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A cross-species comparison of corticogeniculate structure and function

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Abstract

The corticogeniculate circuit is an evolutionarily conserved pathway linking the primary visual cortex with the visual thalamus in the feedback direction. While the corticogeniculate circuit is anatomically robust, the impact of corticogeniculate feedback on the visual response properties of visual thalamic neurons is subtle. Accordingly, discovering the function of corticogeniculate feedback in vision has been a particularly challenging task. In this review, the morphology, organization, physiology, and function of corticogeniculate feedback is compared across mammals commonly studied in visual neuroscience: primates, carnivores, rabbits, and rodents. Common structural and organizational motifs are present across species, including the organization of corticogeniculate feedback into parallel processing streams in highly visual mammals.

Keywords

Corticogeniculate; V1; LGN

Introduction

The corticogeniculate circuit is an evolutionarily conserved feedback pathway that links the visual cortex to the visual portion of the thalamus in the mammalian visual system (Jones, 1985; Sherman & Guillery, 2006; Briggs & Usrey, 2007*a*). Corticogeniculate neurons are a subpopulation of corticothalamic neurons. The term “corticothalamic” refers to all cortical neurons that project axons to thalamic structures (e.g. pulvinar, superior colliculus, basal forebrain), while “corticogeniculate” refers only to cortical neurons that project axons to the lateral geniculate nucleus (LGN) of the thalamus. The cell bodies of corticogeniculate (CG) neurons are located exclusively in layer 6 of the primary and secondary visual cortex (Gilbert & Kelly, 1975; Lund et al., 1975; Lin & Kaas, 1977; Swadlow & Weyand, 1981; Katz, 1987; Conley & Raczkowski, 1990; Jiang et al., 1993; Fitzpatrick et al., 1994; Usrey

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& Fitzpatrick, 1996; Brumberg et al., 2003; Ichida et al., 2014; Kim et al., 2014; Briggs et al., 2016). CG neurons often receive direct feedforward geniculocortical input (Hendrickson et al., 1978; Bullier & Henry, 1980; Blasdel & Lund, 1983; Ferster & Lindstrom, 1983; Briggs & Usrey, 2007*b*; Da Costa & Martin, 2009) as well as local input from neurons spanning the cortical layers (Lund & Boothe, 1975; Katz, 1987; Wiser & Callaway, 1996; Briggs & Callaway, 2001; Zarrinpar & Callaway, 2006; Kim et al., 2014; Briggs et al., 2016). CG neurons are all excitatory neurons, releasing glutamate as their primary neurotransmitter (Sherman & Guillery, 2006). All CG neurons project axons to the LGN and the thalamic reticular nucleus (TRN), where they form modulating synapses (Sherman & Guillery, 1998, 2006). The corticogeniculate circuit serves a vital role in visual information processing by providing the visual cortex the opportunity to dynamically influence its own input. Experimental and theoretical evidence suggests that CG feedback increases the salience of relevant visual stimuli by modulating the gain of LGN neuronal responses, altering the mode, timing, and precision of LGN spiking activity, and sharpening LGN receptive fields (Briggs & Usrey, 2008). The goal of this review is to examine similarities and differences in corticogeniculate anatomy, physiology, and function across commonly studied mammalian species: primates, carnivores, rabbits, and rodents.

Anatomy of CG neurons

Like most cortical areas, primary visual cortex (V1) is a laminar structure with 6 main cortical layers. The deepest layer of V1, layer 6, is relatively large and contains a morphologically diverse neuronal population in mammals (Tombol, 1984; Ferrer et al., 1986*a*,*b*; Briggs, 2010). In primates and insectivores, layer 6 of V1 is further subdivided into tiers based on a separation of distinct corticothalamic neuronal subpopulations with cell bodies in the upper, middle, and lower portions of layer 6 (Conley & Raczkowski, 1990; Fitzpatrick et al., 1994; Usrey & Fitzpatrick, 1996). Morphologically distinct neuronal types in layer 6 receive different patterns of local cortical input (Briggs & Callaway, 2001; Zarrinpar & Callaway, 2006). Additionally, nonoverlapping neuronal subpopulations within layer 6 project axons to different extrastriate cortical and subcortical targets (LeVay & Sherk, 1981; Katz, 1987; Conley & Raczkowski, 1990; Casagrande & Kaas, 1994; Usrey & Fitzpatrick, 1996; Sincich & Horton, 2005; Sherman & Guillery, 2006; Nhan & Callaway, 2012; Olsen et al., 2012).

CG neurons make up a fraction of the total population of excitatory neurons in layer 6 of V1, on the order of ~15% in primates and closer to ~50% in carnivores (Gilbert & Kelly, 1975; Ferster & Lindstrom, 1985; Fitzpatrick et al., 1994). Within the CG neuronal population, there is also diversity in local dendritic morphologies, axonal projection patterns, and stratification of cell bodies within layer 6, described in detail below. Some organizational motifs appear to be conserved across mammals. Figure 1 illustrates schematic representations of CG subtypes in primates, carnivores, and rodents, including local dendritic morphologies, putative axonal projection patterns, and stratification of cell bodies within layer 6.

Morphology and local circuit connections

CG neurons fall into three broad morphological categories: short, tall, and stellate or unusual morphology (Briggs, 2010). Short CG neurons are the most abundant morphological type with cell bodies in the upper tier of layer 6 and apical dendrites targeting layer 4. Tall CG neurons have cell bodies in either the top or bottom tier of layer 6 with apical dendrites extending into layer 2/3, sometimes including apical dendritic tufts. Less abundant and more unusual CG neuronal types include spiny stellate neurons that lack apical dendrites and tilted, sideways, or upside-down pyramidal-like neurons that have been observed in upper and lower tiers of layer 6 and also in the white matter below the cortical layers.

A recent anatomical study performed in macaque monkeys (Briggs et al., 2016) has expanded our understanding of the morphological diversity of CG neurons, including the presence of rare and previously unobserved CG types. In the macaque, CG cell bodies are restricted to the top and bottom tiers of layer 6 (Fitzpatrick et al., 1994). CG neurons with cell bodies in the upper tier include Iβ neurons (Wiser & Callaway, 1996), neurons with large cell bodies, and spiny stellate neurons. Following the general pattern for short CG neurons, Iβ neurons have apical dendrites that terminate in layer 4, where they preferentially target parvocellular stream input layer 4Cβ; and the basal dendrites of Iβ neurons are restricted to the upper tier of layer 6, which is the parvocellular stream input zone within layer 6 (Hubel & Wiesel, 1972; Hendrickson et al., 1978). Large neurons have tall apical dendrites with apical tufts near the pia in layer 1. Their basal dendritic arbor is more extensive than that of Iβ neurons, with basal dendrites targeting all three tiers of layer 6. Stellate CG neurons have dendrites restricted to the upper tier of layer 6.

Briggs et al. (2016) identified two distinct CG morphological subtypes with cell bodies in the bottom tier of layer 6: IC neurons (Wiser & Callaway, 1996) and tilted neurons. IC neurons follow the general pattern for tall CG neurons. Interestingly, the apical dendrites of IC neurons show no preference for the parvocellular or magnocellular stream input sublamina of layer 4C, however the basal dendrites of IC neurons are restricted to the magnocellular stream input zone at the bottom of layer 6 (Hubel & Wiesel, 1972; Hendrickson et al., 1978). Tilted neurons had not been observed previously in monkey V1, however neurons with similar morphologies have been observed in rodent and cat visual cortex (Tombol, 1984; Miller, 1988). Tilted CG neurons are observed less frequently and have unique morphology. First, their oval-shaped cell bodies are restricted to a narrow band in the deepest part of layer 6, often encroaching into the white matter. Second, the apical dendrites of tilted neurons exit at the side of the cell body (rather than the top of the cell body, as for pyramidal neurons) and turn to continue up through the cortical layers toward the pia. The dendritic and axonal analyses performed by Briggs et al. (2016) suggest that CG neurons form local connections with neurons in the same tier within layer 6 and receive segregated parvocellular or magnocellular stream input within those same tiers.

While the majority of CG neurons are in V1, CG neurons have also been identified in V2 of primates (Lin & Kaas, 1977; Briggs et al., 2016) and the homologous area 18 in cats (Gilbert & Kelly, 1975; Updyke, 1975; Murphy et al., 2000). V2 CG neurons probably made up a smaller fraction of excitatory neurons in layer 6 compared to the fraction of CG neurons in V1. V2 CG neurons also include three morphologically distinct subtypes with similar

morphological features as V1 CGs. Short V2 CGs are located in the upper tier of layer 6 while tall and tilted V2 CGs are located in the lower tier (Briggs et al., 2016).

The results of most retrograde labeling studies in primates and insectivores support the notion that distinct CG subtypes are segregated into upper and lower tiers of layer 6 (Conley & Raczkowski, 1990; Fitzpatrick et al., 1994; Usrey & Fitzpatrick, 1996). However detailed data on CG dendritic morphology is only available from a limited number of primate studies. Ichida et al. (2014) performed a morphological analysis of retrogradely labeled CG neurons in galagos and observed only short dendritic morphology patterns, however technical limitations may have led to an under-sampling of superficial arbors. Still, it is possible that some species have more homogeneous CG neuronal populations than others.

CG neurons in cats follow many of the same organizational principals observed in primates. Cat CG neurons are pyramidal neurons with cell bodies restricted to layer 6 and the CG population does not overlap with other corticothalamic projecting neuronal populations (Gilbert & Kelly, 1975; LeVay & Sherk, 1981; Katz, 1987). Katz (1987) observed both short and tall CG neurons (called type II and type I, respectively) in cat V1. Interestingly, the cell bodies of short and tall CGs in cats do not appear to segregate into different tiers of layer 6 (Katz, 1987), suggesting that sub-laminar organization of CG subtypes may be a primate specialization.

Compared to the wealth of anatomical data available about CG neurons in primates and carnivores, relatively little is known about CG morphology in rodents. Similar to other mammals, rat and mouse CG neurons have cell bodies restricted to layer 6 in V1, however CG dendritic morphology may be more homogeneous in rodents (Jiang et al., 1993; Brumberg et al., 2003). Following the recent introduction of the Ntsr1-cre mouse line (Gong et al., 2007), which enables genetic targeting of corticothalamic neurons, more focus has been placed on the CG circuit in the mouse. Olsen et al. (2012) characterized the morphology of Ntsr1 neurons in mouse V1, observing both short and tall pyramidal neurons. It is important to note that while the Ntsr1 population includes CG neurons (Kim et al., 2014; Denman & Contreras, 2015), it also includes additional corticothalamic populations both in layer 5 and layer 6 of the cortex (Olsen et al., 2012). One notable difference between CG neurons in mice *versus* primates and carnivores involves their local connectivity. While CG neurons in primates and cats are strongly reciprocally connected with neurons in layer 4, Ntsr1 neurons in mice are more strongly connected to layer 5 and mediate inhibition across the cortical layers (Katz, 1987; Briggs & Callaway, 2001; Olsen et al., 2012; Bortone et al., 2014; Kim et al., 2014; Briggs et al., 2016). Further characterization of CG neurons in rodents is necessary before detailed comparisons can be made between rodent and primate or carnivore CG neurons. It is important to note that CG neurons in both V1 and V2 project local axons throughout the cortical depth, including the superficial layers and layer 5, both of which contain cortico-cortical projecting neurons. CG neurons are therefore positioned to influence not only visual signals relayed back to the LGN but also feedforward signals transmitted to extrastriate visual cortex.

Axon projections

By definition, CG neurons target the LGN with their axonal projections. Importantly, CG synapses onto LGN relay neurons far outnumber retinogeniculate synapses even though their influence appears to be more modulatory than driving (Guillery, 1969; Erisir et al., 1997*a*; Erisir et al., 1997*b*; Sherman & Guillery, 2006). Given the diversity of morphologically distinct CG subtypes across a variety of mammalian species, it seems reasonable to predict diverse CG axonal projection patterns within the LGN. While CG axonal projection data are largely consistent with the notion of diverse CG subtypes, it is technically challenging to confirm the actual specificity of CG-to-LGN connectivity. Interestingly, in primates, cats, and ferrets, CG axons target the LGN and TRN (Robson, 1983; Claps & Casagrande, 1990; Murphy & Sillito, 1996; Ichida & Casagrande, 2002; Ichida et al., 2014), while in rodents, some CG neurons have axons in the LGN, TRN, and/or the lateral posterior nucleus of the thalamus (Bourassa & Deschenes, 1995; Olsen et al., 2012), suggesting that CG projections in rodents may be less selective or specific than those in more visual mammals. In ferrets and cats, CG axons tend to target multiple LGN layers even though boutons are often clustered (Robson, 1983; Claps & Casagrande, 1990). In primates, CG axons are mainly restricted to individual LGN layers or to functionally-matched layers (e.g., pairs parvocellular layers or pairs of magnocellular layers) although CG axonal arbors often encroach into neighboring koniocellular layers (Ichida & Casagrande, 2002; Ichida et al., 2014). Thus at least in visual mammals such as primates and carnivores, CG axon termination patterns are consistent with distinct CG subtypes targeting select populations of LGN neurons. Whether or not CG axons make functionally stream-specific connections with LGN neurons has not yet been established.

The structure and physiological properties of CG synapses onto LGN relay neurons, LGN interneurons, and TRN neurons have been studied in a number of species, including primates, carnivores, and rodents. For thorough reviews of the ultrastructure and physiology of CG synapses across species, please refer to (Bickford, 2016) and to (Sherman & Guillery, 2006), chapters 3 and 5. The general characteristics of CG synapses appear to be largely conserved across species. While CG synapses outnumber retinal synapses, they display the characteristics of “modulating” rather than “driving” synapses. CG synapses are smaller, contain less synaptic vesicles, and are located further out along distal dendrites of LGN relay neurons compared to retinal inputs. Postsynaptic terminals of CG synapses include both ionotropic and metabotropic glutamate receptors, while postsynaptic terminals of retinal synapses contain only ionotropic glutamate receptors. The fact that these general structural characteristics are conserved across species suggests that the relative contributions of retinal and cortical inputs to LGN relay neurons are also evolutionarily conserved.

Physiology of CG neurons

In visual mammals such as primates and carnivores, there are precise relationships between CG axon conduction latency and visual physiology. Here visual physiology is used to describe the receptive field properties of neurons. One of the most common visual physiological metrics is the classification of V1 neurons as Simple or Complex. Simple cells in V1 have separate receptive field subregions that respond to opposite luminance polarity,

while Complex cells respond equally well to stimuli of opposite luminance polarity within their receptive fields. The distinct CG subtypes defined by axon conduction latencies and visual response properties can be directly related to the feedforward parallel processing streams that are a hallmark of visual systems in highly visual mammals. Similar information is not available in rodents, however CG physiology has been well characterized in rabbits so comparisons between primates, carnivores, and rabbits are described below.

Axon conduction latencies

Measurements of CG axon conduction latencies provide some of the strongest, and oldest, evidence in favor of distinct CG subtypes. Antidromic stimulation studies, where CG axons in the LGN are electrically stimulated and resultant action potentials are recorded at cell bodies in layer 6 of V1, provide valuable physiological information about CG axon conduction speed. In visual mammals such as ferrets, cats, and monkeys, axon conduction latencies correlate with Simple/Complex visual response properties whereby fast-conducting CG neurons are Complex, medium-conducting CG neurons are Simple, and slowly-conducting CG neurons are Complex or nonresponsive to visual stimuli (Harvey, 1978; Tsumoto & Suda, 1980; Grieve & Sillito, 1995; Briggs & Usrey, 2005, 2007*b*). In rabbits, CG axon conduction latencies are generally slower, but similar relationships exist between axon conduction speed and visual response properties (Swadlow & Weyand, 1987). In all of these species studied to date, it is clear that CG neurons with different axon conduction latencies form distinct and nonoverlapping cell types. For example, in the monkey, CG subtypes defined based on axon conduction latency are clear-cut: fast/Complex CGs always have conduction latencies <7 ms; medium/Simple CGs always have conduction latencies between 7–15 ms; and slow/Complex CGs always have conduction latencies >15 ms (Briggs & Usrey, 2007*b*, 2009). Given the diversity in CG conduction latencies that is strictly defined and conserved across many species, it is likely that CG subtypes with different axon conduction speeds contribute to different aspects of visual processing. Along these lines, only fast-conducting CG neurons in primates also receive suprathreshold feedforward input from the LGN, creating a fast, reciprocal loop for transferring visual information between LGN and V1 (Briggs & Usrey, 2007*b*). Accordingly, these fast-conducting CG neurons may contribute primarily to motion perception. The diversity in axon conduction speeds also suggests that CG circuits operate on a variety of timescales, perhaps to accommodate a variety of integration windows for accumulating visual information. As we learn more about the functional contributions of CG circuits to vision, it will be important to consider the variety of timescales over which CG circuits operate.

Receptive field properties

In carnivores, primates, and rabbits, the visual response properties of CG neurons strongly correlate with axon conduction latencies, as described above. For example, CG neurons with fast and medium conduction latencies are often tuned for orientation and direction in cats and rabbits (Tsumoto & Suda, 1980; Swadlow & Weyand, 1987; Grieve & Sillito, 1995). A more systematic study of the visual response properties of CG neurons in alert monkeys revealed that CG subtypes defined based on axon conduction latencies display unique receptive field properties that align with the feedforward magnocellular, parvocellular, and koniocellular processing streams (Briggs & Usrey, 2009). Fast-conducting Complex CGs are

sensitive to low contrast and high temporal frequency stimuli, and thus optimized to process motion signals conveyed by the magnocellular stream. Medium-conducting Simple CGs are less sensitive to contrast, but are orientation tuned and responsive to red and green color signals, in line with signals conveyed by the parvocellular stream. Slow-conducting Complex CGs are poorly tuned for orientation and direction but modulated by blue color signals, aligning with signals conveyed by the koniocellular stream. These data suggest that inputs from the magnocellular, parvocellular, and koniocellular parallel processing streams are segregated through the local circuitry in V1 such that CG feedback maintains stream-specificity.

There is ongoing debate about whether some of the slowest-conducting CG neurons are visually responsive. In ferrets, cats, and rabbits, some slow-conducting CG neurons are not responsive to visual stimuli (Tsumoto & Suda, 1980; Swadlow & Weyand, 1987; Briggs & Usrey, 2005). Lack of responsiveness cannot necessarily be attributed to anesthesia as visually nonresponsive CG neurons are observed in awake rabbits (Swadlow & Weyand, 1987). Interestingly, in alert monkeys, all CG neurons, including slow-conducting CG neurons, are visually responsive (Briggs & Usrey, 2009). The utility of the slowest-conducting CG neurons and whether or not they are responsive to visual stimuli in a variety of species remain unknown.

Stream specificity

A major hallmark of retino-geniculo-cortical circuits in visual mammals is the separation of feedforward signals into parallel processing streams made up of morphologically and physiologically distinct neuronal classes. In primates, the parvocellular, magnocellular, and koniocellular parallel processing streams carry information about form/acuity, motion, and blue color, respectively (Kaplan, 2004). Homologous X, Y, and W streams are present in carnivores (Sherman & Guillery, 2006). Evidence for parallel streams in the visual systems of rodents is less clear (Krahe et al., 2011). Mounting evidence supports the notion that in visual mammals such as primates and carnivores, CG circuits are also organized into parallel streams that align with the feedforward parallel streams. The dendritic arborization and axon projection patterns of primate and carnivore CG neurons, described in detail above, support distinct CG subtypes. Similarly, physiological measurements including axon conduction latency and visual response properties also support distinct CG subtypes with physiological properties aligned with the properties of neurons in the feedforward streams. Together, these data provide strong support for the idea that separate channels of CG feedback preserve the segregation of visual information into distinct feedforward processing streams in highly visual mammals.

In the primate, the alignment of feedforward and CG feedback circuits is precise. The following predictions arise from combinations of morphological and physiological observations in monkeys. CG neurons with fast axon conduction latencies and Complex visual physiology are the presumptive magnocellular-projecting CG neurons. Magnocellular feedforward retino-geniculo-cortical and fast Complex CG neurons have the fastest conducting axons, the greatest contrast and temporal frequency sensitivity, the most surround suppression, the shortest visual response latencies, and the highest firing rates

(Benardete et al., 1932; Schiller & Malpeli, 1978; Kaplan & Shapley, 1982, 1986; Maunsell et al., 1999; Usrey & Reid, 2000; White et al., 2001; Solomon et al., 2002; Briggs & Usrey, 2007*b*, 2009*b*, 2011*b*; Alitto & Usrey, 2008). Additionally, fast Complex CG neurons have sharper orientation tuning and greater direction selectivity, reminiscent of neurons in layer 4Cα that receive direct magno-cellular input from the LGN (Hawken et al., 1988; Merigan & Maunsell, 1993; Gur et al., 2005; Briggs & Usrey, 2009). The presumptive magnocellular-projecting fast Complex CG neurons are also the only CG neurons to receive direct, feedforward suprathreshold LGN input (Briggs & Usrey, 2007*b*). It is likely that the type IC CG neurons, located in the bottom tier of layer 6, are the magnocellular-projecting, fast Complex CG neurons because magnocellular LGN layers receive CG feedback from the bottom tier of layer 6 (Fitzpatrick et al., 1994).

CG neurons with medium axon conduction latencies and Simple visual physiology are the presumptive parvocellular-projecting CG neurons. Parvocellular feedforward retino-geniculo-cortical and medium Simple CG neurons have intermediary axon conduction speeds, low contrast and temporal frequency sensitivity, less surround suppression, slower visual response latencies, intermediary firing rates, and are sensitive to inputs from the L- and M-cones in the retina (Schiller & Malpeli, 1978; Bullier & Henry, 1980; Maunsell et al., 1999; Field & Chichilnisky, 2007; Briggs & Usrey, 2009). The type Iβ CG neurons, located in the top tier of layer 6 are likely the parvocellular-projecting, medium Simple CG neurons because parvocellular LGN layers receive CG feedback from the top tier of layer 6 (Fitzpatrick et al., 1994).

CG neurons with the slowest conducting axons and Complex visual physiology likely project to the koniocellular LGN layers. Like the feedforward koniocellular retino-geniculo-cortical neurons, slow Complex CG neurons have slower axon conduction speeds, intermediate contrast, and temporal frequency sensitivity, some surround suppression, and sensitivity to inputs from the S-cones in the retina (Irvin et al., 1986; White et al., 1998; Solomon et al., 1999; Hendry & Reid, 2000; White et al., 2001; Solomon & Lennie, 2007; Briggs & Usrey, 2009, 2011*b*). Interestingly, slow Complex CGs are not orientation or direction tuned, unlike the other CG subtypes (Briggs & Usrey, 2009). It is likely that a number of morphologically distinct CG subtypes, including stellate, large, and tilted CG neurons, project to the various koniocellular layers in the LGN. However, the tilted CG neurons are presumably the slow Complex, koniocellular-projecting neurons encountered physiologically because these neurons were always located in the deepest part of layer 6 (Briggs & Usrey, 2009).

In primates, and possibly also in carnivores, CG neurons retain physiological signatures of the feedforward parallel processing streams in spite of the fact that V1 contains numerous local circuits that could mix information from the three input streams (Merigan & Maunsell, 1993; Douglas & Martin, 2004; Sincich & Horton, 2005; Callaway, 2014). Accordingly, a clear precedent is set to ensure that CG circuits preserve the specificity of information relayed by feedforward streams. Preservation of segregated information channels through both feedforward and feedback circuits is evident in other species and sensory systems including the whisker/barrel system of rodents and the auditory system of bats (Ghazanfar et al., 2001; Suga & Ma, 2003; Bokor et al., 2008). Stream-specific corticothalamic feedback

may therefore be evolutionarily conserved for neuronal pathways that serve primary senses across a variety of species. Because stream-specificity is likely to be a critical organizational feature of CG feedback, CG function must be considered in the context of parallel processing streams.

Function of CG neurons

In the past 10 years, we have gained significant insight about the structure, organization, and visual physiology of CG neurons, especially in the primate visual system. However the functional role of CG feedback in vision has remained a particularly stubborn puzzle. It is obvious from LGN recordings that the influence of CG feedback on the visual responses of LGN neurons is subtle. The receptive fields of LGN neurons mimic their retinal inputs and not their cortical inputs. For example, individual LGN neurons are not orientation tuned even though many CG neurons are tuned for orientation. Although CG inputs onto LGN neurons are anatomically robust in terms of numbers of synapses, the smaller size and placement of CG synapses on distal dendrites of LGN relay neurons means CG influence is modulatory rather than driving (Sherman & Guillery, 1998, 2006). Until recently, it has also been technically challenging to manipulate CG neurons in a selective and reversible manner. With the advent of optogenetics (Huber et al., 2008; Gradinaru et al., 2009), it is now possible to perform a more causal test of CG function by performing reversible manipulations selectively on CG neurons in intact animals. Results of experimental examinations of CG function, varying in invasiveness and/or selectivity, converge on three general candidate functions for CG feedback: LGN gain modulation, sharpening or shifting of LGN receptive fields, and changes in LGN spiking mode, timing, and precision (Briggs & Usrey, 2008, 2011*a*).

Gain modulation

As the first feedback circuit in the visual system, CG neurons could function as filters that increase the salience of relevant visual signals and suppress the activity of non-relevant visual information. Accordingly, CG feedback could operate by increasing or decreasing the gain of LGN neuronal responses. Changes in both the magnitude and gain of LGN responses have been observed when CG feedback is manipulated (Molotchnikoff et al., 1984; Gulyas et al., 1990; Marrocco et al., 1996; Cudiero et al., 2000; Przybyszewski et al., 2000; Worgotter et al., 2002; Wolfart et al., 2005; Andolina et al., 2007; Li et al., 2011; Olsen et al., 2012; Denman & Contreras, 2015). Specifically, aspirating or cooling V1 in anesthetized cats and primates led to decreased LGN responses to moving visual stimuli without changing LGN tuning preferences (Gulyas et al., 1990; Marrocco et al., 1996). Additionally, cooling V1 in anesthetized monkeys led to a reduction in contrast gain that was specific to parvocellular LGN neurons (Przybyszewski et al., 2000). Similarly, lesioning V1 in anesthetized cats led to decreased contrast adaptation with greater effects on Y than X cells in the LGN (Li et al., 2011). These latter findings support the notion of stream-specific functions for CG subtypes. Interestingly, in the mouse, optogenetic suppression of corticothalamic feedback led to a variety of effects on LGN responses including increases, decreases, and no change in response magnitude and gain (Denman & Contreras, 2015).

A related function for CG feedback could be to convey cognitive signals about attention or arousal state from the cortex to the LGN. Corticothalamic circuits are strongly modulated by arousal state, demonstrating different spiking, and oscillatory modes during sleep and arousal (Steriade, 2001, 2003). Additionally, LGN neurons are modulated by visual attention (Vanduffel et al., 2000; O'Connor et al., 2002; McAlonan et al., 2006, 2008; Ling et al., 2015). The precise role of CG feedback in delivering arousal and/or attention signals to the LGN is not known. However, as the only path by which cortical information reaches the LGN, CG feedback is a good candidate for conveying information about cognitive state.

Receptive field changes

LGN neurons derive their receptive field properties from their retinal inputs, however it is possible that CG feedback sharpens and/or shifts the tuning properties of individual or ensembles of LGN neurons. There is evidence that the spatial receptive field of LGN neurons, with the antagonistic center/surround of the classical receptive field and the extra-classical suppressive surround, may be sharpened or modulated by CG feedback (Murphy & Sillito, 1987; Sillito & Jones, 2002; Webb et al., 2002; Jones et al., 2012; Andolina et al., 2013). CG feedback could sharpen the border between the classical and extra-classical fields (Murphy & Sillito, 1987; Jones et al., 2000; Rivadulla et al., 2002; Webb et al., 2002; Jones et al., 2012). Alternatively, CG feedback could reduce the spatial extent of the classical receptive field and enhance surround suppression as pharmacological inactivation of V1 in anesthetized cats led to an increase in LGN receptive size and a reduction in surround suppression (Andolina et al., 2013). In the mouse, corticothalamic feedback does not modulate LGN receptive field size or surround suppression (Denman & Contreras, 2015).

While the influence of CG feedback on the receptive fields of individual LGN neurons may be subtle, it is possible that CG feedback coordinates the activity of ensembles of LGN neurons to produce "tuning" among small groups of LGN neurons. Experimental evidence suggests that CG feedback enhances the activity of ensembles of LGN neurons with receptive fields clustered along the orientation axis of their CG inputs (Sillito et al., 1993; Wang et al., 2006; Andolina et al., 2007). Theoretical evidence also supports a role for CG feedback in enhancing the activity of ensembles of LGN neurons with retinotopically aligned receptive fields and suppressing neighboring neurons (Bickle et al., 1999). Together, these findings highlight the importance of future studies involving multi-electrode recordings so that the broader impact of CG feedback on populations of LGN neurons can be examined.

A final argument in favor of a role for CG feedback in sharpening or shifting the receptive fields of LGN neurons is that similar functions have been attributed to corticothalamic circuits in other sensory systems. The term "egocentric selection" describes the enhancement and shifting of thalamic responses to match the tuning preferences of activated corticothalamic neurons and suppression of activity among thalamic neurons with nonmatched tuning (Suga & Ma, 2003). Egocentric selection by corticothalamic feedback has been described in the auditory and somatosensory systems (Krupa et al., 1999; Ghazanfar et al., 2001; Suga & Ma, 2003; Li & Ebner, 2007; Wu & Yan, 2007; Temereanca et al., 2008; Zhang & Yan, 2008).

Modulation of LGN spiking mode, timing, and precision

In addition to modulating the gain of LGN response or sharpening LGN receptive fields, CG feedback could influence the feedforward transmission of visual signals by modulating the spike timing of LGN relay neurons. By coordinating the spike latencies and/or increasing the spike timing precision for an ensemble of LGN neurons, CG feedback could enhance the efficacy of visual information conveyed by the coordinated ensemble to V1. One way in which CG feedback could coordinate the activity of LGN neurons is to shift a select group of LGN neurons between burst and tonic modes of firing (Sherman, 1996). In support of this notion is the finding that selective destruction of CG neurons led to a broadening of the inter-spike-interval distribution of tonic spikes recorded during synchronized EEG states (Eyding et al., 2003). However, in the mouse, selectively manipulating corticothalamic feedback had no net impact on tonic or burst spiking (Denman & Contreras, 2015).

Alternatively, CG feedback could coordinate slow timescale fluctuations in membrane potential, leading to an increase in coordinated spiking patterns among LGN ensembles (Destexhe et al., 1999; Bal et al., 2000; Blumenfeld & McCormick, 2000; Destexhe, 2000; Rigas & Castro-Alamancos, 2007). Both experimental and theoretical studies support the notion that CG feedback alters the timing of LGN responses in order to improve the transfer of information from the LGN to V1 (Funke et al., 1996; Bal et al., 2000; Destexhe, 2000; Worgotter et al., 2002; Wolfart et al., 2005; Andolina et al., 2007; Yousif & Denham, 2007). Specifically, Andolina and colleagues (Andolina et al., 2007) observed decreased stimulus modulation and increased response variability in LGN neurons when V1 was pharmacologically inactivated in anesthetized cats. In spite of these advances, exactly how CG feedback alters the timing and/or precision of LGN neurons to improve information transmission remains unclear.

There is some experimental evidence that CG feedback synchronizes the activity of LGN ensembles (Sillito et al., 1994), however the synchrony measurements in this study were confounded (Brody, 1999) and the manipulations of CG feedback were nonselective with limited data. Nevertheless, the hypothesis proposed in this study, that CG feedback selectively synchronizes the activity of LGN ensembles carrying feature-specific information, must be tested using modern techniques. Interestingly, somewhat parallel analyses performed in the mouse, in which pairwise correlations were measured among LGN neurons when corticothalamic feedback was manipulated, yielded no influence of corticothalamic feedback on correlated activity among LGN neurons (Denman & Contreras, 2015).

Finally, CG feedback could play a role in the arrangement of synapses onto LGN relay neurons during development—a function that could have important consequences for LGN spiking synchrony and precision throughout life. A number of recent studies examining the development of visual thalamic circuits in the mouse have provided significant new insight into the timing and influence of CG activity during development. CG axonal innervation of the LGN is delayed relative to innervation of the LGN by retinal inputs (Jacobs et al., 2007; Seabrook et al., 2013). Additionally, CG inputs become stronger during later developmental stages relative to retinal inputs (Jurgens et al., 2012). However, CG inputs are required for correct retinogeniculate innervation of the LGN as retinogeniculate afferents fail to correctly

innervate the LGN in mice lacking layer 6 projection neurons (Shanks et al., 2016). Furthermore, disruptions of CG feedback during development result in over-abundant retinogeniculate innervation of LGN relay neurons, similar to that observed during dark rearing (Thompson et al., 2016). Together these findings suggest that CG activity during specific developmental stages is required for correct retinal and cortical synaptic innervation of LGN neurons, perhaps setting the stage for LGN neuronal synchronization that is critical for visual function throughout life.

Concluding remarks

While a large body of work is now available describing the structure, organization, and physiology of CG neurons, the functional role of these enigmatic neurons in vision remains unresolved. A number of other important questions also remain, including the functional connectivity of CG axons with LGN relay neurons and whether or not CG feedback is functionally stream specific. Any examination of CG function must take into account the fact that CG subtypes operate on very different timescales and are specialized to convey stream-specific signals from V1 to the LGN. Additionally, it will be important to record from ensembles of neurons in the LGN to determine whether CG feedback alters the timing or population tuning properties of select groups of LGN neurons. Finally, as technical approaches improve, studies of CG circuits in alert and behaving animals will provide important new insight into the contributions of CG feedback to contextual and cognitive processes.

There are clear similarities in CG morphology and physiology across highly visual mammals such as primates and carnivores. These similarities suggest that evolution maintains a precedent for preserving the separation of visual information into parallel processing streams throughout the early visual pathways. However, this precedent is not apparent for nonvisual mammals such as rodents, as CG morphology and function appears more homogeneous and less selective. Precise and parallel organization is present in the rodent somatosensory system, however. Further studies of corticothalamic feedback in a variety of sensory modalities and species may provide significant insight into the senses that are must useful for each species and the general strategies employed by corticothalamic circuits to enhance sensory perception.

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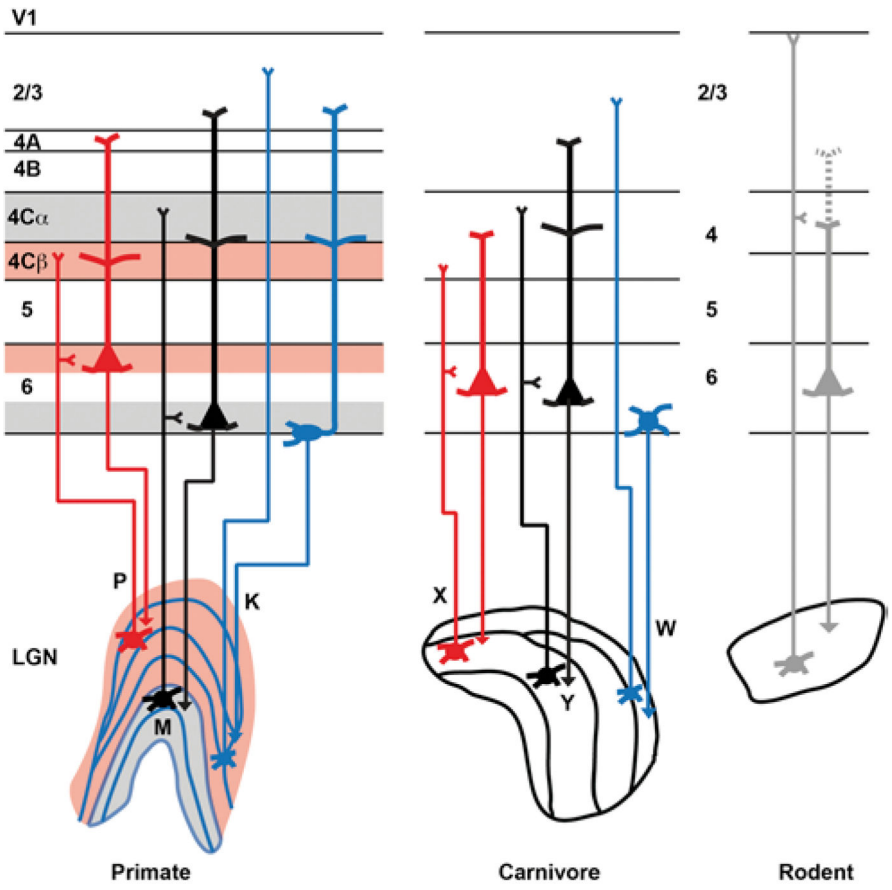

Fig. 1.

Schematic representations of corticogeniculate (CG) subtypes in primates, carnivores, and rodents. Parvocellular (P), magnocellular (M), and koniocellular (K) and homologous X, Y, and W stream neurons are illustrated in red, black, and blue, respectively. Axons are thinner and dendrites thicker. Layers within V1 are indicated to the left for primate V1 and between the laminar boundaries for carnivore and rodent V1. LGN relay axons project to layers 1 and 4 in rodents (thin gray lines). Dashed gray dendrite to layer 2/3 illustrates possible, but yet unconfirmed, arborization of rodent CG neurons.