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Circuits for Multisensory Integration and Attentional Modulation Through the Prefrontal Cortex and the Thalamic Reticular Nucleus in Primates

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SYNOPSIS

Converging evidence from anatomic and physiological studies suggests that the interaction of high-order association cortices with the thalamus is necessary to focus attention on a task in a complex environment with multiple distractions. Interposed between the thalamus and cortex, the inhibitory thalamic reticular nucleus intercepts and regulates communication between the two structures. Recent findings demonstrate that a unique circuitry links the prefrontal cortex with the reticular nucleus and may underlie the process of selective attention to enhance salient stimuli and suppress irrelevant stimuli in behavior. Unlike other cortices, some prefrontal areas issue widespread projections to the reticular nucleus, extending beyond the frontal sector to the sensory sectors of the nucleus, and may influence the flow of sensory information from the thalamus to the cortex. Unlike other thalamic nuclei, the mediodorsal nucleus, which is the principal thalamic nucleus for the prefrontal cortex, has similarly widespread connections with the reticular nucleus. Unlike sensory association cortices, some terminations from prefrontal areas to the reticular nucleus are large, suggesting efficient transfer of information. We propose a model showing that the specialized features of prefrontal pathways in the reticular nucleus may allow selection of relevant information and override distractors, in processes that are deranged in schizophrenia.

KEY WORDS

corticothalamic projections, dual mode of termination, drivers and modulators, inhibitory control, overlap of terminations, mediodorsal nucleus, association cortices

INTRODUCTION

In recent years it has become increasingly apparent that thalamic processing involves a dynamic change of peripheral or cortical input, and is thus more complex than a direct, linear relay of information /23/. Thalamocortical interactions of high-order association cortices, in particular, have an important role in an array of cognitive, mnemonic, and emotional processes /11,51,52,150, 151,182/.

Reciprocal circuits between the dorsal thalamus and the cortex involve first-order thalamic nuclei, which relay information from ascending pathways to the cortex, and high-order thalamic nuclei that receive input from one cortical area and transmit it to other cortical areas. Studies, based largely on the linkage of sensory systems with the thalamus, separate pathways into driver and modulatory. Driver pathways initiate activity in the next processing station, and modulatory pathways change the driving signal. Pathways from the sensory periphery that terminate in first-order thalamic nuclei, which then project to the middle layers of the cortex, are driver pathways. Pathways from the

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thalamus that terminate extensively in the superficial cortical layers, or the prevalent cortical projections from layer VI to the thalamus, are considered to be modulatory pathways. Some studies have provided evidence that driver pathways, at least in the thalamus, have large terminals, whereas modulatory pathways have small terminals /1,68,72,86-88,96,104,113,138,139,151,153/.

Interposed between the dorsal thalamus and the cortex, lies the thalamic reticular nucleus (TRN), a thin sheet of inhibitory neurons that intercept communication between the dorsal thalamus and the cortex. Thalamocortical and corticothalamic axons send collateral branches to TRN, and the TRN projects to the thalamus but not to the cortex. The strategic position of TRN and its unique functional properties that can regulate the activity of thalamocortical neurons through inhibition and disinhibition have fueled the hypothesis that the TRN has a key role in selective attention /39,69, 107,131/. Interestingly, studies in sensory systems suggest that the physiological properties of TRN neurons change during attentional tasks, possibly modulating thalamocortical communications even at early processing stages /108,114-116/.

Attentional mechanisms are thought to be regulated by high-order cortical areas, such as the prefrontal cortex, which has a supervisory function and a key role in selecting relevant information and discarding irrelevant information. In this review we discuss recent findings on widespread, driver- and modulatory-like prefrontal pathways in TRN /184/ and show how they differ from sensory cortico-reticular projections, which appear to be exclusively modulatory. We summarize circuits suggesting novel mechanisms for cross-modal corticocortical, corticothalamic and intrathalamic interactions in TRN that may have a significant role in attentional modulation. The focus is on the interactions of prefrontal and some sensory cortices with TRN in the primate brain, with references to other mammalian species, as necessary.

FEATURES OF THE THALAMIC RETICULAR NUCLEUS

Anatomy and cellular architecture

The TRN develops from the ventral thalamus /84,140/ forming a thin veil that covers most of the dorsal thalamus along its entire antero-posterior extent and separates it from the cortex (Figs. 1, 2A). The nucleus is bordered laterally by the internal capsule, medially by the external medullary lamina, ventromedially by the zona incerta and posteriorly by the ventrolateral geniculate nucleus. The TRN covers the dorsal and lateral parts of the thalamus as an open umbrella with the handle positioned at the midline, between the dorsal thalamus of each hemisphere. It has a similar shape across mammals, appearing round rostrally, is progressively thinner in its central and caudal parts along the medio-lateral dimension and elongated along the dorsoventral axis, and tapers caudally into a narrow spur.

The TRN consists of about 1 million neurons on each side of the adult rhesus monkey brain /184/. Unlike other thalamic nuclei, it is composed entirely of inhibitory neurons, which are GABAergic and most are parvalbumin-positive (PV+) (~70%) /184/ (Fig. 2B). Morphological studies of TRN in monkeys and humans have classified reticular neurons into several groups mainly according to cell body size and dendritic morphology /21,122, 167/ (Fig. 3). The majority of neuronal somata have diameters of 20-50 μm and appear fusiform or ovoid with a markedly invaginated nuclear envelope and thin cytoplasm. Most neurons have long, sparsely branched, aspiny dendrites, emerging from the poles of the soma, but some have beaded structures along their dendrites /21/. The axons of TRN neurons target underlying thalamic nuclei but also send local collaterals within neighboring TRN regions and, interacting through chemical axo-axonic, axosomatic and dendrodendritic synapses inhibit each other /9,43,82,98,123,146,155,168,175, 180/. Moreover, neighboring reticular neurons in rodents are electrically coupled, forming highly synchronized networks /28,95/.

There is no general agreement among studies about the morphology of reticular neurons across species. Some reports suggest that TRN neurons

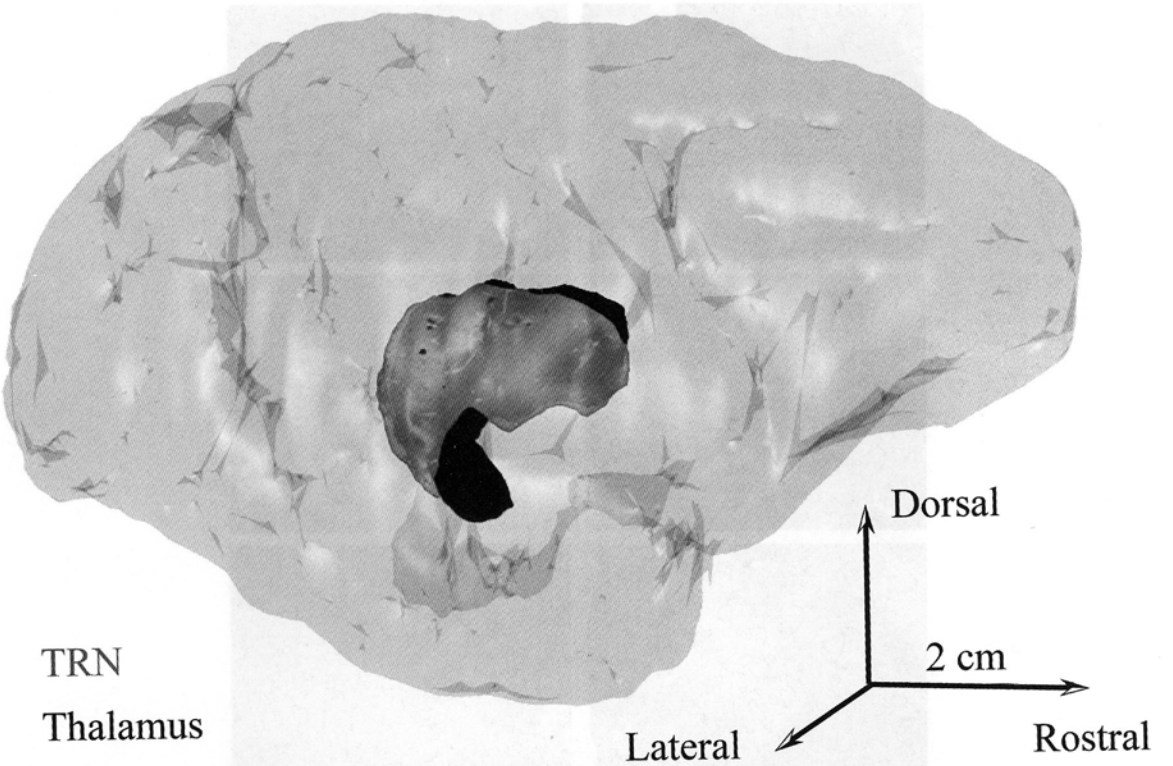

Fig. 1: Position of the thalamic reticular nucleus (TRN) in the rhesus monkey brain. Reconstructed hemisphere shown from the lateral surface, which was rendered transparent to show the position of the TRN (gray) surrounding the thalamus (black).

cannot be classified into separate groups based solely on dendritic morphology and orientation, which extends either dorsoventrally or rostrocaudally and is determined mainly by the shape of the nucleus /103,124/. There is general agreement that reticular neurons conform to the available space, subject to mechanical factors as in other brain regions /46,79/, having round perikarya and multipolar dendrites at the more spacious rostral pole (Fig. 3 top B, C), and elongated and flattened perikarya and dendritic trees in the more cramped central and posterior parts of the nucleus (Fig. 3 bottom B, C). Other studies in rats, rabbits and cats report diversity in the TRN neuronal population, similar to that described in primates /79/. These findings, along with the differential expression of calcium-binding proteins in subsets of TRN neurons for the monkey /184/, and other species (reviewed in /131/), suggest that TRN may be considered an architectonically heterogeneous structure.

Electrophysiological properties

The physiological properties of TRN neurons suggest functional heterogeneity. The TRN contains at least two types of neurons that exhibit two activity modes, burst and tonic. Importantly, the type of activity depends on the animal's behavioral state /45,74,112,119,157,159/. Dual discharge modes have also been observed in thalamic relay neurons but they differ in duration and interval between spikes /47,100/. When the animal is in a state of attentive wakefulness or REM sleep, depolarized reticular neurons fire single action potentials continuously, leading to high background activity in TRN and consequent tonic inhibition of the thalamus /108/. In contrast, during states of drowsiness or slow-wave sleep, activity in TRN is in bursts of intermittent groups of high frequency discharges separated by periods of quiescence, causing bursts of firing after a delay period in the

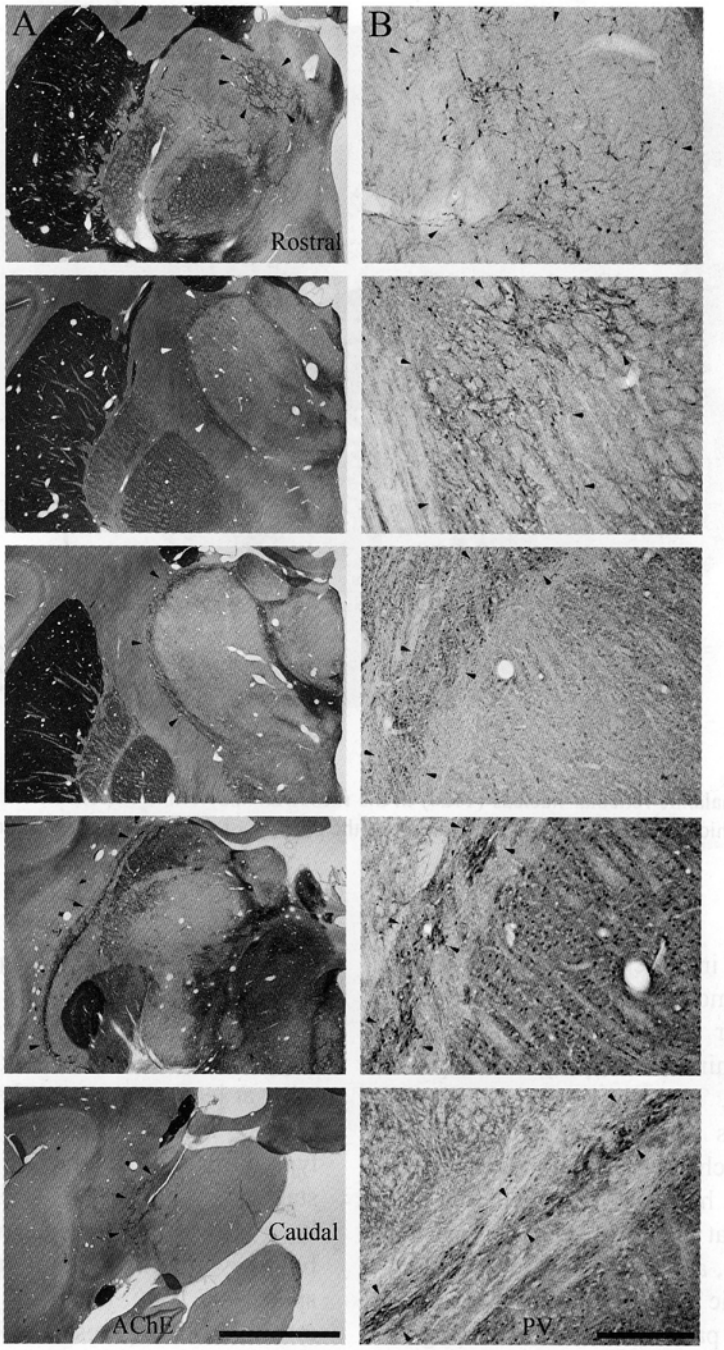

Fig. 2: The thalamic reticular nucleus (TRN) and some of its neurochemical features. Brightfield photomicrographs of coronal sections from rostral (top) to caudal (bottom) levels of the rhesus monkey thalamus showing the TRN in sections treated for: **A:** acetylcholinesterase (AChE) histochemistry, showing TRN as it enveils the dorsal thalamus; **B**: high magnification of sections at the same rostrocaudal levels as in A, immunohistochemically labeled with parvalbumin (PV), showing that the majority of TRN neurons are PV+. Black and white arrows indicate the borders of the TRN. Scale bars: **A** 5 mm; **B** 500 μm.

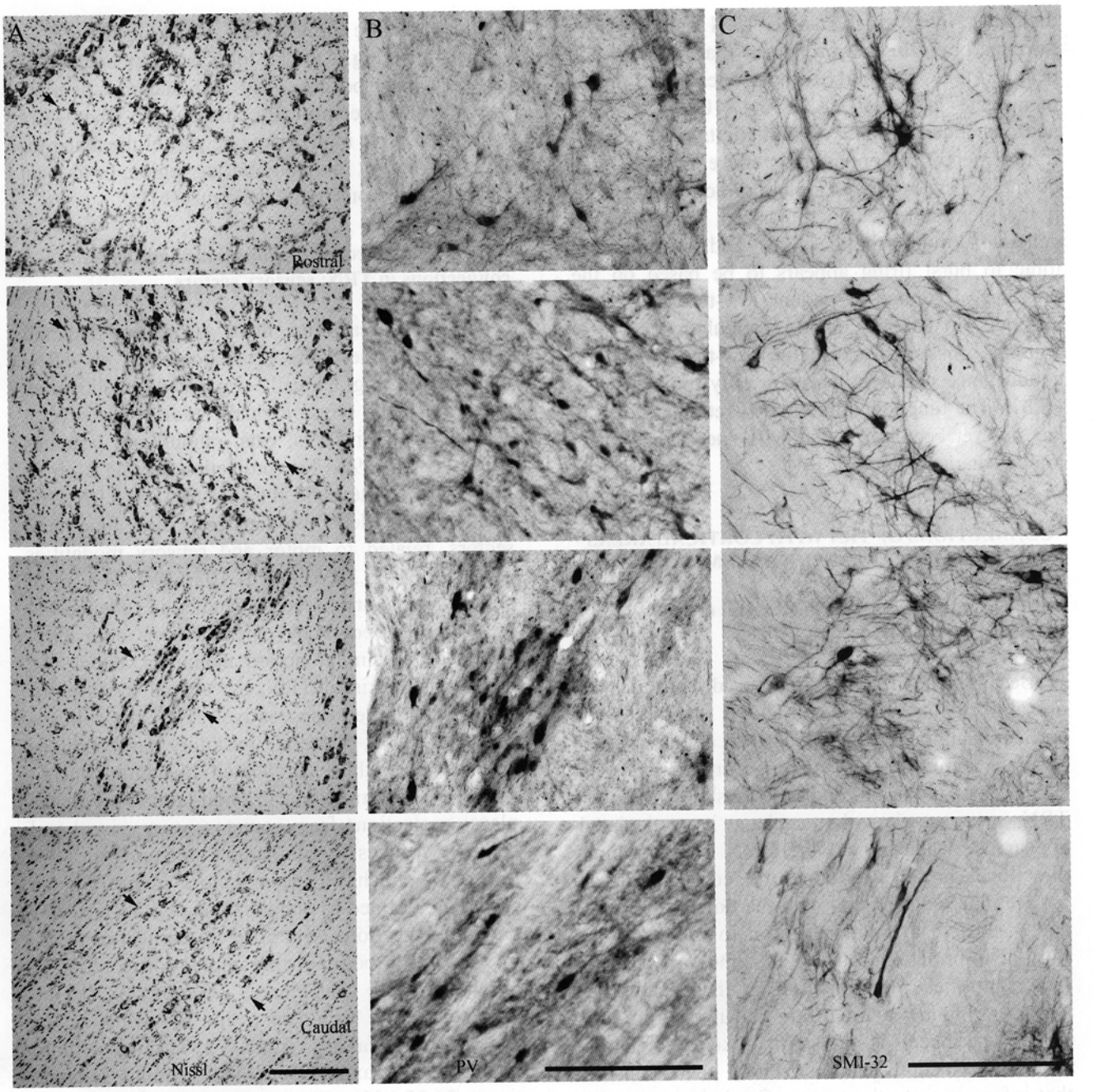

Fig. 3: Features of thalamic reticular nucleus (TRN) neurons. Brightfield photomicrographs showing differences in the morphology of TRN neurons from a rostral to a caudal direction (top to bottom panels), with larger multipolar neurons with round perikarya appearing rostrally (top panels), and smaller, fusiform, bipolar neurons appearing caudally (bottom panels). Coronal sections of a rhesus monkey thalamus stained for: **A:** Nissl; **B:** parvalbumin; **C:** nonphosphorylated neurofilament H (SMI-32). Scale bars: **A** 500 μm; **B** and **C** 200 μm.

thalamus. Interestingly, some TRN neurons have intrinsic physiological properties that allow switch between tonic and burst firing modes based on the membrane potential /8,29,30,47,100/. In these neurons, a depolarizing current elicits tonic activity if the membrane potential is more positive than normal (> -65 mV), and a burst of action potentials if the membrane is hyperpolarized. The ability to generate low-threshold spikes and switch from tonic to burst firing appears to be based on the presence of voltage-dependent, low-threshold, Ca^{2+} channels. In contrast, another population of TRN neurons, possibly lacking the low-threshold Ca^{2+} conductance channels, can fire only tonically /30, 47,81/. The functional diversity of reticular neurons has not yet been correlated with specific morphological characteristics.

CONNECTIONS OF TRN WITH CORTICAL AREAS AND THEIR ASSOCIATED THALAMIC NUCLEI

Basic circuitry linking the cortex and dorsal thalamus with TRN

Because the TRN is interposed between the dorsal thalamus and the cortex, it is crossed by corticothalamic and thalamocortical axons, as well as axons coming to the thalamus from the striatum. The axons that pass through the mesh of inhibitory TRN neurons give the nucleus its reticulated appearance and name. The TRN receives unidirectional projections from the cortex and has bidirectional connections with the dorsal thalamus, and is thus in a unique position to modulate the flow of information between thalamus and cortex. In a simplified representation of these pathways (Fig. 4), input reaching the thalamus from the sensory periphery or the cortex excites thalamocortical projection neurons, which then transmit that information to the cortex. On their way to the cortex, thalamocortical axons give off collateral branches that terminate in TRN. In the feedback loop of this circuit, corticothalamic axons thought to originate from layer VI /70,131/ give off collateral branches that innervate the same TRN regions. The TRN, therefore, receives excitatory input from the cortex and the thalamus and sends inhibitory projections only to the thalamus. These reticulothalamic projections can form closed or open loops (Fig. 5). The loop is considered to be closed when specific TRN and thalamic neurons are connected reciprocally, and is open when TRN neurons receive input from one part of the thalamus and send output to a neighboring region, or to local inhibitory neurons in the thalamus /131/.

Topography of cortical projections and thalamic connections in TRN: sensory sectors

Cortical areas and their associated thalamic nuclei share the same projection sites on TRN, which are topographically organized, as shown in anatomic and physiological studies in several species, including rats, cats, rabbits and primates (reviewed in /69/). The projections create a crude map of the cortex and the thalamus on TRN, and divide the nucleus into anatomic and functional sectors, related to motor and sensory modalities /24,26,27,31-36,38,70,83,101,102,179/. The most detailed maps are based on studies in rodents, but the relative topography of projections onto TRN seems to be similar across mammals. Along the rostrocaudal axis of TRN, the central to posterior sectors are linked consecutively with the somatosensory, visual, visceral, gustatory and auditory cortices and their associated thalamic nuclei. Available information in non-human primates places projections from somatosensory, visual and auditory cortices in comparable positions in TRN (Fig. 6A). Each of these sectors includes tiers, which are defined as subdivisions of a TRN sector having connections with different cortical or thalamic areas, or both. For example, corticoreticular terminals from visual areas V1 and V2 in the primate *Galago* terminate within the visual sector of TRN, but axons from V2 terminate more medially than axons from V1, forming separate tiers /26,27,166/. The topography in TRN is blurred, especially in sectors connected with high-order association cortices or thalamic nuclei, so that connection zones of nearby cortices or thalamic nuclei overlap, allowing indirect modulation of TRN inhibition (reviewed in /35,131/).

The blurred topography is evident in the visual and auditory sectors of the monkey TRN, which are not only connected with temporal visual area TE1

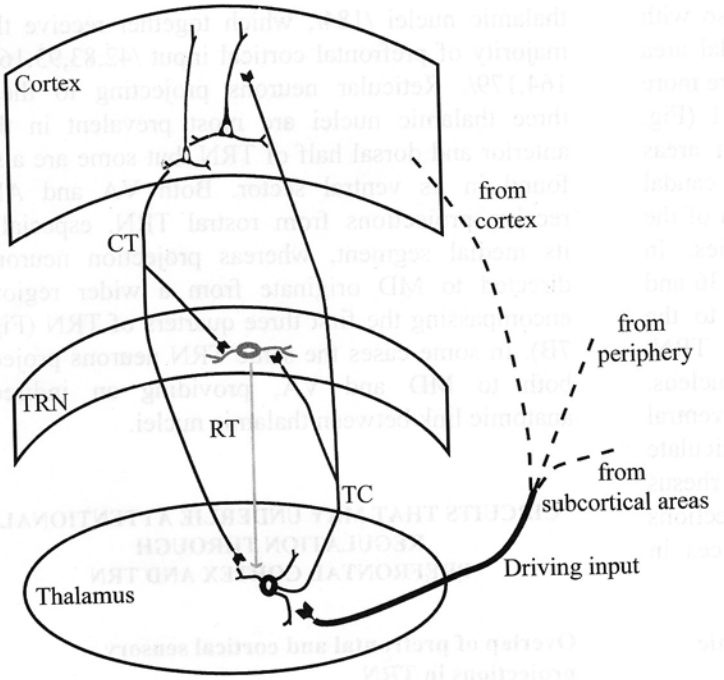

Fig. 4:

Basic circuits linking the thalamic reticular nucleus (TRN) with the cortex and the thalamus. Driving input reaching the thalamus from the sensory periphery, subcortical regions or the cortex, activates thalamocortical projection neurons, which then transmit that information to the cortex. Thalamocortical axons (TC), on their way to the cortex, give off collateral branches that terminate in TRN. In the feedback loop of this circuit, corticothalamic axons (CT) give off collateral branches that innervate the same TRN regions. The TRN sends inhibitory projections only to the thalamus. RT = reticulothalamic connections.

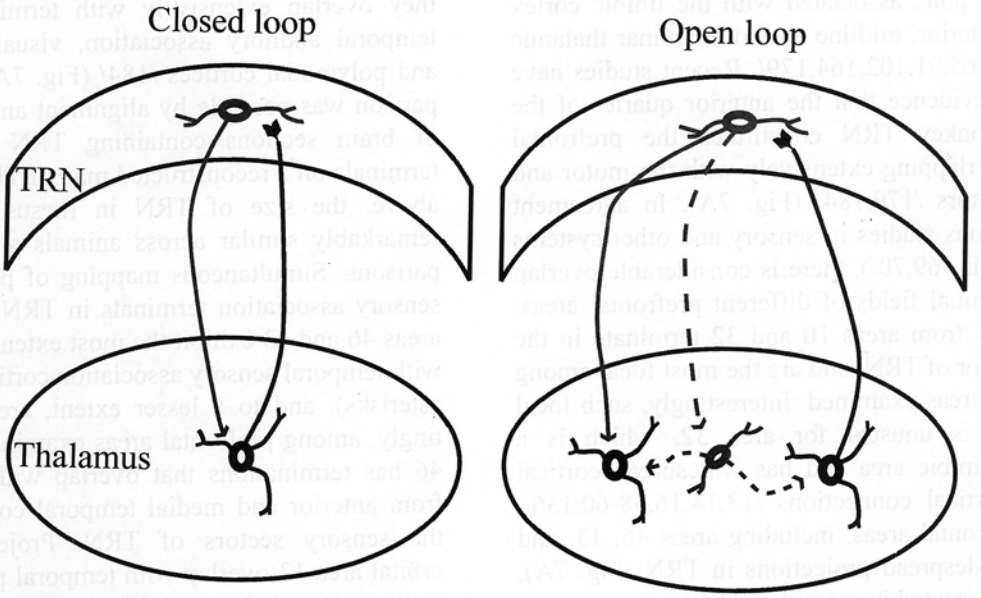

Fig. 5: Thalamic reticular nucleus (TRN) neurons send inhibitory projections (gray line) to thalamic relay neurons that excite them (black line), forming closed loops (left panel). In some cases, a TRN neuron can receive excitatory projections from one thalamic neuron (black line) and send inhibitory projections to another thalamic relay neuron (gray line) or a local inhibitory neuron (dotted gray line), forming open loops (right panel).

and auditory area Ts1, respectively, but also with auditory association area Ts2 and polymodal area 36 /184/. The projections from Ts2 and 36 are more diffuse than projections from TE1 and Ts1 (Fig. 6B). Projections from auditory association areas Ts1 and Ts2 overlap extensively in the caudal sectors of TRN, consistent with the location of the auditory sectors of TRN in other species. In addition, terminations from polymodal area 36 and visual area TE1 are found mainly rostral to the auditory sector, in the visual sector of TRN, situated in the central-caudal parts of the nucleus. These projections are more prominent in the ventral parts of TRN, which include the perigeniculate region. The projections onto TRN in the rhesus monkey have a similar organization as projections from auditory and visual association cortices in other species /25,26,36,38/.

Topography of cortical projections and thalamic connections in TRN: the prefrontal sector

In contrast to the plethora of information on the central and caudal sectors of TRN, the anterior part has received less attention. The anterior TRN includes a motor sector, connected with the motor cortex and the ventrolateral thalamic nucleus, and the rostral pole, associated with the limbic cortex and the anterior, midline and intralaminar thalamic nuclei /24,65,91,102,164,179/. Recent studies have provided evidence that the anterior quarter of the rhesus monkey TRN constitutes the prefrontal sector, overlapping extensively with the motor and limbic sectors /179,184/ (Fig. 7A). In agreement with previous studies in sensory and other systems (reviewed in /69,70/), there is considerable overlap in the terminal fields of different prefrontal areas. Projections from areas 10 and 32 terminate in the rostral sector of TRN, and are the most focal among prefrontal areas examined. Interestingly, such focal projection is unusual for area 32, which is a cingulate limbic area and has widespread cortical and subcortical connections /13,14,16,58-60,136/. Other prefrontal areas, including areas 46, 13, and 9, have widespread projections in TRN (Fig. 7A), which is presented in more detail below.

The same TRN regions that receive prefrontal terminations also project to the mediodorsal (MD), ventral anterior (VA) and anterior medial (AM) thalamic nuclei /184/, which together receive the majority of prefrontal cortical input /42,83,93,160, 164,179/. Reticular neurons projecting to these three thalamic nuclei are most prevalent in the anterior and dorsal half of TRN, but some are also found in its ventral sector. Both VA and AM receive projections from rostral TRN, especially its medial segment, whereas projection neurons directed to MD originate from a wider region, encompassing the first three quarters of TRN (Fig. 7B). In some cases the same TRN neurons project both to MD and VA, providing an indirect anatomic link between thalamic nuclei.

CIRCUITS THAT MAY UNDERLIE ATTENTIONAL REGULATION THROUGH PREFRONTAL CORTEX AND TRN

Overlap of prefrontal and cortical sensory projections in TRN

An unusually widespread pattern of termination in TRN is seen for lateral prefrontal areas 46 and 9 and orbitofrontal area 13. The projections of these prefrontal areas extend beyond the rostral sector of TRN to its second and third quarters, where they overlap extensively with terminations from temporal auditory association, visual association, and polymodal cortices /184/ (Fig. 7A). This comparison was possible by alignment and registration of brain sections containing TRN and labeled terminals on a reconstructed map of TRN. As noted above, the size of TRN in rhesus monkeys is remarkably similar across animals allowing comparisons. Simultaneous mapping of prefrontal and sensory association terminals in TRN showed that areas 46 and 13 exhibit the most extensive overlaps with temporal sensory association cortices (Fig. 7A, asterisks), and to a lesser extent, area 9. Interestingly, among prefrontal areas examined, only area 46 has terminations that overlap with projections from anterior and medial temporal cortices within the sensory sectors of TRN. Projections from orbital area 13 overlap with temporal polymodal or auditory association areas. In contrast, terminations from area 9 show limited overlap with projections from polymodal area 36 and auditory association area Ts2, in dorsal regions of TRN /184/.

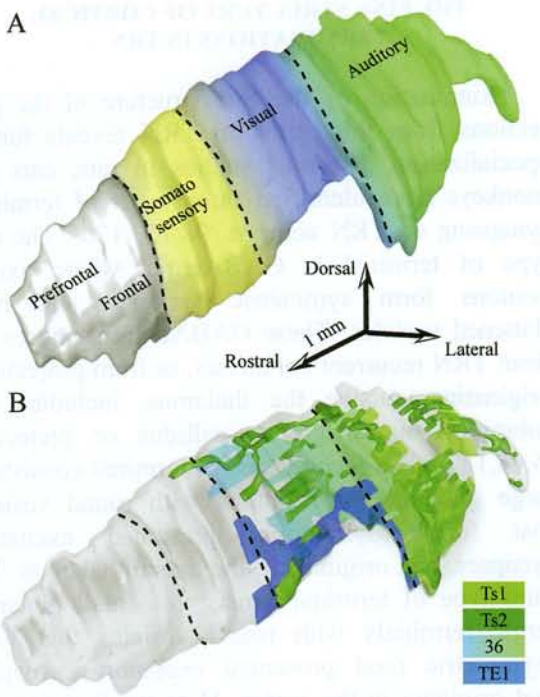

Fig. 6: Sensory sectors of the rhesus monkey thalamic reticular nucleus (TRN). **A:** Three-dimensional reconstruction of TRN (light gray) showing the approximate sectors receiving projections from auditory (green), visual (blue) and somatosensory (yellow) cortices in non-human primates based on available evidence. The colors between the different sectors change gradually to illustrate the blurred topography of the sectors and their overlaps. **B:** Three-dimensional reconstruction of TRN (light gray), which was rendered transparent to show the position of axonal terminations from temporal sensory association cortices, including auditory areas Ts1 (light green) and Ts2 (dark green), visual area TE1 (dark blue), and polymodal area 36 (light green-blue gradient).

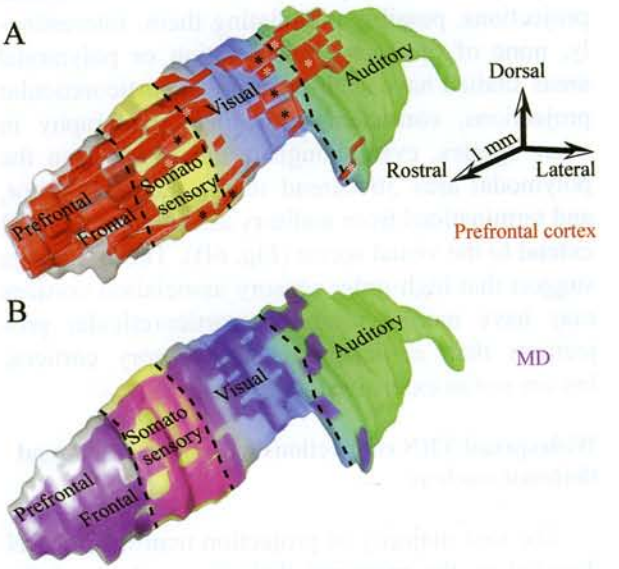

Fig. 7: Widespread prefrontal terminations in the thalamic reticular nucleus (TRN) and projection neurons to the mediodorsal thalamic nucleus (MD) overlap with projections from sensory association cortices. **A:** Three-dimensional reconstruction of TRN (light gray), which was rendered transparent to show the position of axonal terminations from prefrontal areas (red) and their overlaps with somatosensory (yellow), visual (blue) and auditory (green) sectors. Black asterisks indicate some projections from dorsal area 46 and white asterisks indicate some projections from orbital area 13. **B:** TRN neurons projecting to MD (purple) superimposed on a 3D model of TRN with color coded sensory sectors (as in **A**).

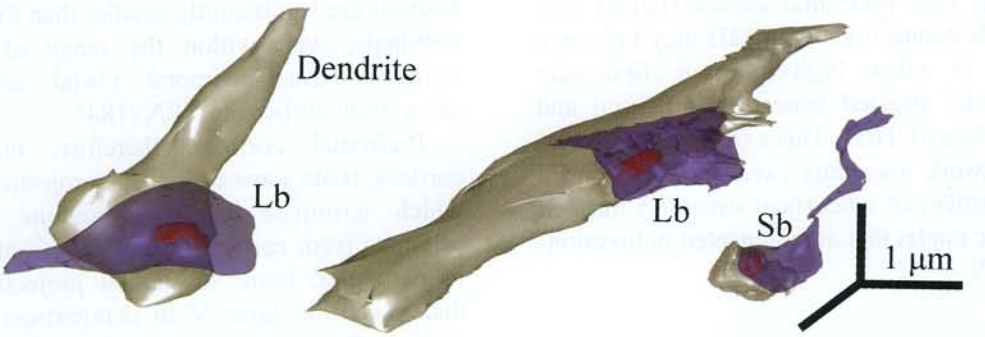

Fig. 8: Large and small bouton populations in the thalamic reticular nucleus (TRN). 3D reconstructions of large (Lb) and small (Sb) boutons (blue), synapsing (red) on parvalbumin-positive dendrites of TRN neurons (gray).

The above evidence suggests that specific prefrontal cortices have widespread projections to TRN, which overlap with other corticoreticular projections, possibly modulating them. Interestingly, none of the sensory association or polymodal areas studied have such widespread corticoreticular projections, consistent with their topography in other species, even though terminations from the polymodal area 36 extend to the auditory sector, and terminations from auditory association area Ts2 extend to the visual sector (Fig. 6B). These findings suggest that high-order sensory association cortices may have more widespread corticoreticular projections than earlier-processing sensory cortices, but are not as extensive as the prefrontal.

Widespread TRN connections with the mediodorsal thalamic nucleus

The vast majority of projection neurons in TRN directed to the principal thalamic nucleus of the prefrontal cortex, the mediodorsal nucleus, are found in anterior loci, but also originate in posterior TRN sectors, albeit to a lesser extent /164,184/. In contrast to other thalamic nuclei connected with prefrontal areas, such as AM and VA, projection neurons in TRN directed to MD extend beyond the rostral sector, encompassing the first three quarters of TRN /184/ (Fig. 7B). Simultaneous mapping in 3D of terminals from prefrontal cortices in TRN, and neurons in TRN that project to MD, reveal considerable overlap in the two projection systems. Superimposed terminations from auditory, visual and polymodal association cortices on the same map show partial overlap with projections from dorsal area 46 and area 13 in the third quarter of TRN, at sites that also project to MD (Fig. 7A, B).

In concert with prefrontal corticoreticular projections, TRN connections with MD may influence relay cells in other high-order or first-order thalamic nuclei situated beneath the central and posterior sectors of TRN. This extensive prefrontal and MD network may thus exert indirect control over other cortices or subcortical structures through their thalamic nuclei that are connected bidirectionally with TRN.

THE FINE STRUCTURE OF CORTICAL TERMINATIONS IN TRN

Examination of the fine structure of the projections from the cortex to TRN reveals further specialization. Previous studies in rats, cats and monkeys have identified three types of terminals synapsing on TRN neurons /98,123,176/. The first type of terminal is GABAergic, where axonal boutons form symmetric synapses and have flattened vesicles. These GABAergic synapses are from TRN recurrent collaterals, or from projections originating outside the thalamus, including the substancia nigra, globus pallidus or pretectum /5,40,127/. The second type of terminal consists of large glutamatergic boutons with round vesicles that form asymmetric, presumed excitatory synapses, and originate in the dorsal thalamus. The third type of terminal consists of small glutamatergic terminals with round vesicles that form asymmetric (and presumed excitatory) synapses that originate in the cortex. Here we focus on the corticoreticular axonal terminals, which are the most abundant and have special characteristics.

Several studies have indicated that projections from sensory or motor cortices to TRN terminate exclusively as small boutons and are thought to originate from layer VI /67-71,89,142-144,151/, which is also the predominant pattern of cortical innervation in other thalamic nuclei. In contrast to projections from sensory association cortices, prefrontal axons in TRN have a dual mode of termination, consisting mostly of small, but also a significant proportion of large boutons (~10% of the total population; /184/) (Fig. 8). Somatosensory corticoreticular terminations are reported to have dual morphology as well /176/, but the large boutons are significantly smaller than the prefrontal terminals, well within the range of the small terminals from temporal visual and auditory association cortices in TRN /184/.

Prefrontal cortices, therefore, unlike other cortices, issue some driver-like projections to TRN, which terminate as large boutons and could originate from cortical layer V. Prefrontal cortices, in particular, issue substantial projections to the thalamus from layer V in comparison with other cortices. Projection neurons in layer V of prefrontal cortices account for about 20% of all neurons

directed to the anterior thalamic nucleus /178/, and about half of those projecting to the ventral anterior thalamic nucleus /179/.

Large boutons have more synaptic vesicles /56, 130,148/ and are more likely to undergo multivesicular release upon stimulation /121,141/, and could thus be more efficient in activating TRN neurons. Large boutons may be present in highly active networks, consistent with their increased mitochondrial content /56,57/, which is activity dependent /165/. Moreover, because neighboring reticular neurons communicate synaptically and can inhibit adjacent TRN regions /183/, subsets of thalamic neurons could be inhibited and others disinhibited, facilitating discrimination of incoming information. In rodents, and possibly other mammals, reticular neurons are additionally coupled by electrical synapses /94,95/, suggesting that even a small number of large boutons could initiate widespread activation in TRN.

CHOLINERGIC AND MONOAMINERGIC INPUT TO TRN

In addition to the glutamatergic projections from the cortex and thalamus, or the GABAergic projections from the substancia nigra, globus pallidus, and pretectum, the TRN receives strong cholinergic and monoaminergic inputs from the brainstem /6, 24,76,92/. These ascending brainstem projections arise primarily from mesopontine cholinergic nuclei /31,128,129,134,162/ and the monoaminergic nuclei locus coeruleus and dorsal raphe /118/. The monoaminergic projection slightly depolarizes TRN neurons, favoring a switch to tonic firing mode, whereas cholinergic input hyperpolarizes them, enabling a switch to burst firing /18,90,111, 112,132/. The effect of cholinergic hyperpolarization of TRN neurons is the removal of their tonic inhibition on thalamocortical projection neurons, leading to increased spontaneous firing in the thalamus. In contrast, noradrenergic depolarization of TRN neurons enables a switch to tonic firing mode, and leads to decreased spontaneous firing of thalamic neurons, reducing noise /80/.

The same neurotransmitter systems and dopamine also robustly innervate thalamic nuclei connected with prefrontal cortices. In contrast to the differential effects on TRN neurons, thalamocortical cells are depolarized by either acetylcholine or norepinephrine /109/. The neurotransmitter projections in the dorsal thalamus have been implicated in the sleep-wake cycle, arousal, attentional mechanisms and the control of vigilance /7,55,75,110,145,161/. A delicate balance of norepinephrine, acetylcholine and dopamine is essential for prefrontal cortical function /4,111,145/ and its disruption is implicated in several diseases, including attention deficit hyperactivity disorder and schizophrenia. The interaction of these neurotransmitter systems with cortical or thalamic afferents in TRN, in conjunction with the widespread prefrontal projections in TRN, may allow extensive modulation of corticothalamic communication.

CORTICAL ACTIVATION AND FUNCTIONAL FLEXIBILITY OF TRN NEURONS

Thalamic, cortical, and other projections to TRN play a critical role in controlling the firing patterns of thalamocortical relay neurons, affecting corticothalamic rhythmic activity and corticocortical communication (for reviews see /47,131/). Recent studies indicate that the predominant synaptic input in TRN is from the cortex, suggesting that the cortex has the greatest modulatory influence on TRN activity /98/. Physiological studies and computational models of reconstructed reticular neurons have shown that the number of glutamate receptor subunits is significantly higher in corticoreticular synapses compared to other corticothalamic synapses. Moreover, the dendrites of TRN neurons have high densities of the low-threshold Ca^{2+} current channel, rendering them highly sensitive to cortical excitatory postsynaptic potentials (EPSPs), but only when the dendrites are hyperpolarized /44,47,64/. As a result, corticothalamic EPSPs easily evoke bursts in reticular neurons and have a net inhibitory effect on thalamic relay cells. Hyperpolarized thalamic projection neurons then respond after a short delay to incoming input with a long-lasting burst followed by prolonged inhibition. This neuronal activity is observed during the early stages of sleep /161/. On the other hand, when the dendrites of TRN neurons

are depolarized, thalamic reticular neurons switch to the tonic mode. In this state, the cortical influence on thalamic relay cells is mostly excitatory, manifested through single spike tonic activity, resulting in desynchronization of thalamocortical oscillations and transition to the alert state.

COMPARISON AMONG SOME SPECIES

Studies in monkeys have shown that about half of synapses between TRN axons in the anterior and mediodorsal thalamic nuclei are on thalamic GABAergic neurons, enabling disinhibition of thalamic relay cells /93,164/. By contrast, in the somatosensory and visual systems of cats, reticular neurons preferentially target projection neurons in several thalamic nuclei, including the ventroposterior, dorsal lateral geniculate, medial interlaminar, lateral posterior, and the pulvinar, and tend to avoid intrinsic inhibitory neurons /99,171/. This evidence suggests that there is a significant difference in the corticothalamic systems of primates and cats. However, one cannot rule out the possibility that these differences are due to examination of different thalamic nuclei in each species.

Thalamic chemoarchitecture may affect the outcome of TRN activation by the cortex

Local circuit inhibitory neurons are found in dorsal thalamic nuclei of primates and cats as well as the dorsal lateral geniculate nucleus of rats, but are absent in other nuclei in rodents /10,20,73,84, 105,117,120,125, 126,156,158,172/. Consequently, cortical activation of hyperpolarized TRN neurons in rodents would inhibit or reduce the excitability of targeted thalamic neurons.

Another significant difference in the thalamus of primates and other mammals is in the dual neurochemical character of the thalamic relay cells, which, in primates, includes neurons positive for the calcium binding protein calbindin or parvalbumin, which often have complementary distributions. These proteins likely play an important role in the regulation of neuronal responses, since they are implicated in the buffering and transport of calcium and in the regulation of related enzyme systems /3,77,78/. In the primate thalamus, these two calcium-binding proteins are not expressed by intrinsic GABAergic neurons and only parvalbumin is expressed by the reticular neurons /85,87,88, 184/. Similar neurochemical specificity is present at least in the medial geniculate complex of rabbits /41/. In contrast, in the cat thalamus, most projection neurons are calbindin-positive, while parvalbumin is expressed in intrinsic GABAergic neurons as well as in reticular neurons, but not the relay neurons of the intralaminar nuclei (reviewed in /87/). In rodents, most thalamic projection neurons are calbindin-positive but many do not express either calbindin or parvalbumin, but some express a third calcium-binding protein, calretinin (reviewed in /87/). These species-specific differences in the expression of calcium-binding proteins may underlie significant differences in the properties of thalamic neurons and the way they respond to cortical and reticular innervation.

ATTENTIONAL MODULATION IN TRN

Through its extensive linkage with the cortex, thalamus and brainstem, the TRN may have a unique role among brain structures in attentional processes. The TRN can potentially regulate the activity of thalamocortical neurons through inhibitory/disinhibitory mechanisms, and determine whether information is relayed through the thalamus unchanged or processed. This gatekeeping role is a result of the circuitry of TRN and depends on the physiological state. The functional activation of TRN is determined largely by the cortex, and by cholinergic and monoaminergic inputs from the brainstem that regulate the membrane potential of TRN neurons. These control mechanisms provide the substrate for the fine-tuning of the excitability of neurons in TRN, endowing this system with the functional flexibility necessary to modulate attention in a constantly changing environment. The involvement of TRN in attentional modulation is exemplified after lesion of the visual sector of TRN, resulting in impairment in selection of relevant targets in attentional orienting tasks /174/. Other studies in the visual system of rats show that when a focus of attention is transmitted from the cortex to the thalamus generating a

core of excitation, there is a concomitant increase in Fos-positive neurons in the associated TRN sector /114,115/. Similarly, there is evidence for an increase in TRN activity during attentional tasks in monkeys /108/ and humans /163,170,173/.

MODEL FOR ENHANCEMENT OF SALIENT STIMULI AND SUPPRESSION OF DISTRACTORS

By what mechanism are relevant stimuli selected and distractors suppressed? There is general agreement that in order to modulate attention, TRN should either enhance relevant stimuli or dampen the noise, increasing the signal-to-noise ratio /39,69,131/. Figure 9 shows a model of circuits through which salient or distracting stimuli may gain access to the cortex or may be dampened in the awake brain in primates. The proposed wiring underlying these circuits is based on the circuitry known from anatomic studies and on physiological studies examining how salient or distracting input entering the thalamus can reach the cortex and initiate a cascade of cortico-reticulo-thalamic activation through open loops (Fig. 9A, C, D) or closed loops (Fig. 9B, C, D). Open loops allow prolonged activation between the thalamus and cortex, and closed loops allow brief thalamocortical activation. Figure 9 shows the possible combinations of salient and distracting input interacting with open or closed loops in the bidirectional linkage between the dorsal thalamus and TRN, and also shows the unidirectional link from sensory and prefrontal cortex onto TRN. Behaviorally salient inputs can have prolonged access to the cortex through open reticulothalamic loops, as shown in Figure 9A, C. In this case, an increase in TRN activity, elicited by the incoming salient signal, would lead to surround inhibition of neighboring thalamic neurons, enhancing the incoming signal, and suppressing distractors (Fig. 9A, C) /93,131,133,164/. In the case of closed loop reticulothalamic projections, a behaviorally salient input would gain brief access to the cortex, before an increase in TRN activity inhibits the thalamic relay neurons that transmit the salient stimulus and prevent further relay to the cortex (Fig. 9B, D). This brief access to the cortex may be enough to guide attention. Alternatively, it has been suggested that during wakefulness, the rhythmic burst firing in thalamic relay neurons initiated after feedback inhibition from TRN may serve as a wake up call to alert the cortex to the presence of behaviorally relevant sensory input /149,152/.

The model also explains how incoming distracting stimuli can be suppressed, or reach the cortex. In the open reticulothalamic loop depicted in Figure 9A, D, a distracting stimulus gains access to the cortex for a prolonged period through activation of thalamocortical pathways. Distractors can also reach the cortex, in the closed loop mode, but only briefly, before a feedback projection from a TRN neuron inhibits the thalamic relay neuron (Fig. 9B, C). The best case scenario for the selection of relevant information and suppression of distractors is presented in Figure 9C, where salient input gains prolonged access to the cortex, through activation of open reticulothalamic loops, and distracting input accesses the cortex only briefly, through activation of closed reticulothalamic loops. Figure 9D presents the worst case scenario, in which the transmission of salient and distracting inputs is reversed.

Model of prefrontal influence in attentional modulation through TRN

The above discussion shows how salient stimuli may reach the cortex and distractors suppressed or passed on to the cortex by virtue of activity in sensory cortices through the thalamus, TRN and cortex, consistent with previous findings /108,114-116/. Prefrontal pathways can perform both functions more effectively, as summarized on the basis of recent findings /184/, in Figure 9 (blue pathways). Prefrontal pathways serve three key functions. First, through their widespread small and large terminals onto TRN, prefrontal pathways can increase the drive for the salient stimuli and ensure passage to the cortex (Fig. 9A-D). Second, through the same mechanism, prefrontal pathways to TRN can increase the drive of reticular neurons, effectively inhibiting distractors in both open loop (Fig. 9A, D) and closed loop (Fig. 9B, C) circuits. Third, prefrontal activation of MD, which maps broadly on the same TRN sites as the prefrontal pathways, also enhances transmission of relevant signals and eliminates distractors. Given that

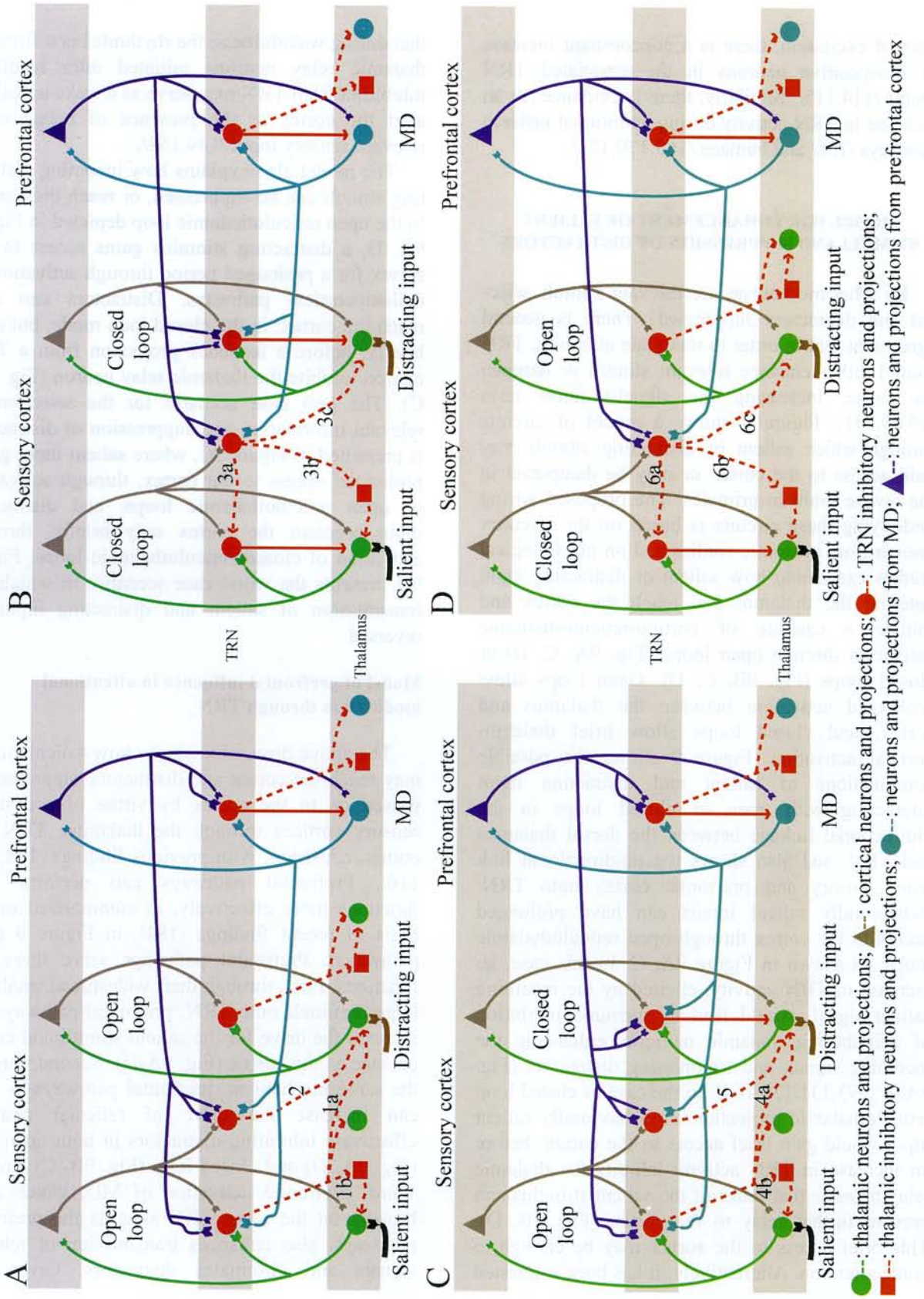
A
Sensory cortex
Prefrontal cortex
Open loop
Salient input
Distracting input
MD
TRN
Thalamus
1a
1b
2
B
Closed loop
3a
3b
3c
C
4a
4b
5
D
6a
6b
6c
--: thalamic neurons and projections; --: cortical neurons and projections; --: TRN inhibitory neurons and projections;
--: thalamic inhibitory neurons and projections; --: neurons and projections from MD; --: neurons and projections from prefrontal cortex

Fig. 9: Schematic diagram summarizing the involvement of prefrontal and sensory systems in attentional mechanisms through the thalamic reticular nucleus (TRN). **A-D** depict all possible combinations of salient (black) and distracting (brown) inputs interacting with open or closed reticulothalamic loops. Reticulo-mediodorsal thalamic nucleus (MD) loops can be either closed or open. **A:** Salient and distracting inputs interact with open reticulothalamic loops. Salient and distracting input is relayed from the thalamus to the cortex (green dots and lines) and back (gray triangles and lines); Activated TRN neurons inhibit other thalamic neurons (dotted red lines) or thalamic GABAergic neurons (red squares), allowing prolonged access of the stimulus to the cortex. The sensory system can suppress distracting stimuli if reticular neurons activated by the salient signal inhibit neighboring thalamic neurons that transmit distracting signals (1a). Dimorphic prefrontal input (blue), through small and large terminals, and input from MD (cyan) can also activate neighboring reticular neurons and inhibit the thalamic neurons that relay distractors (2) and disinhibit thalamic neurons relaying relevant information (1b). **B:** Salient and distracting inputs interact with closed reticulothalamic loops, reaching the cortex briefly before they are inhibited by TRN neurons. Input from prefrontal cortex and MD can reverse this outcome by activating neighboring TRN neurons that inhibit the TRN neurons, that prevent transmission of the salient input (3a), or by inhibiting thalamic GABAergic neurons and disinhibiting the relay of salient input (3b). Prefrontal-MD input could also lead to increased inhibition of distractors (3c). **C:** Salient input has prolonged access to the cortex, interacting with open reticulothalamic loops, and distracting input reaches the cortex briefly, interacting with closed reticulothalamic loops. This is the best case scenario for selection of relevant information and suppression of distractors, and can occur even at early processing stages. Input from the prefrontal cortex and MD to TRN results in enhancement of selection of relevant stimuli by activating TRN neurons that suppress distractors (4a, 5) or disinhibit neurons relaying salient input (4b). **D:** Salient input reaches the cortex briefly, before TRN feedback inhibition through closed loops, and distracting input has prolonged access to the cortex, interacting with open reticulothalamic loops. Projections from prefrontal cortex and MD to TRN provide a mechanism to allow prolonged passage of relevant input, through lateral inhibition in TRN (6a) or disinhibition of the thalamus (6b). The same projections have a concomitant consequence of suppressing distractors (6c).

sensory and other systems can modulate attention at early processing stages, interactions of the prefrontal system with TRN may be especially necessary in complex situations involving cognitive and emotional processing.

Classic studies have shown that detection of novel stimuli evokes large negative slow potentials in the prefrontal cortex and correlated positive slow potentials in rostral TRN /154,181/. According to these authors (reviewed in /22/), selective intermodal attention might be realized by prefrontal control over TRN through the inferior thalamic peduncle. A potential problem for this hypothesis was thought to be in the topography of prefrontal cortical input to the rostral part of TRN, while the processing of salient or distracting sensory stimuli takes place in more posterior parts of the thalamus, in sensory related nuclei. Since there are no direct connections between dorsal thalamic nuclei, another link between the anterior and the posterior part of TRN is needed to provide an anatomic substrate for selective attention. The recent findings of strong and widespread prefrontal projections in TRN that overlap extensively with projections from other cortical and thalamic pathways provide a link between different sectors of TRN /184/ (Figs. 7, 9). Moreover, some TRN neurons project simultaneously to more than one thalamic nucleus, such as the MD and VA /184/. Consistent with the circuitry, there is evidence that stimulation of neurons in sensory- or motor-related dorsal thalamic nuclei robustly inhibits other dorsal thalamic nuclei of the same or different modalities through disynaptic inhibition mediated by TRN /35,37/.

The prefrontal corticoreticular pathway has two unique characteristics that other corticoreticular pathways lack. The first is its dimorphic termination into many small but also a significant proportion of large terminals, which may be more efficient in affecting information processing. Large terminals could override input from small terminals arising in sensory, motor or even other prefrontal cortical areas promoting the relay of relevant stimuli over distracting stimuli. The nature of prefrontal corticoreticular interactions, combined with the properties of TRN neurons, favor the searchlight hypothesis proposed by Crick in 1984 /39/. According to Crick's hypothesis, the TRN acts as an attentional searchlight in the brain that can discover action 'hotspots' in the cortex and the thalamus, intensify the 'hotspot' activity, and then rapidly turn off and repeat the same process for the next field of attention. This integration and intensification of relevant cues was thought to occur through rapidly modifiable synapses that are 'strengthened' to temporarily coordinate two already connected neurons, when those neurons fire in a highly correlated manner. The large terminals of prefrontal pathways may facilitate selection of specific loops through TRN and provide the flexibility needed to direct attention to relevant stimuli, creating 'hotspots' through the thalamus and cortex.

The second unique feature of some prefrontal corticoreticular pathways is their widespread extent, poised to modulate relevant signals from several modalities, as shown in Figure 7. The evidence presented suggests involvement of these pathways in attentional mechanisms through direct interaction of prefrontal terminals, MD, and temporal sensory association areas in TRN. It seems plausible that, through these overlaps in TRN, prefrontal areas 46, 13, and 9 may help modulate signals conveyed by projections from temporal sensory association cortices in the same TRN sites, guiding the selection of relevant and motivationally significant signals.

The uniquely widespread circuitry of some prefrontal cortices and MD with TRN may contribute to the functional specialization of the prefrontal cortex in executive control. Pathways linking area 46 with MD, in particular, are active when animals must hold information temporarily in mind to solve the task at hand /2,48-50,53,62/. The interdependence of prefrontal cortex and MD is exemplified after cooling and incapacitating lateral prefrontal cortex, leading to disruption of activity in MD related to working memory /2/. In addition, area 46 processes detailed sensory information, necessary for discrimination, and has connections with premotor cortices for action /15,106/. Interestingly, axonal terminations from area 46 overlap in TRN with projections from inferior temporal cortices associated with visual perception and visual memory /54,66/. On the other hand, area 13 has robust connections with limbic structures and is associated with emotional processing and evalu-

ation of reward contingencies /12,17/. The widespread prefrontal projections to TRN from these cortices may help focus attention on relevant and motivationally salient stimuli. In schizophrenia, both lateral prefrontal cortex and MD are disrupted /19,61,63,97,135,137,147,169,177/, potentially impairing the ability to effectively select relevant stimuli and suppress distractors.

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