■ HYPOTHESIS

The Thalamic Intralaminar Nuclei: A Role in Visual Awareness

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We briefly review the anatomy and functional properties of the intralaminar nuclei (ILN) of the thalamus and the neurological disorders associated with their dysfunction. The ILN project over a wide range of cortical territories and are connected to several subcortical structures that place the ILN within the distributed networks underlying arousal, attention, working memory, and gaze control. The temporal structure of the spike discharges of ILN neurons can be controlled by levels of arousal and visuomotor behavior. Taken together, the anatomy, cellular physiology, and clinical data suggest that in the state of wakefulness, the ILN neurons promote the formation of an "event-holding" function in the cortex. In the prefrontal cortex, this function facilitates the storage of target location in working memory. In the frontal eye fields, the function produces sustained activation that anticipates the onset of intended eye movements. In the posterior parietal cortex, the sustained activation can be boosted at the start of the intersaccadic interval and can operate as an attentional gate regulating the flow of information back to the prefrontal cortex. The attentional gate is of limited capacity, as is working memory, and is best utilized during the intersaccadic interval. The ILN may help to synchronize the eye movement commands of the frontal eye fields with the episodic dynamics of the attentional gate and working memory. NEUROSCIENTIST 3:8–15, 1997

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The operation of the cortex is inextricably linked to its interactions with the thalamus. Perhaps one of the most compelling puzzles posed by the thalamocortical system is the role played by a small set of nuclei located in the paramedian thalamus, the intralaminar nuclei (ILN). For six decades, the ILN have been thought to play a role in consciousness, attention, and sensory-motor integration on the basis of both anatomical connectivity and physiological properties (1, 2). The ILN were originally seen primarily as the rostral extension of the brain stem reticular activating systems generating arousal and rhythmic electrical activity distributed across the cortex (2). Over the last 50 years, a gradual shift toward an expanded role in higher integrative functions associated with consciousness has occurred (3–7). In the 1940s and 1950s, Jasper et al. identified the ILN within a diffuse projection system distributing arousal inputs to the cortex. Penfield's hypothesis of a ''centrencephalic integrating system'' highlighted a similar role for the intralaminar thalamus but drew criticism for assigning such a central role to an ''ancient'' and small set of nuclei (8). The contribution of these subcortical structures to higher cognitive functions has been neglected during the past four decades, during which most research has concentrated on regional cortical studies (9). In the last 20 years, however, several studies have suggested an essential role for the ILN in visuospatial awareness, attention, memory, and development (10–14). Recently, interest in the role of the ILN has reemerged (3–5, 7).

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Anatomy

The ILN can be divided into an anterior and posterior group. The anterior group projects widely throughout the neocortex to primary sensory and motor areas, and association cortices. The posterior group projects mainly to sensory-motor and premotor areas, and striatal targets (Fig. 1). The anterior IL group includes the central lateral nucleus (CL), which projects to the frontal eye field (FEF) and, more heavily, to the posterior parietal cortex (PPC). Projections to prefrontal cortex (PFC) and anterior cingulate cortex arise, as well, from the anterior intralaminar group. The CL is also known to project to the primary visual cortex in the cat and monkey (15). The posterior group is dominated by the centromedian-parafasicularis complex (Cm-Pf), which undergoes a notable expansion in primates (the CL also expands and develops further subdivisions in primates) (16). This system projects strongly to the caudate (from Pf), putamen (from Cm), and prefrontal and parietal association cortices. A small projection (Pf) also goes to the FEF (15). The ILN projections to the striatum per se are considered the principle efferent connections of the ILN and include anterior group projections to the caudate, as well.

The ILN receive ascending inputs from several components of the ascending reticular arousal system, including the pedunculopontine cholinergic group (lateral dorsal tegmentum), mesencephalic reticular formation, locus ceruleus, and dorsal raphe. Also received by the ILN are nociceptive, cerebellar, tectal, pretectal, and rhinencephalic inputs (5). Descending inputs reciprocally relate components of the ILN with their cortical projections.

Although each cell group within the ILN projects broadly to cortical targets, each neuron of the ILN has a narrowly elaborated projection and receives its cortical feedback from the same restricted area. The reciprocal projections between the ILN and cortex have a distinctive laminar pattern that differs from the more well-known pattern of the reciprocal projections of the relay nuclei. The ILN neurons synapse in Layer I on the terminal dendritic tufts of layers III and V pyramidal cells (17) and in layers V and VI (17), whereas neurons of the relay nuclei terminate primarily in cortical layers III and IV. Feedback to ILN neurons originates in Layer V, but feedback to the relay nuclei originates in Layer VI (18). In the cat, the dominant corticothalamic input to the CL originates in the PFC, whereas the visual areas, including area 17, also project directly to the CL (18).

The ILN participate in major neural circuits underlying gaze control. Both the CL and the Pf project to the FEF, and the CL sends a strong projection to the PPC.

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Repetitive stimulation of the CL yields contraversive head turning and saccadic conjugate contraversive eye movements (12). Pf receives substantial afferents from the FEF, and the CL receives an ascending projection from the superior colliculus and descending projection from the PPC (6). Because of the projection of Pf to the caudate, the ILN also projects back to the superior colliculus via inputs to the substantia nigra from the caudate. A feedback circuit to the FEF has been proposed via CL to reciprocate a direct corticotectal projection from FEF (Fig. 1) (6).

Neurological Disorders

Visuospatial awareness allows us to orient to objects and events in our world and to navigate through our surroundings. To be visually aware, we must be awake (aroused), focused (attending), and remembering the immediate past (using working memory). Many neurological disorders of the ILN impact on at least one and usually several of these functions. The syndrome of hemineglect associated with unilateral paramedian thalamic injury (usually right-sided) is characterized by the loss of awareness or inattention to multimodal sensory inputs originating from intra- or extrapersonal space contralateral to the lesion (19). The principle lesion is thought to be the disruption of Cm-Pf and tonic arousal inputs to this intralaminar nuclear group from the mesencephalic reticular formation. Thalamic neglect is, therefore, frequently attributed to an arousal or activation defect (19). However, specific integrative problems in visuospatial awareness are seen with posterior thalamic lesions thought to involve the ILN (14). Animal studies support a specific integrative role for the ILN in visuospatial awareness, as well, with strong contributions from the CL (6, 12).

The ILN have been identified with the generation of absence or "petit mal" seizures since the work in the 1940s by Jasper and associates (1, 21). Absence seizures are characterized by amnesia and loss of vigilance; during an "absence," patients fix their eyes forward in a stare for five to ten seconds, followed by an abrupt recovery. Cellular models (22–23) identify the reticular nucleus (RN) of the thalamus as the generator of 3/s spike and wave paroxysms typical of absence seizures. The transition from RN spike and wave to cortical spike and wave is thought to be mediated by both the ILN (and other nonspecific nuclei) and the specific relay nuclei. Abolition of the intrinsic cellular activity of the ILN by 3/s spike and wave may explain the profound disruption of sensory processing and awareness seen in the absence seizure, possibly resulting in a loss of critical control signals necessary for binding of cortical information in the PPC and the frontal lobe. The stare associated with the absence can be explained as a failure of gaze control signals from the ILN (6). In a review of animal models of amnesia, Mair (4) points to a critical role of the ILN in working memory. In humans, working memory disorders have been associated with ischemic insult to the ILN, specifically the left Cm-Pf (4, 24). In many theories of amnesia, subcortical structures are thought to provide signals that synchronize disparate cortical sites during the process of memory consolidation (4). The amnesia characteristic of absence seizures may reflect the disruption of such synchronizing signals from the ILN (25).

The ILN also convey strong arousal inputs to the cortex. Acute bilateral loss of function in the ILN leads to immediate coma (posterior IL group) or profound disruption in arousal and consciousness (anterior group) (26). Recovery generally results in amnesia and memory disorders with anterior group lesions or in more severe impairments, including disturbances of arousal and motor intention (akinesia), with posterior group lesions. Gradual compression of the brain stem, as occurs in incipient downward central brain herniation, is heralded by an early diencephalic stage characterized by changes in attention and arousal, and the loss of fast saccadic eye movements. The eyes rove, unyoked by attention in the comatose state (if no direct damage to the oculomotor centers has been sustained), and they similarly rove in the persistent vegetative state in which the arousal component of consciousness is preserved without attention or awareness (27). These clinical observations emphasize the link between impaired attention, arousal, and eye movements. Given their anatomical connections and location in the dorsal thalamus, the ILN may mediate the changes in saccadic eye movements, arousal, and attention seen with early rostral compression of the thalamus.

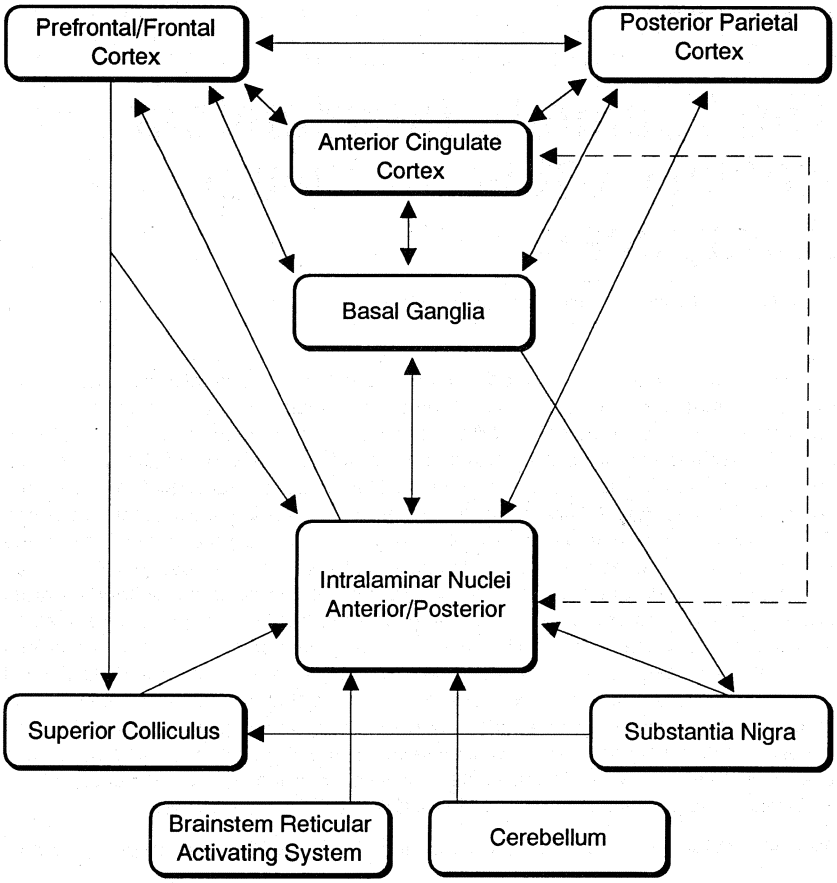

Fig. 1. Anatomical connections of the intralaminar nuclei with distributed circuits underlying arousal, attention, and gaze control. See text for details. Adapted from The neurobiology of saccadic eye movements, New York: Elsevier 1990;361–390.

Classical neuropsychological studies also indicate a close relationship of eye movements with attentional and memory systems. Such observations include the appearance in some subjects of lateralized eye movements during recall of memories and task-specific problem-solving (28). Additionally, there is evidence for a strong link between the rapid eye movement (REM) stage of sleep and attentional processes. During REM sleep, eye movements are closely linked to attentional and memory processing (29). This link was demonstrated in a study comparing the REMs of patients who had hemispheric (frontoparietal) lesions that produced neglect with patients who had similar lesions but no neglect. The neglect group exhibited a severe loss of contralesional REMs, despite their ability to make leftward saccades during free viewing restricted to the intact hemifield (30). These data support a role of the attentional system in the generation of REMs and suggest a role of the ILN because of its known connectivity to brain stem REM generators and frontoparietal areas critical to attention and eye movement control (15). One could speculate that both observations might reflect an overflow of patterned neural activity into the ILN secondary to increased attentional and memory processing (29, 31). REM sleep is known to generate overflow of neural activation into other brain stem circuits that are incompletely suppressed (32).

Physiology

Thalamocortical Circuits and Intrinsic Membrane Properties

All thalamic neurons (specific and nonspecific nuclei) are embedded in the same type of local circuit (Fig. 2): cortically projecting axons of the principal cells make collateral excitatory connections to inhibitory neurons of the RN, and, in turn, neurons of the RN send inhibitory inputs back to the principal cells. The cortical feedback axons send excitatory collaterals into the RN, and the neurons of the RN are interconnected through dendrodendritic synapses. As detailed above, the thalamocortical circuits of the specific and nonspecific nuclei differ in the precise nature of their reciprocal connections with the cortex.

Through the basic thalamocortical circuit and the intrinsic membrane properties common to all thalamic neurons, the principal neurons of the ILN are capable of two modes of spike-firing behavior (34–35) (Fig. 3). When hyperpolarized, ILN neurons fire short high-frequency bursts superimposed on slower and lower-amplitude Ca^{++} spikes. During sleep, neurons of the nonspecific thalamic nuclei (e.g., dorsal CL) are shifted into the hyperpolarized mode. The low-amplitude Ca^{++} spikes occur 7–14 times per second, and the bursts appear with almost every Ca^{++} spike. When depolarized, ILN neurons fire spikes one at a time, at a more regular rate determined by the level of depolarization. During quiet wakefulness and REM sleep, the ILN neurons are switched into the depolarized mode and fire at a baseline rate of 20–40 times per second, with the spikes riding on a membrane potential oscillating in the same range of frequencies (35–37). During visually guided behavior in alert monkeys, the baseline firing rate of some ILN neurons is influenced by eye position, and of others, by the amplitude and direction of saccades (10). The baseline firing rate of another class of neurons (described below) goes to zero during a saccade, followed by a high-frequency burst after the saccade (10). These neurons appear to go through a transition, from the depolarized to the hyperpolarized and back to the depolarized mode of spike-firing behavior, during the course of saccade execution (Fig. 3). Thus, the same ILN neuron membrane properties that allow the brain stem to switch the cortex from sleep to wakefulness seem to be exploited in visuomotor integration. We suggest below that high-frequency bursts at the end of the saccade could boost the cortical activity in the parietal cortex timed to the start of the intersaccadic interval.

Cortical Activation Linked to the ILN

The diffuse thalamocortical projections radiating from the ILN allow signals generated within the thalamus to be distributed simultaneously to many cortical sites. Some of these signals produce synchronized activation in these cortical areas, and some do not. For example, the rhythmic oscillations associated with drowsiness (7–14 Hz) are generated by the intrinsic properties of the RN neurons (22–23). Through recruitment of the ILN, the RN is able to produce slow, synchronized cortical oscillations in many regions (38). The faster oscillatory rhythms seen in the ILN during arousal and REM sleep are also seen in cortical field-potential and extracellular unit recordings in the anesthetized cat (38). However, there is much less inter-regional cortical synchronization of this activity. Paired electrode recordings reveal that the fast field-potential rhythms are synchronized intracortically within columns and for 1–2 mm along the cortical surface. But if the electrode pairs are separated by more than a few millimeters, the synchronization between the two recording sites is abolished. Interregional synchronization of narrowband (including 40-Hz) fast cortical rhythms has also not been seen in electroencephalograms (39) and multisite local field-potential recordings from awake monkeys (40). In contrast, Llinas and co-workers (3, 41) have described a globally coherent (across the cortical hemispheres) 40-Hz activity of brief duration (≈200 ms) in humans engaged in an auditory attention task and during REM sleep. Distributed source analysis of their multichannel magnetoencephalography data led them to conclude that the 40-Hz signals were generated by activity in recurrent thalamocortical circuits involving the ILN.

The dynamics of cortical activation are now understood in the context of an expanded version of the thalamocortical circuit (Fig. 2) (3). The expanded circuit includes components from the specific thalamic nuclei and the nonspecific nuclei. Modeling studies show that activation of both the specific and nonspecific nuclei are required to produce sustained bouts of rhythmic discharge in pyramidal cells (3). The pyramidal cells tend to follow the output of the specific nuclei more closely, with the ILN neurons firing at much higher rates. The ILN is thought to play largely a modulatory role, preparing the cortex for incoming signals from the specific nuclei and, as we suggest below, from other cortical regions.

Visuomotor Function of the ILN

Schlag-Rey and Schlag (10–11) first described visuomotor functions in the rostral ILN of alert monkeys. They identified different cell types from single-unit recordings in animals trained to a variety of behavioral tasks. One population of neurons ceased firing during a saccade and then rebounded with a burst of action potentials at the start of the next intersaccadic interval (Fig. 3). For most of these neurons, neither the direction nor amplitude of the saccade affected the dynamics of the response. This property differed from other neighboring visuomotor neurons in the ILN (eye position and saccadic

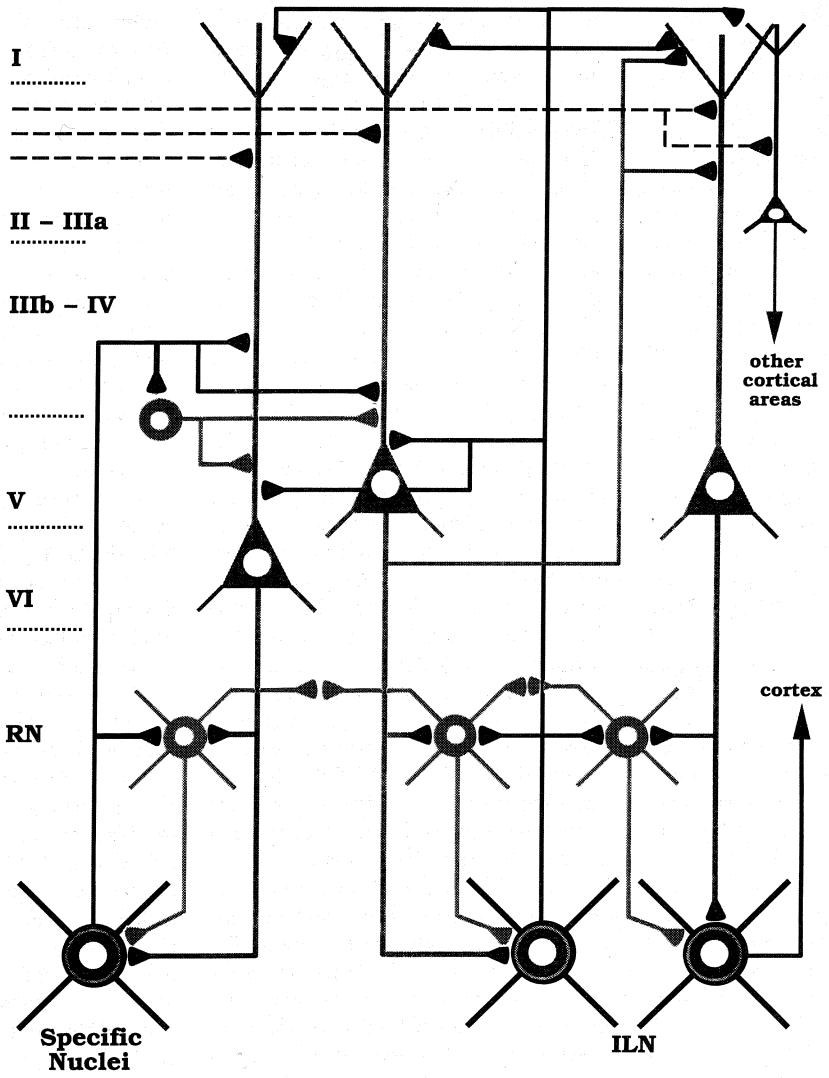

Fig. 2. Expanded version of the thalamocortical circuit (adapted from Temporal coding in the brain, New York: Springer 1994;251–290 and Rev Neurosci 1994;5:105–140). This figure illustrates the relationship between the thalamocortical circuits of the specific nuclei and of the nonspecific intralaminar nuclei (*ILN*). Also shown are two corticocortical circuits that may interact with inputs from the ILN to produce sustained activation (event-holding functions) in local cortical circuits. All excitatory synapses are indicated by a *triangle with a gray border.* All the inhibitory synapses are shown *in blue.* The principal cells of the thalamus appear at the bottom of the figure. The inhibitory neurons of the reticular nucleus (*RN*) of the thalamus are shown in the second row. Four cortical pyramidal cells are shown, one in Layer *VI*, two in Layer *V*, and one in the supragranular layers. One inhibitory interneuron (*in blue*) is shown receiving inputs from the *specific nuclei* and sending outputs to the apical dendrites of two of the pyramidal cells. The Layer *V* pyramidal cell on the left sends ascending axon collaterals to the apical dendrite of the Layer *V* pyramidal cell on the right (33). The other corticocortical circuit is depicted by the *horizontal dashed lines* running through the *II–IIIa* layers. These lines represent afferents from other cortical areas. The corticocortical output of the local circuit is represented by the pyramidal cell in the supragranular layers at the top right of the figure. Note the close juxtaposition in the supragranular layers between synapses arising from the *ILN* and synapses arising from both local and long-range corticocortical connections.

burst cells) that were very sensitive to the parameters (amplitude and direction) of the saccade. Most pause-rebound units also had the same responses, regardless of whether the monkey was performing its tasks in the light or dark. Those that did show an attenuation of the rebound burst in the dark did so only after several seconds. Thus, the rebounds could not be explained by visual stimulation caused by the saccades themselves. Schlag and Schlag-Rey concluded that the pause-rebound neurons primed "visual cortical neurons in the anticipation of acquiring and processing new information after saccades" (10). In their view, the ILN was at least partly responsible for distributing to the cortex control signals related to the timing of saccades and fixation periods. Another cell group that generated visually evoked sustained responses during a fixation interval also fulfilled this role. These neurons had a sustained response that began before a targeting saccade, terminated before or at the same time fixation was broken, and persisted even if the stimulus disappeared while fixation was maintained.

Linking the visuomotor behavior of the ILN to that of the rest of the oculomotor system is beyond the scope of this

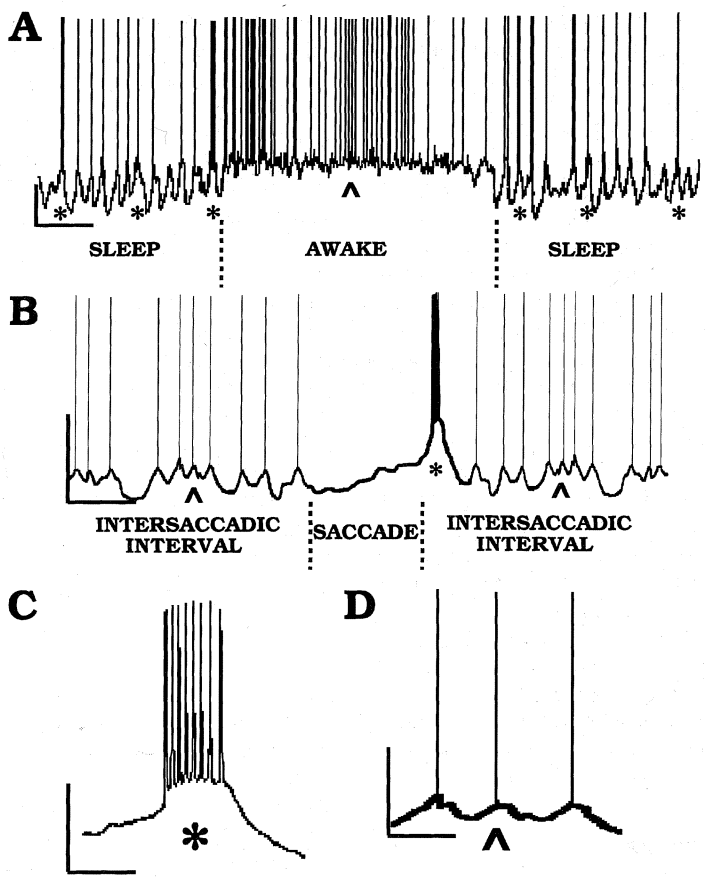

Fig. 3. Two firing modes of intralaminar nuclei: intracellular recordings (adapted from Neuroscience 1993;56:1–9). *A*, intracellular recording from a dorsolateral central lateral nucleus (CL) cell obtained from a cat during epochs of sleep and wakefulness. The neuron passes through two modes of spike firing behavior during the ~3.5 s of the recording. During the first second, the cat is asleep, and the neuron is hyperpolarized. The neuron fires low-threshold calcium spikes at a rate of about 8/s. Riding on many of these calcium spikes are high frequency bursts of action potentials. When events like those marked by the *asterisk* are expanded in time, one observes what is illustrated in part *C*. The *asterisk* was placed below only three of the calcium spikes for the sake of clarity. After ~1.2 s into the recording, the cat awakes. The neuron depolarizes and begins to fire tonically at a rate of ~30 spikes/s. This segment of the recording (marked with a ^) is expanded in time in part *D*. The cat slips back into sleep ~1.7 s later, and the neuron repolarizes and returns to the burst-firing mode. The resting membrane potential at the start of the recording was −75 mV. The *vertical bar* is 20 mV, and the *horizontal bar* is 0.5 s. *B*, a hypothetical intracellular recording of a pause-rebound neuron. This "recording" is a pastiche of intracellular recording traces collected from Neuroscience 1993;56:1–9. Pause-rebound neurons were described in extracellular unit recordings made in the dorsolateral CL of the alert rhesus monkey (10). The intracellular recordings of Steriade and co-workers (37) were made in the dorsolateral CL of cats. The purpose of this synthetic image is to suggest that the ILN may exploit the two spike-firing modes in two very different capacities: 1) generating states of sleep and wakefulness in the cortex; 2) signaling the cortex about the beginning of periods of visual fixation and providing tonic drive to the cortex during fixation. During the intersaccadic interval, the neuron is depolarized and fires tonically, similar to its behavior in the state of quiet wakefulness. During the saccade, the neuron becomes hyperpolarized below the threshold of the low-threshold calcium spike. As the saccade terminates, the neuron begins to depolarize above the calcium spike threshold, leading to the generation of a calcium spike and a high-frequency burst at the start of the intersaccadic interval. The neuron then settles back into the tonic firing mode during the subsequent period of visual fixation. The *vertical scale bar* indicates 20 mV, and the *horizontal scale bar* is 50 ms. *C*, the low-threshold calcium spike and high-frequency burst seen in an expanded time scale. The vertical bar is 20 mV and the horizontal bar is 10 ms. *D*, the depolarized/tonic-firing mode on an expanded time scale. The *vertical bar* is 20 mV, and the *horizontal bar* is 10 ms.

review. However, the ILN contain both neurons that would be useful for establishing a head-centered spatial coordinate system (42), the eye-position encoding units, and neurons that would be useful for a retinotopic spatial coordinate system, the sustained fixation units. The sustained fixation units have many of the "predictive mapping" response characteristics seen in neurons of the lateral intraparietal (LIP) area (43): they change their activity before the saccade is initiated, and they retain a "memory" of the target, even if it is extinguished before the saccade sweeps it into the receptive field. Because both a head-centered and retinotopically centered coordinate system may contribute to maintaining constancy in visuospatial relationships, the ILN may play a key role in visuospatial awareness. Human lesions of the thalamus thought to involve the ILN show specific impairments in the use of extraretinal eye position signals to produce accurate memory-guided saccades (20).

Attentional Processing and Sustained Activation

For individuals to be fully engaged in their surroundings and not just relaxed and awake, they must be capable of selecting particular stimulus attributes or targets for further inspection and directed action. Selective attention is the process by which this becomes possible. The ILN have been linked directly to selective attention through the use of positron emission tomography (PET). In a study by Kinomura and co-workers (7), changes in regional blood flow were seen in the prefrontal, frontal, and parietal cortices; the mesencephalic reticular formation; and the ILN when scans collected during periods of quiet wakefulness were compared with scans made during an attention-demanding reaction-time task. These patterns of activation were seen for both visual and somatosensory cued tasks. This result highlights the participation of the ILN in a modality-independent distributed system for attending to behaviorally relevant external events.

The result of the study by Kinomura et al. was novel for demonstrating with PET the activation of the brain stem reticular activating system and the ILN by a selective attention task. In general, however, attentional tasks involving visual orienting and search produce local increases in cerebral blood flow in the parietal cortex and frontal lobes (44). What does this suggest? Changes in regional cerebral blood

flow that can be measured with PET are only produced by prolonged periods of neural activity, on the order of at least several seconds. Thus, tasks requiring focal attention must involve local regions of sustained cortical activity. The result of the study by Kinomura et al. also carries with it the interpretation that the ILN must be tonically active during tasks utilizing selective attention and that this activity must be more vigorous than the sustained firing seen during quiet wakefulness.

A common feature of neural responses found in the monkey's PFC (45), FEFs (46), and PPC (42, 47) is a period of sustained activation in the interval between presentation of a peripheral target and a subsequent saccade to the target's location. It is possible that the sustained activation is a physiological signature of selective attention being directed to this location. Selective attention is of limited capacity (48) and, thus, must be allotted to some stimuli or tasks at the expense of others. To compensate for the bottleneck imposed by its limited capacity, selective attention can be shifted between stimulus attributes and locations. Shifting between locations amounts to something like closing one entrance to a movie theater and opening another—the ensuing stampede will pile through the newly opened gate after a short delay. The attentional gate to a cued spatial location opens within about 100 ms and remains open for about 1 s (49). While the gate is open, stimulus features at the cued location are passed to working memory, where they can be used for solving a task or programming the next attentional shift. The shift of the gate's location can be performed in conjunction with or without a saccade, but when saccades are involved, perceptual identification is better at the new location, even if the target is extinguished before the fovea arrives (50). Moreover, a successful shift of attention (leading to perceptual identification) to one location is impossible if the saccade is directed to another location (50). These results suggest that attentional shifts are greatly facilitated by saccadic eye movements.

In a memory-guided saccade paradigm, the monkey has to remember the position of a target presented in its movement field and then saccade to this position some time after it has been turned off. The neuron begins firing upon presentation of the target, rapidly increases its firing rate to a maximum before or after the target is turned off (depending on the delay), and maintains its firing rate close to this level until signaled to make the saccade. The neuron will keep firing, even if the signal to make the saccade is given nearly 3 s after the target initially appears. This type of neural response has been interpreted as an ''intention-to-move'' signal or as a memory trace of the target's position (51). The ''intention-to-move'' interpretation arises from the fact that without a saccade, the neuron does not discharge. But it has also been shown that the target can be brought into the neuron's movement field by the saccade, and, still, a period of sustained activation is initiated prior to the eye movement (43). Even if the target is turned off, the neuron will generate a period of sustained activation upon completion of the saccade. Taken together, these results suggest that the location of the target, whether it initially resides in the neuron's movement field or not, is being marked for directed action (a saccade) and for further processing. The attentional shift can occur before or after the saccade, depending on the exact timing of the events and the nature of the visual cues in the behavioral paradigm.

Hypothesis

We hypothesize that the ILN, through their connections with the PFC, FEF and PPC, facilitate and, perhaps, trigger sustained periods of activation in these cortical regions. In the PFC, sustained activation is used for working memory and for directing attentional shifts in more posterior cortical areas. In the FEF, sustained activation prepares saccadic eye movements to attended targets, and in the PPC, it acts as an attentional gate. It is not novel to suggest that the thalamus has a role in visual attention (52) or that attention involves ''amplification'' of cortical activity (44). We do, however, suggest that the ILN, together with the specific nuclei, are essential components of the distributed attentional system and that their participation is required for sustained activation (amplification or event-holding) to occur to link eye movements and working memory with the attentional gate.

There are several plausible mechanisms for how an event-holding process (13) could be generated (4). One of these involves the action of N-methyl-D-aspartate (NMDA) receptors in the upper layers of the cortex. In the adult cortex, NMDA receptors are found almost entirely within layers I-III on the apical dendrites of pyramidal cells. ILN axons are thalamocortical; thus, they presumably synapse predominantly at sites with non-NMDA receptors, but they are unlike the relay nuclei in that their axons synapse in a cortical layer rich in NMDA receptors. The action of ILN axodendritic synapses may be to produce a sufficient enough depolarization in the apical tufts to allow for the activation of the NMDA-linked channels in the superficial cortical layers. These synapses are driven largely by axon collaterals from other pyramidal cells in the local circuit and from afferents originating in other cortical areas (Fig. 2). As previously described, simultaneous activation of ILN and specific thalamic afferents is thought to be required to produce tonic activation in a single pyramidal cell (3). If we now embed that pyramidal cell in a local cortical network, regenerative, sustained activation will be produced in the local population of pyramidal cells (33). This activity would be further enhanced if volleys of action potentials arrive from other cortical areas. The sustained activation could also produce oscillatory firing patterns if local inhibitory circuits are recruited by the specific nuclei (Fig. 2) and $GABA_A$-mediated currents in the pyramidal cells are activated (53). Layer V pyramidal cells send the output of the recurrent excitation in the local circuit back to the ILN. Layer VI pyramidal cells send the output back to the specific nuclei, and the output from layers III/V/VI is sent to other cortical areas. The sustained activation in the local circuit eventually fails because of a reversible decline in transmitter-release probability (33). At firing rates in the range of 20–100 spikes/s, this could lead to a decrease to baseline firing rates within 1 s. In the absence of the ILN input, excitation through the NMDA receptors tends to generate pair-pulse inhibition in pyramidal-to-pyramidal cell circuits (33). As a consequence, recurrent excitation does not develop in the local circuit. In the absence of ILN inputs, the pyramidal cells are also unable to follow the drive of the specific thalamic nuclei.

One can imagine the following scenario (refer to Fig. 4). You are sitting in front of a computer screen that is blank except for a small cursor in the screen's center. You are asked to stare at the cursor and wait for a small, patterned square to appear somewhere on the screen. The wait can be anywhere from 1–10 s. During this period, you are in a state of high vigilance. The ILN in your thalamus are in their quiet wakefulness mode, the principal neurons tonically firing away and setting up diffuse areas of activation in the PFC, FEF, and PPC.

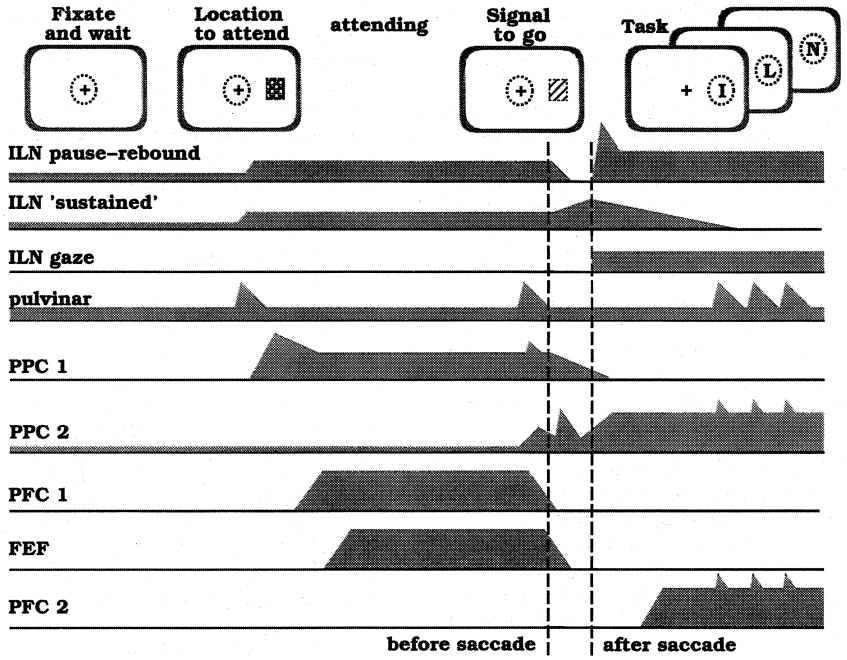

Fig. 4. Timing chart for cortical and subcortical activation during a visual attention task. Imagine that it would be possible to monitor the extracellular unit activity at nine sites within the brain during the performance of the task. Three of the sites are within the intralaminar nuclei (*ILN*), one within the pulvinar, two within the posterior parietal cortex (*PPC 1* and *PPC 2*), two within the prefrontal cortex (*PFC 1* and *PFC 2*), and one within the frontal eye fields (*FEF*). Heights of the *shaded regions* along the time lines indicate the strengths of activation in spikes/s. The *wedges* represent more transient responses, and the *blocks* indicate patterns of sustained activation. For clarity, the time line is dilated at the time of the saccade (*vertical dashed lines*) and at the time of the presentation of the sequence of letters on the screen. This was done to represent more of the dynamics of the responses. The *dashed circle* on the screen at the top of the figure represents the position of the fovea during the trial. See text for details.

The small, patterned square now appears somewhere on the screen, but your instructions are to not look at it until the pattern changes. Within 100 ms of the square's appearance, a subset of neurons in the PPC receives a burst of activation from both the pulvinar (specific nucleus for extrastriate visual cortex) and other extrastriate areas. Through the thalamocortical loop, the ILN increase their levels of firing, causing a wind-up of activation in a local region of the PPC. This region of the PPC encodes the spatial location of the square. Your instructions are to make a saccade to the square as soon as its pattern changes because at that location a sequence of tiny letters will appear in rapid succession and you will have to remember the sequence to spell out a word—a sort of visual Morse code.

The waiting time is now 1–3 s. During this waiting period, a shift of attention and the programming of the saccade takes place. The sustained activation in the PPC recruits a subset of neurons in the PFC through direct corticocortical connections. The neurons in the PFC wind up their activity through their interaction with the ILN and the PPC, and mark the location of the square for directed action and subsequent processing. Output from the PFC to the FEF helps to select those neurons that will generate the appropriate saccade. These FEF neurons wind up their activity during the delay period through their ILN thalamocortical loops. Output from the PFC to the PPC is directed away from the neurons in the PPC encoding the location of the cursor to the neurons that encode the location of the square. The increased sustained activation at the site in the PPC encoding the location of the square now acts as an attentional gate, highlighting this location in the visual maps of other cortical areas in anticipation of a change in the square's pattern (52).

The square now changes from checks to diagonally oriented lines. Once the PFC receives the change in pattern information, the FEF is directed to execute a saccade. At about the same time, neurons in the ILN and PPC that will have the location of the square in their receptive fields following the saccade begin to discharge to prepare a new attentional gate. Other neurons in the ILN become silent during the saccade. As the saccade ends, a burst of activity comes out of the ILN, starting a new region of sustained activation in the PPC. This hot spot of activity opens a new attentional gate synchronized to the start of the intersaccadic interval. Other ILN neurons signal the change in eye position within the orbit. The attentional gate directs the passage of the neural representation of the letter sequence into working memory in the PFC. The PFC may be primed to receive the information by a spread of activity mediated by the RN from the CL neurons projecting to the PPC to the CL neurons projecting to the PFC. This wave of activity may be part of the fast rostral-caudal sweep of RN/ILN activation hypothesized by Llinas and co-workers (3, 41) to underlie cognitive processing. Once the stream of letters is finished, the screen goes blank, and you report the word that was spelled out letter-by-letter on the screen.

Our hypothesis and the scenario described above are supported by the location of ILN within the distributed networks underlying arousal, attention, and gaze control, and by the resulting loss of visuospatial awareness seen with neurological lesions of the ILN. The intimate connection of the ILN with the ''ancient'' brain stem arousal system suggests a rationale for the devastating effects of injuries to these nuclei and the prominent but limited role advocated for them here: the brain takes a system that in some behavioral states produces only a generalized arousal of the cortex and uses it in other behavioral states to promote the formation of local areas of sustained activation in the cortex. Through this latter role, the ILN are able to facilitate the proper channeling of information among specific sets of cortical sites and to promote the synchronization of eye movements with working memory and attention. This makes the ILN critical for visual awareness.

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