

Paying attention to the thalamic reticular nucleus

R.W. Guillery, S.L. Feig and D.A. Lozsádi

The thalamic reticular nucleus can be divided into a number of sectors, each concerned with a different function (sight, touch, hearing, movement or 'limbic' functions). Each sector is connected to more than one thalamic nucleus and to more than one cortical area, and each sector has topographically mapped connections with the thalamus and the cortex. We consider the known details of these connections and show: (1) that they are not the same for each sector; (2) that the reticular nucleus serves as a nexus, where several functionally related cortical areas and thalamic nuclei can interact, modifying thalamocortical transmission through the inhibitory connections that go from the reticular cells to thalamic relay cells; and (3) that we need much more detailed information about these highly organized connections before we can understand exactly how the thalamic reticular nucleus might be influencing thalamocortical pathways in attentional mechanisms or in other, as yet undefined, roles.

Trends Neurosci. (1998) 21, 28–32

THE THALAMIC RETICULAR NUCLEUS (TRN) forms an essential part of the circuits that link the thalamus to the cerebral cortex. Although these circuits have been implicated in attentional mechanisms¹, their functional role in the transmission of information through the thalamus to the cerebral cortex is still largely undefined. The reticular nucleus lies like a shield between thalamus and cortex (Fig. 1), so that all of the fibers passing either way between thalamus and cortex must go through the TRN. This gives the nucleus the structure of a sieve rather than a real shield. Many of the fibers that go through the TRN give off side branches to supply excitatory, glutamatergic synapses to the cells of TRN and these cells, in turn, send inhibitory, GABAergic fibers back to the thalamus^{2,3}. The basic circuit, shown in Fig. 1, can be seen as crucial in the control of messages reaching the cerebral cortex.

In this review we present evidence that the topographic organization of connections with cortex and thalamus within TRN is important in the control of thalamocortical circuits. We suggest that each of the major thalamocortical systems has its own characteristic pattern of organization in TRN, a pattern that probably relates to the functional properties of that system. That is, understanding the different organizational patterns within TRN might show how each part of TRN can act upon all or just a part of its related thalamocortical pathways.

The TRN was long regarded as a diffusely organized structure, having global rather than localized actions on thalamocortical pathways^{4,5}. However, there is now evidence that the nucleus is divided into several distinct sectors, each related to a particular functional group of thalamocortical pathways², and that in each of the sectors there is a topographically ordered representation of relevant cortical areas and thalamic nuclei^{6–14}. Visual, auditory, somatosensory and motor sectors can be recognized in the TRN, as well as separate sectors for other nuclei like the anterior and mediodorsal thalamic

nuclei; and for each sector the topography of cortical and thalamic connections is beginning to be defined.

The afferents to TRN from thalamus and cortex, together with those from brainstem and basal forebrain (see Fig. 1; Refs 15,16), play a critical role in controlling the firing patterns of thalamocortical relay cells, which can be in either a 'tonic' or a 'burst' mode^{17,18}. In the tonic mode, there is a relatively unmodified, linear information transfer through the thalamic relay from ascending pathways to cortex. The burst mode has been characteristically seen during sleep or epileptic discharges⁵ and has therefore been considered to be a global mechanism that prevents the relay of information to cortex. However, recent observations show that even in the burst mode the thalamocortical relay cells can respond to sensory stimuli^{19,20}. Although this transmission is non-linear, the afferent activity is transmitted to cortex and, perhaps most significantly, the signal-to-noise ratio is higher than in the tonic mode. That is, in the burst mode the system is primed to react to changes in input activity rather than to transfer this activity reliably to cortex for analysis. For the latter, the system needs to switch to the tonic mode and it appears that this switch can occur in animals that are awake²¹.

Thus, two features have recently been added to our knowledge of thalamo-reticular circuits: one is the capacity of the thalamic cells, when in the burst mode, to respond to novel activity patterns and then change to the tonic mode so that the new stimuli can be accurately transferred to the cortex; the other is the localization of connections to and from topographically well-defined parts of TRN. Together they provide a basis on which the thalamo-reticular circuitry can respond to specific, localized, active parts of the environment or other brain centers. This is in contrast to the seemingly more global action of afferents that come from the brainstem. We are here concerned with the topographically organized connections that allow a highlighting of limited parts of thalamo-reticular circuits and can be

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closely related to Crick's 'searchlight hypothesis' about TRN action in attention¹. Whatever functions will eventually be assigned to the reticular nucleus, and there might be more than one, the topographic order seen in its connections, and its consequent capacity to focus on limited parts of the environment or of other brain parts, are likely to play key roles.

Multiple inputs to single sectors of TRN

For any single functional thalamocortical pathway and its related TRN sector, there is usually more than one connected thalamic nucleus or cortical area. Thus, visual, auditory and somatosensory systems have many cortical areas^{22–24} and more than one related thalamic nucleus connected to TRN (Refs 6,9–12). The way in which several thalamocortical circuits relate to each other in TRN must be crucial to the influence that any one cortical area can exert on the modulation going from a TRN sector back to any one of the related thalamic nuclei, and then on to cortex.

Figure 2 uses the visual system as an example to show that thalamic nuclei and their associated cortical and reticular connections can be categorized as either first order or higher order²⁵. The lateral geniculate nucleus (LGN) is a first-order nucleus. It receives primary, functional driving afferents from retina (green in Fig. 2), and sends to primary visual cortex (V1). The pulvinar, in contrast, is a higher-order nucleus. It receives primary driving afferents from the cerebral cortex (green), specifically from branches of descending axons of layer-5 pyramidal cells^{26–28} and sends to peristriate cortex. Both first-order and higher-order nuclei receive modulatory afferents (orange) from cells in layer 6 of their related cortical areas^{27–29}, and these are the afferents that send collaterals to TRN (Ref. 27). In contrast, thalamocortical fibers from layer 5 innervating the higher-order nucleus have no direct input to TRN (Ref. 27), and in this they resemble the ascending afferent fibers^{2,15}.

For the auditory pathways, the pars ventralis of the medial geniculate nucleus (MGv) is a first-order relay to cortical area A1 (Refs 2,10) and for the somatosensory pathways it is the ventrobasal nucleus (VB) (Refs 2,12), which sends to cortical area S1. Parts of the dorsal division of the medial geniculate nucleus (MGm) can be regarded as a higher-order relay to secondary auditory areas^{11,30,31}. For the somatosensory system, the medial division of the posterior group (POm) can be seen as a higher-order relay^{9,10,27,32}, connecting to the second somatosensory area (S2). Detailed studies might show that some or all of these higher-order relays have some first-order ascending connections, but the important point for the present is that there are different sorts of circuits going through TRN: some are primarily first-order circuits driven by ascending afferents, others are higher-order circuits driven by descending afferents from layer 5 of cortex. Current evidence suggests that the relationship of these circuits within TRN is not the same for each sector. The visual, somatosensory and auditory sectors appear to receive strikingly different connectional patterns, and so do the rostral parts of TRN that relate to motor thalamus, anterior and medio-dorsal thalamic nuclei, and to the midline and intralaminar nuclei. These will each be considered in turn.

The visual sector

There is evidence for visuotopic connections to TRN for rabbit, *Galago* and rat^{6,11,33–35}. Each has two parts to the visual sector: an outer or lateral tier occupies about

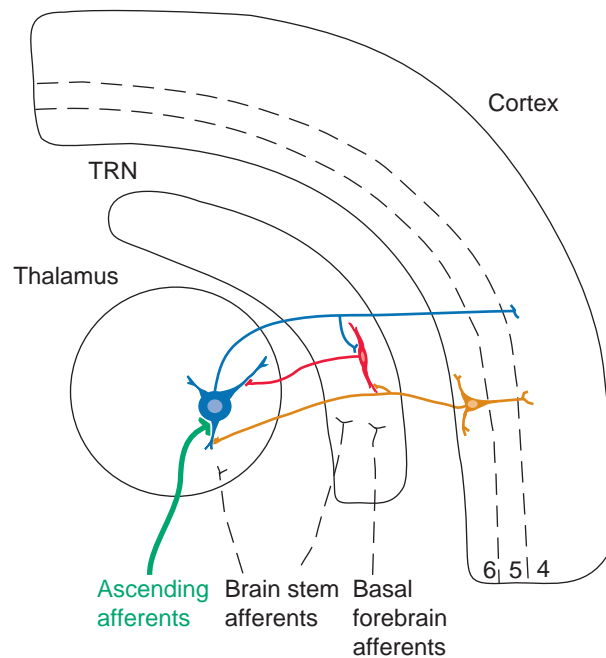


Fig. 1. The major connections between thalamic relay cells (blue), cells of the thalamic reticular nucleus (TRN; red) and the cerebral cortex (orange). Cortical layers 4, 5 and 6 are indicated by numbers.

two-thirds of the thickness of TRN and receives first order afferents from cortical area 17 (V1) and from LGN. Within this outer tier, each small area of V1 or small column of geniculate gives origin to reticular terminals that form a narrow slab in the plane of the TRN (Figs 3,4). The horizontal meridian is represented perpendicular to the thickness of the nucleus, peripheral vision at the outer border of the nucleus and central

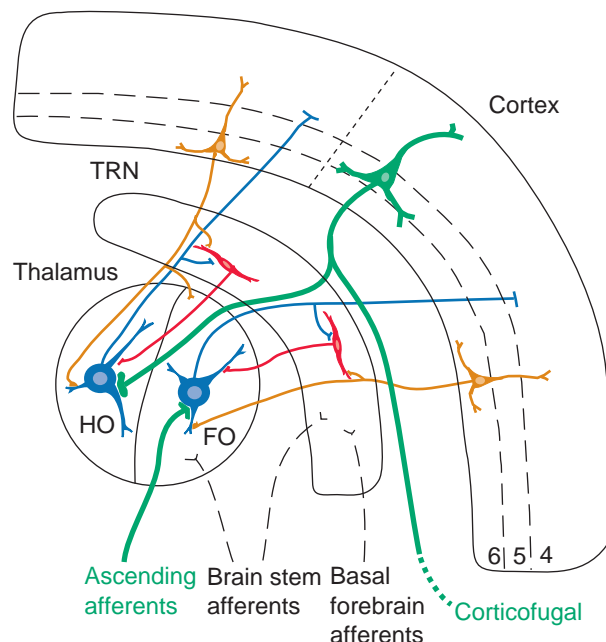


Fig. 2. Some thalamic nuclei, called 'first-order' (FO) nuclei, receive their main 'driving' afferents (green) from ascending specific afferents, whereas others, the 'higher-order' (HO) nuclei, receive their main (green) driving afferents from layer 5 of the cerebral cortex. Note that both FO and HO nuclei receive modulatory afferents from layer 6 of the cortex, and that these corticothalamic cells (orange) as well as the thalamocortical cells (blue) send branches to TRN, whereas the primary afferents (green) whether coming from cortex or from ascending pathways send no branches to TRN.

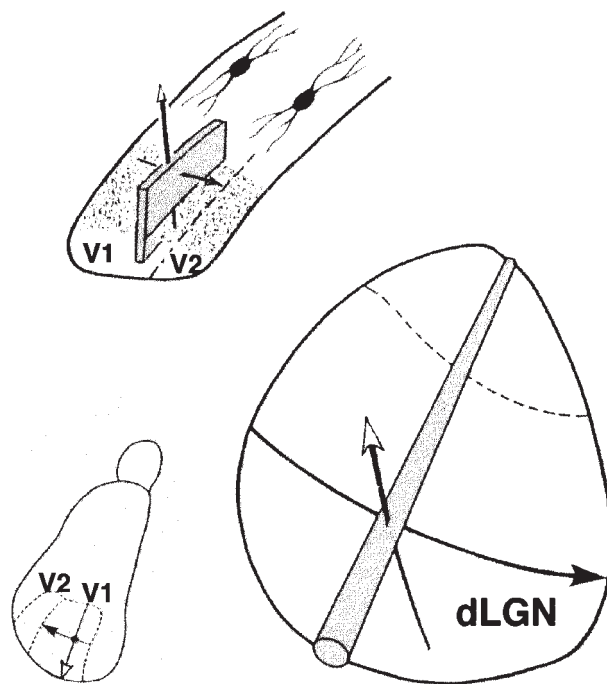


Fig. 3. A small area of visual cortex (V1 or V2 in bottom left), which receives from a corresponding small area of the visual field, relates to a single column in the dorsal lateral geniculate nucleus (dLGN) (bottom right) and to a slab within either the outer tier of the thalamic reticular nucleus, as shown here for V1, or to the inner tier, for V2 (top). The dendritic arbor of the reticular cells tends to match the shape of the slabs (see Fig. 5). From Mitrofanis and Guillery³⁶ (based on data from Crabtree and Killackey⁶).

vision at the junction of the outer and inner tiers. Movements upward in the visual field are represented by movements dorsally in the sector. The cells within any one slab send their axons to the part of the lateral geniculate nucleus from which they receive their afferents.

Whereas the two tiers have relatively well-defined borders, the slabs do not. Slabs are revealed only when connections from small cortical areas or thalamic volumes are labelled, and the larger the area that is labelled, the larger the slab. Therefore one cannot ask about the size of a slab, or see how slabs relate to individual TRN cells. However, in the main part of TRN (including the visual, auditory, somatosensory and motor sectors) cells have discoid dendritic arbors, with the dendrites stretched parallel to the slabs (Figs 3,5)^{12,37}. The relationship of reticular cells to axons that contribute to the slabs is important, but currently undefined.

The tier forming the inner third of the visual sector receives higher-order afferents from extrastriate visual areas and from the pulvinar. The inner and outer representations in TRN could be mirror reversals of each other about the vertical meridian, but the topography of the higher-order projections to the inner tier is still in question. Conley and Diamond¹¹ have suggested that the inner tier lacks any topographic organization. It is clear that for all three species there are two distinct tiers in the reticular nucleus, an outer one relating to first-order circuits, and an inner one connected to higher-order circuits.

The somatosensory sector

The somatosensory sector has been studied in cat, rat and rabbit^{7,9,12,27}. This sector appears to have a single tier in cat and rabbit⁷⁻⁹, but in the rat there is evidence for two tiers, an outer first-order tier and an inner higher-order tier^{12,27}, as seen in the visual sector (Fig. 4B). The first-order circuits have topographically organized reticular connections, leg representations connect to the outer parts of TRN, face areas to the inner parts, and arm in between. Higher-order circuits are established with S2 and POM. In TRN S2 matches the topography of S1, but it appears that the topography of the connections with POM is less accurate or absent^{9,12,27}. Single reticular cells can send axon branches to both VB (mapped) and to POM (unmapped, or poorly mapped); these branched axons might be less common in rat than cat^{9,12}, possibly because of a greater separation of the first- and higher-order connections in the rat.

The auditory sector

Evidence about the auditory sector is based on studies in *Galago*¹¹ and show a more complex relationship between first- and higher-order circuits. Essentially three distinct tiers are recognizable in this sector (Fig. 4C). First-order afferents from thalamic nucleus MGv form topographically organized slabs in the middle tier. Higher-order afferents from thalamic nucleus MGm and cortical area A2 distribute to the outer and inner tiers, forming a U-shaped surround to the middle tier. They show no evidence for topographic order. The first-order afferents from area A1 do show a topographical order but, surprisingly, extend across all three tiers. At present, evidence about auditory connections of TRN is available only for *Galago*, where we know relatively little about functional maps in thalamus or cortex.

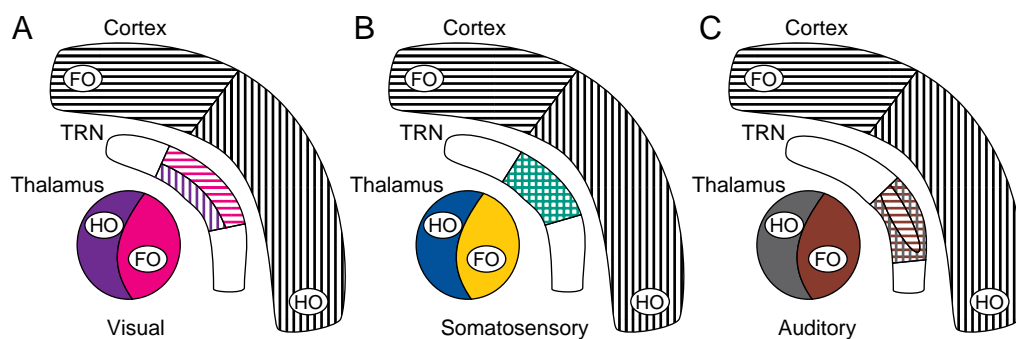


Fig. 4. The different relationships established by visual (A), somatosensory (B) and auditory (C) pathways in the thalamic reticular nucleus (TRN). Note that the three sectors of the reticular nucleus illustrated in the figure occupy different parts of TRN. The somatosensory sector lies rostral to the visual sector, and the auditory sector lies in the ventral and caudal parts of TRN. (A) First-order pathways are shown in red for the thalamus and as horizontal lines for the cortex. Higher-order pathways are shown in purple for thalamus and as vertical lines for cortex. Within the TRN one can see two distinct tiers, a larger outer tier receiving from first order thalamus and cortex, and smaller inner tier, receiving from higher order thalamus and cortex. Tiers are defined as subdivisions of a reticular sector having connections to different cortical areas or different thalamic nuclei, or both. Tiers are distinct from slabs: slabs represent a subdivision of the reticular nucleus relating to a part of any one cortical area or thalamic nucleus. Slabs are experimentally definable and have no functionally recognizable boundaries. (B) Only a single tier can be recognized in the thalamic reticular nucleus of cat and rabbit. Both first-order (yellow) and higher-order (blue) thalamic relays project to this single sector, which is shown as green. The cortical areas, again shown as horizontal and vertical lines, show complete overlap in the reticular nucleus. Connections in the rat resemble those shown in A and are not illustrated. (C) Three tiers can be recognized in the auditory sector of the TRN. A central tier receives from the first order nucleus (brown) and from a part of the first-order cortex (horizontal stripes). Inner and outer tiers receive from higher-order thalamus (black) and from parts of first-order cortex (horizontal stripes), and from the whole of higher-order cortex (vertical stripes).

Comparisons with other species should prove especially valuable.

The anterior parts of the reticular nucleus

The anterior parts of the reticular nucleus include a motor sector connected topographically to motor cortex and ventrolateral thalamic nucleus in rat and monkey^{14,38}. In the monkey there is evidence for slabs from motor cortex, but connections to other motor areas remain to be defined. The most rostral pole of TRN has topographically mapped connections to limbic cortex and to the anterior thalamic nuclei in the rat^{13,39}. These can be regarded as first-order circuits that are driven from the mamillothalamic tract. They show no slabs, suggesting that there are some different organizational principles in this region. Higher-order circuits are represented by connections to the laterodorsal and mediodorsal nuclei, and possibly by connections to the midline and intralaminar nuclei⁴⁰. A single reticular cell can send axonal arbors to lateralis dorsalis and anterodorsalis (D. Pinault and M. Deschênes, pers. commun.), perhaps comparable to the dual projection described for the somatosensory sector. The reticular connections of these important parts of thalamocortical pathways, dealing with higher functions of frontal and limbic cortex, are still largely undefined and merit detailed study. They are likely to illuminate the way in which the relevant cortical areas relate to each other.

Functional implications

At present, evidence on details of reticular connections is incomplete. One reason for writing this article is to stress the importance of defining the connections. It is clear that no simple general rule governing cortical and thalamic connections in TRN applies to all sectors. Each sector appears to follow distinct rules. To understand how any one sector responds to its several inputs and then produces modulatory effects in the thalamus, we have to look at its particular pattern of organization. A clue to understanding reticular connectivity could perhaps be seen in the visual sector, on the basis of the special importance of central vision. In TRN this is where the first- and higher-order pathways are immediately adjacent to each other, so that there is likely to be some interaction between the two pathways for central vision. In contrast to this, the somatosensory systems of cat and rabbit have nothing that corresponds to central vision: the parts of the body are treated as more or less equivalent, and first- and higher-order pathways interact in all parts of TRN in approximately the same way. The rat, with its large vibrissal input, might treat this more like an area centralis, showing some of the reduplication around a sensory focus that characterizes the visual pathways. The auditory sector is perhaps the most puzzling. One would have expected a correspondence between the representations from first-order MGv and A1, because there is a topographically organized projection from MGv to A1. Instead there would appear to be a central portion of A1 that relates to the first-order thalamic inputs, and two outer sectors of A1 relating to higher-order thalamic inputs. We do not know what particular aspects of auditory function are mapped in the connections that have been described for *Galago*, but it is reasonable to look for local differences in the properties of cortical area A1 that do not correspond to anything seen in the medial geniculate nucleus. There is evidence in species other than *Galago* of a non-uniform distribution of properties such as bandwidth values,

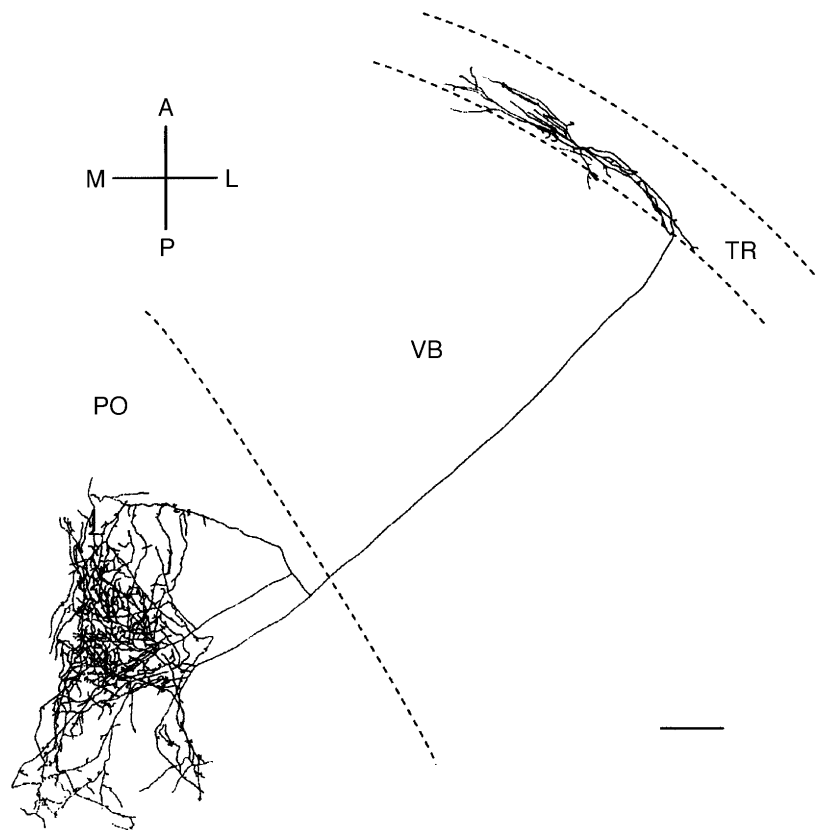


Fig. 5. Cell from the thalamic reticular nucleus, filled with biocytin to show the dendritic arbor and the axonal terminals in the ventrobasal nucleus. From Pinault et al.¹² PO, posterior group; TR, thalamic reticular nucleus; VB, ventrobasal complex.

frequency scatter and threshold scatter, which all show minima for a central part of cortical area A1 (Ref. 41). These variables have not been defined for *Galago*, and it is likely that studies of reticular connections in cat or primate, where more is known about thalamic and cortical auditory functions, will help to clarify the significance of the connections.

We suggest that details of connectivity in each sector of TRN merit close attention because they will reveal how the parts of any one group of thalamocortical pathways, whether implicated in attentional mechanisms⁴², or in other mechanisms that have yet to be defined, interact to control thalamocortical transmission in related thalamic relays. We need to know the topographical relations of first- and higher-order pathways in each sector, and we also need to understand the details of their synaptic organization within TRN. How do thalamic and cortical afferents relate to individual reticular cells? There is evidence that thalamic fibers have larger terminals ending closer to the reticular cell body than do cortical fibres (Ref. 3 and D. Lozsádi and R. Guillery, unpublished observations), but whether or not this pattern is common to all of TRN and is the same for first- and higher-order circuits is undefined. The extent to which reticular dendrites cross the boundaries of tiers has not been defined, nor do we know how the oriented arbors of reticular cells relate to small or large slabs. The specificity and complexity of the inputs to individual reticular cells still remains to be studied, as do details of possible connections between cells in TRN (Ref. 43).

Concluding remarks

The organization of TRN involves the interaction of several thalamocortical circuits for each functionally

distinct sector of TRN. We have discussed two cortical areas and two thalamic nuclei for each sector, but generally more cortical areas and more thalamic nuclei are involved in any one sector. The important point is that each sector provides a nexus for the interaction of several thalamocortical and corticothalamic circuits, and will prove to be a key site where many cortical areas concerned with one modality can interact. The nature of interactions in this nexus is likely to prove crucial for the cortical and reticular control of relay properties of thalamic cells as these switch from one mode of firing to another, possibly changing as attentional foci shift across cortical areas and within cortical areas. It has recently been shown that the pattern of thalamic reticular connections to the auditory thalamus of the cat resembles that of the somatosensory pathways in this species⁴⁴. However, the cortical connections in the auditory sector of the cat have not yet been defined.

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Acknowledgements

This work was supported by grants from the Wellcome Trust and the NIH (EY11494). We thank Dr D. Pinault for a critical reading of the manuscript.

Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates

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There are two views as to the character of basal-ganglia processing – processing by segregated parallel circuits or by information sharing. To distinguish between these views, we studied the simultaneous activity of neurons in the output stage of the basal ganglia with cross-correlation techniques. The firing of neurons in the globus pallidus of normal monkeys is almost always uncorrelated. However, after dopamine depletion and induction of parkinsonism by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), oscillatory activity appeared and the firing of many neurons became correlated. We conclude that the normal dopaminergic system supports segregation of the functional subcircuits of the basal ganglia, and that a breakdown of this independent processing is a hallmark of Parkinson's disease.

Trends Neurosci. (1998) 21, 32–38

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ALTHOUGH THE CRUCIAL ROLE played by the basal ganglia in the pathogenesis of various movement disorders such as Parkinson's and Huntington's diseases has been known for many years^{1,2}, the basic mechanisms of information processing by the basal ganglia in health

and disease are still under debate. Here, we first highlight the open questions on information processing by the basal ganglia and then summarize our studies of the simultaneous activity of several neurons in the basal ganglia of normal and parkinsonian primates. Finally,