvocellular layers), they may exist in the C layers or koniocellular layers, which have received considerably less attention. In support of this possibility, anatomical and physiological studies have revealed a much greater diversity of RGCs with projections to these layers compared to the principal layers (reviewed in Dacey

& Packer 2003; Wässle 2004; Masland 2011, 2012; Crook et al. 2014). Thus, results from the mouse may provide insight into the broader range of possible processing strategies utilized across mammals.

GENERAL PROPERTIES OF RETINOGENICULATE SYNAPSES

Although retinal axons provide a minority of synapses onto LGN neurons, RGCs are the primary drivers of LGN activity (Hubel & Wiesel 1961; Cleland et al. 1971a,b; Kaplan & Shapley 1984; Mastronarde 1987; Kaplan et al. 1987; Usrey et al. 1999; Rathbun et al. 2010; for review, see Sherman & Guillery 2009). Results indicate that more than 95% of LGN spikes are directly evoked by retinal inputs (Kaplan & Shapley 1984, Sincich et al. 2007). RGCs provide strong glutamatergic input onto the proximal dendrites of both LGN relay neurons and LGN local inhibitory neurons. Retinal excitatory postsynaptic potentials (EPSPs) are, relatively speaking, enormous; indeed, they are often sufficiently large that they can be measured using extracellular recording methods. These events, called S-potentials (Bishop et al. 1962), can be measured simultaneously with LGN action potentials and have therefore been useful for studies examining the responses of synaptically connected RGCs and LGN neurons.

The specificity and strength of retinal synaptic inputs onto LGN neurons can also be determined from simultaneous recordings from inside the eye and from the LGN (Cleland et al. 1971a,b). One advantage of this dual recording technique over S-potential recordings is its ability to study retinogeniculate communication for cell pairs with either strong or weak connections (Mastronarde 1987, Usrey et al. 1999). This feature is useful because the ensemble of RGCs that provide convergent input onto an LGN neuron usually includes one cell with strong connectivity and the remainder with weaker connectivity (Cleland 1986, Usrey et al. 1999). From these types of recordings, the strength of connectivity can be quantified using measures of efficacy (the percentage of retinal spikes that evoke an LGN response) and contribution (the percentage of LGN spikes evoked by a particular RGC) (Cleland et al. 1971a,b). Using S-potential and dual recording methods, the range of contribution values calculated for weakly and strongly connected cell pairs is 1–100% (Kaplan & Shapley 1984, Kaplan et al. 1987, Mastronarde 1987, Usrey et al. 1999, Levine & Cleland 2001, Rowe & Fischer 2001, Sincich et al. 2007, Weyand 2007, Rathbun et al. 2010). As might be expected, the similarity between presynaptic and postsynaptic receptive fields increases as the strength of connection increases (Usrey et al. 1999, Rathbun et al. 2010).

NONRETINAL SYNAPTIC INPUT TO THE LATERAL GENICULATE NUCLEUS

Although retinal inputs are the primary driver of spiking responses in the LGN, most synaptic inputs onto LGN neurons come from nonretinal sources (reviewed in Sherman & Guillery 2009). Nonretinal inputs onto LGN neurons include various forms of thalamic inhibition, feedback from the cortex, and diffuse modulatory systems.

Thalamic Inhibition

LGN relay neurons receive inhibitory input from two classes of neurons: local inhibitory interneurons within the LGN and inhibitory neurons within the thalamic reticular nucleus (TRN). Within the LGN, 20–30% of neurons are inhibitory interneurons that provide local GABAergic input to neighboring relay neurons. Similar to relay neurons, LGN interneurons receive direct monosynaptic excitation from the retina; unlike relay neurons, however, this input is received by both ionotropic and metabotropic glutamate receptors (Cox & Sherman 2000, Acuna-Goycolea et al. 2008). LGN inhibitory neurons form two types of synaptic connections with relay neurons, commonly referred to as F1 and F2 terminals, based on their flat anatomical shape (Gray 1969, Sherman & Guillery 2009, Cox 2014).

F2 terminals typically belong to synaptic triads, unique structures involving elements from three cells: a retinal cell, an LGN relay cell, and a local inhibitory neuron. These triads comprise a retinal (or cholinergic) synapse onto the dendrite of an LGN relay cell and an F2 terminal on the dendrite of a local inhibitory neuron that is postsynaptic to the retinal (or cholinergic) axon and presynaptic to the relay cell dendrite. Importantly, F2 terminals are found on the distal dendrites of LGN interneurons. As LGN interneurons are not electrotonically compact, synaptic activity at the F2 terminal may occur in isolation from both the integration of other synaptic inputs and the generation of action potentials that underlie transmission at F1 terminals. F2 terminals in distal dendrites are not completely isolated, however: Under certain conditions, somatically activated action potentials can back propagate through the distal dendrites and stimulate neurotransmitter release from F2 terminals (Casale & McCormick 2011, Cox 2014).

Another source of inhibitory input to LGN neurons is the TRN, a thin nucleus that forms a sheath around the dorsal thalamus (Jones 2006). Although the TRN lacks anatomically well-defined boundaries, TRN connectivity with the LGN is retinotopically organized and is distinct from TRN regions that are interconnected with other thalamic nuclei. Neurons in the TRN do not receive direct input from the retina; instead, they receive visual signals from collaterals of geniculocortical axons and corticogeniculate axons (reviewed in Jones 2006). Given this organization of input, TRN neurons appear well poised to monitor activity levels in the LGN and cortex and to influence geniculocortical communication. This influence is likely complex, as TRN synapses involve both $GABA_A$ and $GABA_B$ receptors on relay neurons and are often located in close proximity to those of corticogeniculate axons (Sherman & Guillery 2009, Ulrich et al. 2007). Moreover, TRN neurons receive cholinergic input from the brain stem and basal forebrain (Parent et al. 1988, McCormick 1992, Guillery et al. 1998), thereby providing a route for arousal mechanisms to influence geniculocortical transmission.

Cortical Feedback

The single greatest source of synaptic input to the LGN comes from corticogeniculate feedback axons (Guillery 1969; Eri ir et al. 1997a,b). In contrast to retinal excitation, the influence of cortical feedback on visual processing in the LGN is poorly understood. Both LGN relay neurons and interneurons receive monosynaptic excitation from corticothalamic axons. As mentioned in the previous subsection, corticothalamic axons also target inhibitory

neurons in the TRN, which in turn provide inhibition to LGN neurons. Thus, cortical feedback has both a direct excitatory and disynaptic inhibitory influence on LGN relay neurons. Relative to retinal axons, corticothalamic axons have a much larger arborization, approximately 2–3 times the spread of retinal axons (Murphy & Sillito 1996). Consequently, individual corticogeniculate axons influence activity across a larger pool of LGN neurons than do individual axons from the retina. Although corticogeniculate synapses outnumber retinogeniculate synapses, unitary EPSPs from corticogeniculate axons have significantly smaller amplitudes than those from retinal axons do (reviewed in Sherman & Guillery 2009). In addition, corticogeniculate synapses are located more distally on the dendrites of relay cells than retinogeniculate synapses. For these reasons, and because the receptive fields of LGN neurons more closely resemble those of RGCs and not cortical cells, the corticogeniculate pathway is generally considered a modulatory pathway rather than a driving pathway (Sherman & Guillery 2009).

In primates, corticogeniculate feedback respects the segregation of feedforward parallel pathways traversing the LGN. In particular, parvocellular LGN neurons receive cortical feedback from V1 pyramidal neurons whose cell bodies are located in the upper half of layer 6, whereas magnocellular neurons receive input from the pyramidal neurons in the lower half of layer 6 (Conley & Raczkowski 1990, Fitzpatrick et al. 1994). Corticothalamic feedback inputs are not only anatomically separated but also physiologically distinct; feedback neurons supplying the parvocellular and magnocellular layers of the LGN have response properties that parallel those of their target neurons (Briggs & Usrey 2009). These results indicate that corticogeniculate feedback is able to exert a stream-specific influence on the feedforward transmission of visual signals to the cortex on the basis of its filtering properties.

Diffuse Neuromodulators

LGN neurons receive a variety of inputs from nonvisual neuromodulatory areas in the brain stem, including noradrenergic input from the reticular formation, serotoninergic input from the dorsal raphe nucleus, and cholinergic input from the parabrachial nucleus. Although these inputs do not drive LGN responses directly, they play an important role in adjusting LGN responses as a function of alertness and the sleep–wake cycle. As we discuss below (see the section titled "Behavioral State and the Gating of Sensory Information in the Lateral Geniculate Nucleus"), they also play an important role in modulating network interaction between the LGN and cortex.

TRANSFORMATION OF RETINAL INFORMATION IN THE LATERAL GENICULATE NUCLEUS

Although the receptive fields of LGN neurons generally resemble those of their retinal afferents, some important differences between the spatial domains of these receptive fields accompany more dramatic differences in the temporal properties of presynaptic and postsynaptic spike trains.

Stronger Classical Surrounds in the Lateral Geniculate Nucleus

Although the receptive fields of most LGN cells resemble those of their retinal afferents in terms of spatial location and center–surround organization, one consistent difference between the receptive fields of presynaptic and postsynaptic neurons is the strength of the classical surround. Originally reported by Hubel & Wiesel (1961), the stronger classical surrounds of LGN receptive fields are believed to play an important role in shifting the spatial frequency response functions of LGN neurons toward higher frequencies (Moore et al. 2014). Moreover, because the onset of responses in the classical surround is delayed relative to the onset of responses in the center, there is a temporal cascade in coarse- to fine-tuning for preferred spatial frequencies between the retina and LGN (Moore et al. 2014). Cellular mechanisms underlying the increased classical surround likely include feedforward disynaptic inhibition via LGN interneurons. Indeed, in an elegant series of experiments, Hirsch and colleagues (Wang et al. 2011a,b) used whole-cell recording methods to study the subthreshold response properties of LGN neurons and identified clear push–pull antagonism in the LGN, whereby nonpreferred stimuli presented in the classical surround evoked synaptic inhibition.

Stronger Extraclassical Suppression in the Lateral Geniculate Nucleus

As described above (see the subsection titled "Nonlinear Receptive Field Properties"), extraclassical suppression is a form of nonlinear suppression that overlaps and extends beyond the classical receptive field of LGN neurons. This form of suppression contributes to gain control in the LGN and can be quantified from area summation response functions using patches of sinusoidal stimuli that match the preferred spatial frequency of the neuron but differ in diameter. Circuit mechanisms that contribute to extraclassical suppression in the LGN have been the subject of intense investigation, and the results of these investigations thus far paint a complex picture. On the one hand, the results of studies of surround suppression and response gain in the cat and the mouse have indicated a prominent role for corticogeniculate feedback circuits in strengthening extraclassical suppression and in modulating neuronal responsiveness in the LGN (Sillito & Jones 2002, Olsen et al. 2012). On the other hand, the results of studies performed in monkeys have suggested that the strength of surround suppression in the retina is comparable to that in the LGN and, moreover, the onset of surround suppression in the LGN is too fast for circuits involving the cortex (Alitto & Usrey 2008). Further, extraclassical suppression in the LGN has been successfully modeled as an expression of retinal contrast gain control (Bonin et al. 2005). Although future work is needed to untangle these results, the identification of multiple mechanisms for extraclassical suppression in the LGNs of different species underscores the important role extraclassical suppression plays in visual processing.

The Role of Spike Timing in Enhancing Communication and Information Processing Between the Retina and the Lateral Geniculate Nucleus

Although the percentage of LGN spikes directly evoked from the ensemble of RGCs that provide monosynaptic input may exceed 95%, not all retinal spikes generate LGN action potentials (reviewed in Usrey 2002a,b). Indeed, individual RGCs typically fire two to three times more spikes than their target neurons in the LGN do (Rathbun et al. 2010). Thus,

postsynaptic potentials from some retinal spikes cross the spike threshold, and others do not. By comparing the spike trains of synaptically connected RGCs and LGN neurons, researchers have determined the time course of interaction between retinal spikes in driving LGN responses. Results show that retinal spikes that follow the shortest interspike interval (ISI), set by the refractory period of a cell, have the highest efficacy in driving LGN spikes, and the enhanced efficacy of second spikes in a pair persists for interspike intervals of up to 20–30 msec (Mastronarde 1987; Usrey et al. 1998; Levine & Cleland 2001; Rowe & Fischer 2001; Sincich et al. 2007, 2009; Weyand 2007; Rathbun et al. 2010). Moreover, retinal spikes that occur at ISIs of more than 40 msec rarely generate suprathreshold spiking responses (Sincich et al. 2007). Although retinogeniculate synapses studied in vitro display prominent synaptic depression, this depression appears to be saturated at activity levels associated with visual processing in vivo. Relatedly, modeling efforts indicate that the ISI-dependent enhancement of the second spike in a pair can be accounted for entirely by postsynaptic temporal summation (Carandini et al. 2007).

An important consequence of the enhanced efficacy of retinal spikes following short ISIs is a high-pass filtering of the retinal spike train—an effect that serves to increase the signal-to-noise ratio of LGN spikes relayed to the cortex relative to those supplied from the retina (Sincich et al. 2009, Rathbun et al. 2010, Wang et al. 2010). Similarly, retinal spikes that occur following short ISIs generate stronger response maps than do those that occur following longer ISIs (Rathbun et al. 2007, 2010). Relayed retinal spikes are also more reliable and have less temporal jitter than nonrelayed spikes do. Taken together, these results indicate that relayed retinal spikes are much more likely to be driven by visual stimulation of the retina than by random fluctuations in the membrane potentials of retinal cells that result from non-stimulus-related processes.

Remapping the Retinal Mosaic Increases the Efficacy and Resolution of the Visual Signal

As mentioned above (see the section titled "General Properties of Retinogeniculate Synapses"), the retinogeniculate projection does not maintain a 1:1 relationship between presynaptic and postsynaptic neurons. Individual RGCs often innervate multiple LGN neurons (anatomical divergence), and individual LGN neurons often receive input from multiple RGCs (anatomical convergence). Together, this divergence and this convergence result in remapping the representation of visual space by individual neurons across the LGN. This remapping appears to serve a practical role; computational analyses of the retinogeniculate projection indicate that the representation of visual space in the LGN is improved beyond the computational limits of the retinal mosaic (Martinez et al. 2014). In other words, convergence and divergence generate an interpolated map of visual space in the LGN that can facilitate the detection of stimulus position in the presence of sensor noise. Note that too much divergence and convergence in the retinogeniculate pathway would be problematic, as extreme levels would cause every LGN neuron to have the exact same receptive field. Interestingly, estimates of the optimal amount of divergence to maximize both the coverage of visual space and receptive field diversity (Martinez et al. 2014) match the amount of divergence reported by in vivo studies (reviewed in Reid & Usrey 2004).

Anatomical Divergence Produces Synchronous Activity in the Lateral Geniculate Nucleus and Strengthens Geniculocortical Communication

Divergence from a single RGC to multiple LGN neurons promotes a tight form of synchrony (<1 msec) in the responses of postsynaptic neurons (Alonso et al. 1996, Usrey et al. 1998). Multielectrode recording studies demonstrate that this form of synchrony is present only for LGN neurons with highly overlapping receptive fields and is greatest for LGN neurons of the same class (e.g., two X cells). When these criteria are met, pairs of LGN neurons that receive common input from the retina can fire up to 40% of their spikes synchronously. Functionally, synchronous firing between LGN neurons facilitates feedforward communication to target neurons in layer 4 of the visual cortex, as evidenced by studies demonstrating that the time course for interaction between spikes arriving from converging LGN axons onto a cortical target neuron is ~7 msec (Usrey et al. 2000). Thus, synchrony may serve to strengthen the relatively spare geniculate input (~5% of synapses) onto cortical target neurons. Synchrony could also serve to increase the amount of information conveyed to the cortex; information theoretic analysis shows that more information can be extracted from the spiking activity of pairs of cells when temporal correlations are taken into account (Dan et al. 1998).

BEHAVIORAL STATE AND THE GATING OF SENSORY INFORMATION IN THE LATERAL GENICULATE NUCLEUS

When an animal is alert and actively processing sensory information, the primary job of first-order thalamic nuclei, such as the LGN, is to transmit sensory information from the periphery to the cortex. The preceding sections have described how visual information from the retina is transformed in the LGN before reaching the cortex. Although these transformations have important implications for visual processing, perhaps the most significant transformation of the retinal signal in the LGN is that which takes place as a function of behavioral states such as arousal, sleep, and attention.

Thalamic Processing Shifts with Arousal

The importance of behavioral state in determining the response properties of LGN neurons was made readily apparent from early experiments by Livingstone & Hubel (1981). These scientists recorded from individual LGN neurons in cats that drifted between periods of sleep and wakefulness and documented both an increase in firing rate and a decrease in high-frequency bursts that accompanied arousal from slow-wave sleep. We now recognize that these differences in the LGN neuron response profiles represent shifts between two modes of thalamic activity: burst mode and tonic mode.

Whether or not an LGN neuron is in burst mode or tonic mode depends on the recent membrane potential history of the neuron and on the state of its low-threshold, T-type Ca^{2+} channels (Jahnsen & Llinás 1984a,b; Guido et al. 1992; Lu et al. 1992). When the resting membrane potential of an LGN neuron is relatively depolarized (approximately −70 mV), as is the case during arousal and wakefulness, LGN neurons generate a train of tonic spikes when the excitatory drive reaches the threshold for opening voltage-gated Na^+ channels. In contrast, when the resting potential of an LGN neuron is hyperpolarized (approximately −85

mV), for example, when animals are asleep, drowsy, or anesthetized, T-type Ca^{2+} channels that were otherwise in an inactivated state become deinactivated. Upon deinactivation, these channels open in response to excitatory input and generate a Ca^{2+} plateau potential that can trigger a burst of Na^+ spikes.

Although the frequency of burst activity decreases dramatically with alertness (Weyand et al. 2001, Ruiz et al. 2006, Alitto et al. 2011), the occurrence of bursts during active vision has been suggested to play an important role in ensuring the transmission of visual signals between the LGN and the cortex (Sherman 2001). Along these lines, a recent study indicates that stimulus novelty may increase the frequency of LGN bursts during a visual detection task (Ortuño et al. 2014). Although not examined in alert animals, further support for a possible role for bursts in visual processing comes from physiological recordings in anesthetized animals. These recordings demonstrate that (*a*) LGN burst spikes have greater efficacy in driving cortical responses than tonic spikes do (Swadlow & Gusev 2001), (*b*) the recent history of visual stimulation can prime LGN neurons to generate burst spikes (Alitto et al. 2005), (*c*) naturalistic stimuli evoke a greater percentage of burst spikes than unnatural stimuli evoke (Lesica & Stanley 2004, Denning & Reinagel 2005), and (*d*) cortical feedback can modulate the occurrence of LGN burst activity (Andolina et al. 2013).

In addition to shifting LGN neurons between burst and tonic activity modes, alertness also affects other features of visual responses in the LGN. This topic has been studied extensively in the awake rabbit, in which frequent transitions between alert sensory processing and quiescence can be monitored in real time using electroencephalogram (EEG) recordings in conjunction with extracellular recording from neurons in the LGN and/or cortex (Zhuang et al. 2014). When the cortical EEG becomes desynchronized, burst frequency decreases, the strength of visual responses in the LGN increases, and basic receptive field properties such as direction selectivity are enhanced, indicating an increase in behavioral vigilance (Bereshpolova et al. 2011, Hei et al. 2014). Similarly, the enhancement of activity in mouse V1 that occurs with locomotion (Niell & Stryker 2010, Ayaz et al. 2013, Polack et al. 2013) has been extended to include enhancement of activity in the LGN (Erisken et al. 2014). Thus, alertness and physical activity play a prominent role in visual processing in the LGN.

Thalamocortical Oscillations During Quiescence and Sleep Disrupt Geniculocortical Transmission

One of the primary functions served by thalamic bursts is their participation in thalamocortical network oscillations that dominate during sleep and, to a lesser extent, periods of low arousal (Steriade 2003). During wakefulness, the cortical EEG is dominated by small-amplitude, high-frequency activity that is associated with cognition and active sensory processing. In contrast, during sleep, the cortical EEG is transformed and becomes dominated by high-amplitude, low-frequency activity. This low-frequency activity represents oscillations that are generated locally in the thalamus (in relay nuclei and in the TRN) and in the cortex and that interact to form highly structured and interdependent oscillations (Steriade 2006). The transformation from wakefulness to sleep is complex and involves a variety of subcortical structures (Brown et al. 2012). In the thalamocortical pathway, this transformation begins with the withdrawal of cholinergic input from the brain stem and basal

forebrain (Steriade 2004, Jones 2004, Brown et al. 2012). This withdrawal results in the hyperpolarization of LGN relay neurons as local muscarinic receptors are silenced and inhibition supplied from the TRN increases. Cortical feedback to the LGN is also affected as cortical neurons become hyperpolarized and begin to display slow-wave oscillations. Consequently, large populations of thalamic relay neurons burst en masse, disconnecting thalamic neurons from their peripheral drivers.

Although a detailed discussion of the utility of these oscillations, and of sleep more generally, is beyond the scope of this review (for more information, see Steriade 2004, Brown et al. 2012, McCormick et al. 2015), these oscillations are important to consider when discussing the functional implications of anatomical connections in sensory systems. Thalamocortical network oscillations that occur during quiescence and sleep do not play a role in active visual processing. Rather, they serve to disrupt the thalamus from transmitting sensory information and to essentially disconnect the cortex from the periphery. Thus, when one asks how nonretinal inputs influence sensory processing in the LGN, a significant part of the answer is that these inputs play a role in the generation of thalamocortical oscillations that disrupt the transmission of sensory information to the cortex. This is true not only for neuromodulatory inputs from the brain stem, but also for nonretinal inputs to the LGN that typically carry visual signals, including corticogeniculate feedback projections and projections from the TRN.

Thalamocortical Oscillations During Active Visual Processing

Although some forms of oscillatory activity serve to disrupt the transmission of visual information between the thalamus and the cortex during periods of quiescence and sleep, other forms of this activity may actually aid the transmission of information. For instance, gamma oscillations (30–100 Hz) in the cortex of alert monkeys have been proposed to facilitate the encoding of information within local subnetworks of neurons and to enhance the communication of signals between cortical areas (Bastos et al. 2015b). Given the robust organization of feedback projections from V1 to the LGN, it has been tempting to speculate that gamma activity in V1 might entrain similar activity in the LGN, perhaps providing a mechanism to adjust dynamically the functional connectivity between the LGN and V1. In support of this possibility, strong gamma oscillations have been observed in the local field potential (LFP) and single-unit activity of LGN neurons in anesthetized animals (Neuenschwander & Singer 1996, Castelo-Branco et al. 1998, Koepsell et al. 2009); however, these oscillations are largely absent in similar recordings from alert animals (Bastos et al. 2014). Instead, oscillations in nongamma frequency bands seem to contribute to feedforward and feedback communication between the LGN and V1: Feedforward coherence is seen in the beta band (15–30 Hz), and feedback coherence is seen in the alpha band (8–14 Hz) (Bastos et al. 2014). Interestingly, although a functional role for these rhythmic interactions has yet to be demonstrated, interareal cortical recordings from alert animals have identified comparatively high-frequency oscillations associated with feedforward communication and low-frequency oscillations associated with feedback communication (van Kerkoerle et al. 2014, Bastos et al. 2015a).

Influence of Attention on Visual Response Properties in the Lateral Geniculate Nucleus

Covert spatial attention, the ability to direct visual attention to specified retinotopic locations, can improve the ability to detect and discriminate visual stimuli at attended locations compared with unattended locations. Within the cortex, spatial attention typically (*a*) increases neuronal responses to visual stimuli at the attended location (e.g., McAdams & Maunsell 1999) and (*b*) increases coherence between single-unit activity and the LFP, often in the gamma band (30–100 Hz) (e.g., Fries et al. 2008).

Although the effects of spatial attention are generally stronger in extrastriate cortical regions (e.g., V4, MT, VIP), attention also influences neuronal activity in V1 and in subcortical structures including the LGN. For instance, both single-unit recordings of LGN neurons in macaque monkeys and fMRI measures of the blood-oxygenation-level-dependent (BOLD) response in the LGN in humans revealed increased activity with spatial attention (O'Connor et al. 2002, McAlonan et al. 2008, Schneider & Kastner 2009). In monkeys, the influence of attention on LGN activity points to a pathway that involves the TRN and the GABAergic projections from the TRN to the LGN. In particular, whereas spatial attention directed toward the receptive fields of TRN neurons suppresses activity (McAlonan et al. 2006), attention directed toward the receptive fields of LGN neurons enhances activity (McAlonan et al. 2008), presumably by releasing the suppressive influence of the TRN on the LGN. Interestingly, the enhancement of LGN activity occurs throughout the entire response profile, beginning at onset and continuing through later stages of the analyzed time period, whereas attentional modulation of the TRN activity is seen only in the initial period of the visual response. This temporal relationship has implications for the circuitry involved in the modulation of LGN activity, and it suggests that other sources of input, likely corticogeniculate feedback, contribute to later stages of attentional modulation in the LGN.

Attention Enhances Geniculocortical Communication

Spatial attention also modulates the efficacy of geniculocortical communication. A recent investigation in which electrical stimulation of LGN relay neurons was paired with simultaneous recordings from postsynaptic neurons in layer 4 of the macaque V1 demonstrated that spatial attention increases the transfer of electrically evoked presynaptic spikes to suprathreshold postsynaptic responses (Briggs et al. 2013). Although the mechanisms underlying this enhanced communication are unknown, analyses suggested involvement beyond changes in postsynaptic resting potential, including a possible role for cholinergic input onto the presynaptic terminals of LGN axons. In addition to the attention-dependent enhancement of geniculocortical communication, attention was also found to increase a fast form of polysynaptic inhibition within cortical layer 4, an effect that appears to play a role in decreasing the temporal jitter of postsynaptic responses among geniculocortical target neurons (Briggs et al. 2013).

In summary, the LGN serves an essential function, transmitting visual information from the periphery to the cortex. Although the visual signal sent to the cortex largely reflects the complex processing that occurs within the retina, the LGN transforms and selectively transmits visual information based on the statistics of the visual stimulus and on the behavioral state of the animal. Given the relatively simple anatomical organization of the

LGN, one main source of synaptic drive (RGCs) and one main postsynaptic target (V1), it is not surprising that the general function of the LGN is fairly well understood. However, many issues clearly remain open to investigation. For instance, despite extensive investigation into the role(s) played by corticothalamic projections, their function is still being revealed (Crandall et al. 2015). We are also just beginning to understand the role of the TRN in regulating LGN activity dynamically across behavioral states (Halassa et al. 2014). Finally, LGN processing is strongly affected by neuromodulators such as vasopressin, and the functions of these neuromodulators are largely unclear (Freeman et al. 2014).

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SUMMARY POINTS

1. The LGN is located between the retina and primary visual cortex and is the gateway through which visual information reaches the cerebral cortex.

2. Divergence and convergence in the pathway from the retina to the LGN increase the resolution of visual space beyond the limits of the retinal mosaic and establish coordinated activity among ensembles of LGN neurons, thereby facilitating geniculocortical communication.

3. The LGN transforms the temporal structure of retinal spike trains to increase the signal-to-noise ratios of visual signals.

4. Center–surround interactions, first established in the retina, are strengthened by local thalamic inhibition involving polysynaptic circuits.

5. Geniculocortical functional connectivity is strongly modulated by various behavioral states, including sleep, arousal, and spatial attention.
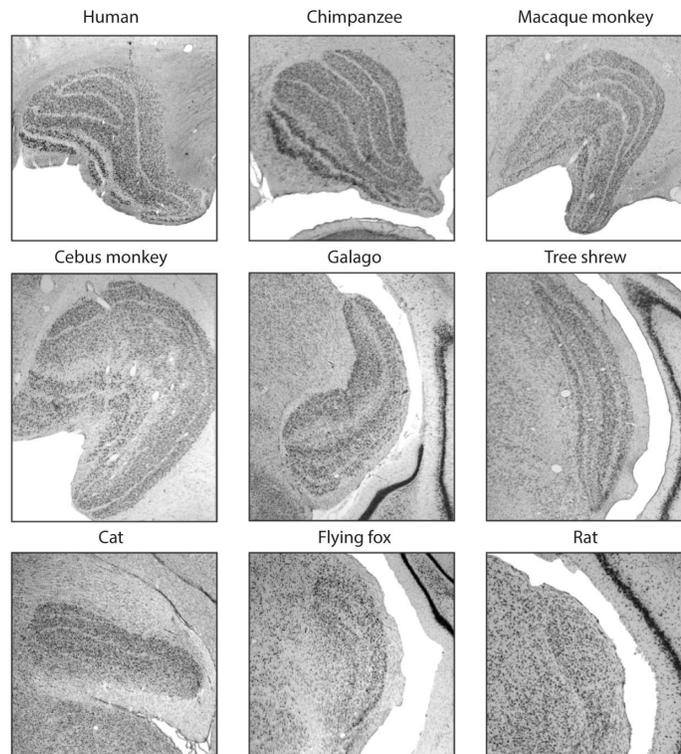
Figure 1.
Nissl-stained sections of the lateral geniculate nucleus (LGN) from nine different species: (*top row*) human, chimpanzee, rhesus macaque; (*middle row*) cebus monkey, galago, tree shrew; (*bottom row*) domestic cat, flying fox, rat. Adapted with permission from Usrey (2002a).