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Review

The thalamic reticular nucleus: structure, function and concept

Didier Pinault*

Laboratoire d'anatomo-électrophysiologie cellulaire et intégrée, INSERM U405, psychopathologie et pharmacologie de la cognition Faculté de Médecine, 11 rue Humann, F-67085 Strasbourg, France

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Abstract

On the basis of theoretical, anatomical, psychological and physiological considerations, Francis Crick (1984) proposed that, during selective attention, the thalamic reticular nucleus (TRN) controls the internal attentional searchlight that simultaneously highlights all the neural circuits called on by the object of attention. In other words, he submitted that during either perception, or the preparation and execution of any cognitive and/or motor task, the TRN sets all the corresponding thalamocortical (TC) circuits in motion. Over the last two decades, behavioural, electrophysiological, anatomical and neurochemical findings have been accumulating, supporting the complex nature of the TRN and raising questions about the validity of this speculative hypothesis. Indeed, our knowledge of the actual functioning of the TRN is still sprinkled with unresolved questions. Therefore, the time has come to join forces and discuss some recent cellular and network findings concerning this diencephalic GABAergic structure, which plays important roles during various states of consciousness. On the whole, the present critical survey emphasizes the TRN's complexity, and provides arguments combining anatomy, physiology and cognitive psychology.

Theme: Motor systems and sensorimotor integration
Topic: Thalamus

Keywords: Anatomy; Biological electrical rhythms; Cerebral cortex; Electrophysiology; Mammals; Selective attention

Contents

Abbreviations: CT, corticothalamic; TRN, thalamic reticular nucleus; TC, thalamocortical

* Tel.: +33-3-90-24-32-45; fax: +33-3-90-24-32-56.
E-mail address: pinault@neurochem.u-strasbg.fr (D. Pinault).
URL: http://www-ulpmed.u-strasbg.fr/laec/.

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More than a century ago, Kölliker [127] identified a nucleus at the thalamus–white matter interface with sets of crossing bundles of axons. He called this nucleus the Gitterkern (from the German word "Gitter", meaning lattice). Subsequently, the term "nucleus reticularis" was introduced by Munzer and Wiener [178], but it was supplanted by "noyau rayé" or "noyau grillagé" which was used by Ramon y Cajal [212] to describe the nucleus' anatomical characteristics in rabbits and mice. The thalamic reticular nucleus (TRN) originates embryologically from the ventral thalamus [219] and then migrates dorsally to envelop mainly the anterior and lateral parts of the thalamus, and partly its dorsal and ventral parts [118]. This shell-shaped nucleus is found in all mammals [9,101,106]. It is adjacent ventromedially to the zona incerta and caudally to the ventrolateral geniculate nucleus [119].

The TRN occupies a key position for thalamocortical (TC) and corticothalamic (CT) operations since it is located at the thalamus-white matter interface - between the internal capsule and the external medullary lamina- where TC and CT axons intersect [92] and where these give off collaterals to innervate TRN cells (Fig. 1). The reticular nucleus (or TRN) is a reservoir of GABAergic cells [60,107]. In the following, the term "thalamus" implicitly means "dorsal thalamus", otherwise it will be clarified.

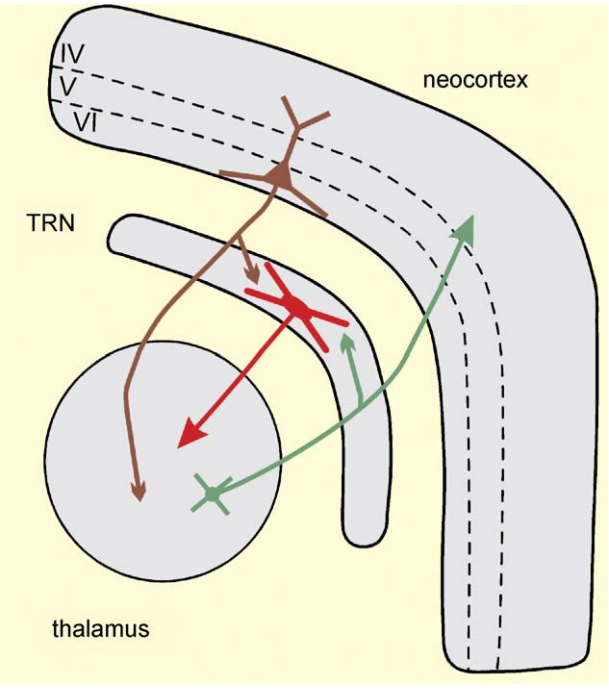

Fig. 1. General organization of the three principal neurons that make the corticothalamic, thalamocortical and reticulothalamic systems. In this rough schema, the size of the neurons and of their ramifications and that of the structures are not at the same scale.

1. Virtually all functional modalities

The TRN is concerned with almost if not all functional modalities. Moreover, electrophysiological studies have demonstrated the existence of at least seven sectors in the TRN, five sensory (auditory, gustatory, somatosensory, visceral and visual), one motor and one limbic. Shosaku et al. [234,235] performed comprehensive physiological studies in the rat showing the topographic organization of the somatosensory, auditory (also see Ref. [267]) and visual sectors (Fig. 2). The large size of the visual sector (dorsocaudal part of the TRN) has been confirmed using an anterograde and retrograde tracer [38]. The latter study has further revealed that the visual sector is divided into subsectors, each receiving inputs from distinct cortical visual areas. Using anatomical means, Hayama et al. [102] and Stehberg et al. [245] revealed a taste-related region located in the ventromedial-most portion of the TRN and a visceral sector in the intermediate part of the TRN at the mid-dorsoventral level, respectively. Whether or not there is an olfactory sector is an unresolved question but olfactory inputs have been identified in the rat in the medial dorsal nucleus of the thalamus [208], a nucleus that is reciprocally connected with the rostral part of the TRN [42,89,199]. The motor and limbic sectors, which have not yet been well defined, are located in the rostral part of the rat's TRN [84,85,199].

Each sector has its own anatomical organization, which is determined by its input and output relationships with the corresponding, first-order and higher-order, thalamic nuclei and related cortical areas (see reviews by Crabtree [51] and by Guillery et al. [94]). Both "first-order nuclei" and "higher-order nuclei" were first defined by Guillery [91] on the basis of their principal "driver" inputs (also see Ref. [186]). The main driver inputs of first-order thalamic nuclei are prethalamic inputs (e.g., somatosensory, auditory and visual inputs), whereas those of higher-order nuclei emerge from cortical layer V cells. The thalamic-projecting axon collateral of the latter cortical neurons cross the TRN without innervating it and their terminal axonal arbors have morphological features to drive restricted thalamic regions, like prethalamic afferents [22,23,186]. Regarding this nomenclature, one should not exclude that some first-order and

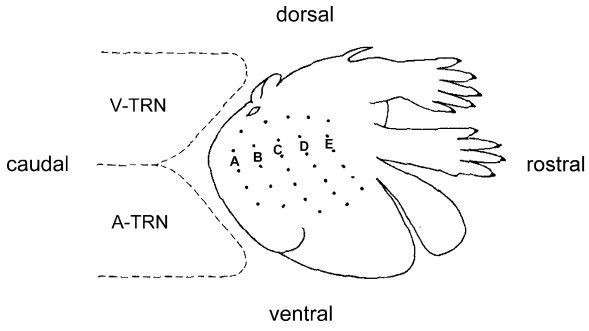

Fig. 2. Schematic representation of the somatosensory, visual (V-TRN) and auditory (A-TRN) sectors of the TRN (lateral view). Rows of whiskers are indicated by A–E. Adapted from Ref. [235].

higher-order nuclei probably also contain higher-order and first-order circuits. For instance, this is the case for intralaminar nuclei, which receive their principal driver inputs from both the periphery and the neocortex [4,21,153,192]. Such nuclei may be considered as "mixed" nuclei [231].

Reticular sectors can be subdivided into anatomical recipient regions of distinct but functionally related thalamic nuclei and cortical areas (see review by Guillery et al. [94]). One typical example is the rat's somatosensory sector, which contains three tiers (internal, intermediate and external). They are interconnected with the first-order thalamic nuclei (ventral, posterolateral and posteromedial, nuclei) in an ordered fashion whereas only the internal tier is interconnected with the posterior thalamic nuclear group, a higher-order nucleus (Fig. 3C). Reticular tiers projecting to first-order nuclei display a well-defined topography whereas those projecting to higher-order nuclei seem not to [49]. In cats and rabbits, the somatosensory sector seems to have only one tier [47–49].

2. Receptive field properties

Reticular cells generally have larger receptive fields than TC neurons [207,224,240,260,277,279]. Although the experimental conditions (e.g., type and depth of anaesthesia) modulate the characteristics of the receptive field(s) of any given neuron in some way, the data currently to hand demonstrate that a small percentage of TRN cells can respond to two sensory modalities, probably those that are located within a region that is common to two adjacent sectors. Moreover, the existence of poly-sensory interactions suggests that adjacent sectors are not sharply bounded. Overlaps between sectors were observed using electrophysiological studies [207,245,251]. For instance, Sugitani [251] found about 1% of the units in the rat's TRN responding to either somatosensory and visual inputs, or somatosensory and auditory inputs. The physiological significance of bimodal units remains, however, to be determined.

A somatotopic representation of the body surface is present in the TRN of rats [235,236], cats and monkeys [207]. In cats and monkeys that are awake, distinct TRN loci representing different parts of the body can have overlapping receptive fields [207]. Under urethane-anaesthesia, three different response patterns of vibrissae TRN units (ON-tonic, ON-phasic and ON-OFF-phasic) have been recorded, some of which also respond to visual or to auditory inputs [251]. In the visual sector of the anaesthetized cat TRN cells are binocular and exhibit both ON and OFF visual responses [224,240,260,277]. In urethane-anaesthetized or lightly narcotized rats, TRN cells transiently fire at both the onset and the offset of whisker deflection [99,232]; in addition, they display robust tonic firing during sustained whisker deflection. To compare, TC neurons of the corresponding somatosensory thalamic nucleus display a weaker tonic pattern and usually exhibit tonic suppression. Thalamocortical and TRN neurons are selective for deflection angle and display best responses to a particular direction [99]. These observations clearly show that TRN cells play a key role in the processing of submodalities, particularly in a way limiting the duration of TC responses.

3. Diverse somatodendritic architectures

From a morphological viewpoint, it is not yet clear whether the TRN contains a homogeneous or heterogeneous cellular population. When investigating the architecture of rabbit and mouse TRN cells with the silver chromate method, Ramon y Cajal [212] highlighted the long hairy and sparsely divided dendritic processes emerging from a fusiform or triangular cell body. Using Golgi impregnation of thalamic pieces of adult cats, Scheibel and Scheibel [226] identified tightly packed dendritic bundles in the dorsolateral portion of the TRN but not in its anterior pole, showing the heterogenic nature of this nucleus. Such bundles were also observed in the dorsolateral TRN following juxtacellular multi-unit staining (Fig. 4). Today, we have no idea how far such singular structures extend, nor do we know anything about their functional significance. Dendritic bundles seem to be formed by parallel dendritic components that belong to neighbouring cells, which are remote within a range of a few tens to a few hundreds of micrometers.

Using Nissl stain, Golgi impregnation, retrograde transport of horseradish peroxidase following thalamic injections, GABA immunocytochemistry and in vitro intracellular stainings with HRP-filled micropipettes, Spreafico et al. [243,244] found three morphological types of TRN cells in the adult rat: (1) a small fusiform "f" type characterized by an elongated perikaryon, and a dendritic arborization extending in the rostrocaudal and dorsoventral planes. This type was observed almost exclusively in the medial third of the dorsoventral extent of the nucleus; (2) large fusiform "F" neurons with dendrites arborizing mainly in the horizontal plane were seen throughout the whole extent of the nucleus; (3) cells with round perikarya and with multipolar

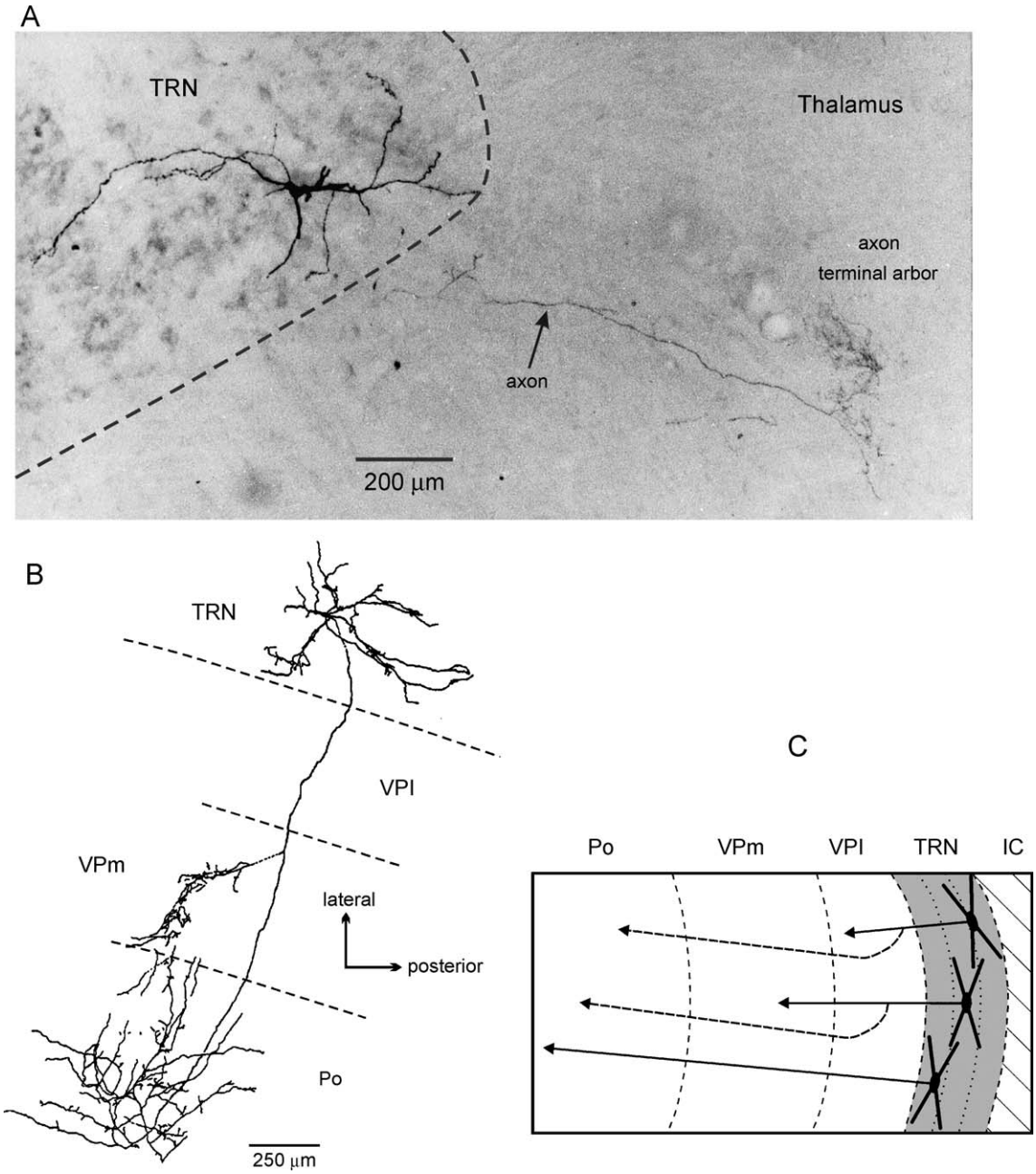

Fig. 3. Axonal projections of TRN neurons. (A) Photomicrograph of a typical single cell juxtacellularly labelled in the rostral pole of the rat's TRN. Parts of its dendrites and axon are contained in the same 100-μm-thick section. (B) Reconstruction of another TRN cell innervating two, first-order and higher-order, thalamic nuclei. (C) Schematic drawing of the axonal projections from the three TRN tiers to first-order and higher-order thalamic nuclei of the rat's somatosensory system. Thick and truncated lines represent principal and occasional axonal TRN projections, respectively. Note that the dendrites of every TRN cell can extend into adjacent tiers (see text for further details). IC, internal capsule; Po, posterior thalamic nuclear group; VPl, ventral posterolateral thalamic nucleus; VPm, ventral posteromedial thalamic nucleus. Adapted from Refs. [194,199]).

dendrites were found predominantly in the rostral pole of the nucleus.

On the other hand, following intracellular injection of TRN cells in fixed thalamic slices of three species (rat, rabbit and cat), Lubke [149] found no obvious basis for classification of neurons in the mammalian TRN according to dendritic morphology. Furthermore, after observing the 3D reconstruction of cells retrogradely labelled in the whole TRN of adult rats, Ohara and Havton [183] concluded that all TRN cells have a similar dendritic morphology and orientation, that is, dendritic arbours with a planar discoid-like architecture and extending either dorso-ventrally or rostro-caudally.

Having individually labelled more than 100 TRN cells using the juxtacellular technique and reconstructed more than a few tens of them in 3D in a previous study [199], it is

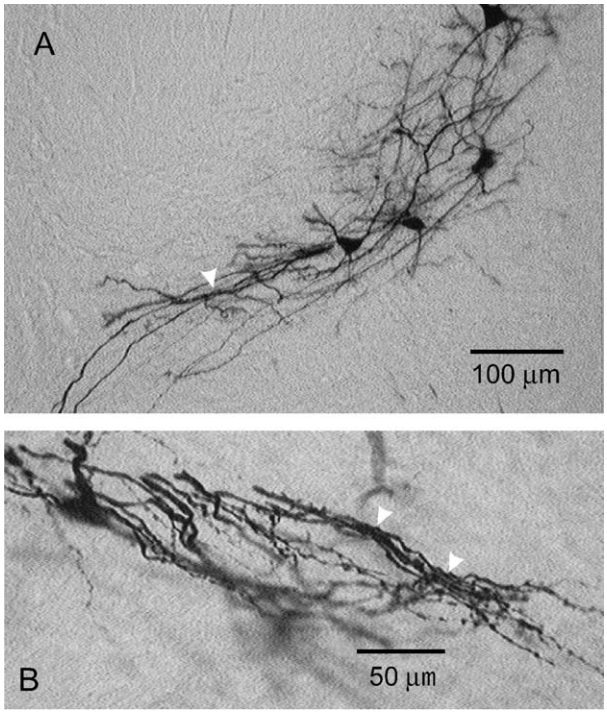

Fig. 4. Juxtacellular multi-unit labelling of nearby cells in the dorsolateral region of the rat's TRN. Note the parallel organization of dendrites, which can form dendritic bundles (white arrowheads) in these horizontal sections (A and B).

tempting to show that the TRN contains at least three types in terms of their dendritic architecture: (1) cells with dendritic ramifications which mainly extend dorso-ventrally (Fig. 5B), (2) cells with dendritic ramifications which mainly extend rostro-caudally and (3) cells with dendritic ramifications extending in nearly all directions (Fig. 5D). While the first two types are observed in almost all TRN regions (also see Ref. [183]), the third type is observed especially in the rostral and ventral regions where the TRN space is the largest [199,243]. These 3D data further show that even when a "pure" architectural type does exist (e.g., only dorso-ventral or rostro-caudal extension of the dendrites), intermediary types also do exist (Fig. 5C).

In conclusion, taken together these morphological findings are somewhat controversial. They show that the dendritic shapes that are seen may depend on the section plane of the curve-shaped TRN (see Fig. 5A). Therefore, it is important to perform 3D reconstruction of any labelled neuron to gain a better idea of its real architecture. Any architectural type may belong to a continuum adapting itself to the available space, which is larger in the rostral pole than in the caudal pole; furthermore, each sector has its own anatomical input–output relationships, and the orientation of the dendritic arbours appear to match the organization of the related TC and CT inputs. These are known to form ordered slab-like arrangement in sensory sectors [47,48] (see also reviews by Crabtree [51] and by Guillery and Harting [92]) but not in the limbic sector [147]. It is also important to note that, whatever the cellular type, most of its dendrites usually span more than one tier (Fig. 5) (also see Ref. [244]), implying that any TRN cell may combine information from several different kinds of thalamic and cortical inputs (e.g., first-order and higher-order). Thus, from an architectural viewpoint the TRN may be considered as a heterogeneous structure. As we shall see below, immunocytochemical and electrophysiological data support this notion.

4. Cellular neurochemical diversities

The heterogeneity of the TRN has also been demonstrated using immunocytochemical stainings, in particular of Ca^{2+}-binding proteins (calbindin, parvalbumin and calretinin), which are present in different subsets of TRN neurons in various species [37,72,77,140,161,215,274]. Calcium-binding proteins are important molecules acting like buffers to modulate dynamics of cytosolic Ca^{2+} transients [13]. Such intracellular proteins can have significant functional consequences on the membrane potential, firing pattern and synaptic transmission [13,33,124]. In rodents, the postnatal maturation of calbindin and parvalbumin is relatively slow [77], like that of the thyrotropin-releasing hormone [162].

The complexity of the TRN is also accounted for by the pharmacological properties of its neurons. This consideration has not been developed herein but would be an appropriate subject for another review. Six intriguing points can, however, be mentioned. (1) The glutamate is usually viewed as the most important classical excitatory neurotransmitter in the CNS. Since it is the prime neurotransmitter liberated by both TC and CT inputs in the TRN, its overall net effect is of course excitatory. It is worth mentioning that the glutamate can have a small inhibitory effect in some TRN cells mediated through the activation of group II metabotropic glutamate receptors, as demonstrated using an in vitro slice preparation [43]. (2) Dopamine receptors, which are the main targets of therapeutic drugs used to treat schizophrenia, are present in the TRN [108,174], but the source of eventual dopaminergic inputs in the TRN has not yet been identified [108] and the physiological action of these receptors remains elusive [74]. (3) The mRNA of the thyrotropin-releasing hormone receptors are prominently expressed in the TRN [105], and the corresponding hormone is immunocytochemically present in TRN cells [134,162]. These molecular studies suggest that the thyrotropin-releasing hormone is a major GABA partner during TC operations, perhaps acting directly from one TRN cell to another. (4) Somatostatin is a well-known peptide that is present in GABAergic cells, including those in the TRN of various species, from rodents to human beings [19,30,88]. It operates in different sites with brake effects on oscillations, suggesting that it may play a major role in physiological and pathological cellular and network activities [253]. (5) Cholecystokinin, which is present in cortical and thalamic

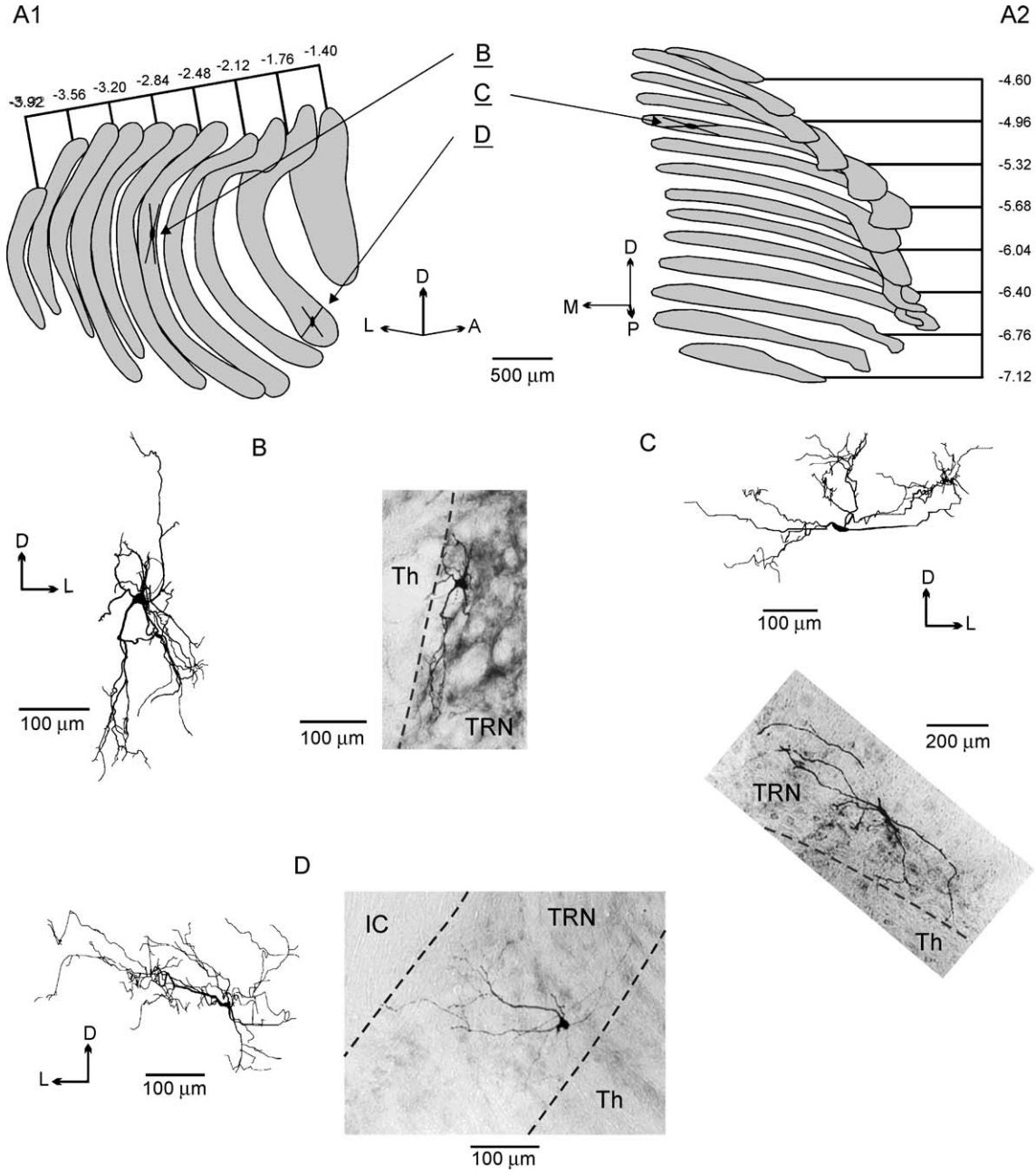

Fig. 5. At least three distinct types of somatodendritic architectures. The architectural type is defined on the basis of the major orientation of the dendrites observed following 3D reconstruction of juxtacellularly marked individual TRN cells [199]. (A1 and A2) Approximate location of three typical TRN cells, which have mainly either a dorso-ventral (B), rostro-caudal (C) or dorso-ventral + rostro-caudal (D) extension of their dendritic arborization. The drawings are made from a series of frontal and horizontal rat's sections (left [A1] and right [A2] TRN). The negative numbers correspond to the rostrocaudal (A1) or dorsoventral (A2) distances (in mm) between the bregma and the frontal or horizontal TRN sections, which are set equally apart of about 0.2 mm, referring to the Paxinos and Watson's atlas [191]. (B, C or D) Each photomicrograph shows parts of the marked cell's dendritic field on a single 80–100-µm-thick section (B and D = frontal sections, C = horizontal section). The 3D reconstruction of each cellular type is seen from a posterior view. Note that about two-thirds and one-third of the dendrites of cell C extend in the horizontal and vertical planes, respectively. A, anterior; D, dorsal; IC, internal capsule; L, lateral; M, medial; P, posterior; Th, thalamus.

neurons [111,227], exerts a depolarizing action in rats' TRN cells by suppressing a K^+ conductance [44]. The majority of cholecystokinin immunostaining is confined to axon terminals, which apparently belongs to TC neurons (Acsady, unpublished observation). (6) Other peptides such as vasoactive intestinal [31], prolactin-releasing [218] peptides and neuropeptide Y [164,172] are also present in the TRN. The modulatory and/or transmitter actions of neuropeptides are far from being understood. It has recently been shown that endogenous neuropeptide Y can be released from TRN cells following burst activity and directly generates IPSPs in TRN cells but not in relay neurons [254]. Since neuro-

peptides can cause long-lasting modulations of neuronal activities, their precise functional role should be assessed further during different functional states of the TC system.

5. Corticothalamic and thalamocortical inputs

The TRN receives monosynaptic glutamatergic inputs mainly from both the cerebral cortex [26,69,75] and the thalamus [76,125]. The only source of CT inputs is layer VI [22,73]. The CT and TC inputs are recognized as being mainly excitatory [2,66,83,157,179]. They are topographically organized, with some exceptions, particularly where inputs from higher-order structures are concerned (reviewed by Crabtree [51] and by Guillery et al. [94]). Also, TRN sectors receive convergent inputs from different cortical areas. Roughly, CT and TC axonal projections are topographically organized, forming multiple maps, which have not yet well been defined [231]. First-order and higher-order thalamic inputs can overlap each other, meaning that TRN cells may integrate information from both sources. However, in the visual sector, first-order and higher-order visual cortical areas are represented in distinct subsectors in rabbits [53] and rats [38]. Developmental studies have shown that the mapping of the CT and TC axons is determined early on (E14–E19 in rats) by a group of peri-TRN cells located laterally to the TRN [163]. Such a mapping has not yet been demonstrated in the visual sector. At the cellular level every single TC axon innervates, within the TRN, a locus whose size tends to fit in approximately with the field occupied by a single TRN dendrite (Fig. 6). A single TC neuron is therefore expected to innervate dendritic subfields of more than one TRN cell (also see Ref. [97]). This might explain why TRN neurons usually have large receptive fields, giving credence to the notion that a given TRN cell is an integrator.

Furthermore, individual layer VI CT axon collaterals are organized in the TRN in a fashion [22] that appears to be similar to that of single TC axon collaterals. However, CT axons are much more numerous by far than TC axons by a magnitude of about 10 [90,119], meaning that, in the TRN, the number of CT synapses is much greater than that of TC synapses. Layer VI CT neurons are more effective in generating larger excitatory synaptic conductances in TRN than in TC neurons [83]. The latter findings support the notion that CT neurons play an important role during TC operations.

The synaptology of the TRN of different species (rats, cats and monkeys) has been extensively studied since the beginning of the eighties [110,137,184]. In the TRN neuropil, the majority of terminals are excitatory and form asymmetric synapses on all portions of TRN dendrites. In general, these electron microscope studies could distinguish between large (L) and small (S) terminals forming asymmetrical synapses throughout the TRN dendritic trees. A combination of immunocytochemistry and degeneration and axonal tracing methods led to the finding that the L and S types of axon terminals in the TRN neuropil are from TC and CT neurons, respectively [137,165,182,184]. However, it cannot be ruled out that some of these terminals might also originate from other sources (e.g., brainstem nuclei). It should be emphasized that possible differences in the ultrastructural characteristics of first-order and higher-order thalamic inputs were not distinguished in any of these studies.

Correlating light and electron microscope observations, Pinault et al. [204] found that the hillock and initial segment of some TRN axons were densely covered with GABA-negative terminals forming asymmetric synapses, a finding that is in keeping with previous electron microscope observations [182]. The corresponding presynaptic terminals were of the L type and this thought to serve as a major constraint on the output of TRN cells. Because this large type was presumed to belong to TC neurons, we examined juxtacellularly labelled TC boutons. Though this matter is still being investigated, the exact source of excitatory synaptic inputs on the axon hillock of TRN neurons has yet to be established.

6. Other afferents

In addition to the cortical and thalamic glutamatergic afferents, the TRN also receives GABAergic [11,58,79,190], cholinergic and monoaminergic inputs [10,56,96,108,136,275], most of these being involved in the control of vigilance. Some functional aspects of these modulatory inputs are available elsewhere [156].

7. Parallel and divergent axonal projections

Ramon y Cajal [212] observed in Golgi impregnated pieces of brain tissue that TRN axons took a ventro-caudal direction, which to all appearances was not the way toward the cerebral cortex. Using similar histological techniques, Scheibel and Scheibel [225] confirmed that TRN axons project to thalamic nuclei (see also Ref. [160]). The principal axon of TRN cells emerges from the soma or a dendrite and usually penetrates the thalamus perpendicularly to the thalamus–TRN interface (see Fig. 3A–C).

Reticular axonal projections to the dorsal thalamus have long been regarded as being almost exclusively ipsilateral. However, retrograde and anterograde labelling experiments have suggested the presence of TRN commissural axonal projections to contralateral thalamic nuclei in various mammalian species [17,35,104,188,213,217]. On the other hand, multiunit [103] and single-unit [199] anterograde labelling procedures revealed instead that the contralateral component of some TRN axonal projections seem not to be noticeable if indeed they are present at all. Whether or

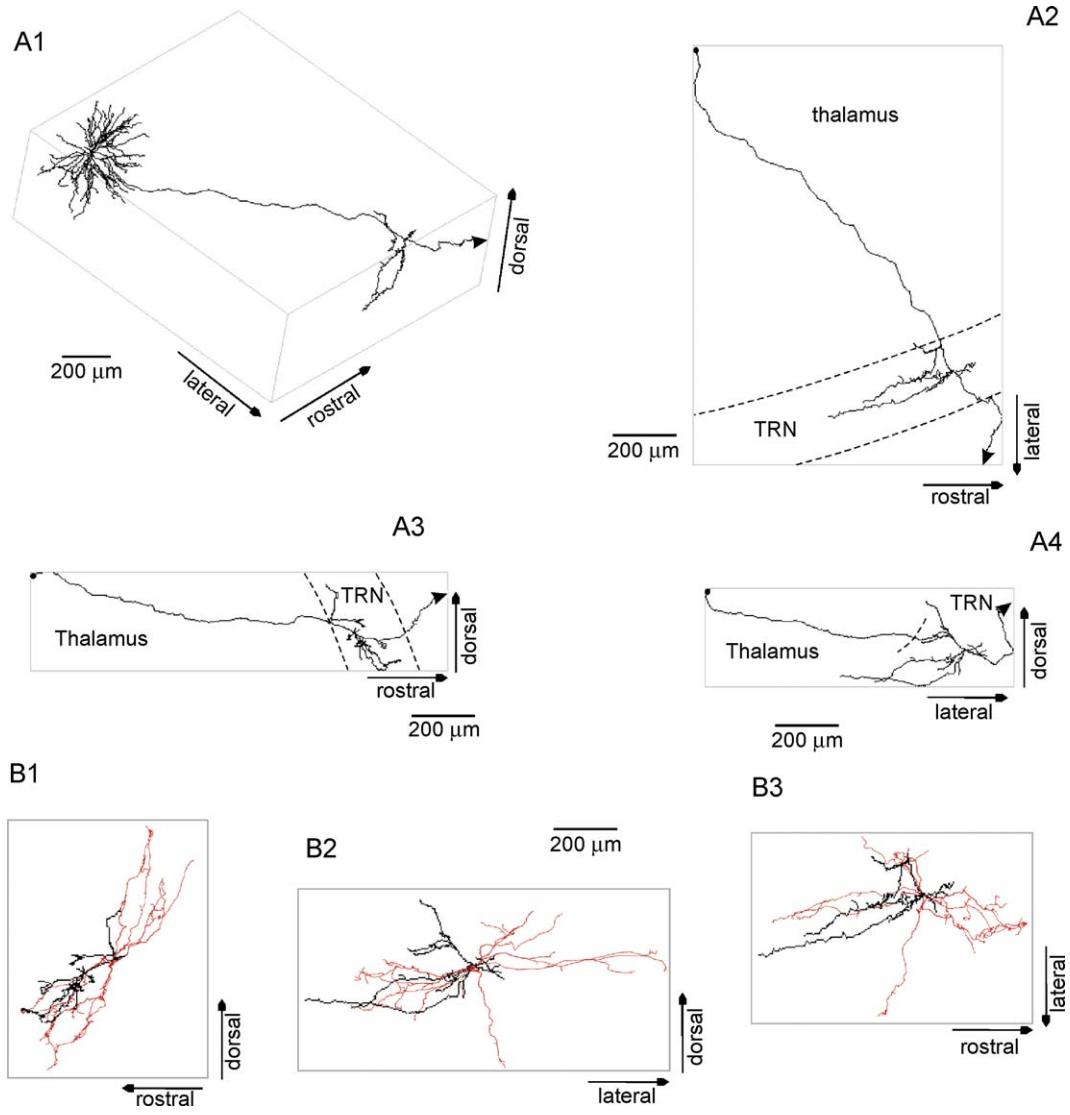

Fig. 6. Individual TC axonal projections in the TRN. (A1–A4) Different view angles of a three-dimensional reconstruction of a juxtacellularly stained TC neuron that innervates parts of the internal and intermediate tiers of the somatosensory sector of the TRN. This neuron originates in the posterior thalamic nuclear group (dendrites not shown in A2–A4). The arrowhead indicates the entrance of the main TC axon into the internal capsule. (B1–B3) The TC axon collaterals (in black) innervate a TRN locus whose size is inferior than that occupied by the whole dendritic field of a TRN cell (in red) individually labelled in the approximate target region of the TC neuron. Adapted from Ref. [239].

not a significant population of TRN neurons innervates both thalami is a fundamental question that is worth probing further.

It should perhaps be said that, for years, it was believed that the TRN does not project into the anterior thalamus, at least in the cat [189,247,266]. At variance with this longstanding concept, several anatomical studies have demonstrated that the TRN does project topographically to the anterior thalamic nuclei in rats, monkeys [84,85,129] and seemingly in cats [266]. In view of these data, it might be questioned whether or not the innervation of anterior nuclei by the TRN is important in felines. Further anatomical studies are needed to clarify this issue.

In parallel with the development of modern anatomical procedures, it is well established that, in various species, TRN axons project into nearly all the anterior, dorsal, intralaminar, posterior and ventral thalamic nuclei according to a loose parallel pattern with a certain degree of divergence [85,95,118,129,199,212,225,247,255,266]. More accurately, adjacent TRN cells with non-overlapping somatodendritic arbours project to two adjacent distinct districts in the corresponding thalamic nucleus (Fig. 7A1); TRN cells with overlapping somatodendritic arbours have overlapping axon terminal fields (Fig. 7A2).

Two intriguing features were noticed during the course of a single-cell anatomical study [199,204]: (1) about 2% of stained cells had two axons emanating from two distinct, somatic and dendritic, locations that projected to the same thalamic target; (2) the main axon of about 3% of neurons originated from a distal dendrite and bore

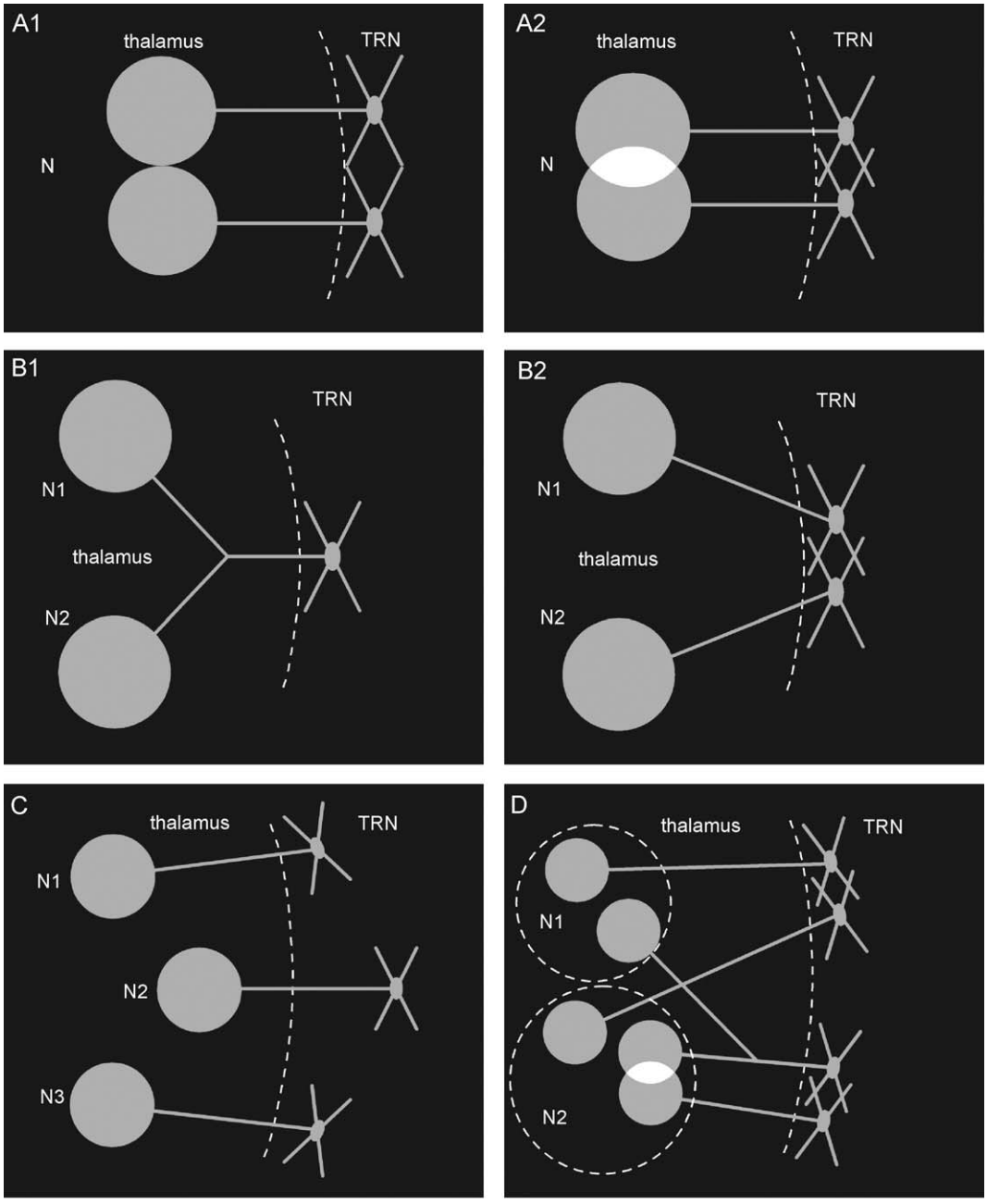

Fig. 7. Organization of TRN axonal projections. (A1) Two TRN cells with adjacent somatodendritic fields innervate two adjacent districts within a given thalamic nucleus (N). (A2) Two TRN neurons having overlap of their dendritic arbours have overlapping axon terminal fields. (B1) A TRN cell can display two distinct axonal arbours into two separate thalamic nuclei (N1 and N2). (B2) Two TRN cells with overlapping dendritic fields can innervate two distinct thalamic nuclei (N1 and N2). (C) Three TRN cells from distinct sectors project to separate thalamic nuclei (N1, N2 and N3). An anteroposterior, dorsoventral or mediolateral shift in the position of a somatodendritic arbour in the TRN is generally and roughly accompanied by a similar shift in the position of its parent axonal arbour inside the thalamus. (D) A thalamic nucleus (N1 or N2) can receive TRN inputs from two distinct TRN loci. Adapted from Ref. [199].

varicosities just like it as if they were a "dendrite" arborizing into the thalamus. The functional significance of TRN cells with a dendrite-like axon arborizing into the thalamus is unknown. If we assume that these structural features are not just developmental errors, they are intriguing because they raise questions about the respective functional properties of the somatodendritic and of the axonal arbours of such TRN cells.

The pattern of TRN axonal projections that emerged following intracellular or juxtacellular staining varied within a single nucleus, from one nucleus to another, between species and during development. Scheibel and Scheibel [225] observed Golgi-impregnated TRN cells of young animals (kittens, rats and mice) with diffuse axonal projections through first-order and higher-order thalamic nuclei. In young rats, the projection patterns of individual

axons deriving from the somatosensory sector were categorized into three types, ranging from compact to diffuse [45]. Since this in vitro study was performed in young animals, it might be questioned whether these three types are still present in the adult or whether they represent an accumulation of all the stages of brain development. In adult cats, cells in the visual sector have robust and/or sparse axonal components in the related thalamus [260]; those of the somatosensory sector display diffuse branches in the related thalamic nuclei [278,279]. In adult rats, TRN cells in both the somatosensory and the visual sectors form clear-cut, dense axon terminal fields in the corresponding thalamic nuclei [202,203]. The latter studies demonstrate that, at cellular level, TRN axonal projections are highly segregated, albeit primarily in a parallel manner (also see Ref. [199]). This does not, however, exclude overlapping between individual focused axonal projections inside a given thalamic nucleus (Fig. 8), suggesting the existence of well-organized innervations within a space continuum.

Divergence of axonal projections was first suggested by Scheibel and Scheibel [225] following observation of Golgi impregnated neurons. Retrograde labelling experiments in whole animal preparations indicated that a given TRN locus may give rise to divergent axonal projections to intralaminar and midline nuclei in both rats [128] and cats [247]. In the cat the dual projections toward the posterior nuclear group and the ventrobasal complex are said to result from 50% to 70% of the TRN cells scattered throughout the somatosensory sector [49]. By means of in vitro intracellular labellings in the visual sector [260], it was demonstrated that TRN cells project almost exclusively into the A-laminae of the cat visual thalamus and that some neurons display a second axonal branch, which presumably runs toward another visual-related thalamic nucleus, perhaps a higher-order thalamic nucleus (posterior nuclear group and/or lateral posterior). Moreover, using the juxtacellular technique in anaesthetized rats, Pinault and Deschênes [199] revealed that a minority of TRN cells (<5%) had an axon that split into two branches innervating a first-order nucleus (e.g., ventral posteromedial nucleus) and a functionally related higher-order nucleus (e.g., posterior nuclear group; Fig. 3B); in addition, TRN neurons with overlapping dendritic arbours could project into two separate thalamic nuclei involved in the same function (Fig. 7B2). From a functional viewpoint, the TRN may be viewed therefore as a "hub" [143], marshalling ongoing TC information not only into a parallel process but also with a degree of interactions between pathways involving distinct but functionally related thalamic nuclei (Fig. 7B1,B2,C,D).

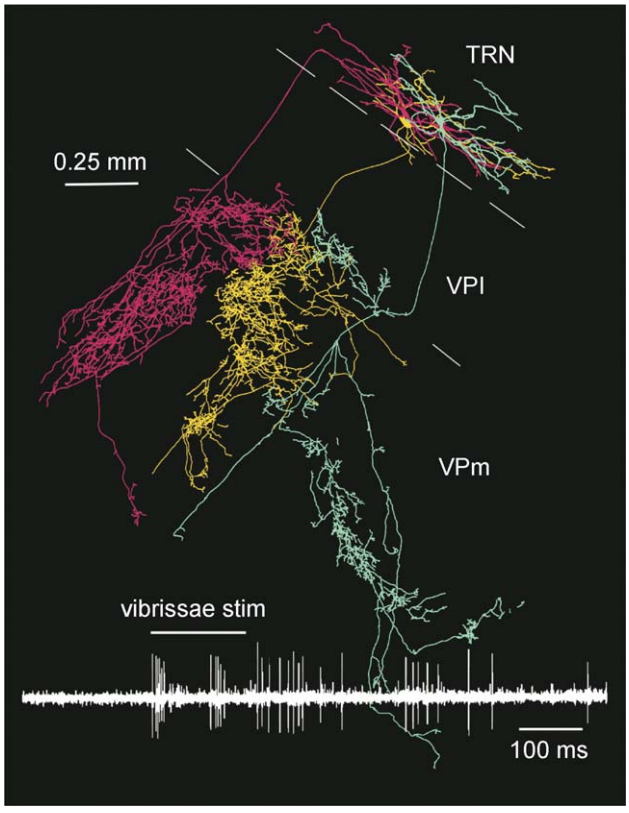

Fig. 8. Overlapping TRN neurons. These three adjacent TRN cells have been reconstructed following juxtacellular multi-unit staining with Neurobiotin. Before tracer application, at least three TRN cells fired in response to natural stimulation of contralateral vibrissae (vibrissae stim). VPl, ventral posterolateral thalamic nucleus; VPm, ventral posteromedial thalamic nucleus. Adapted from Ref. [195].

Structural and morphometric analysis of juxtacellularly stained rats' TRN axon terminal arbours demonstrated that the clustering of boutons optimally matches the somatodendritic architecture of the corresponding postsynaptic TC neurons [199]. Within the axonal patches, boutons tend to form grape-like clusters or strings according to the tufted or linear architecture of the postsynaptic dendrites, and it is very probable that the purpose of this is to ensure that the corresponding synaptic and integrative functions are sufficiently enhanced. This rule seems to apply both to the first-order (e.g., ventrobasal complex) and to the higher-order (e.g., lateral posterior and/or posterior nuclear group) thalamic nuclei, which contain bushy and star-like relay cells, respectively (Fig. 9). Terminations of TRN axons make Gray type II axodendritic and axosomatic synaptic contacts with TC neurons [57,98,139,169,185,193]. It is worth mentioning that some thalamic nuclei include GABAergic interneurons [231], which do not seem as being the major synaptic target of TRN axon terminals [139,269]. These local circuit cells are much greater in number in felines and primates than in rodents [119,231].

In conclusion, it is tempting to propose that the TRN may perform at least two types of control over information on its way to the cerebral cortex: (1) one type seems to involve the ordered parallel TRN axonal projections toward first-order and higher-order thalamic nuclei (parallel processing), while (2) the second appears to be a more complex form of

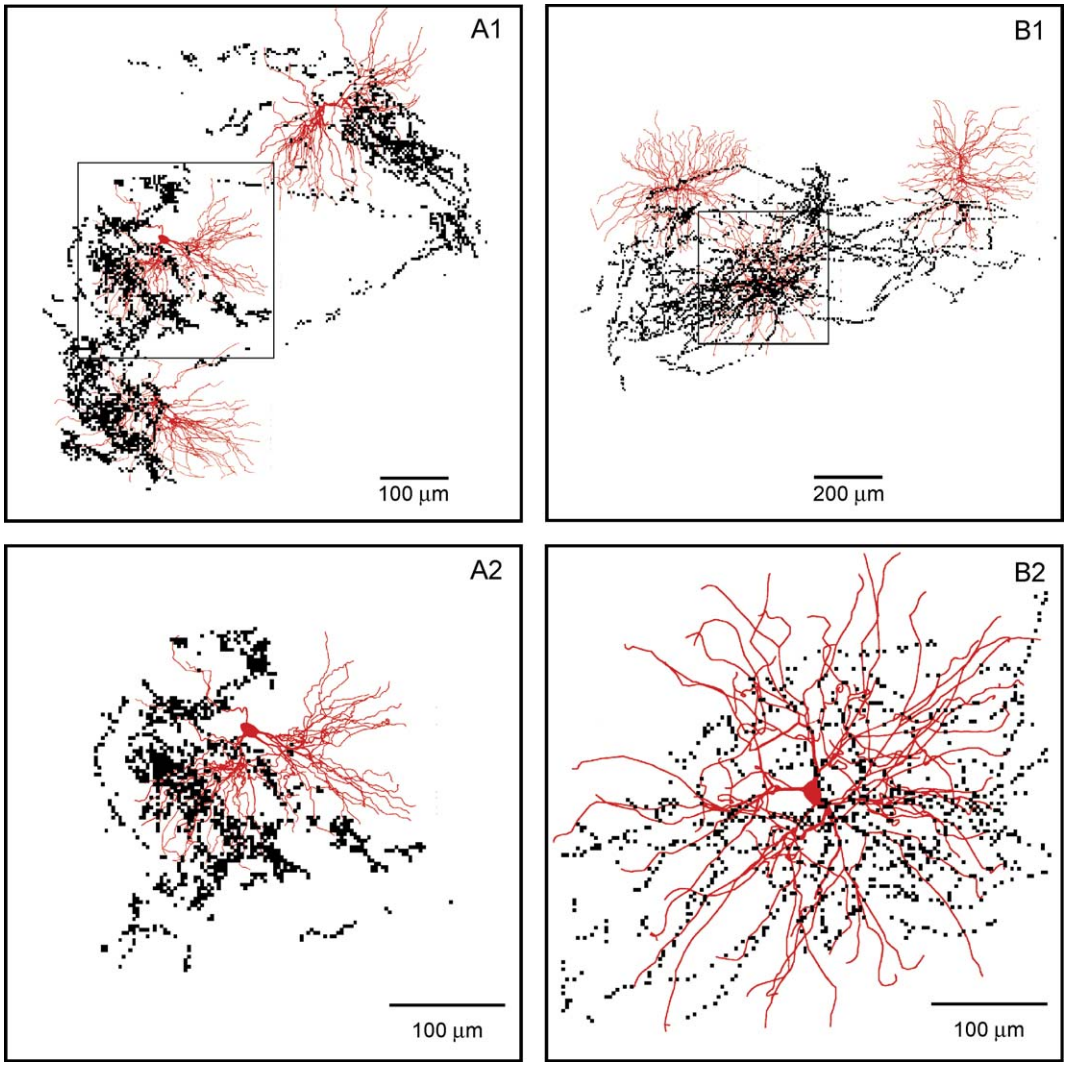

Fig. 9. The distribution of TRN axonal terminations fits in with the somatodendritic architecture of target TC neurons. (A1) Posterior view of a 3D-mapping of all the boutons (in black) belonging to a ventrobasal-projecting TRN cell. The boutons are segregated into three major dense patches. The three somatodendritic arbours (in red) are three different views of a 3D-reconstructed, juxtacellularly labelled ventrobasal TC neuron. The framed area is shown at higher magnification in A2. In A2, all the TRN boutons are contained in a 200-µm-thick tissue block. (B1) Lateral view of a 3D-mapping of all the boutons (in black) belonging to a lateral posterior-projecting TRN cell. The boutons are segregated into a patch and a peripheral, more diffuse component. The three somatodendritic arbours (in red) are three different views of a 3D-reconstructed, juxtacellularly labelled lateral posterior TC neuron. The framed area is shown at higher magnification in B2. In B2, all the TRN boutons are contained in a 200-µm-thick tissue block. Adapted from Ref. [199].

control, also involving divergent axonal projections toward at least two separate nuclei (combining processing). The functional properties of these two potential controls are unknown.

8. Closed- and open-loop thalamo-reticulo-thalamic circuits

It is usually argued that the thalamus and the TRN are reciprocally connected [95,118,230]. The reciprocal thalamus-TRN relationship does not, however, fully apply at the cellular level when examining both the anterogradely and the retrogradely labelled neuronal elements following juxtacellular applications of a compound containing biotin [200] (also see Fig. 10). Furthermore, an anatomical study aimed at labelling both afferent and efferent axonal projections from cat TRN loci showed that the distribution of marked neurons and anterograde labelling did not completely overlap between the pulvinar-lateralis posterior complex and the related TRN sector [71]. Taken together, these data demonstrate that between themselves TC and TRN neurons form open- and closed-loop connections. Those two circuits represent the anatomical substrates of mechanisms of lateral and feedback inhibition, respectively (Fig. 10C1,C2). Neither the relative importance nor the actual functional significance of these two types of inhibition have yet been determined in any TC system or

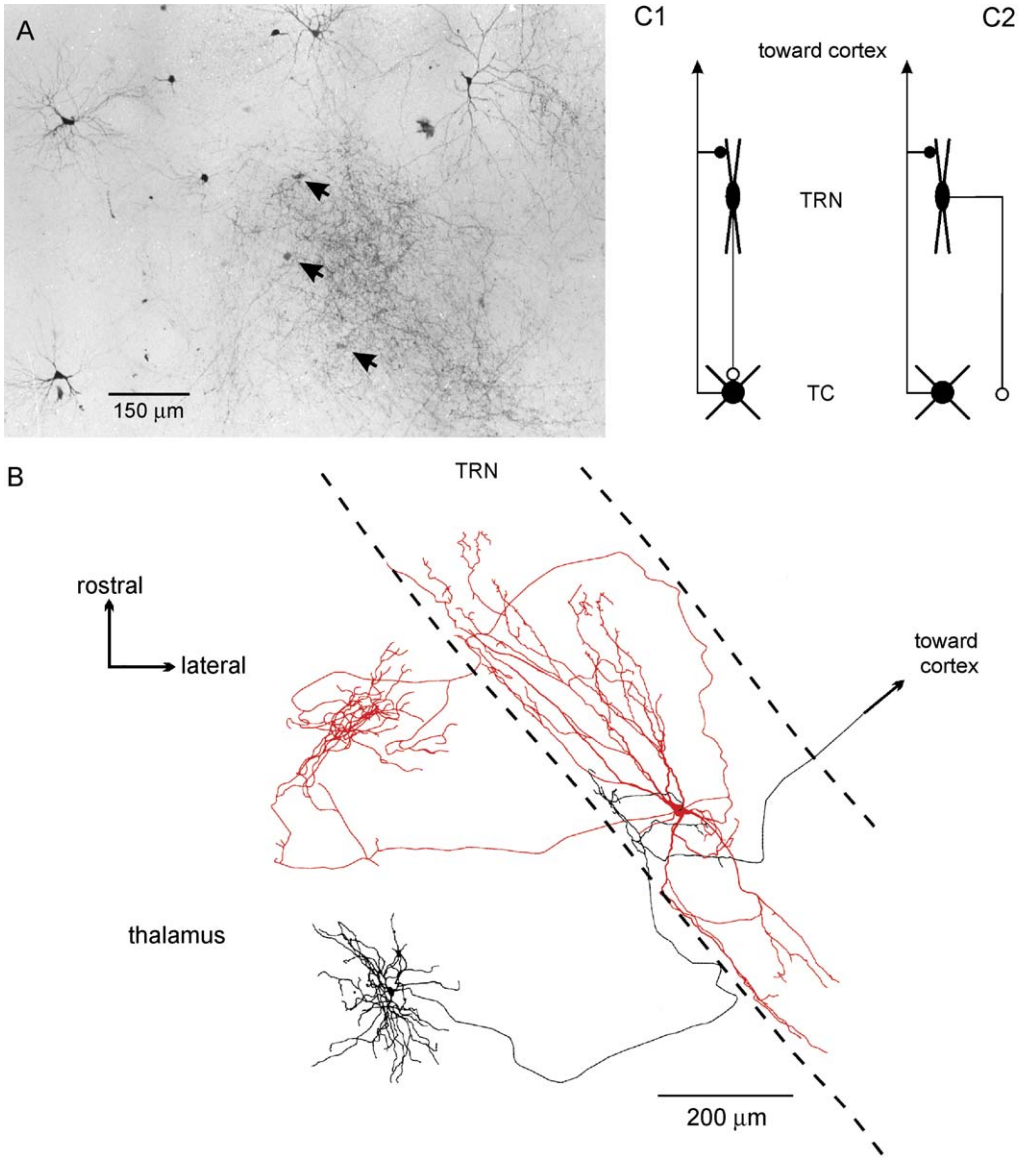

Fig. 10. Anatomical evidence of thalamic recurrent and lateral inhibitions. (A) Photomicrograph showing simultaneous anterograde and retrograde labellings following extracellular application of a biotin-containing compound into the TRN of an anaesthetized rat. Note the presence of strongly and lightly (black arrows) stained thalamocortical somatodendritic arborizations outside and inside the TRN axon terminal arbours within the thalamus, respectively. (B) Reconstruction of two simultaneously juxtacellularly stained neurons, an anterogradely stained TRN cell (the recorded target unit, in red) and a retrogradely stained thalamocortical neuron (in black). (C1, C2) Drawings illustrating likely feedback and lateral inhibitory circuits, respectively. Adapted from Ref. [200].

species. It is worth saying that, in some thalamic nuclei, GABAergic interneurons should somehow interfere with the functional role of TRN cells during TC operations, an issue that merits investigation.

These anatomical findings are in line with in vitro [81,145] and in vivo [233,236] physiological data revealing a small proportion of TC-TRN cellular pairs with closed disynaptic loops (about 7–17% and 20%, respectively). In urethane-anaesthetized rats, Shosaku [233] used paired recordings and cross-correlation analysis to show that TRN and TC neurons with receptive fields on the same vibrissa could interact with each other (excitations and/or inhibitions). The excitation–inhibition pattern, which presumably represented reciprocal interactions, was seen in a few instances (7 out of 34). Furthermore, no significant functional interaction could be detected between TRN and TC neurons having receptive fields on different vibrissae. Shosaku [233] concluded that TRN axonal projections' convergence and divergence from a significant number of thalamic neurons with receptive fields on the same vibrissa play a role in channelling ongoing sensory information in the TC system. By means of extracellular and intracellular recordings in slices of the ferret visual thalamus, it was shown that reciprocal interactions between subsets of hyperpolarized TC and TRN neurons were responsible for generating rhythmic burst-firing in

the TC system [268]. Intracellular recordings of TC neurons in slices of the cat visual thalamus revealed a post-action potential long-lasting hyperpolarization, which was bicuculline-sensitive, in only a few geniculate cells [145]. This postsynaptic event was wisely interpreted as being the manifestation of either an actual feedback inhibition, or a lateral inhibition generated by a coincident action potential in another TC neuron. In none of those electrophysiological studies was the corresponding anatomical correlate demonstrated. Neither do they tell us how closed- and open-loop circuits work.

The vibrissal TC sensory system of rodents is highly segregated, representing an excellent model of modular organization from periphery to cortex [23,63,131,262,264,265,276]. In other words, one given whisker is principally represented by a thalamic module (or "barreloid", a term introduced by Van der Loos [261]) and by a cortical module (or "barrel", a term introduced by Woolsey and Van der Loos [276]). The role played by TRN cells in this modular organization is far from understood. By means of a double-labelling protocol in adult rats, it has recently been demonstrated that the axon of a TRN cell responding to the principal whisker of its receptive field projects within the limits of the whisker-related module [63]. It is important to note that the relay cells' dendritic field extends into adjacent modules [264]. Furthermore, the corresponding distal dendrites receive GABAergic inputs from TRN cells whose principal receptive field is an adjacent whisker. These closed-loop connections are thought to be the anatomical substrate of crosstalk inhibitions between adjacent thalamic modules, which might involve the following two inhibitory mechanisms (Fig. 11): (1) a recurring inhibition of the proximal dendrites of the relay cells responding to the principal whisker of its receptive field; (2) a lateral inhibition of the distal dendrites of the relay cells whose principal receptive field is an adjacent whisker. These findings, however, raise at least three questions: (1) Since TRN cells with overlapping somatodendritic arbours have overlapping axon terminal fields (Fig. 8), and reticular and relay neurons have receptive fields defined by one main and a few adjacent whiskers [8,65,237], it might be that these closed-loop connections represent one extreme of a continuum between closed-and open-loop connections. Such a loose parallel pattern certainly cries out for physiological studies. (2) Somatosensory-related TRN cells display focused axon terminal fields of at least two types, one occupying approximately the space of a module, the other segregated into patches, each of which is approximately the size of a module [199,202,203]. Therefore, it cannot be ruled out that a given TRN cell may be involved in both recurrent and lateral inhibitions.

In conclusion, the question of how lateral and recurrent inhibitory mechanisms work is still open to debate. Both mechanisms may function in isolation or in concert during normal TC operations. They are presumed to generate their counterpart, that is, disinhibitions adjacent to inhibitions. These mechanisms, which are schematically represented in Fig. 12, are likely valid in thalamic nuclei that do not contain interneurons, which are known as being a source of inhibitory inputs in TC neurons (e.g., see Ref. [46]). In the vibrissal system, closed-loop connections might be involved simultaneously in at least two subtle levels of integration: (1) a modular integration of information generated by the inputs activated by the principal whisker of the receptive field and (2) a more general integration of information generated by the inputs activated by adjacent whiskers. The functional relationship

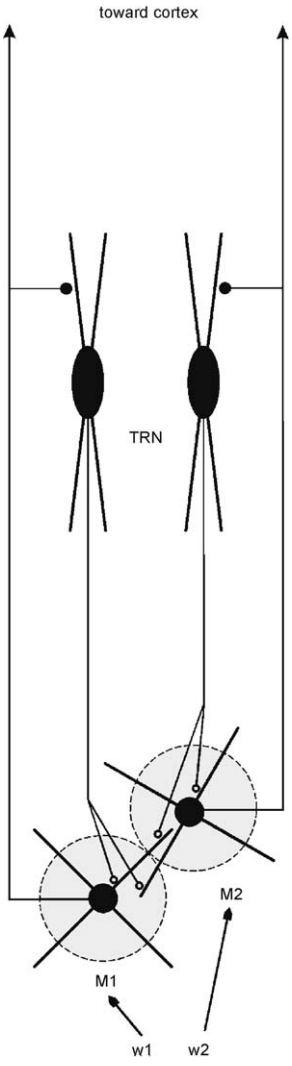

Fig. 11. Crosstalk inhibitions between adjacent thalamic modules in the somatosensory system. Two adjacent modules (M1 and M2) correspond to two adjacent whiskers (w1 and w2). For simplicity, in this drawing, one module contains the cell body and the proximal part of its somatodendritic arbour of one relay neuron. Each TRN cell is involved in a recurrent inhibition mechanism that occurs on the proximal dendrites of each relay cell responding to the principal whisker of its receptive field. The same TRN cell is also involved in a lateral inhibition mechanism on the distal dendrites of the relay cells whose principal receptive field is an adjacent whisker.

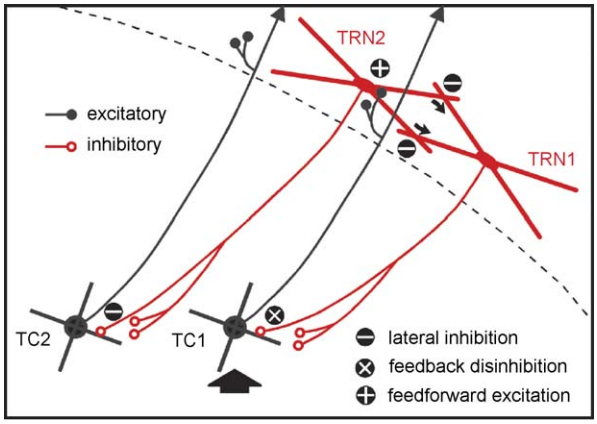

Fig. 12. Likely synaptic relations between single thalamocortical (in black) and TRN (in red) neurons in the case of lateral inhibition. These drawn nerve cells, which are respectively excitatory and inhibitory, form an open-loop circuit. Some of the terminal axonal boutons of one TC neuron contact one TRN cell, and some terminal boutons of one TRN cell make synaptic contacts with one TC neuron. Activation of the open-loop starts with neuron TC1, for instance following an afferent discharge on a specific prethalamic input (black arrow). This cell, via its axon collateral, excites cell TRN2, which then inhibits cell TC2 (lateral inhibition). The neuron TRN2 presumably inhibits cell TRN1 (via dendrodendritic GABAergic synapses), which then would disinhibit the neuron TC1 (feedback disinhibition). Adapted from Ref. [200].

between the open- and closed-loop circuits still has to be determined, however, at both modular and regional levels. Another important point worthy of special attention is that the inhibitory mechanisms involved in any integration process depend on the state of the corresponding networks [100]. It is also tempting to speculate that during physiological processing both inhibitory mechanisms may work independently and/or sometimes in concert whereas during certain neurological and psychiatric disorders they may systematically function together as a whole, for instance during high-voltage synchronized oscillations (e.g., during episodes of sleep or generalized epileptic seizures).

9. Large-scale thalamo-reticulo-thalamic circuits

It is generally thought that, unlike to cortical areas, TC neurons do not interact with each other. Crabtree et al. [52,54] have demonstrated recently in thalamic slices of young rats that glutamate-induced activation of neurons in a thalamic nucleus is associated with inhibition of cellular activities in another distinct but functionally related thalamic nucleus, and conversely. The inhibition is mediated through activation of $GABA_A$ receptors. Because the thalamic slices were free of reciprocal connections with the cerebral cortex, these intrathalamic functional interactions are likely to involve a disynaptic pathway passing through the TRN. Moreover, both thalamic nuclei project to the same TRN sector, and that sector projects to both nuclei. These intrathalamic functional connections occur in a reciprocal manner either between first-order and higher-order, sensory-related or motor-related, nuclei or between higher-order nuclei. As it is known that one TRN locus can innervate two thalamic nuclei and that TRN loci are reciprocally connected with their respective target regions, it might be surmised that a given disynaptic pathway passing through an TRN locus operates in both directions. These TC–TRN–TC circuits might allow modality-related and cross-modality modulation of ongoing information through diverse thalamic nuclei (Fig. 13). Anatomical studies strongly suggest that some of these pathways are likely to be present in the adult [49,50,128,148,199,247]. Such circuits would represent a powerful tool for the TRN to select the appropriate intrathalamic pathways for any sensory, motor and cognitive task.

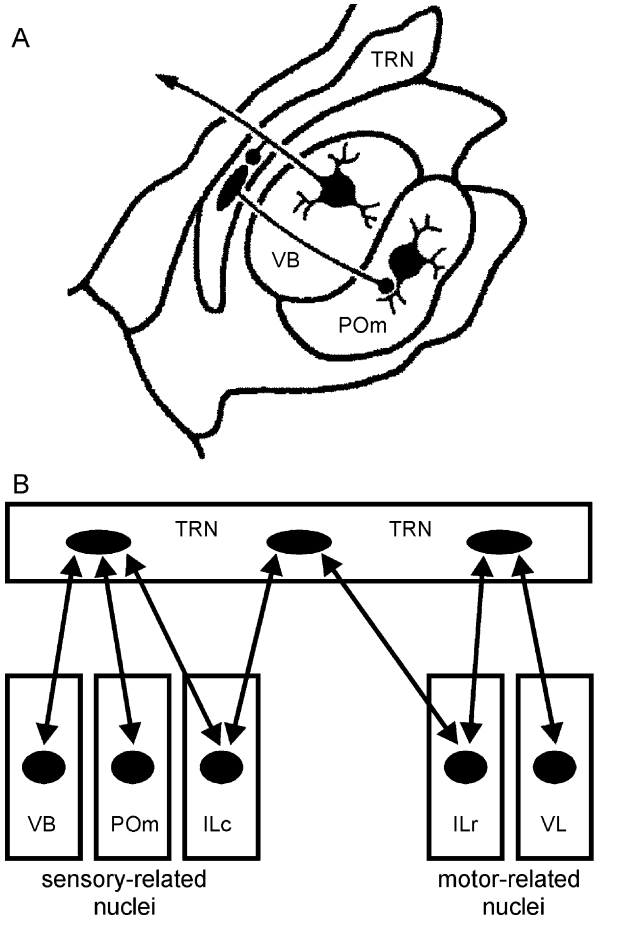

Fig. 13. The thalamic reticular nucleus, a potential combinatory matrix ensuring spatial and temporal bindings during sensorimotor operations involving thalamocortical circuits. (A) Drawing of a horizontal thalamic section showing an intrathalamic pathway linking the ventrobasal complex (VB) with the medial division of the posterior complex (POm). Both thalamic cells project to the cerebral cortex and give off axon collaterals into the TRN. For simplicity, the axon of the POm cell is not shown. (B) Schema showing likely intrathalamic pathways. ILc, caudal intralaminar nuclei; ILr, rostral intralaminar nuclei; VL, ventrolateral nucleus. Adapted from Refs. [52,54].

10. Intrinsic cell–cell communications

Various anatomical and functional studies have attempted to show that TRN cells communicate synaptically between each other through dendrodendritic and/or axodendritic synapses. Mutual inhibitory synaptic interactions between TRN cells in the visual sector were first recorded in anaesthetized adult cats [3]. Indeed, electrical stimulation of the optic tract induced a short-latency excitation in TRN cells followed by an inhibitory period, during which the excitatory response that followed electrical stimulation of the related visual cortex was no longer recorded. Local application of glutamate in the ferret's perigeniculate nucleus (visual sector of the TRN) maintained in vitro induced $GABA_A$-dependent IPSPs in cells located in the neighbourhood of the application [223] (Fig. 14). One cannot exclude that in some TRN cells such IPSPs occasionally include a small $GABA_B$-mediated component [259]. In the presence of $GABA_A$ receptor blockade, glutamate-induced excitation of a perigeniculate locus produces $GABA_B$ -dependent IPSPs in a subset of perigeniculate cells [223]. The blockade was achieved using the $GABA_A$ receptor antagonist bicuculline methiodide, which also blocked an $I_{K(Ca)}$ in TRN cells directly [59]. Disynaptic or polysynaptic $GABA_A$-mediated inhibitions have recently been recorded in mouse TC slices' TRN cells following focal electrical stimulation of layer VI in the related cortex [281]. Taken together, these findings strongly suggest that excitation of a pool of TRN cells can trigger widespread inhibitions in the TRN. Sohal and Huguenard [241] demonstrated in rat thalamic slices that intra-TRN inhibitions limit the number and synchrony of TRN cellular bursts. Mutual GABAergic inhibitions between TRN cells are thought to be mediated by intrinsic axodendritic synapses (see below). In another separate in vitro study, dual single-cell recordings in thalamic slices of young rodents (rats and mice) were, however, unable to reveal the presence of inhibitory chemical synaptic connections between adjacent TRN cells [132]. Therefore, assuming that lateral synaptic interactions do exist, the question is whether intranuclear inhibitory interactions involve nearby and/or remote neurons.

Paired-cell recordings (inter-cell distance: up to 35 μm) in thalamic slices of young rodents (rat and mouse, P14–P21) have recently demonstrated the presence of functional electrical cellular couplings in the TRN (Fig. 15), with strong low-pass filtering characteristics [132]. Such couplings have not been recorded in mice with a null mutation for the connexion-36 gene. They are thought to play a significant role in intra-TRN cellular synchronizations especially of low-frequency events such as low-threshold Ca^{2+} spikes. Such electrically generated synchronizations (in the range of 10 Hz) concern small clusters of TRN cells [146]. Although their morphological substratum is thought to be gap junctions, such electrical synapses have not yet been seen during ultrastructural analyses of the TRN in various species [62,138,182,184,204,279]. Connexin-36 has recently been observed at focal sites on plasma membranes of TRN dendrites and somata in postnatal mouse brain without any association with identifiable gap junctions [138]. It is worth to say that such close membrane junctional

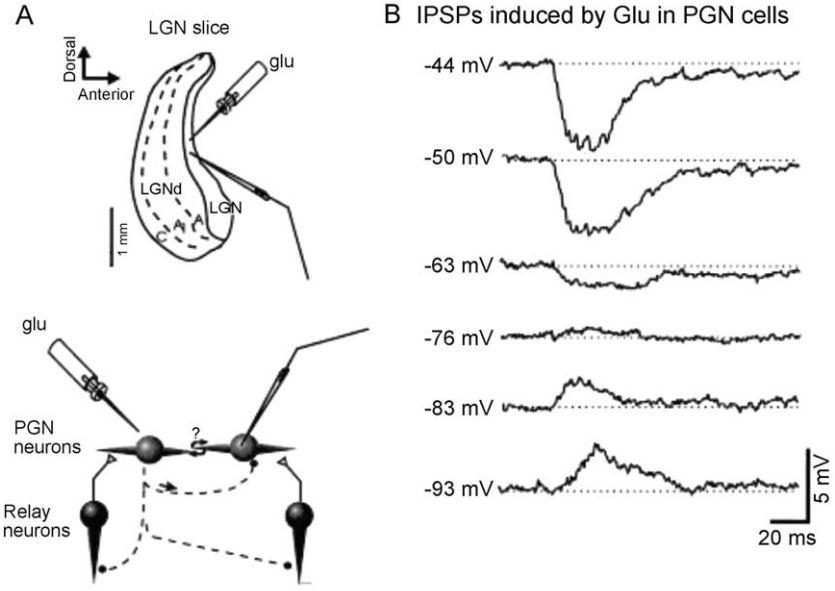

Fig. 14. Pharmacological evidence of lateral inhibition into the ferret's perigeniculate nucleus. Local application of glutamate in the visual sector of the ferret TRN maintained in vitro (A) induces a barrage of IPSPs in a perigeniculate cell (B). Note that the reversal potential is close to −76 mV. In A at the bottom, the dashed lines represent likely axonal projections and the question mark indicates a doubt about the existence of dendrodendritic synapses between perigeniculate cells (see text for further details). Adapted from Ref. [223].

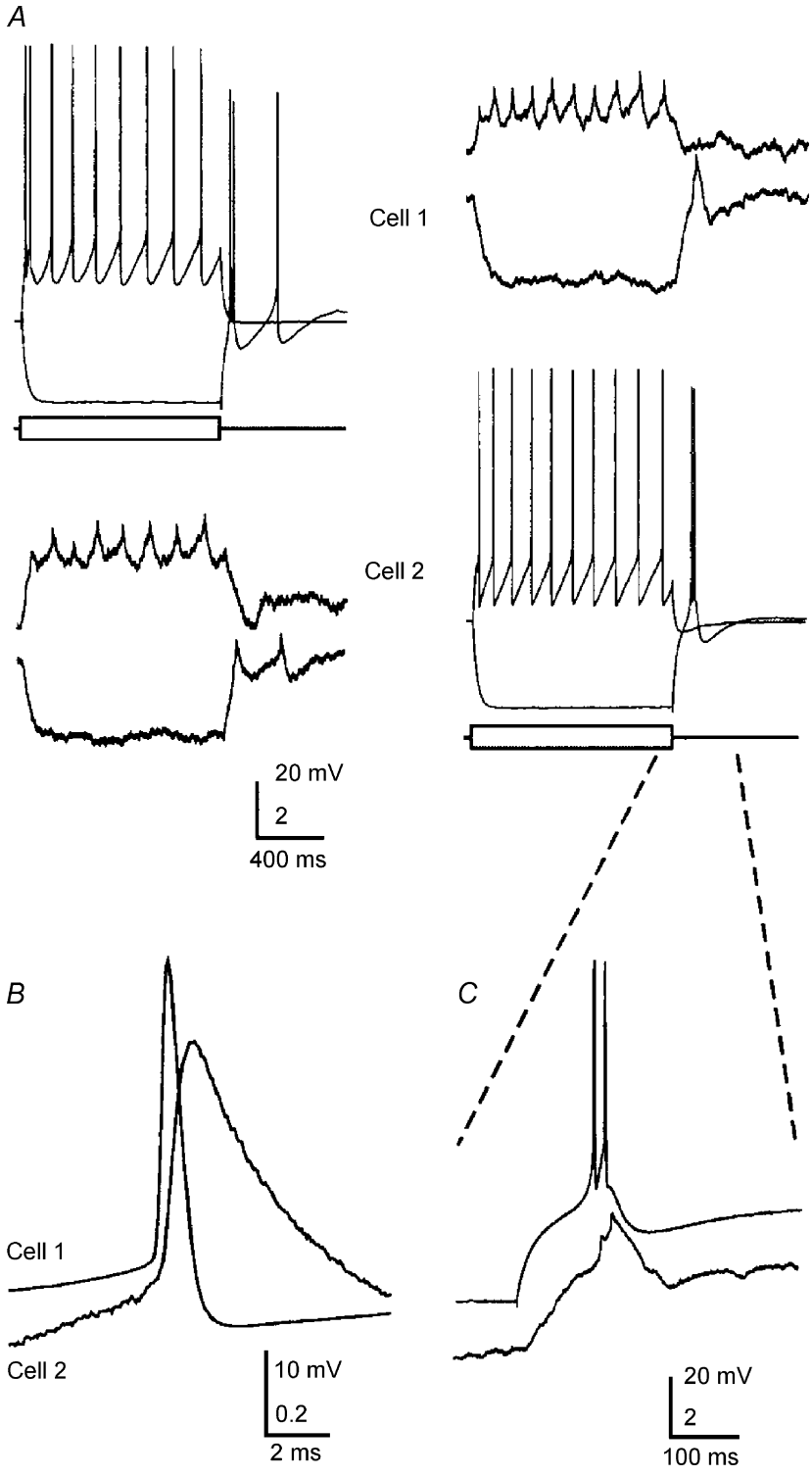

Fig. 15. Electrophysiological evidence of electrical coupling between two intracellularly recorded adjacent cells (cell 1 and cell 2) of rat TRN maintained in vitro. (A) Intracellular square current pulses to evoke firing in cell 1 induces an attenuated voltage oscillation (set of spikelets) in cell 2 (left traces); on the right, current pulses that evoke firing in cell 2 likewise induces a set of spikelets in cell 1. (B) A single presynaptic action potential recorded in cell 1 and an averaged spikelet recorded in cell 2. (C) The rebound high-frequency burst of action potentials generated in cell 2 and the corresponding coupling potential recorded in cell 1. Adapted from Ref. [132].

complexes are difficult to see in the brain, even in the cerebral cortex [256]. Therefore, the basic mechanism underlying electrical couplings using gap junctions between adjacent TRN cells in young rodents still eludes us. Again, it is possible that these potential electrical couplings are present in the adult, but no evidence of cell–cell coupling

was observed following juxtacellular staining of a large number of individual TRN cells in anaesthetized adult rats using neurobiotin [195], a junction-permeant tracer [263].

To date, the anatomical substrate of potential synaptic cell–cell communications in the TRN has not yet been established. On the basis of light microscope examination of Golgi-impregnated neurons in adult animals, Scheibel and Scheibel [226] postulated that dendrodendritic interactions might take place in the TRN. In line with this hypothesis, electron microscope analyses in adult cats revealed that TRN cell dendrites form a local network of symmetric dendrodendritic synapses [62,110,170,279]. In contrast few, if any, dendrodendritic synapses have been seen in the TRN of monkeys [182,273] or rats [137,184] when examined in single ultrathin sections. However, an analysis of serial ultrathin sections (60 nm) of dendritic bundles cut along their longitudinal plane in rat TRN revealed dendrodendritic synapses and numerous nonsynaptic puncta adhaerentia between component dendrites [204]. The observed dendrodendritic synapses are relatively short (<240 nm), making them unlikely to be seen in single sections. The functional correlates of both the puncta adhaerentia and the dendrodendritic synapses are unknown.

Puncta adhaerentia represent an intriguing singular morphological characteristic of the TRN. They may be an important structural substrate for synaptic (electrical and/or chemical) and non-synaptic functions. Currently, we can only speculate as to what the functional significance of such membrane appositions is. For instance, they might increase extracellular resistance, thereby facilitating non-synaptic (ionic and/or electric) interactions. Furthermore, if we assume that the TRN dendrites' membrane contains unpaired connexon channels, they may operate in at least two ways: (1) They might form transient gap-junctional intercellular channels, which would be involved in Ca^{2+}-related oscillatory activities (see review by Goodenough and Paul [86]); and/or (2) such hemichannels might be involved in the control of, for instance, dendritic Ca^{2+} currents, assuming that these connexons are numerous enough to generate efficient current sinks [123].

As for the dendrodendritic synapses, they are generally thought to be involved in lateral inhibition (Fig. 12). However, the possibility cannot be ruled out that some of these, perhaps those located in distal dendrites, may be excitatory since GABA induced depolarizations were recorded in vitro in TRN cells of young rats [243]. The excitatory or inhibitory role of GABAergic synapses can be determined by the value of chloride gradient through the neurons' membrane [5,27].

It is currently believed that, in rats [137], ferrets [223] and in monkeys [273], TRN cells can communicate with each other by means of axodendritic synapses. However, an important point to bear in mind is that such synapses have not yet been demonstrated in a conclusive manner. Light-microscope examination of individually labelled TRN neurons suggested that they possess intrinsic beaded axon collaterals and dendrites ending in fine varicose processes resembling synaptic terminals (''axon-like processes'') in rats [243] and cats [139,149,177,260,279]. When using the electron microscope to examine synaptic inputs on intracellularly labelled cells in the rat TRN, Liu and Jones [137] identified GABA immunoreactive F terminals, which formed symmetrical synaptic contacts on cell bodies and dendrites. Again using the electron microscope, Williamson et al. [273] observed GABA immunoreactive terminals in the monkey TRN, which also formed axodendritic and axosomatic symmetric synaptic contacts. The morphological features of the corresponding presynaptic elements also resembled F terminals. Since the TRN receives GABAergic inputs from external sources [11,190], the origin of the F presynaptic terminals observed in both studies still has to be determined. On the other hand, when observed at the ultrastructural level in the rat, the boutons of axon-like processes that were juxtacellularly labelled in the TRN had the morphological features of postsynaptic elements [204].

Furthermore, during the examination of the axonal ramifications of a large number of juxtacellularly labelled TRN neurons in the adult rat, we noticed that about 10% of these cells display short-range, poorly ramifying varicose local axon collaterals, which remained indistinguishable from parent distal dendrites, raising the question as to whether their varicosities were presynaptic terminals [204]. Correlated light- and electron-microscope observations of at least the proximal part of such intrinsic varicose axonal segments revealed that their varicosities and intervaricose segments were in fact postsynaptic structures, which were contacted by a large number of boutons that, for the most part, formed asymmetric synapses [204]. On the other hand, it has been reported that, in young rats, about 65% of TRN neurons give rise to intrinsic axon collaterals [45]. This is entirely keeping with Scheibel and Scheibel's observations [225] of a dense network of intrinsic axon collaterals in Golgi-stained TRN neuropil of young animals. All these data suggest therefore that some intrinsic axon collaterals have the propensity to disappear during brain maturation, possibly as a consequence of an experience-dependent pruning mechanism, and those that remain might in fact be fine dendritic ramifications. In conclusion, at least in adult rats and cats, dendrodendritic junctions seem to be the main anatomical substrate underlying intercellular communications in the TRN. However, the functions of dendrodendritic synapses in the TRN still have to be investigated.

Do cells in the visual sector innervate with each other with axodendritic or dendrodendritic synapses? Sanchez-Vives et al. [223] examined axonal ramifications of biocytin-filled perigeniculate cells in ferrets. They observed beaded axon collaterals within the internal border of the perigeniculate nucleus, that is, in the region adjacent to the visual thalamus' A lamina, in which the stained TRN axons profusely arborized. Sanchez-Vives et al. [223] wisely interpreted their observations by stating as follows in their

discussion "...the precise physical substrate of the PGN to PGN cell inhibition demonstrated here may require closer examination; it will be particularly important to determine the postsynaptic targets of intra-PGN axon collaterals".

11. Cellular electrophysiological properties

Reticular cells are endowed with a set of at least 6 voltage-dependent ionic conductances: two classical for Na^+ and K^+, a non-inactivated for Na^+, a low-threshold for Ca^{2+}, a Ca^{2+}-dependent for K^+ and a Ca^{2+}-dependent non-selective cation current [12,14,176,243]. Low-threshold Ca^{2+} conductance is well known to underlay high-frequency bursts of up to 15 action potentials (200–500 Hz) with an acceleration-deceleration pattern [12,41]. This transient Ca^{2+} conductance, which might be generated mainly in dendrites [64], inactivates much more slowly than that recorded in TC neurons [109]; furthermore, this low-threshold current of TRN cells has different voltage dependence features to those recorded in TC neurons.

Single-cell recordings in the TRN of diverse mammals indicated that it is composed of diverse cellular types distinguished by their spontaneous firing pattern. During stereotaxic surgery of parkinsonian patients who where awake, recorded TRN cells were categorized into three groups (A, B and C): irregular for type A, short (10–30 ms) high-frequency bursts of action potentials (200–500 Hz) for type B and long (up to 2s) high-frequency trains of action potentials for type C [211]. It is possible, however, that the firing pattern of the latter type was the result of an injury discharge induced by the metallic microelectrode. Indeed, the high-frequency character (200–500 Hz) of the corresponding long train discharges of action potentials, which was unchanged during verbal or sensory stimuli [210], has never been recorded during experimental studies, including ones involving unanaesthetized cats (see below). Type A was no longer observed when the level of consciousness was decreased, that is, during short-term anaesthesia [211], and it was activated in a tonic manner during the verbal command to perform a movement and during its execution [210]. The type B was inhibited during the command presentation whereas it was activated during motion. Positive cross-correlations were detected during the simultaneous recordings of two A units whereas the activities of nearby A and B units were negatively correlated. These results showed the involvement of the TRN in the transmission of a signal triggering speech-mediated voluntary acts in humans and further emphasized the heterogeneity of the TRN cellular population on the basis of its firing patterns.

In urethane-anaesthetized adult rats, three categories of cells were distinguished on the basis of the firing pattern [197]: (1) cells discharging high-frequency bursts of action potential ($N=2–15$ at 200–500 Hz) in isolation or in short rhythmic sequences at about 10 Hz; (2) other units irregularly discharging single action potential with occasional bursting episodes; (3) the remaining units (about 34%) emitting a single action potential in a regular fashion at 25–60 Hz. The latter cells could switch their firing into the burst mode and vice versa. Simultaneous recordings of two nearby cells usually could reveal the absence of synchrony, even when the cells belonged to a same category. Under urethane anaesthesia cortical neurons are rather silent [130] and TC neurons usually exhibit high frequency bursts of action potential ($N=2–4$ at 200–500 Hz [201]). So, the fact that two nearby TRN units, which are supposed to share the same excitatory and inhibitory inputs, do not display the same firing pattern at the same time suggests that the activity of most recorded TRN cells is largely dominated by their intrinsic properties, which may be different from one cell to another (see below). This inference is well borne out by multi-unit recordings conducted in diverse animals, including in human beings (Fig. 16).

In stereotaxically restrained and unanaesthetized cats, two types (fast and slow) of TRN cells were recorded [16]. Whereas the slow type fired no more than 15 action potentials per second during wakefulness or paradoxical sleep, the fast type had the propensity to fire much above that frequency. Also, the slow type had an intra-burst frequency much higher than that of the fast type (158 vs. 62 Hz). In freely moving cats, single-cell recordings in the caudal part of the TRN revealed that the mean cellular firing rate, which was in the range of 40 Hz, was nearly the same during both the waking and the REM sleep states

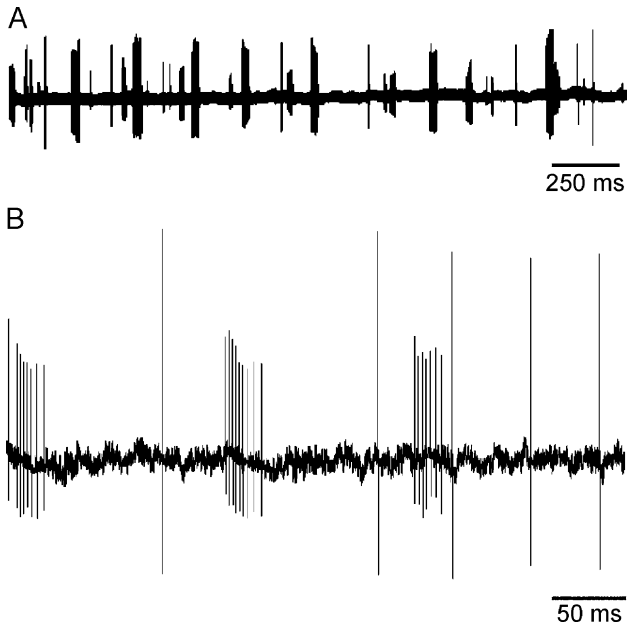

Fig. 16. Different firing patterns in simultaneously recorded adjacent TRN units. (A) Unit activities recorded with tungsten microelectrodes in the TRN of dyskinetic patients who are awake [210]. (B) Two adjacent units recorded with a sharp glass micropipette in the TRN of a neuroleptanalgesied rat [187].

[175]. In freely moving cats [248] and rats [152], TRN cells usually fire in the burst mode during sleep episodes whereas they fire in the single action potential mode during the waking state; furthermore, during the development of REM sleep these reticular cells have a propensity to discharge in a more tonic manner than during deep sleep.

In vivo and in vitro intracellular recordings revealed two distinct types of TRN cells according to their intrinsic properties. In cats anaesthetized using urethane, intracellular recordings showed two classes of cells, which were distinguished by their ability to develop short-lasting (up to 100 ms) high-frequency bursts of action potential (up to 200 Hz). If they were able to do so they were classed as bursting cells—type 1—and if they were unable they were classed as tonic cells—type 2 [40]. Using whole-cell patch clamp recordings in thalamic slices of young rats, Brunton and Charpak [28] revealed that, in contrast to type 1, type 2 rarely generated a low-threshold spike at the removal of hyperpolarizing pulses (Fig. 17). Furthermore intracellular recordings in guinea pig thalamic slices showed that some TRN cells had a low-threshold spike (presumably mediated by Ca^{2+} conductances), which was partly deinactivated at the resting membrane potential and did not have a non-activating Na^{+} conductance [141].

In addition, as they have a set of powerful intrinsic ionic conductances, TRN cells can behave like resonators. For instance, in the study on Genetic Absence Epilepsy Rats from Strasbourg, spike-and-wave discharges emerged from TC medium-voltage 5–9 Hz oscillations [206]. During absence seizures CT neurons play a primary role in the synchronized excitation of TC and TRN neurons [196]. Furthermore, during the generation of the 5–9 Hz rhythm TRN cells start to fire robust, high-frequency bursts of action potential and almost always do so before TC neurons (Fig. 18A,B). Intracellular recordings revealed that such TRN bursts are usually caused by a depolarizing wave (underlain by at least a low-threshold Ca^{2+} spike), which is triggered by a barrage of EPSPs principally induced by CT inputs (Fig. 18D). Because TRN cells exhibit such synaptically induced intrinsic bursts much more frequently than TC neurons (Fig. 18A,C,D) (see also Ref. [205]), they may be considered as powerful resonators, which are partly responsible, for instance, for the generation of absence-related spike-and-wave discharges [196].

In conclusion, the powerful intrinsic electroresponsive properties of TRN cells allow them to switch to any one of a number of electrophysiological behaviours (see below). The above-mentioned electrophysiological data indicate that the TRN contains at least two types of cells, one of which has a greater ability to generate robust high-frequency bursts of action potential than the other (also see Ref. [180]). Unfortunately, there are as yet no defined anatomical and morphological correlates of these two types of TRN neurons. Because Spreafico et al. [243] could not record any electrophysiological difference between morphologically distinct cellular types, it might be suggested that the different electrophysiological properties observed are correlated with certain network properties. Moreover, TRN cells are well known as being a principal target of TC and CT inputs [231]. Furthermore, the electroresponsive properties of TRN cells might also depend on the neuronal network to which they belong. Indeed, in urethane-anaesthetized rats, TRN cells in the visual sector were categorized into two types following electrical stimulation of the optic tract [252]: (1) some, which were selectively excited from area 17 of the visual cortex and projected to the dorsal lateral geniculate (first-order) nucleus, responded with a short latency (2.3–6.1 ms); (2)

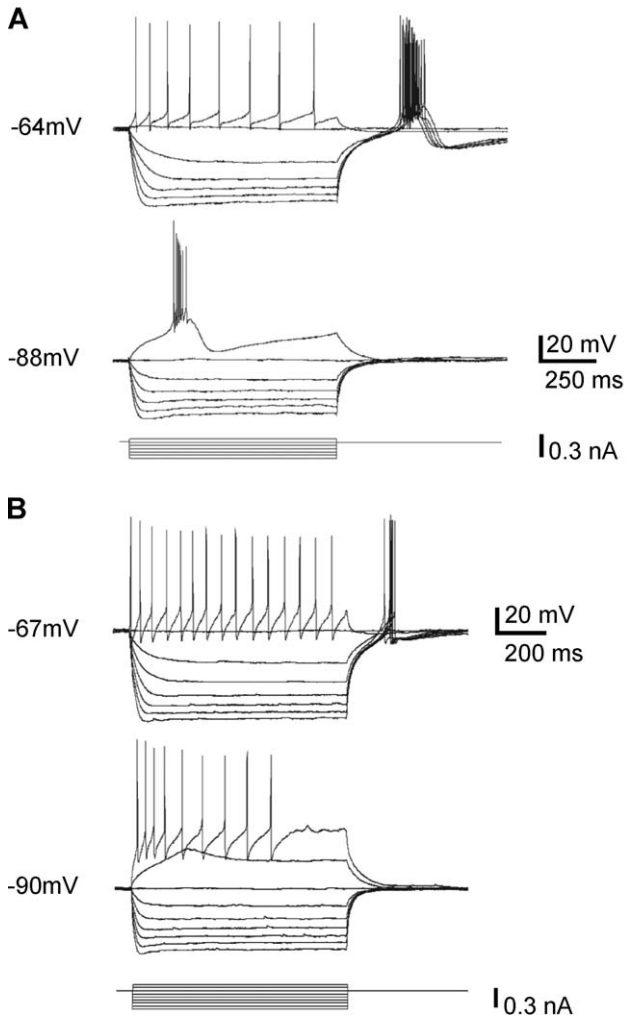

Fig. 17. Two functionally different types of TRN cells. (A) This type is a bursting cell since it usually emits a high-frequency burst of action potentials at both the offset of hyperpolarizing current pulses and the onset of depolarizing pulses (from a strongly hyperpolarized level). (B) That unit is a tonic cell since it does not fire a burst discharge of action potentials at both the offset of hyperpolarizing current pulses and the onset of depolarizing pulses (from a strongly hyperpolarized level). Adapted from Ref. [28].

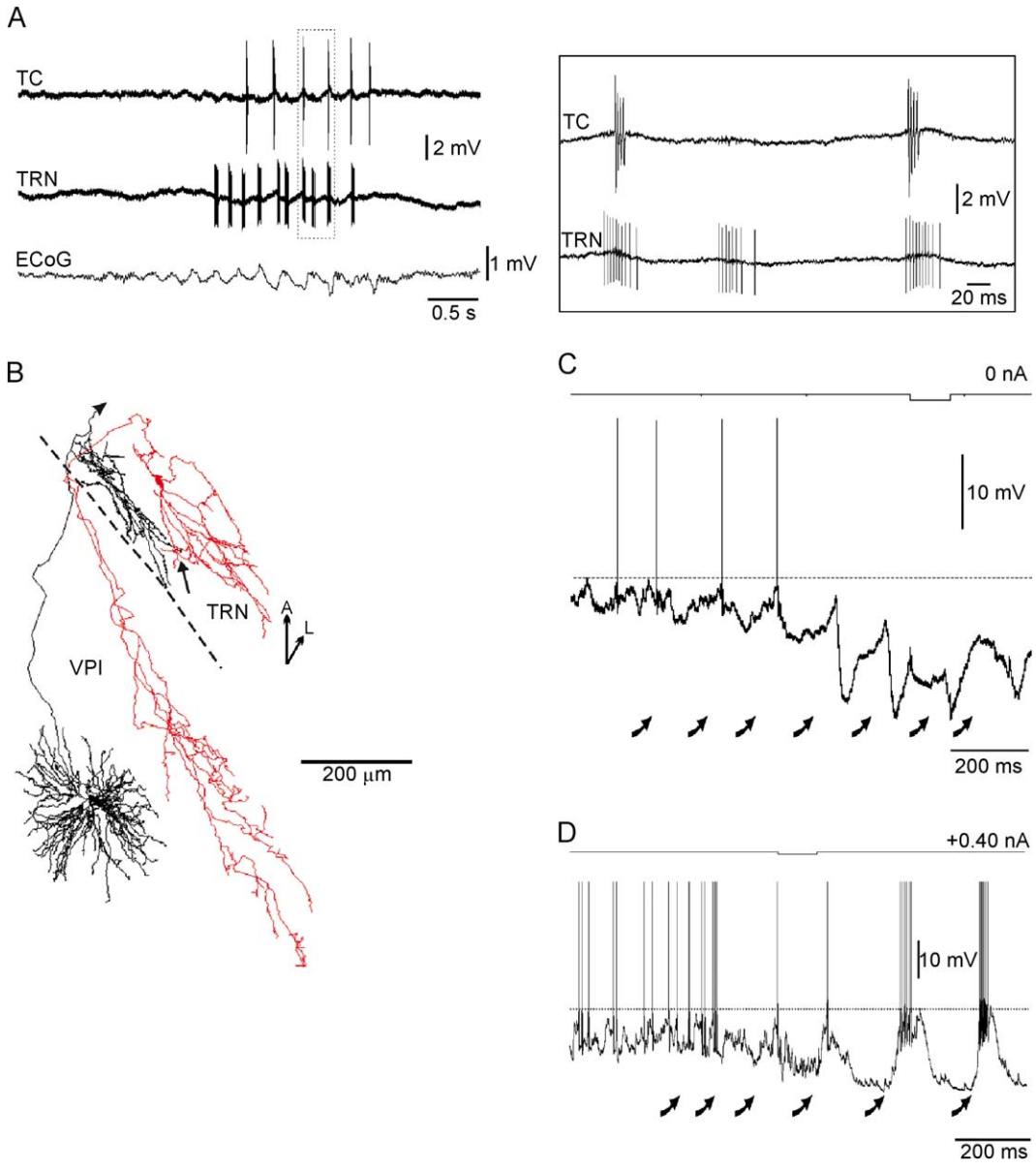

Fig. 18. Thalamic reticular nucleus cells can function as resonators. (A) Paired single-cell extracellular recording of thalamocortical (TC) and TRN neurons of the somatosensory system during spontaneously occurring medium-voltage 5–9 Hz oscillations in the related surface electrocorticogram (ECoG) in a neuroleptanalgesied adult rat. The framed area is expanded on the right. (B) Three-dimensional reconstruction of these two cells, which were individually labelled following juxtacellular application of Neurobiotin. Note that one branch of the TC axonal arbour ends (black arrow) into the dendritic field of the TRN cell (in red). (C and D) Intracellular recording of somatosensory-related TC and TRN neurons, respectively, during the generation of 5–9 Hz oscillations in a neuroleptanalgesied rat. The curved arrows indicate barrages of EPSPs, which are mainly provoked by rhythmic corticothalamic inputs. Note that the TRN high-frequency bursts of action potentials are caused by a low-threshold depolarizing spike, which is triggered by individual depolarizations of small amplitude. The action potentials are truncated in C and D. A, anterior; L, lateral; VPl, ventral posterolateral thalamic nucleus. A and B are adapted from Ref. [206], and C and D from Ref. [196].

others, which were selectively excited from area 18a and projected to the lateral posterior (higher-order) nucleus, responded with a longer latency (5.2–15.3 ms). The latter cells were located in the most posterior part of the visual sector. There is a mean latency difference of 0.7 ms, suggesting the involvement of one additional synapse likely due to indirect activation through the superior colliculus (see discussion by Sumitomo et al. [252]). The hypothesis that the TRN is composed of various types of neurons is clearly worth testing at functional, anatomical and network levels.

12. Thalamocortical oscillations

At the end of the 19th century, Richard Caton [34] discovered that the brain is an extraordinary machine producing spontaneous electrical waves. Hans Berger [20]

characterized the human alpha oscillations, which were modified by activation of sensory systems. He believed that electrocortical rhythms were intracortically generated (also see Refs. [115,214]). Since then several other rhythms have been recorded in association with the wake–sleep cycle, with cognitive tasks and/or with clinical disorders (e.g., Refs. [18,32,82,135,272]). Studies by Adrian and Matthews [1] and by Bremer [25] led electrophysiologists to conclude that rhythms recorded on the brain surface were generated by deep structures, including the thalamus [6,117,171, 173,209]. Moreover, Jasper [117] considered the thalamus and the TRN to be the rostral extension of the reticular activating system identified by Moruzzi and Magoun [173]. During the late 1960s, it was taught that TC oscillations are accounted for by network properties. Andersen and Andersson [6] proposed that alpha neuronal activities resulted from inherent properties of interconnected excitatory and inhibitory neurons, which were presumed to generate a sequence of synaptic activities. The rhythmic character of alpha activity was believed to be the result of propagation of an EPSP–IPSP sequence from one set of interconnected cells to another. This theory was based upon the discovery of a powerful recurrent inhibitory system in the thalamus and the assumption that single neurons cannot generate rhythmic activities [7].

Since the 1980s, in vitro and in vivo intracellular recordings of individual neurons have demonstrated that TC and TRN cells are endowed with intrinsic electrophysiological properties [61,113,142], leading to new concepts of TC oscillations. More specifically, TC oscillations mainly reside conceptually in the intrinsic capacity of neurons to generate oscillatory activities. Moreover, the Steriade laboratory proposed that the TRN is the pacemaker of sleep spindles because spindle activity was preserved in the TRN when it was disconnected from cortical and thalamic inputs [249]. The theory is that the pacemaker activity of TRN cells is characterized by the alternance of two main intrinsic currents, I_T and $I_{K^+}(Ca^{2+})$, which have been well characterized in in vitro conditions [109,114]. However, we should bear in mind that TRN neurons do not behave electrophysiologically like true pacemaker cells—like those of the suprachiasmatic nucleus and of the sinoatrial node—since their intrinsic currents need adequate inhibitory and/or excitatory activities to operate in a rhythmic mode without damping. Steriade and Deschênes [246] arrived at the conclusion that the thalamus is a neuronal oscillator, a theory combining network and synaptic properties, and intrinsic cell properties. This conclusion has been borne out further by electrophysiological studies performed on thalamic slices from ferrets [268] and mice [270]. In particular, it has been demonstrated from thalamic slices from ferrets that reciprocal functional connections between TC and TRN neurons, which involve synaptic and intrinsic cell properties, are essential for generating spindle-like thalamic activities [15,126,268]. This demonstration, which was based on the cutting of connections between TC and TRN neurons, is a strong counterargument to the proposal that the TRN is an autonomous structure for generating spindle-like oscillations. Nowadays, the cellular and network mechanisms responsible for spindle oscillations may be a contentious issue simply because both the terms "spindle" and "spindle-like" are sometimes used in a misleading fashion. Indeed, they are used for any kind of TC rhythmic activity recorded specifically in in vitro conditions (e.g., Refs. [112,257,268]), whereas true sleep-related spindle oscillations have an intra-spindle frequency of 10–15 Hz and last no more than 2 s, at least in humans [181], cats [249] and rats [80,206].

Furthermore, feline anterior thalamic nuclei do not appear to generate spindle-like activities [176]. Yet, it has been demonstrated in rodents [84], felines [266] and primates [129] that the rostral part of the TRN projects to these anterior nuclei. This is at variance with previous anatomical and electrophysiological data obtained in the cat [189,247]. Thus, assuming that the TRN is the leading structure in the generation of sleep-related spindle activity, it may be questioned whether or not cells projecting into the anterior thalamus and caudal cells projecting into the dorsal thalamus share similar functional properties.

Nowadays, it is well known that the electrophysiological behaviour of TRN cells varies from one moment to the next (e.g., Ref. [250]). For instance, in anaesthetized rats, TRN cells usually display rhythmic burst activity during medium-voltage synchronized oscillations (Fig. 19). During these episodes, two burst firing patterns (long-lasting 5–9 Hz and short-lasting 10–16 Hz) are easily distinguishable [206]. Intracellular recordings revealed that layer VI CT neurons play a leading role in the generation of 5–9 Hz oscillations in the TRN [196]. Thus, the question is whether the short-lasting 10–16 Hz oscillations—which are believed to correspond to spindle-like activity [206]—are generated by similar cellular and network mechanisms. Additional experimental studies are required to increase our understanding of the cellular mechanisms responsible for these two distinguishable rodent rhythms.

Gamma (20–80 Hz) oscillations have been recorded in the TC system during attentional processes in the cat [24] and during cognitive tasks in humans [216]. Furthermore, in the cat, TRN cells discharge in the gamma frequency band when the animal fixes its attention on a motor task [151]. It has been demonstrated in anaesthetized rats that the gamma frequency firing of TRN cells is generated by a voltage-dependent mechanism, which operates within a voltage range close to the action potential triggering threshold [197], which in turn has also been found in in vitro studies [14,158]. This intrinsic behaviour operates under the control of diverse neurotransmitters, including monoaminergic and cholinergic inputs [198], which are involved in the control of vigilance [10,56,96,136,275]. However, the role of the TRN in electro-corticographic gamma activities still has to

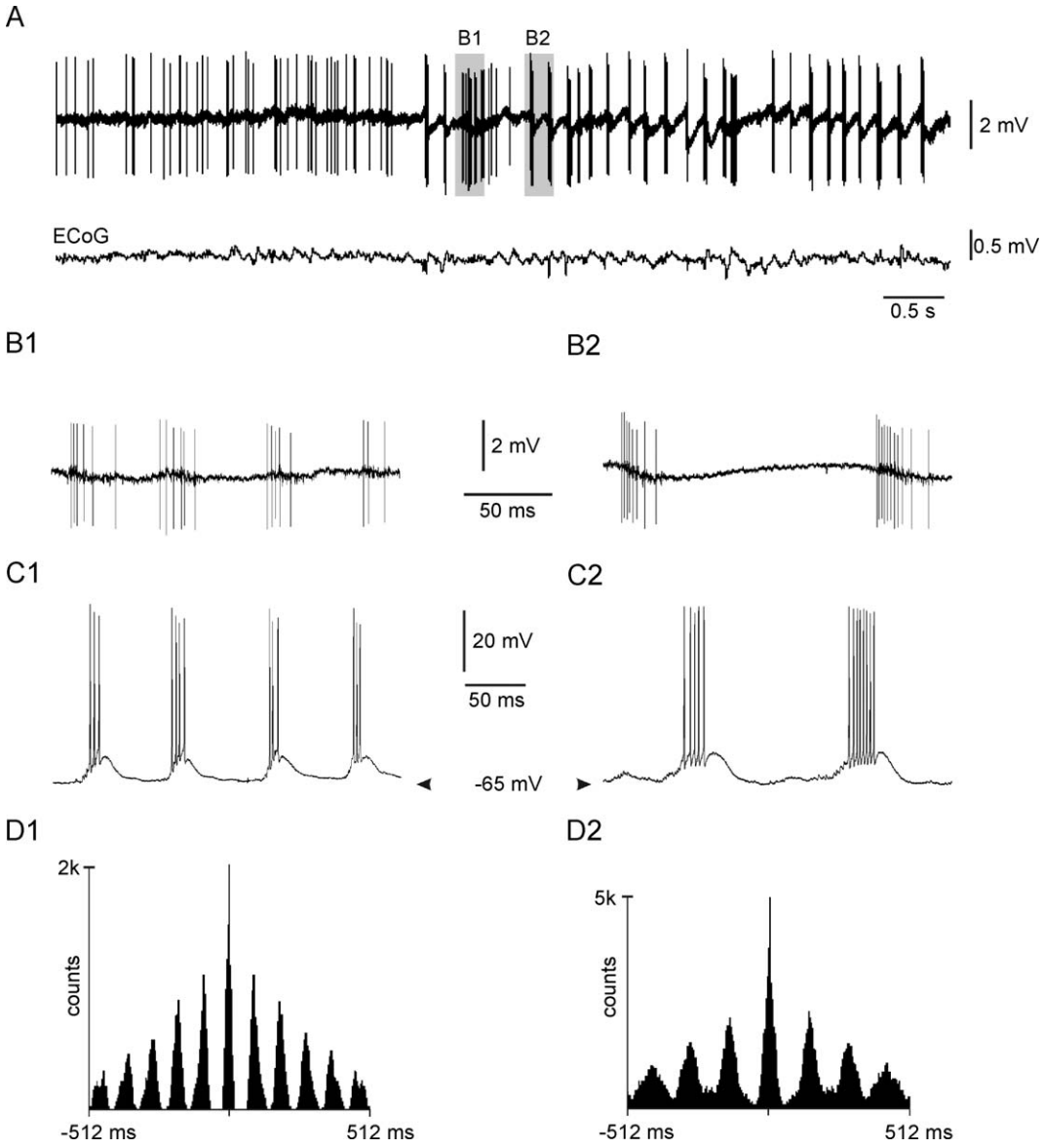

Fig. 19. Two distinct reticular burst firing patterns during medium-voltage electrocorticographic (ECoG) oscillations of the related cerebral cortex. (A) Tonic firing spontaneously alternates with burst firing in neuroleptanalgesied rats. During the occurrence of rhythmic high-frequency bursts of action potentials (200–500 Hz), two patterns are distinguishable (in grey). One (B1) is characterized by a burst frequency of 10–16 Hz (auto-correlogram in D1) and never lasts over 2 s; the other pattern is characterized by a burst frequency of 5–9 Hz (auto-correlogram in D2) and usually last well over 2 s. (C1 or C2) Intracellular recordings reveal that each burst is caused by a depolarizing wave. Adapted from Refs. [196,206].

be determined. Interestingly, high-frequency stimulations of discrete loci in the auditory and somatosensory sectors of the TRN evoke gamma oscillations in the related cortical areas [150].

13. An ideal substrate for selective attention?

That the TRN is involved in attentional processes is supported by recent findings. McAlonan and Brown [155] revealed that a given attended conditioned sensory stimulus induces in the corresponding TRN sector a significant increase of the number of neurons immunoreactive to the Fos protein. The involvement of the TRN in cognition is highlighted further following directly and indirectly induced neuronal lesions. Lesions of TRN regions usually induce forms of behavioural neglect, suggesting that the TRN is involved in attentional processes [29,39,78,159,271]. Before the Scheibels' discovery of the reticulothalamic projections [225], it was believed that TRN axons project diffusely into the whole cerebral cortex and this led to the proposal that this diencephalic structure was the terminal part of the ascending activating system [36,116,221]. That belief derived from observations that were mistakenly interpreted as retrograde degeneration occurring subsequently to cortical lesions [133,220]. Clin-

ical studies have shown that after severe head injuries, a selective loss of TRN cells was found in nearly all examined cases, supporting the notion that loss of TRN cells might contribute to some cognitive deficits observed following brain trauma [222].

Because the TRN occupies a strategic position between the neocortex and the thalamus and controls TC activities through inhibitory/disinhibitory mechanisms (see Fig. 12), it has been viewed as a key structure for selective attention for more than three decades [55,94,120,154,166,197,225,280]. This concept was crystallized by Crick [55] in the form of "the searchlight hypothesis". The notion of an internal attentional searchlight derives from psychophysical studies of cognitive mechanisms, particularly those conducted by Treisman and Gelade [258] and Julesz [121].

What is the "searchlight"? According to Francis Crick [55], the TRN endowed with neurons having extensive inhibitory axon collaterals, which are supposed to generate large-scale intra-TRN cellular interactions, and successive thalamic burst discharges are what is required of a searchlight. This concept is nowadays brought into question by at least two types, anatomical and functional, of findings recently available. First, in contrast to the interpretation of anatomical data obtained from the rapid Golgi method [225], individual labelling of TRN cells revealed that only a weak proportion (about 10%) of neurons display short-range local axon collaterals, whose proximal part have the ultrastructural properties of postsynaptic structures [204]. Therefore, there is no compelling evidence that these collaterals are indeed involved in intra-TRN cellular interactions (see Section 10). Second, rhythmic burst activity in thalamic neurons, which include TRN cells, usually occurs during states of drowsiness and sleep [248], whereas attentive wakefulness and cognitive tasks are usually associated with gamma oscillations in TC systems [24,151,216]. Such fast oscillations are usually thought to reflect rhythmic single action potential activity rather than burst activity, at least in TRN cells [197]. Accordingly, the Crick's hypotheses that "the expression of the searchlight is the production of rapid firing in a subset of active thalamic neurons" and that "the searchlight is controlled by the reticular complex of the thalamus" should be rethought on the basis of recent cellular and network findings.

Therefore, it is tempting to place some above-mentioned anatomical considerations on the scene and to put forward some ideas, which may help to reformulate the heuristic concept of Francis Crick, as follows:

- Virtually all the functional modalities are represented within the TRN. Although there appear to be overlaps between adjacent sectors, one might wonder how, at a given time, the TRN combines all the modalities required for a given motor or mental task with the appropriate individual synaptic capacities. This combination requires, at the least, widespread and reliable interaction between remote TRN cells. Because the TRN itself seems unable to take on such interaction, it is likely that thalamic and cortical structures at least are also involved.
- The fact that a given TRN cell can respond to two sensory modalities suggests that, during attention, such a reticular cell might selectively and simultaneously set various thalamic regions into "excitation", through inhibitory (e.g., surround inhibition)/disinhibitory mechanisms, thereby shaping the transfer of the multi-modal TC information that is required by the current brain processing. Divergences of TRN axonal projections do exist and appear to be involved in only one functional modality [49,199,200]. These findings also raise the question as to whether such diencephalic GABAergic neurons might be responsible for spatial and temporal bindings during TC operations.
- The closed- and open-loop thalamo-reticulo-thalamic circuits allow the TRN to shape thalamic activities through lateral and feedback, GABA-dependent, inhibition mechanisms. These circuits seem to be able to operate at both modular and global scales. In this way, subsets of TRN cells are thought to synchronize subpopulations of TC neurons through oscillatory mechanisms, and this process is supposed to result in hotspots in different cortical regions. What binds these hotspots together during focused attention is still open to debate.
- The TRN controls neuronal activities in a focused manner within nearly all thalamic nuclei, and it is bombarded by all the functionally related cortical areas and thalamic nuclei. Assuming that the TRN is the searchlight operator, functional data suggest that the operator is probably driven by layer VI CT inputs [83,167,168,196].
- Whatever the TRN sector, most cells have dendrites spanning more than one tier, and this is probably the result of a developmental arrangement with TC and CT inputs of diverse origins (from first-order and higher-order regions). This suggests that TRN cells can be excellent integrators of diverse information coming from thalamic and cortical, first-order and higher-order, regions.
- All TRN neurons have powerful intrinsic electrophysiological features. Furthermore, the timing and the pattern of a cell's firing can be independent of its neighbours. It is tempting therefore to speculate that the reason why all TRN cells are endowed with intrinsic electrophysiological properties is to allow them to fire in a given fashion at a particular moment, independently of their neighbours. On the basis of the intrinsic and extrinsic connections of TRN cells, it can be said that any TRN neuron belongs to more than one neuronal circuit. Every TRN cell may therefore be a potential elementary searchlight, which might be able to connect itself to the appropriate network in which it is required to enter into action, for instance during focused attention.
- Is the searchlight the result of a resonance phenomenon between the relevant TC systems associated with a given

action? According to current opinion, a searchlight should be able, at the ms scale, to detect the attention-related neuronal demands within, among others, TC systems and to shape the corresponding thalamic activities accordingly so that they can reach simultaneously diverse cortical areas responsible for preparing and for executing the action (cognitive and/or motor task). The searchlight's activity is thought to be ephemeral and combinatory, working both sequential and in parallel.

- Taken together, the diverse and numerous, in vivo and in vitro studies conducted in this area have resulted in great strides in the understanding of some of the anatomical and functional, cellular and network, properties of the TRN. Nevertheless, its actual functioning is still far from being understood. On the basis of the data currently available, it is tempting to suggest that this diencephalic GABAergic structure is a set of elementary searchlights, which are under the permanent control of inputs from the cortex, the thalamus, the brainstem and the basal forebrain. Since the TRN innervates several thalamic nuclei [199,247], since TRN loci can be intermediary communication sites between two distinct thalamic nuclei [54], since neighbouring and remote TRN cells are somehow capable of communicating with each other [132,223], and since most if not all of these GABAergic neurons are endowed with powerful, synaptic and intrinsic, electroresponsive properties [12,177], the TRN may be viewed as a "hub" [143], marshalling relevant TC channels required for action.
- Cognitive tasks are generally associated with cortico-cortical relations, which involve hierarchical neuronal processing from first-order to higher-order systems [70,122]. Two conflicting views attempt to explain the neural bases of cortico-cortical synchronizations. The first views it as a mechanism involving a feed-back loop from a common site, which is thought to be the thalamus [144,216], while the second sees it is a mechanism involving intracortical lateral connections, including the corpus callosum [67,68,87,228,238,242]. The hypothesis that the thalamus is involved in large-scale cortico-cortical synchronizations is now convincingly supported by anatomical data [93]. This important matter should be investigated at the anatomo-functional level.
- The thalamus has long been considered as a gateway to the cerebral cortex and the TRN as the guardian of that gateway. On the basis of the currently known anatomical and functional properties of TRN cells, it is tempting to submit that such diencephalic GABAergic neurons may also be involved in large-scale cortico-cortical connections. Indeed, TRN neurons are massively innervated by cortical inputs arising from layer VI and modulate the activity of a great number of TC cells within thalamic nuclei that receive cortical inputs not only from layer VI but also from layer V [93]. The spatio-temporal dynamics of the corresponding neuronal interactions remain, however, to be explored. From a pathological viewpoint, the TRN should be considered as one key structure in cognitive deficits, which include those associated with schizophrenia [229].

At any rate, the exciting Crick's concept still provides an incentive for challenging research work relating to all forms of sensory, motor and cognitive processing. In the context of our current anatomical knowledge of the TRN, the suggestion of possible existence of several separate searchlights [55] is interesting.

14. Concluding comments

The TRN is a diencephalic GABAergic nucleus, which is composed of neuronal elements endowed with diverse architectural, functional, neurochemical and pharmacological properties. Thus, it might be reasonable to define a TRN cellular type on the basis of its morphological, anatomical, neurochemical and physiological properties.

Nowadays, with single-cell electrophysiological studies conducted in in vitro and in vivo preparations great strides have been made in the understanding of certain integrative and oscillatory properties of thalamic neurons. The integrative properties of TRN cells are not well understood, but it seems that some units can combine more than one functional modality and submodality, which would allow them to have control over certain spatial and temporal bindings involved during global brain operations. Furthermore, it appears that the integrative properties of TRN cells also depend on the plexus of intercrossing TC and CT axons. Since TRN cells are involved in both recurrent and lateral inhibitions, they might have the ability to generate and to sharpen, in a space continuum, task-related peaks of increased TC firings reaching the cerebral cortex. For example, in the sensory systems, TRN cells can merely shape the receptive field of TC neurons accordingly to the functional context by adjusting their level of polarization and excitation through the activation of $GABA_A$ and $GABA_B$ receptors. To sum up, TRN cells might operate as integrators with a wide range of complexity levels.

The reticular and thalamic neurons themselves form closed-loop and open-loop circuits, which are the anatomical substrata of feedback and lateral GABA-mediated inhibitions. It is generally thought that GABAergic neurons usually produce inhibitory effects in their targets, but we should bear in mind that TRN cells effectively have two main effects on TC neurons, namely inhibitory and excitatory effects. (1) Thalamocortical GABA A and GABA B inhibitions that are driven by CT and TC inputs in TRN cells are the direct post-synaptic result of TRN firings; (2) TRN cells too can produce indirect excitation, that is, a post-inhibitory rebound transient discharge (resulting from a low-threshold Ca^{2+} spike) in their target TC cells and/or

discharge of varying duration in non-target TC cells (e.g., through a disinhibition that is presumed to be the counterpart of feedback or lateral inhibition). Furthermore, TRN cells have powerful intrinsic electrophysiological properties to fire in an oscillatory mode and to resonate in a wide range of frequencies; and many studies have demonstrated that the TRN, which occupies a key position in the TC system, plays a leading role in the generation of TC-dependent EEG physiological and pathological oscillations. Furthermore, the structural substrata of cell–cell communications within the reticular nucleus are far from being well understood. A particularity of the TRN is the presence of interwoven dendrites forming bundles. These might conceal synaptic (chemical and/or electrical) and non-synaptic mechanisms of intrinsic cell–cell communications. Whether or not such intra-nuclear interactions specifically occur between adjacent and/or remote neurons is open to debate.

Another intriguing finding is the potential existence of two distinct functional cellular types, "burst" and "tonic", with no apparent correlation with architectural, anatomical, and neurochemical characteristics. However, we should bear in mind at least that any bursting cell can switch its firing into the tonic mode, depending upon its state of polarization. Whether the converse exists is a fundamental question that requires further investigation. That two adjacent TRN cells, which are supposed to share excitatory and inhibitory inputs, can simultaneously fire in different manners at the same time is also intriguing. This suggests that every TRN neuron is endowed with intrinsic electrophysiological properties allowing it to display a firing pattern at a given moment, thereby defining the status of a given set of TC neurons.

The reticular nucleus has anatomical and functional properties that are designed in some way to ensure that the spatio-temporal dynamics of inter-structure communications are coherent; this occurs "horizontally" within the thalamus and then "vertically" between the thalamus and the neocortex, with important consequences for cortico-cortical relations. In other words, under the influence of diverse inputs from the cerebral cortex, the thalamus, the brainstem and from the basal forebrain, the TRN is thought to be able, at both spatial and temporal scales, to sample and integrate neuronal attention-related demands and set up the corresponding TC circuits. Since the TRN includes virtually all the functional modalities and occupies a strategic position in the highly distributed TC systems, it might act like a combinatory matrix. Because the latter systems receive information both from the periphery and from the neocortex, the TRN might be involved in both bottom-up and top-down processing.

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