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### Neural Mechanisms of Spatial Attention in the Visual Thalamus

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The Oxford Handbook of Attention

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### Abstract and Keywords

Neural mechanisms of selective attention route behaviourally relevant information through brain networks for detailed processing. These attention mechanisms are classically viewed as being solely implemented in the cortex, relegating the thalamus to a passive relay of sensory information. However, this passive view of the thalamus is being revised in light of recent studies supporting an important role for the thalamus in selective attention. Evidence suggests that the first-order thalamic nucleus, the lateral geniculate nucleus, regulates the visual information transmitted from the retina to visual cortex, while the higher-order thalamic nucleus, the pulvinar, regulates information transmission between visual cortical areas, according to attentional demands. This chapter discusses how modulation of thalamic responses, switching the response mode of thalamic neurons, and changes in neural synchrony across thalamo-cortical networks contribute to selective attention.

Keywords: attention, oscillations, synchrony, pulvinar, lateral geniculate nucleus, thalamic reticular nucleus, diffusion tensor imaging, multi-electrode recordings

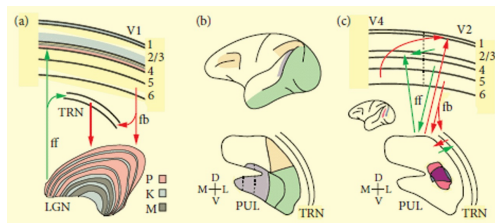
### Introduction

THE thalamus has been extensively studied in terms of its anatomical organization, efferent and afferent connectivity patterns, basic neural response properties, and synaptic, biochemical, and molecular characteristics (Jones 2007; Sherman and Guillery 2006). However, its role in cognitive processes such as spatial attention has remained poorly understood. Studies in awake, behaving monkeys during the last decades have focused almost exclusively on defining the roles of cortical areas in cognition. Similarly, human neuroimaging studies have heavily emphasized the functions of cortical rather than subcortical networks, partially due to technical limitations in terms of spatial resolution. The emphasis on studying cortical function ultimately led to a concept assuming a major, if not exclusive role for cortical networks in cognition. This notion has begun to be revised during the last few years due to the development of functional magnetic resonance imaging (fMRI) at high resolution that permitted for the first time the study of the human thalamus in some detail (reviewed in Saalmann and Kastner 2009, 2011), followed by a renewed interest of physiologists in thalamic function in awake, behaving monkeys (e.g. McAlonan et al. 2006, 2008). In this chapter, we will focus on the visual thalamus as a model system to exemplify the changing views of the thalamus's role in cognition and particularly in spatial attention, which have begun to emerge from these studies.

The visual thalamus consists of three main nuclei, the lateral geniculate nucleus (LGN), the thalamic reticular nucleus (TRN), and the pulvinar. These three structures are characterized by differences in their efferent and afferent connectivity patterns (Jones 2007; Sherman and Guillery 2006). The LGN is considered a first-order thalamic nucleus because it transmits peripheral signals to the cortex along the retino-cortical pathway. In addition to retinal afferents that form only a minority of the input to the LGN, it receives projections from multiple sources including primary visual cortex (V1), the TRN, and brainstem. Thus, the LGN represents the first stage in the visual

pathway at which modulatory influences from other sources could affect information processing. The TRN forms a thin shell of neurons that covers the lateral and anterior surface of the dorsal thalamus, and it receives input from branches of both thalamo-cortical and cortico-thalamic fibers. The TRN in turn sends its output exclusively to the thalamus and is positioned to provide inhibitory control over thalamo-cortical transmission. The pulvinar is the largest nucleus in the primate thalamus and is considered a higher-order thalamic nucleus because it forms input-output loops almost exclusively with the cortex. The extensive and reciprocal connectivity with the cortex suggests that the pulvinar serves in aiding cortico-cortical transmission through thalamic loops. Thus, from an anatomical perspective, the visual thalamus is ideally positioned to regulate the transmission of information to the cortex and between cortical areas, as was originally proposed more than twenty years ago (Crick 1984; Sherman and Koch 1986; Singer 1977). Based on its anatomical connectivity the thalamus may be able to strongly influence cortical networks involved with cognitive processing. The experimental evidence in favour of such a functional role will be reviewed in the following sections that are organized by thalamic nucleus.

### LGN: Early Modulation of Visual Information



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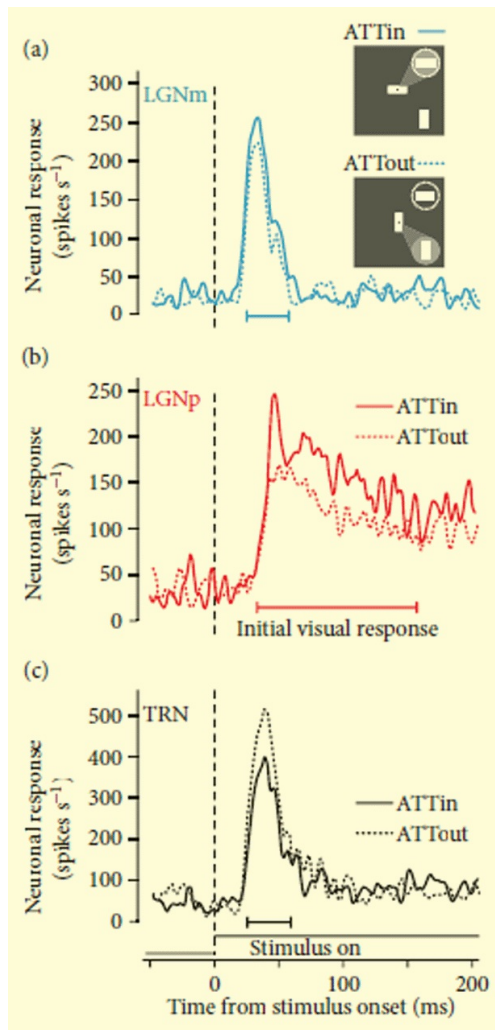
**Figure 14.1** Thalamo-cortical connectivity. (a) Feedforward (ff) projections from parvo-, konio-, and magnocellular (P, K, M) neurons in the LGN target specific layers in V1 (colour-coded). Layer 6 feedback (fb) from V1 respectively targets P, K, and M layers of the LGN. (b) Frontoparietal (yellow), mediotemporal (violet), inferotemporal and occipital (green) cortical regions preferentially connect with different divisions of the pulvinar (PUL). The ventro-lateral and ventro-central divisions shown in green are retinotopically organized. Note that there are alternative parcellation schemes of the pulvinar based on neurochemical criteria (Gutierrez et al. 1995; Stepniowska and Kaas 1997; Adams et al. 2000); however, there is reasonable agreement on subdivisions of the ventro-medial pulvinar (dotted lines). (c) Direct cortico-cortical connections (top) and indirect cortico-pulvino-cortical loops exemplified by V2-pulvino-V4 circuitry. Tracer injections into V2 (blue) and V4 (pink; inset) showed overlapping (purple) projection zones in the pulvinar (bottom). (c) Adapted from *Journal of Comparative Neurology*, 419 (3), Michelle M. Adams, Patrick R. Hof, Ricardo Gattass, Maree J. Webster, and Leslie G. Ungerleider, Visual cortical projections and chemoarchitecture of macaque monkey pulvinar, pp. 377–93, figure 8 © 2000, Wiley-Liss, Inc.

LGN topography and the response properties of LGN neurons have been extensively studied in anaesthetized non-human primates (e.g. Connolly and Van Essen 1984; Kaas et al. 1972; Malpeli and Baker 1975). The LGN is typically organized into six main layers, and each layer receives input from either the contra- or ipsilateral eye. The four dorsal layers contain small (parvocellular) neurons that are characterized by sustained discharge patterns and low contrast sensitivity, largely processing form and colour information. The two ventral layers contain large (magnocellular) neurons that are characterized by transient discharge patterns and high contrast sensitivity, largely processing motion and depth information (Creutzfeldt et al. 1979; Derrington and Lennie 1984; Dreher et al. 1976; Merigan and Maunsell 1993; Shapley et al. 1981; Wiesel and Hubel 1966). In addition, there are six thin LGN layers, located ventral to each of the parvo- and magnocellular layers, that contain very small (koniocellular) neurons, some of which carry signals from short-wavelength-sensitive (blue) cones (Hendry and Reid 2000; Martin et al. 1997; Roy et al. 2009; Xu et al. 2001). These three LGN cell classes target different cortical layers (Fig. 14.1a). Parvocellular and magnocellular neurons project to layer 4 and to a lesser extent to layer 6, while koniocellular cells project to layers 1 and 3 of area V1 and to extrastriate areas as well (reviewed in Callaway 2005).

In addition to retinal afferents, the LGN receives modulatory input from multiple sources. Cortico-thalamic feedback projections from V1 comprise about 30% of the input to the LGN, and inhibitory input from the TRN and local interneurons contributes another 30% of LGN input (Sherman and Guillery 2006). Both V1 and TRN represent visual information in retinotopically organized maps and can thereby influence LGN responses in spatially specific ways. Moreover, V1 feedback arises from three classes of neurons, each selectively targeting parvo-, magno-, or

koniocellular LGN neurons (Briggs and Usrey 2009). This finding suggests that cortico-thalamic feedback may differentially modulate information processing in parvo-, magno-, and koniocellular afferent pathways, and thus be more selective than the TRN input to LGN. A third major modulatory influence that represents another 30% of input to the LGN arises from brainstem nuclei, that is, the pedunculopontine tegmentum and the parabigeminal nucleus. These cholinergic projections are more diffusely organized than the V1 and TRN projections (Bickford et al. 2000; Erisir et al. 1997) and, consequently, are likely to influence LGN responses with less spatial specificity. Due to the multiple modulatory inputs, the LGN is well positioned for early regulation of visual information transmission.

### Attentional response modulation



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**Figure 14.2** Attention effects on macaque LGN and TRN neurons. (Inset) Monkeys were cued to direct their attention to a visual stimulus inside (ATTin) or outside (ATTout) the receptive field (circle). Selective attention increased spike rates of (a) magno- and (b) parvocellular LGN neurons, but reduced spike rates of (c) TRN neurons. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, 456 (7220), Kerry McAlonan, James Cavanaugh and Robert H. Wurtz, Guarding the gateway to cortex with attention in visual thalamus, pp. 391–394, figure 1, copyright (2008), Nature Publishing Group.

Human fMRI studies provided the first compelling evidence of cognitive tasks that modulated LGN responses. In a series of attention experiments, O'Connor et al. (2002) showed that selective attention affects visual processing in at least three different ways, similar to the modulatory effects observed in visual cortex: by enhancing responses to attended relative to ignored stimuli, by suppressing responses evoked by unattended stimuli, and by increasing baseline activity in the absence of visual stimulation and in anticipation of an upcoming stimulus (see Beck and

Kastner, chapter 9, this volume). The finding of attentional modulation in the human LGN has been corroborated by a subsequent single-cell recording study in the macaque LGN that provided a more space- and time-resolved view of the attention effects (McAlonan et al. 2008). The spike rate of LGN neurons increased for attended stimuli relative to unattended stimuli, with slightly stronger effects on magnocellular neurons (11% enhancement) than parvocellular neurons (9%; Fig. 14.2a and b) across the population. Selective attention also influenced magnocellular neurons earlier than parvocellular neurons (the influence of attention on koniocellular neurons is not known). The attention effects varied over time, as evidenced by an early period of attentional modulation within the first 100 ms after stimulus onset, and a later period of modulation starting around 200 ms, possibly reflecting different sources of modulatory input. Based on the response patterns of TRN and V1 neurons, it is possible that the early period of attentional effects in the LGN is attributable to TRN influences, whereas the late period may reflect feedback from V1 (Fig. 14.1a).

### Burst and tonic response modes

Modulating the response magnitude of LGN neurons is one mechanism by which information transmitted to the cortex can be influenced depending on behavioural context. Switching the response mode of LGN neurons potentially represents another important mechanism to regulate thalamo-cortical transmission. Thalamic neurons respond in one of two modes, tonic or burst firing mode, depending on a calcium current ( $I_T$ ) through a low threshold calcium channel (T channel). The calcium channel is inactivated when the neuron is depolarized and de-inactivated when the neuron is hyperpolarized for at least 50 ms. When the calcium current is inactivated, the neuron responds linearly to its input, with a relatively steady train of action potentials (tonic mode). When the calcium current is activated, the neuron responds to its input in a less linear fashion, with a burst of action potentials (burst mode); that is,  $I_T$  activates a  $Ca^{2+}$ -dependent spike, activating a burst of  $Na^+$  spikes (Huguenard 1996). For example, suppressive stimuli may cause sufficiently prolonged hyperpolarization of an LGN neuron to de-inactivate low-threshold calcium channels. A subsequent depolarizing input is then more likely to induce the LGN neuron to burst fire (Alitto et al. 2005; Denning and Reinagel 2005; Lesica and Stanley 2004). Because bursts are more efficacious in activating thalamo-cortical synapses than tonic spikes (Swadlow and Gusev 2001), burst firing mode may be useful for initially detecting stimuli (Fanselow et al. 2001). After stimulus detection, a switch to tonic firing mode would allow thalamic neurons to be more faithful to their retinal input, reliably transmitting information from retinal afferents to the cortex, for more detailed information processing. Such switching of firing modes has been shown in the cat LGN, in which most bursting occurred during early responses to a visual stimulus, followed by tonic firing (Guido and Weyand 1995). The degree of vigilance also appears to influence the firing mode of thalamo-cortical neurons. LGN neurons tended to burst more when rabbits were in a low vigilance state than in an alert state; and this switch in firing mode occurred within one second of the EEG-defined state transition (Bezudnaya et al. 2006). The increased bursting may allow the detection of stimuli that are relevant for ongoing behaviour even when in an inattentive state. Importantly, both cortical feedback as well as cholinergic brainstem influences have been shown to depolarize LGN neurons (Scharfman et al. 1990) and thus are able to switch their firing mode from burst to tonic (Lu et al. 1993; McCormick and von Krosigk 1992; Varela and Sherman 2007). However, little is known about the way in which selective attention and other cognitive processes may impact the firing mode of thalamic neurons.

### Neural synchrony and oscillations

Thus far, we have considered influences on response magnitude and firing mode as mechanisms to modulate the efficacy of thalamic drive to the cortex. Synchronizing thalamic output represents yet a third relevant mechanism, which may be particularly effective in light of the reported low efficacy of thalamo-cortical synapses (Bruno and Sakmann 2006). Accordingly, simultaneous recordings from the LGN and V1 in anaesthetized cats have found that correlated spiking of LGN neurons increased their efficacy in driving cortical neurons (Alonso et al. 1996). Neurons with greater overlap of their RFs showed greater synchrony. A recent modelling study estimated that as few as five to ten synchronized LGN cells may be sufficient to drive a cortical neuron (Wang et al. 2010). Thus, modulating the synchrony of a group of thalamic neurons may be a potent mechanism to regulate information transmission to cortex.

Synchronizing the activity of two groups of neurons can also increase their information exchange (Gregoriou et al. 2009; Saalmann et al. 2007; Tiesinga and Sejnowski 2009; Womelsdorf et al. 2007). Spikes are more likely to be

relayed if those from presynaptic neurons arrive during periods of reduced inhibition of postsynaptic neurons. This spike-timing relationship can be achieved by synchronizing oscillatory activity of pre- and postsynaptic neurons with an appropriate phase lag. Consequently, synchrony between thalamic and cortical neurons, with LGN leading, may increase the efficacy of thalamic input to cortex. Consistent with such a gain control mechanism, it has been found that attentive viewing synchronizes beta frequency oscillations of LFPs in cat LGN and V1 (Bekisz and Wrobel 1993; Wrobel et al. 1994). Such synchrony largely seems to occur between interconnected groups of neurons in each area (Briggs and Usrey 2007; Steriade et al. 1996), offering the possibility of spatially specific control of information transmission.

LGN synchrony and oscillations are controlled by the areas that provide modulatory inputs to the LGN, that is, V1, TRN, and cholinergic brainstem nuclei. Importantly, these sources may differentially influence different oscillation frequencies (the TRN input is discussed in its own section below). For example, evidence suggests that the cholinergic input to the thalamus regulates alpha oscillations in the LGN, as evidenced by activation of muscarinic cholinergic receptors that induce alpha oscillations of LFPs in the LGN (Lorincz et al. 2008). Thalamo-cortical cell firing appears to be correlated with these alpha oscillations, with different groups of LGN neurons firing at distinct phases of the alpha oscillation (Lorincz et al. 2009). Thus, cholinergic inputs to the LGN may influence thalamo-cortical transmission by changing the synchrony of LGN neurons (Hughes and Crunelli 2005; Steriade 2004). Because cholinergic tone increases with vigilance (Datta and Siwek 2002), cholinergic influence on thalamo-cortical transmission may be modulated by behavioural context. Moreover, the thalamus is critically involved in generating cortical alpha rhythms (Hughes and Crunelli 2005), which are linked to spatial attention bias and stimulus visibility (Mathewson et al. 2009; Romei et al. 2010; Thut et al. 2006). In comparison, feedback from V1 may influence alpha oscillations in the LGN to a lesser degree (Lorincz et al. 2009). However, feedback from V1 appears to play an important role at higher frequencies. For instance, inter-areal synchrony in the beta frequency range can help route information during selective attention (Buschman and Miller 2007; Saalman et al. 2007). Accordingly, feedback from V1 has been reported to modulate beta oscillatory activity in the LGN according to attentional demands (Bekisz and Wrobel 1993).

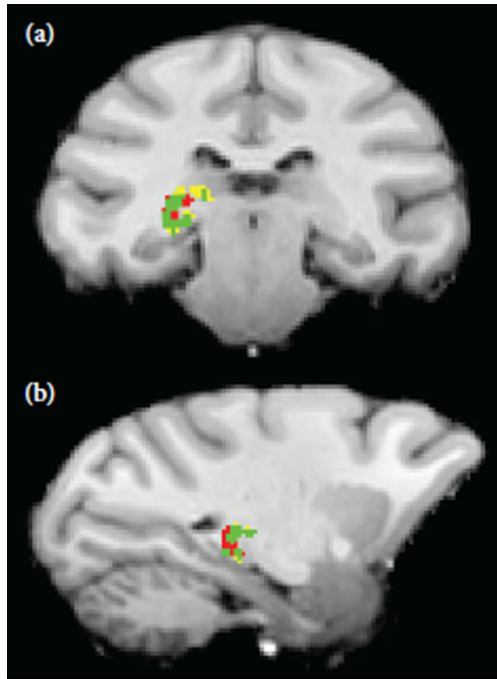
In summary, there is growing evidence from human fMRI and macaque physiology studies that the response magnitude of LGN neurons is influenced by attentive processing. Thus, the LGN may regulate information transmission from the retina to visual cortex according to behavioural context. Although the spike timing of LGN neurons is important in influencing thalamo-cortical transmission, modulation of spike timing by selective attention in the LGN of awake, behaving primates has been largely unexplored.

### **Pulvinar: Modulation of Information Transmission between Cortical Areas**

Traditionally, the pulvinar has been divided into medial, lateral, inferior, and anterior areas. However, these cytoarchitectonically defined divisions do not correspond well with divisions based on connectivity, neurochemistry, or electrophysiological properties (Adams et al. 2000; Gutierrez et al. 1995; Stepniewska and Kaas 1997). Based on retinotopic organization and cortical connections, at least four visual areas of the pulvinar have been differentiated. There are two areas with clearly organized retinotopic maps in the lateral and inferior parts of the pulvinar, which connect with ventral visual cortex. The other two pulvinar areas do not show clear retinotopy: an inferomedial area that connects with dorsal visual cortex (areas MT, MST, and FST); and a dorsal area that connects with the posterior parietal cortex (PPC) and frontal eye fields (Fig. 14.1b). The RF size of pulvinar neurons appears to roughly correspond to that of cortical neurons to which they connect (Bender 1982; Petersen et al. 1985). The majority of pulvinar neurons respond phasically to the onset of visual stimuli, although a number of pulvinar neurons show more tonic responses (Petersen et al. 1985). Pulvinar neurons have been reported to show broad orientation tuning and weak directional preference for moving stimuli; and a subset of neurons show colour-sensitivity, including colour-opponent responses (Bender 1982; Felsten et al. 1983; Petersen et al. 1985).

The pulvinar is heavily connected to the cortex and forms cortico-thalamo-cortical pathways. As a general principle, directly connected cortical areas will be indirectly connected via the pulvinar (Fig. 14.1c; Sherman and Guillery 2006; Shipp 2003). Cortical areas project to restricted zones within the pulvinar, and directly connected cortical areas have overlapping projection zones in the pulvinar. Originally investigated using anatomical tracers, the cortical projection zones in the pulvinar can now be visualized *in vivo* using diffusion tensor imaging (DTI). For

example, Saalmann and colleagues (2012) performed probabilistic tractography on DTI data to map probable connections between the pulvinar and the directly connected cortical areas V4 and TEO. Figure 14.3a and b show pulvinar zones connected with V4 (yellow) and TEO (red), as well as the region of overlap (green) through which the V4-pulvinar-TEO pathway likely traverses. V4 and TEO predominantly connect with the ventral pulvinar, and there is substantial overlap between V4 and TEO projection zones in the pulvinar, with the TEO projection zone extending more caudally. These probabilistic tractography results are broadly consistent with previous anatomical tracer work (Baleydier and Morel 1992; Shipp 2003). However, the probabilistic tractography data has the advantage of delineating projection zones specific to individual monkeys, which cannot be precisely ascribed based on tracer data from the literature.



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**Figure 14.3** Pulvino-cortical networks defined using DTI. (a) Coronal and (b) sagittal slices containing pulvinar voxels with high probability of connection with V4 (yellow), TEO (red), or both (green). Broadly consistent with published anatomical tracer results (Baleydier and Morel 1992), the probabilistic tractography on the DTI data had the advantage of showing projection zones in the pulvinar specific to the individual monkeys participating in our study. This allowed us to target electrodes to interconnected pulvino-cortical network sites, improving the precision of the simultaneous multi-site electrophysiological recordings. From *Science*, 337 (6095), Yuri B. Saalmann, Mark A. Pinsk, Liang Wang, Xin Li, and Sabine Kastner, The Pulvinar Regulates Information Transmission Between Cortical Areas Based on Attention Demands, pp. 753–6, figure 1 (c) 2012, AAAS. Reprinted with permission from AAAS.

The direct cortico-cortical feedforward connections originate in layer 3 and terminate in layer 4 in a higher cortical area (Felleman and Van Essen 1991). In parallel, the putative feedforward pathways through the pulvinar originate in cortical layer 5 and terminate in layer 4 of the higher cortical area as well. There are also direct and indirect feedback pathways between cortical areas. The direct cortico-cortical feedback connections commonly project from layer 6 to layer 1 of the lower cortical area. Cortical layer 6 also provides feedback to the pulvinar, which itself projects to cortical layer 1 (Benevento and Rezak 1976; Lund et al. 1975; Shipp 2003). The fact that the direct and indirect pathways terminate in similar cortical layers presents an opportunity for the two pathways to interact. Due to the overall connectivity pattern, the pulvinar is positioned to regulate cortico-cortical transmission according to behavioural context.

### Effects of pulvinar lesions

Arguably the most compelling evidence for the pulvinar playing an important role in visual perception and behaviour comes from lesion studies in humans and monkeys. Cortical lesions involving the posterior parietal

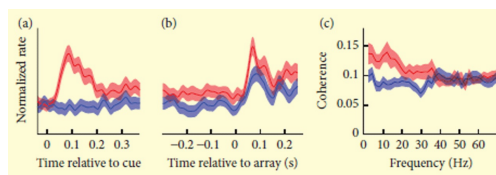
cortex (PPC) may lead to profound attentional deficits such as visuospatial hemineglect, a syndrome associated with a failure to direct attention to contralesional space (see Vallar and Bolognini, chapter 33, this volume). Neglect is not only associated with cortical lesions, but can also occur after thalamic lesions that include the pulvinar (Karnath et al. 2002; Petersen et al. 1987). More specifically, the PPC is interconnected with the dorsal pulvinar and, accordingly, inactivation of the dorsal pulvinar in monkeys leads to deficits in directing attention to contralateral space (Wilke et al. 2010). Even though thalamic neglect in humans is rare and severe attentional deficits that occur as a consequence of pulvinar lesions typically do not persist, a milder deficit that may be a residual form of thalamic neglect has been observed as a slowing of orienting responses to contralesional space (Danziger et al. 2001; Rafal and Posner 1987).

More generally, patients with pulvinar lesions present with deficits in coding spatial information in the contralesional visual field. They have difficulty localizing stimuli in the affected visual space and these difficulties extend to the binding of visual features based on spatial information (Ward et al. 2002), which is one of the most fundamental operations that the visual system has to perform in order to integrate visual information across various feature dimensions. For example, these patients may have difficulties binding the appropriate colour to each of multiple shapes that are presented simultaneously: a red square and a blue circle may be mistaken to be a blue square or red circle. Such errors in binding information from different feature dimensions that require accurate spatial coding are classically associated with PPC lesions (Friedman-Hill et al. 1995), but appear to be associated with pulvinar lesions as well (Arend et al. 2008; Ward et al. 2002). Interestingly, the spatial coding deficits have been observed in different spatial reference frames (e.g. retinotopic or object-based), thus underlining the close functional relationship between the (dorsal) pulvinar and PPC (Ward and Arend 2007).

In accordance with its role in visual attention, patients with pulvinar lesions also show deficits in filtering distractor information. While these patients have no difficulty discriminating target stimuli when shown alone, discrimination performance is impaired when salient distractors are present that compete with the target for attentional resources, consistent with a difficulty in filtering out the unwanted information present in the visual display (Danziger et al. 2004; Snow et al. 2009). Similar filtering deficits have been observed after PPC lesions in humans (Friedman-Hill et al. 2003) and after extrastriate cortex lesions that include area V4 in humans (Gallant et al. 2000) and monkeys (De Weerd et al. 1999), suggesting that the pulvinar is part of a distributed network of brain areas that subserves visuospatial attention.

Taken together, lesion studies point to the critical involvement of the pulvinar, not only in selective attention, but in a number of fundamental cognitive functions, including orienting responses and the exploration of visual space, and the spatial coding of visual information necessary for feature binding. These studies indicate that the pulvinar is an integral subcortical part of multiple large-scale networks that regulate behaviour.

### Behavioural response modulation



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**Figure 14.4** Spatial attention modulated the spike rate of pulvinar neurons and their synchrony. Population activity ( $\pm$  standard error) aligned to (a) cue and (b) target onset. Mean of 51 pulvinar cells. The monkey's attention was drawn to the location of the spatial cue and maintained there until target presentation. In (b), the preferred stimulus appeared at the RF, flanked by congruent distractors. (c) Population average of the transformed spike-field coherence in the pulvinar, calculated in the 300 ms window prior to target onset. Red, attention at RF; blue, attention away from RF. From Science, 337 (6095), Yuri B. Saalmann, Mark A. Pinsk, Liang Wang, Xin Li, and Sabine Kastner, The Pulvinar Regulates Information Transmission Between Cortical Areas Based on Attention Demands, pp. 753–6, figure 2 (c) 2012, AAAS. Reprinted with permission from AAAS.

The findings from lesion studies are corroborated by physiology studies showing that neural responses in the pulvinar reflect the behavioural relevance of stimuli. It has been demonstrated that spatial attention modulates the response magnitude of neurons in dorsal, lateral, and inferior parts of the pulvinar. Evoked neural responses



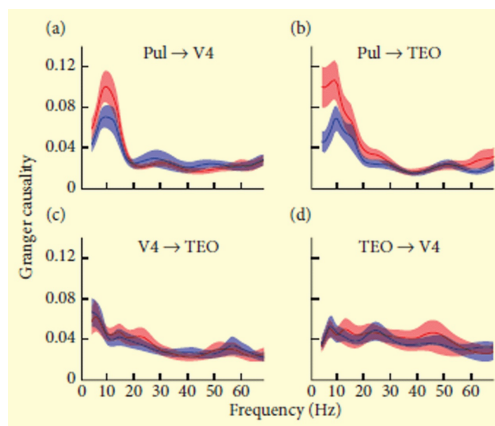
typically increased by up to 25% or more and, in some cases, spontaneous activity was also affected (Bender and Youakim 2001; Petersen et al. 1985). When attention was maintained in the absence of visual stimuli, many pulvinar neurons showed a small but significant elevation in spiking activity (Fig. 14.4a and b; Saalmann et al. 2012). In addition to response magnitude, the timing and variability of pulvinar responses is likely to influence information transmission to the cortex. Accordingly, pulvinar neurons show reduced response variability during peripheral attention and saccade tasks (Petersen et al. 1985). During spatial attention, increased synchrony between pulvinar neurons may increase the efficacy of pulvinar influence on the cortex (Fig. 14.4c; Saalmann et al. 2012).

Like other thalamic cells, pulvinar neurons are able to respond in burst or tonic firing modes. Because the activity of the low-threshold calcium channel depends on cell membrane potential, modulatory inputs to the pulvinar may influence the firing mode. Cholinergic inputs will likely depolarize most pulvinar neurons, switching their firing from burst to tonic mode (Varela and Sherman 2007). However, unlike the LGN, muscarinic activation hyperpolarized about one fifth of rat pulvinar neurons, suggesting that cholinergic inputs can induce bursting in these neurons (Varela and Sherman 2007). In addition, inhibitory input to the pulvinar from sources such as the TRN, anterior pretectal nucleus, and the zona incerta (Bokor et al. 2005; Power et al. 1999) may sufficiently hyperpolarize pulvinar neurons, to enable burst firing. Although data on the relationship between pulvinar burst firing mode and behaviour is lacking, it has been shown that pulvinar neurons are more frequently in burst firing mode than LGN neurons (Ramcharan et al. 2005), and thus burst firing may play a larger role in cortico-cortical transmission than retino-cortical transmission.

### Regulation of cortico-cortical transmission

The direct cortico-cortical pathways are commonly thought to be the major routes for the transmission of visual information between cortical areas (but see, e.g., Sherman and Guillery 2006). Given that these direct pathways are paralleled by indirect pathways through the pulvinar, it is important to ask what function these cortico-thalamo-cortical pathways may serve. *In vitro* studies have shown that microstimulation of the indirect pathways strongly activated cortical areas (Theyel et al. 2010). Moreover, inactivation of the thalamic projection zone that two interconnected cortical areas share led to a failure of cortico-cortical communication, raising the possibility that all cortico-cortical information transmission may strongly depend on thalamic loops (Theyel et al. 2010).

How does pulvinar output influence cortical activity? Simultaneous recordings from the lateral posterior-pulvinar complex and visual cortex of cats performing a spatial discrimination task have demonstrated inter-areal synchrony of beta-band oscillations when the animal anticipated the visual target (Wrobel et al. 2007). Similarly, simultaneous recordings from the pulvinar and visual cortex of macaques performing a spatial attention task have shown synchrony in a pulvino-cortical network predominantly in the alpha frequency range (Saalmann et al. 2012). In anaesthetized cats, deactivating the pulvinar has been reported to disrupt oscillatory activity in visual cortex (Molotchnikoff and Shumikhina 1996; Shumikhina and Molotchnikoff 1999). Together, these results suggest that the pulvinar may facilitate oscillatory activity in visual cortical areas.



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Figure 14.5 Strong pulvino-cortical influences and weak cortico-cortical influences during the maintenance of attention in the absence of visual stimuli. Population average of the conditional Granger



causality for (a) pulvinar influence on V4, (b) pulvinar influence on TEO, (c) V4 influence on TEO, and (d) TEO influence on V4, calculated in the 200 ms window before target onset. The pulvinar influenced both V4 and TEO oscillatory activity predominantly in the alpha frequency range. Because V4 and TEO activity synchronized in the same frequency range, these results suggest that the pulvinar regulates neural synchrony between cortical areas according to the locus of attention. Red, attend in; Blue, attend out. From Science, 337 (6095), Yuri B. Saalmann, Mark A. Pinsk, Liang Wang, Xin Li, and Sabine Kastner, The Pulvinar Regulates Information Transmission Between Cortical Areas Based on Attention Demands, pp. 753–6, figure 4 (c) 2012, AAAS. Reprinted with permission from AAAS.

What may be the functional role of such oscillatory activity in cortico- thalamo-cortical communication? Simultaneous recordings from two cortical areas suggest that the selective routing of behaviourally relevant information across the cortex depends on the degree of synchrony between cortical areas (Buschman and Miller 2007; Gregoriou et al. 2009; Saalmann et al. 2007). Saalmann and colleagues tested whether the pulvinar synchronized oscillations between interconnected cortical areas according to attentional demands, thereby modulating the efficacy of cortico-cortical information transfer. To do this, simultaneous recordings were obtained from two interconnected cortical areas along the ventral visual pathway, V4 and TEO, as well as from the corresponding projection zone in the pulvinar of macaques performing a spatial attention task (Saalmann et al. 2012). Recording electrodes targeted pulvinar sites interconnected with the cortical areas, as determined by probabilistic tractography on DTI data (Fig. 14.3a and b). While monkeys maintained spatial attention, cortical areas V4 and TEO synchronized in the alpha frequency range and to a smaller extent in the gamma frequency range. At the same time, the pulvinar causally influenced oscillatory activity in both V4 and TEO predominantly in the alpha frequency range (Fig. 14.5a and b), suggesting that the pulvinar controlled the alpha frequency synchrony between cortical areas. Pulvinar influence on the cortex may also extend to gamma frequencies through a cross-frequency coupling mechanism. Pulvinar-controlled alpha oscillations in the cortex modulated gamma frequency activity in both V4 and TEO, likely contributing to the synchrony observed between these cortical areas in the gamma frequency range. Thus, the pulvinar may be able to regulate information transfer between cortical areas based on attentional demands. Because direct and indirect feedforward pathways project to cortical layer 4 and direct and indirect feedback pathways project to cortical layer 1 (Fig. 14.1c), the pulvinar is well positioned to regulate both feedforward and feedback cortical pathways.

Together, these results provide evidence for an important role of the pulvinar in regulating cortico-cortical information transmission through the modulation of inter-areal synchrony during cognitive tasks. The prevailing view that information about our visual environment is transmitted through a network of cortical areas for detailed processing needs to be revised by considering extensive pulvino-cortical loops that regulate the information transmitted between each cortical stage of visual processing. Because of common cellular mechanisms and thalamo-cortical connectivity principles across sensorimotor domains, a general function of higher-order thalamic nuclei may be regulation of cortical synchrony to selectively route information across cortex.

Pulvinar control of cortical processing challenges the common conceptualizing of cognitive functions as being restricted to cortex. During maintained spatial attention in the delay period between a cue and subsequent target, pulvino-cortical influences were strong, predominantly in the alpha frequency range (Fig. 14.5a and b), whereas direct cortico-cortical influences were weak (Fig. 14.5c and d). This suggests that internal processes such as maintenance of attention in expectation of visual stimuli and short-term memory rely heavily on pulvino-cortical interactions. Pulvinar regulation of alpha activity is consistent with the important role ascribed to alpha oscillations in these internal processes (Palva and Palva 2011; von Stein et al 2000).

In summary, lesion studies have shown that the pulvinar is critically involved in visual perception, attention, and visually guided behaviour. Electrophysiology evidence suggests that the neural mechanisms supporting these visual functions involve the pulvinar synchronizing distributed groups of cortical neurons, to selectively transmit behaviourally relevant information across the cortex. How the different subdivisions of the pulvinar contribute to cognitive processing remains to be clarified.

### **TRN: Modulator and Pacemaker of Thalamo-cortical Signals?**

The TRN is subdivided into sectors, each associated with a different thalamo-cortical pathway. The visual sector of the TRN receives cortical input from layer 6 as well as thalamic input from the LGN and pulvinar in the form of collaterals from descending or ascending fibers. However, the TRN only projects to the thalamus, providing

inhibitory input to the LGN and pulvinar. The TRN contains topographically organized representations of the visual field, with the RF size of many TRN neurons comparable to that of LGN neurons (McAlonan et al. 2006). The TRN input to the LGN is retinotopically organized (Crabtree and Killackey 1989; Montero et al. 1977), suggesting that the TRN can influence thalamic processing at specific locations in the visual field. However, the TRN is unlikely to selectively modulate magno-, parvo-, or koniocellular pathways, because an individual TRN axon projects to multiple LGN layers (Uhlrich et al. 2003). In contrast with the high spatial specificity of the TRN's input to the LGN, the TRN input to the pulvinar appears to be only roughly topographically organized (Fitzgibbon et al. 1995). Tracer studies have shown that there are reciprocal connections between the TRN and the LGN or pulvinar, forming closed loops. Nonetheless, incomplete overlap in thalamic labelling after the injection of retrograde and anterograde tracers into the TRN suggests that a number of TRN neurons synapse on thalamo-cortical neurons which do not project back to the same TRN neurons, consequently forming open loops (Fitzgibbon et al. 1995; Pinault and Deschenes 1998). Such open and closed loops offer lateral and feedback inhibition, respectively. In addition to these loops formed between the TRN and an individual thalamic nucleus, there are pathways between different thalamic nuclei via the TRN. These disynaptic, intrathalamic pathways can connect first-order and higher-order thalamic nuclei within the same modality, or connect two nuclei of different modalities. These pathways inhibit the target nucleus, thereby providing a means to facilitate information transmission through one thalamic nucleus, while suppressing another one (Crabtree et al. 1998; Crabtree and Isaac 2002).

TRN neurons respond transiently and with short latency to visual stimuli (McAlonan et al. 2006), suggesting that the TRN can influence early evoked responses of LGN and pulvinar neurons. TRN neurons also have high spontaneous activity (McAlonan et al. 2006), consistent with a tonic inhibition of thalamic nuclei. There is growing evidence for modulation of TRN responses depending on stimulus context. For example, in anaesthetized rats, TRN neurons have been reported to habituate to repetitive stimuli (Yu et al. 2009a) and to increase their response to deviant stimuli in an oddball paradigm (Yu et al. 2009b). The TRN receives input from the prefrontal cortex, visual cortex, superior colliculus, and cholinergic brainstem nuclei (Kolmac and Mitrofanis 1998; Montero 2000; Zikopoulos and Barbas 2006), which may enable the TRN to integrate information from various processing levels and to modulate its output according to behavioural needs.

### Attentional modulation

The TRN has been implicated in playing an important role in selective attention by regulating thalamo-cortical information transmission (e.g. Crick 1984; Guillery et al. 1998; Yingling and Skinner 1976). The effects of TRN lesions are consistent with such a role. For example, like in humans, the reaction times of rats to visual targets that are cued are faster than those to targets that are not. However, a unilateral TRN lesion has been shown to abolish this behavioural advantage for the cued stimulus, suggesting that the TRN normally contributes to directing attention to a cued location (Weese et al. 1999). Rat TRN lesions have also been reported to impair orienting responses and, more generally, to reduce exploratory behaviour (Friedberg and Ross 1993).

There is converging evidence from metabolic mapping and electrophysiology studies that selective attention modulates the activity of TRN neurons. Increased activity, as gauged by the number of Fos-labelled cells, has been observed in the visual sector of the rat TRN for attended visual stimuli relative to unattended stimuli (McAlonan et al. 2000). Moreover, increased deoxyglucose uptake has been demonstrated in the TRN of macaques performing a feature-based attention task (Vanduffel et al. 2000). Single-neuron recordings in macaques using cues to guide their attention directly show specific modulatory effects of attention on TRN neuronal responses. When visual and auditory stimuli were simultaneously presented, the spike rate of neurons in the visual sector of the TRN increased when monkeys directed attention to the visual stimulus relative to when they attended to the auditory stimulus (McAlonan et al. 2006). When a monkey attended to one of two visual stimuli presented simultaneously, the spike rate of TRN neurons decreased relative to that evoked by the same stimulus when unattended (Fig. 14.3c; McAlonan et al. 2008). Although magnocellular LGN neurons tended to have a slightly shorter response latency to the visual stimuli, the attentional modulation started in the TRN before LGN, suggesting that the TRN contributed to the attention effects on the LGN. Interestingly, the attentional modulation of TRN responses in the intra-modal attention task differed in sign relative to that found in the cross-modal attention task. The implications of these modulatory effects on thalamo-cortical neurons will be further discussed below.

### Response modes and oscillatory activity

Like LGN and pulvinar neurons, TRN neurons fire in burst or tonic modes depending on the level of vigilance. Importantly, the firing mode can significantly influence the TRN response to sensory stimulation. TRN neurons reach their peak response rate more rapidly for sensory stimulation during tonic mode relative to burst mode. Considering the corresponding time courses of inhibition exerted on thalamo-cortical neurons, tonic mode may thereby facilitate rapid changes in thalamo-cortical signalling, while burst mode may permit an initially strong evoked response from thalamo-cortical neurons (Hartings et al. 2003).

TRN neurons are critically involved in initiating and sustaining thalamo-cortical oscillations. For example, a deafferented TRN is able to self-generate oscillations in the 7–15 Hz range (spindles; Steriade et al. 1987). Moreover, interactions between TRN and thalamo-cortical neurons sustain oscillations, that is, TRN neurons inhibit thalamo-cortical neurons, which rebound fire to excite TRN neurons, thereby initiating another oscillatory cycle (Steriade et al. 1993). In addition to its prominent role in spindle generation, the TRN has been shown to oscillate at lower (Amzica et al. 1992) and higher frequencies, including the beta/gamma frequency range (Pinault and Deschenes 1992). These different oscillation frequencies manifest during different behavioural contexts. Spindles and lower frequencies commonly occur during states of low vigilance, while beta/gamma frequencies are more associated with increased vigilance (Steriade et al. 1993). It appears that spindle oscillations may contribute to reduced efficacy of information transfer across retino-thalamic synapses, by decorrelating retinal input from thalamic output (Le Masson et al. 2002). A more specific role of response modes and oscillatory TRN activity in selective attention remains to be defined.

### Influences on thalamo-cortical transmission

TRN neurons may influence thalamo-cortical neurons of the LGN and pulvinar in a number of ways. First, TRN neurons reduce the spike rate of thalamo-cortical neurons through direct inhibition. For example, the responses of TRN neurons evoked by stimuli at unattended locations were shown to increase, while the responses of LGN neurons decreased (McAlonan et al. 2008), thus suppressing thalamo-cortical transmission of information at unattended locations. In the case of an attended visual stimulus, the converse response pattern was found. That is, responses of LGN neurons increased, while the responses of TRN neurons decreased, thus facilitating the transmission of information at attended locations. Such an inverse correlation has also been reported in anaesthetized cats between simultaneously recorded neurons in the LGN and the perigeniculate nucleus, the equivalent of the TRN's visual sector in the cat (Funke and Eysel 1998).

Second, it is possible that TRN neurons increase the responses of thalamo-cortical neurons through disinhibition. Disinhibition of thalamo-cortical neurons has been shown to arise from TRN neurons inhibiting other TRN cells via dendrodendritic synapses (Pinault et al. 1997) or from TRN neurons synapsing on local inhibitory thalamic neurons, which constitutes about 10% of the synapses formed by TRN neurons projecting to the dorsal thalamus of the cat (Liu et al. 1995; Steriade et al. 1986). Such disinhibitory mechanisms may facilitate the thalamo-cortical transmission of relevant information (Steriade 1999).

Third, TRN neurons may contribute to switching the firing mode of thalamo-cortical neurons. Direct TRN input hyperpolarizes thalamo-cortical cells, which typically invokes burst firing (Huguenard 1996). Consequently, modulation of TRN activity may change the firing mode of thalamo-cortical neurons and the way information is transmitted to cortex (Yu et al. 2009b).

Finally, the TRN may impact the synchrony and oscillatory patterns of thalamic neurons. TRN inhibitory input to LGN and pulvinar neurons may constrain their spike times to time windows following periods of inhibition, thereby helping to synchronize thalamic output (Steriade et al. 1996). Furthermore, it has been argued that the TRN might function as a pacemaker of thalamo-cortical oscillations (Fuentetaja and Steriade 2005). For thalamo-cortical synchrony at spindle frequencies, cortical feedback appears to drive TRN-mediated inhibition and rebound firing of thalamic neurons. Thus, these neurons are recruited into thalamo-cortical spindle oscillations during states of low vigilance (Destexhe et al. 1998). In contrast, thalamo-cortical synchrony at higher frequencies, in the beta/gamma band, may rely more on direct cortical feedback providing excitatory input to thalamo-cortical neurons. In this case, the role of the TRN neurons may be to influence thalamo-cortical beta/gamma oscillations by resetting their phase (Pedroarena and Llinas 1997). Such a phase reset may help to synchronize localized beta/gamma oscillations between the thalamus and cortex, thereby increasing information exchange during states of increased vigilance. This is consistent with the localized enhancement of gamma oscillations in sensory cortex that has been

reported after electrical stimulation of the TRN (Macdonald et al. 1998). Such an account is also supported by a recent computational model showing that the TRN, via other thalamic nuclei, is well positioned to help synchronize areas of the cortex (Drover et al. 2010). However, a functional role of such TRN influences on thalamo-cortical synchrony and oscillations in perception and cognition remains to be determined.

In summary, the TRN forms cortico-reticular-thalamic loops that allow the TRN to influence both the LGN and pulvinar, and this may include playing the role of a pacemaker coordinating the visual thalamus. Although the empirical evidence is sparse, the TRN has a rich mechanistic infrastructure to flexibly control both thalamo-cortical and cortico-thalamic signal transmission according to behavioural context.

### Conclusion

The overall evidence that has emerged during recent years suggests that the visual thalamus serves a fundamental function in regulating information transmission to the cortex and between cortical areas according to behavioural context. Selective attention has been shown to modulate LGN activity, thus indicating that the LGN filters visual information before it reaches the cortex. Behavioural context appears to even more strongly modulate pulvinar activity and, due to its connectivity, the pulvinar is well positioned to influence feedforward and feedback information transmission between cortical areas. Because the TRN provides strong inhibitory input to both the LGN and pulvinar, the TRN may control and coordinate the information transmitted along both retino-cortical and cortico-cortical pathways.

Although the experimental evidence in support of some of these notions is still sparse and there are many unanswered questions about the role of the thalamus in cognitive processing, converging evidence from neuroimaging, physiological, anatomical, and computational studies suggests that the classical view of cognitive functions exclusively depending on the cortex needs to be thoroughly revised. Only with detailed knowledge of thalamic processing and thalamo-cortical interactions will it be possible to fully understand cognition.

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