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Introduction

1.A. Thalamic Functions: What Is the Thalamus, and What Does It Do?

1.A.1. The Classical View of the Thalamus

The thalamus is the major relay to the cerebral cortex. It has been described as the gateway to the cortex. Almost everything we can know about the outside world or about ourselves is based on messages that have had to pass through the thalamus. The thalamus forms a relatively small structure on each side of the midline (figure 1.1) and can be divided into several distinct cell groups, or “nuclei,” each concerned with transmitting a characteristic type of afferent signal (visual, auditory, somatosensory, cerebellar, etc.) to a structurally and functionally distinct, corresponding area or group of areas of the cerebral cortex (figures 1.2 and 1.3) on the same side of the brain. The thalamus relates to the largest part of the cortex, the neocortex, and it is the relationships between thalamus and neocortex that are explored in this book. Other areas of cortex, olfactory cortex and hippocampal cortex, are not neocortex and do not receive comparable thalamic afferents. Olfactory afferents represent the only pathway of a sensory system that does not have to go through the thalamus before it can reach the cortex.

This view of the thalamus was developed during the 70-plus years up to about 1950. It has served us well, and is still the view presented in most textbooks. It was based on clinical observations related to post-mortem study of the brain and on relatively crude experimental neuroanatomical methods: the Nissl method, which shows the distinct nuclei in normal material and shows them undergoing degenerative changes after their axons in the cortex have been cut, and the Marchi method, which stains degenerating myelin in pathways that have been cut or injured. These methods give results in terms of large populations

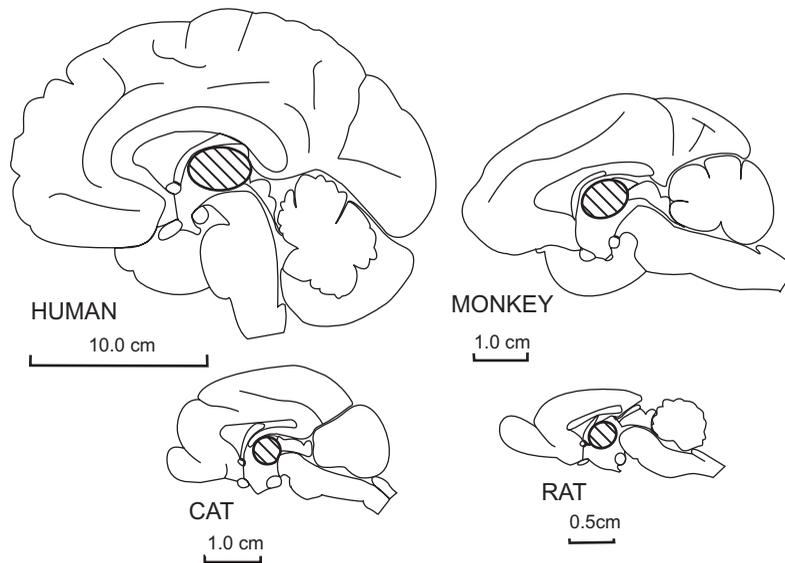


Figure 1.1

Midsagittal view of the cerebral hemisphere of a human, a monkey, a cat, and a rat (in inverse size order) to show the position and relative size of the thalamus, which is indicated by diagonal hatching.

of cells or axons and large areas of thalamus or cortex. Perhaps it was fortunate that modern methods for studying detailed connectivity patterns of single cells or small groups of cells were not available when the thalamic connections were first being defined. If they had been, it is probable that no one would have been able to see the larger thalamic forest for the details of the connectional trees. We shall start with the forest.

The schematic view of thalamocortical relationships, summarized in Walker's great book (Walker, 1938) and in Le Gros Clark's earlier review (Le Gros Clark, 1932), provided a powerful approach to understanding thalamic function. Even though it was heavily dependent on relatively gross methods, this schematic view showed how to divide up the thalamus and how to relate each of the resulting major thalamic nuclei or nuclear groups to one or another part of the cerebral cortex (see figures 1.2 and 1.3). Above all, this classical view of the thalamus showed how the functions of any one part of the neocortex depend on thalamocortical inputs. We present the basic structure of the classical view of the thalamus in the next section, where we provide an abbreviated account

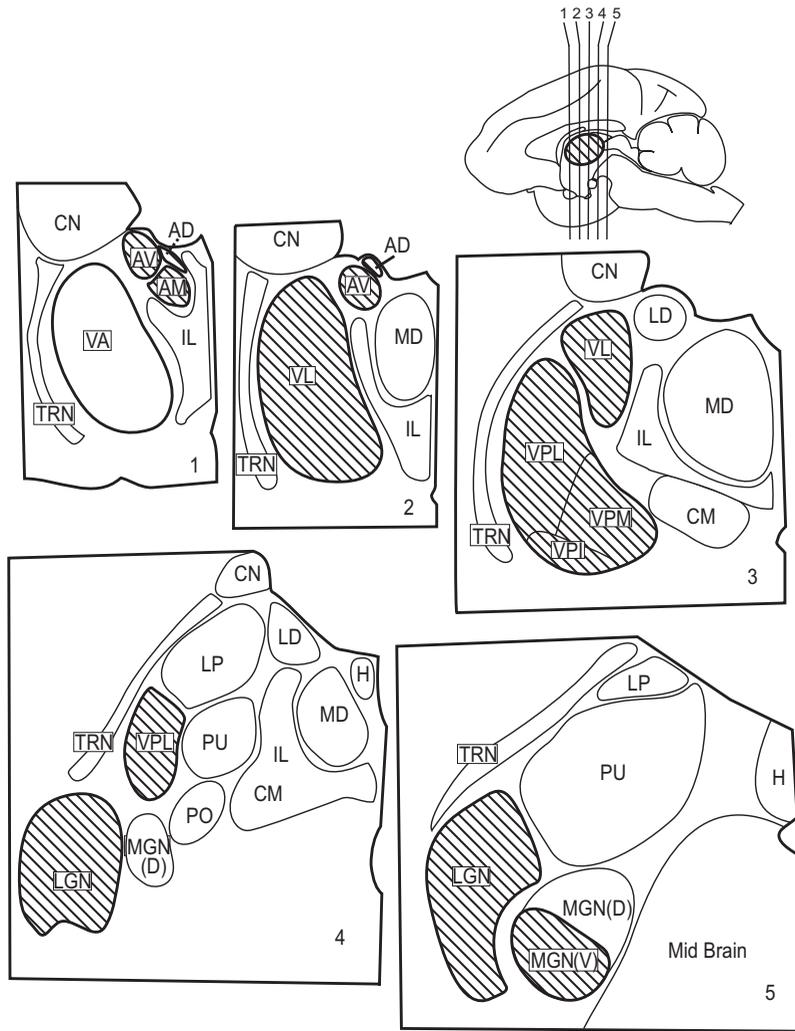


Figure 1.2

Schematic view of five sections through the thalamus of a monkey. The sections are numbered 1 through 5 and were cut in the coronal planes indicated by the arrows in the upper right midsagittal view of the monkey brain from figure 1.1. The major thalamic nuclei in one hemisphere are shown for a generalized primate. The nuclei that are outlined by a heavier line and filled by diagonal hatching are described as first order nuclei (see text), and the major functional connections of these, in terms of their afferent (input) and efferent (output) pathways to cortex, are indicated in figure 1.3. Abbreviations: AD, anterior dorsal nucleus; AM, anterior medial nucleus; AV, anterior ventral nucleus; CM, center median nucleus; CN, caudate nucleus (not a part of the thalamus); H, habenular nucleus (part of the epithalamus); IL, intralaminar (and midline) nuclei; LD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; LP, lateral posterior nucleus; MD, medial dorsal nucleus; MGN, medial geniculate nucleus; PO, posterior nucleus; PU, pulvinar; TRN, thalamic reticular nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPI, VPL, and VPM, inferior, lateral, and medial parts of the ventral posterior nucleus.

Note: The ventral anterior nucleus, although in receipt of some cerebellar afferents, receives significant driver inputs from cortex and is therefore not shown as a first order nucleus.

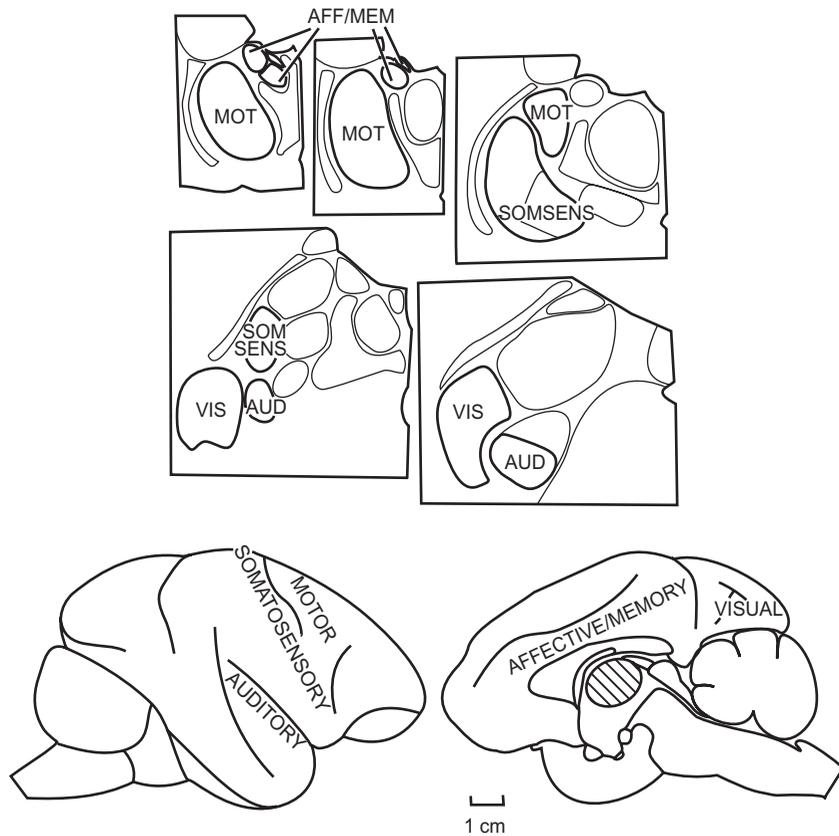


Figure 1.3

The upper part of the figure shows the nuclei illustrated in figure 1.2 and the lower part shows a lateral (left) and a medial view of the hemisphere in a monkey to indicate the functional connections of the major first order thalamic nuclei.

of the major thalamic nuclei, their functions, and their afferent and efferent connections.

Although this classical view of thalamic nuclei provides a useful practical guide, it is, after more than 70 years of refinement, added detail, new terminology, and the demonstration of ever more complex connectivity patterns, which will be introduced in the later parts of this book, beginning to be less useful than it was in the past.

1.A.2. Defining Thalamic Nuclei

The concept of the thalamic nucleus as a single structural, functional, and connectional entity has barely survived advancing techniques and new information. We stay with the thalamic nuclei as one of our prime analytical tools because, as yet, we have little to use in its place. Almost any one of the classical thalamic nuclei can be shown to be made up of several functionally and connectionally distinct cell types; many recent staining methods reveal functionally distinct cell groupings or scattered cell types that cut right across classical nuclear borders. There are cells scattered through the nuclei that simply do not fit the classical rules, and there are puzzling borders between nuclei where one has learned to be on the lookout for novel and surprising connections. It is probable that eventually we will have to treat the pathways that go through the thalamus to cortex in terms of many functionally distinct parallel pathways, several of which may often share a single nucleus, even though they may show no significant interactions within the shared nucleus.

We stress these exceptions as a warning, not because we devote a significant part of the book to them, and not because we have insights that allow us to fit them into new interpretative views of the thalamus, but because we recognize, and think it important for the reader to recognize, that the schematic representation of the thalamus presented in the next section in terms of its nuclei is inadequate. However, it is the best we have at present. This book is not planned to present the thalamus in classical terms, nor is it planned to explore the inadequacies of the classical nuclei in any detail. We start with the classical picture of the thalamic nuclei and their connections because that is still the best starting point, but we have other aims for the book. There follows a brief outline of these aims to orient the reader and to provide a rough guide that will explain the nature of and the need for the rather detailed analysis provided in the rest of the book.

1.A.3. Major Topics Addressed in This Book

A key question concerns the thalamic circuitry that acts on messages arriving along the input pathways and sends them on as outputs to cortex, giving each recipient cortical area particular and characteristic functional properties. Although we recognize that there are differences between the parts of the thalamus (and between species) in the detailed circuitry, we stress that the thalamus is a developmental and a functional

unit and that there is a common, basic plan, from one nucleus to another, made plain especially by physiological recordings from thalamic cells and by studies of the morphological detail of the cells and their interconnections. This basic plan allows us not only to trace how messages pass through the thalamus, but also to look at how thalamic circuitry allows transmission to be modified in relation to current behavioral needs or constraints. This requires a close examination of the cells in the thalamus, the relay cells that send their axon to the cortex, and also the local interneurons that act on the relay cells. The circuitry is complex and depends not only on the precise connections that are established but also on the transmitters, the receptors, and the membrane properties that are involved in the synaptic interactions in the thalamus. Further, understanding thalamic circuits requires identification of the functionally significant input.

It may seem surprising that, for a large part of the thalamus, we know little about what the crucial input for transmission to cortex actually is. It is important to distinguish the functional input that carries the messages for transmission to the cortex, which we call the driver, from the many other inputs, the modulators, which can modify the way in which the message is transmitted without significantly changing the basic functional characteristics of the message that reaches cortex. Thus, for the main sensory relays of the thalamus (visual, auditory, somatosensory), the drivers bring messages about the relevant sensory events. Identifying functional and morphological criteria that will help to distinguish drivers from modulators becomes of prime importance. One such criterion, which in terms of classical views of the thalamus is surprising, is that in the thalamus, where neurons do not fire at very high rates, inhibitory axons cannot, for reasons outlined in chapter 7, be drivers.

Throughout the thalamus, modulators far outnumber drivers in terms of the numbers of synaptic connections, and once rules for recognizing drivers are established, then it becomes clear that much of the thalamus, whose connections were largely undefined in the past, receives its drivers not from subcortical centers but from cerebral cortex and is therefore concerned with sending messages from one cortical area to another. The importance of this pathway, which allows one cortical area to receive inputs from another cortical area through a thalamic relay that can be modulated in accordance with behavioral constraints, is not widely appreciated and has been but poorly explored.

Once we think of the thalamus in terms of the functionally distinct driver pathways that pass through it, we can begin to see one alterna-

tive to the classical nucleus. That is, we can start to think of the thalamus, or of any one part of the thalamus, often one of the classical nuclei, as a relay for transmitting information to cerebral cortex along functionally parallel driver pathways. Where such pathways lie in close relationship to each other, we have to ask about the nature of possible interactions. We also have to consider interactions between the parts of any one such pathway.

Many of the functional pathways through the thalamus, possibly all of them, are mapped. That is, there is a topographic order to the inputs, the thalamic circuits, and the thalamocortical outputs that we refer to as *local sign*. Understanding the maps in any one pathway allows for an investigation of how the parts relate to each other, and knowing the maps in two or more related parallel pathways provides clues as to how these may interact. Currently there is little evidence for such interactions between functionally distinct parallel pathways within a thalamic nucleus, but critical evidence is lacking for most of the thalamus. However, for any one functional mapped pathway, lateral interactions occur, either in the thalamus itself or on the way to the cortex.

One important feature that becomes apparent once one identifies the functional drivers for the many distinct parallel pathways that pass through the thalamus is that many of the drivers, possibly all, give off branches to centers in the spinal cord or brainstem concerned directly or indirectly with the control of movement. This branching pattern leads us to consider the thalamus not just as a sensory relay in the classical sense but rather as also bringing to cortex information about current motor instructions. We apply this view not only to the ascending pathways going to primary cortical sensory areas but also to the transthalamic corticocortical pathways (described earlier), which are then seen as carrying to higher cortical areas information about the current outputs of lower cortical areas.

When it is recognized that the classical “sensory” functions are intimately linked to instructions that are on their way to motor centers even before the sensory messages can reach the cerebral cortex, it becomes necessary to look at a conundrum long discussed by philosophers—how perceptual processes may be linked to action. In the final chapter we consider this problem. We cannot address all of the issues that have been discussed on this subject, but we can cast a new light on them by showing that there are anatomical connections that speak directly to the often puzzlingly close link between action and perception.

1.B. Thalamic Nuclei and Their Connections: The Classical View

Figure 1.1 shows the thalamus in relation to the rest of the cerebral hemisphere. The thalamus is small relative to the whole cerebral hemisphere in all mammals. There are a great many more neocortical cells than there are thalamic cells, even though the neocortex depends on the thalamus for its major inputs.¹ Each major neocortical area depends on a well-defined thalamic nucleus or group of nuclei, and these nuclei in turn receive their input from a well-defined path into the thalamus. In the evolutionary history of mammals, an increase in the size of any one part of cortex generally corresponds to an increase in the related thalamic nuclei. The functionally best-defined cortical areas (visual, auditory, motor, etc.) depend for their functional properties on the messages to that cortical area from the thalamus. The visual cortex is visual because it receives visual messages from the retina through its thalamic relay, and this relationship holds for the other thalamic nuclei outlined in bold and hatched in figure 1.2, which shows some of the major thalamic nuclei in a simplified, schematic form for a generalized primate.

Details concerning the thalamic nuclei differ for each species, and there are a number of nuclei that are not included in figure 1.2 because they play no significant role in the rest of this book. However, the general relationships shown apply to all mammals. Figure 1.3 shows how some of these major thalamic nuclei are linked to specific, functionally or structurally defined cortical areas. Further details on individual thalamic nuclei and their connections can be found in Berman (1982) and Jones (1985).

Figures 1.2 and 1.3 show that for some, but by no means all, of the thalamic nuclei, we can identify the dominant or functionally “driving” afferents. That is, figure 1.3 shows that the lateral geniculate nucleus is visual, the medial geniculate nucleus is auditory, and the

1. From the evidence available for the geniculocortical pathway to the primary visual cortex (variously called V1, area 17, or striate cortex) it appears that there are about $350\text{--}460 \times 10^6$ cortical nerve cells in V1 of each hemisphere in the monkey, and about $55\text{--}70 \times 10^6$ in the cat. The numbers of nerve cells for one lateral geniculate nucleus are about 1.6×10^6 and 0.45×10^6 , respectively. Since not all geniculate cells project to V1, the projecting geniculate cells represent 0.5% or less of the total number of cortical cells in the area receiving the projection. See Rockel et al. (1980) for cell densities in cortex, Duffy et al. (1998) for area V1, Matthews (1964) for cell numbers in the monkey lateral geniculate nucleus, and Bishop et al. (1953) for the cat.

ventral posterior nucleus² is somatosensory, which is to say that the ascending pathways concerned with tactile stimuli and with stimuli related to body position and movements (kinesthesia) go to this nucleus, as do pathways concerned with pain and temperature. We treat these several sensory pathways as the “drivers,” because they are the afferents that determine the receptive field properties of the thalamic relay cells that pass the messages on to cortex. Other afferents, which we treat as “modulators,” can modify the way that the message is transmitted, but they are not responsible for the main qualitative nature of the message conveyed to cortex. Each thalamic nucleus has drivers and modulators, and identifying the drivers for thalamic nuclei whose function is still poorly defined is likely to be a key to understanding their functions. For reasons detailed in chapter 3, we treat the afferents from the cerebellum to the ventral lateral and ventral anterior nuclei as drivers related to movement control, and axons of the mamillothalamic tract as drivers sending information to the anterior thalamic nuclei about ongoing activity in the mamillary bodies. These, and the main sensory afferents mentioned earlier, represent the major known ascending driver inputs to the thalamus. Afferents to the other main thalamic nuclei, indicated with lighter outlines and no hatching in figure 1.2 and unlabeled in figure 1.3, are less straightforward; they are considered in more detail in chapters 3 and 8. These nuclei receive their major driving afferents from the cerebral cortex itself and therefore act as relays on corticocortical pathways, not as relays of subcortical afferents to cortex (Sherman & Guillery, 1996; Guillery & Sherman, 2002a). They are “higher order” relays (figure 1.4). First order relays are defined as those that send messages to the cortex about events in the subcortical parts of the brain, higher order relays as those that provide a transthalamic relay from one part of cortex to another. In primates, the nuclei that contain higher order circuits form more than half the thalamus. The relationship of these transthalamic corticocortical relays to the more widely studied direct corticocortical connections is a challenging question considered in chapters 8 and 10. It is

2. The lateral and medial parts of the ventral posterior nucleus are often referred to as part of the ventrobasal complex, and a distinction is made between a nuclear complex, or group of nuclei, and a thalamic nucleus that has no further subdivisions. The term “complex” has been rather inconsistently applied in the past and is difficult to apply rigorously; the same is true when the term “nucleus” is used to apply to a cell grouping and to its subdivisions. For the purposes of this book, these problems are not important, and we will stay with the term nucleus throughout.

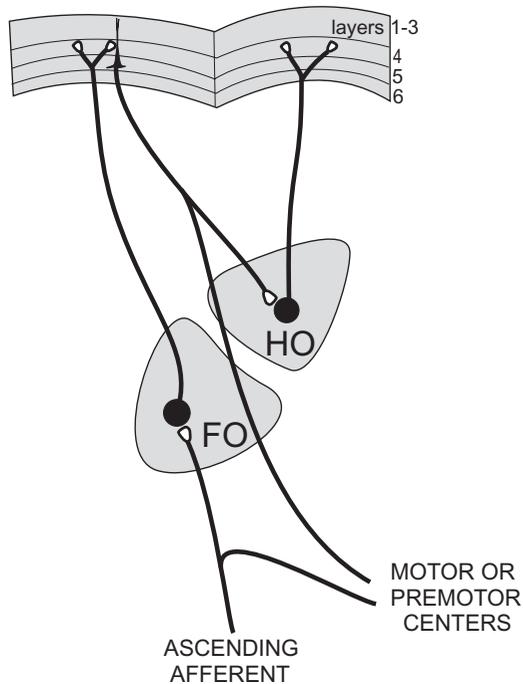


Figure 1.4

Schematic representation of first order (FO) and higher order (HO) thalamic relays. The first order relay receives driving afferents from ascending pathways, whereas the higher order relay receives driving afferents from layer 5 of the cortex. Both of these driving afferents send branches to subcortical motor or pre-motor centers.

important to stress that some of the nuclei shown without hatching in figure 1.2 are likely to contain a mixture of first and higher order relays (see chapter 8), so that it may not be appropriate to speak of higher order *nuclei* but instead to consider specific *relays*.

Although for many of the thalamic nuclei we can show how they serve to connect different cortical areas to sensory surfaces of the body or to other parts of the brain, we cannot readily demonstrate what it is that the thalamus does for the messages that are passed from ascending pathways to the cerebral cortex. Why don't the ascending pathways go straight to the cortex? This question was always present, but was brought into striking focus in the 1960s when electron microscopists showed the complexities of the synaptic relationships in the thalamus (Szentágothai, 1963; Colonnier & Guillery, 1964; Peters & Palay, 1966).

Only about 20% of the synapses in the major relay nuclei, such as the lateral geniculate or the ventral posterior nucleus, were then seen to come from the major ascending pathways (Guillery, 1969a), and recent figures are significantly lower (Van Horn et al., 2000). Complex synaptic formations involving serial synapses and connections from local or distant inhibitory cells characterize all of the thalamic nuclei (e.g., Jones & Powell, 1969; Ralston & Herman, 1969; Morest, 1975; Jones, 1985), and most thalamic nuclei, in accordance with their shared developmental origin, have more or less the same general organizational plan.

The complexity of thalamocortical pathways was further increased by the demonstration of the connections shown in figure 1.5. Not only is there a massive input from the deeper layers of the cerebral cortex back to the thalamus, but there is a specialized cell group adjacent to the thalamus, the thalamic reticular nucleus, which receives excitatory branches from the corticothalamic and thalamocortical axons and sends inhibitory axons back to the thalamus (Jones, 1985).

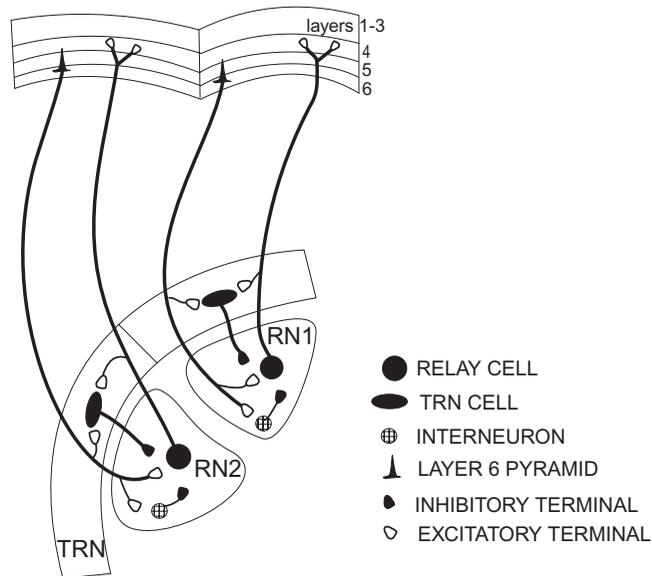


Figure 1.5

Schematic view of the interconnections of two thalamic relay nuclei (RN1, RN2) layer 6 of the cerebral cortex, and the thalamic reticular nucleus. Thalamic nuclei RN1 and RN2 are connected with distinct sectors of the reticular nucleus and with distinct cortical areas. Details of the connections within the nuclei are discussed in chapter 3 (see figure 3.16).

The functional role of the reticular connections and of the complex synaptic arrangements found in the thalamus represented (and still represents) a challenging puzzle, a challenge that was greatly increased in recent years by the discovery of diverse transmitters, voltage and ligand gated ion channels, and receptors that contribute to the synaptic organization in the thalamic relay (see Sherman & Guillery, 1996, and chapters 4 through 6). The functional control of membrane conductances depends on a highly complex interplay of afferent activity and local conditions that will be considered in chapter 4. These conditions in turn determine the way in which a thalamic cell responds to its inputs, and thus determines how messages that come into the thalamus are passed on to cortex. This, the manner in which a thalamic cell passes messages on to cortex, is not constant but depends on the attentive state of the whole animal (awake, drowsy, or sleeping), and probably on the local salience of a particular stimulus or group of stimuli, as well; are the stimuli new, threatening, interesting, or merely a continuation of prior conditions? This question is addressed in chapter 6.

When one considers the factors relevant to how the transfer of messages is controlled or gated in the thalamus, it is probable that more than one functionally significant mechanism will become apparent once we have a clear understanding of these aspects of thalamic organization. That is, there are likely to be several more or less distinct functional roles for the synaptic arrangements present in the thalamus. Particular patterns may be active at different times, or they may have concurrent effects. Two that have received significant attention in the recent past occur in sleep and in the production of epileptic discharges (Steriade et al., 1993b; McCormick & Bal, 1997). A third aspect that has come into focus recently and is addressed in chapter 6 concerns how the role of the relays may change in relation to different behavioral states, and relate to attentional mechanisms. All three involve the circuit going through the thalamic reticular nucleus that was mentioned earlier (figure 1.5; see also Jones, 1985). We anticipate that the role of first and higher order thalamic circuits in passing messages to the cortex will follow the same basic ground rules. That is, whatever it is that the thalamus does for the major ascending pathways, it is likely to be doing something very similar for corticocortical communication. Understanding what it is that the thalamus does should help us to understand not only the functional organization of sensory pathways in relation to perception but should also throw new light on perceptual and cognitive functions that in the past were largely or entirely ascribed to corticocortical interconnections

(Zeki & Shipp, 1988; Felleman & Van Essen, 1991; Salin & Bullier, 1995).

There is one interesting corollary to the above. If the thalamus acts to control the way that information is relayed to the cortex, then it may be a mistake to expect it to act as an integrator of distinctive inputs as well. At present, the most detailed information available on thalamic relays shows that information from the ascending pathways is passed to cortex without a significant change in “content.” That is, there are thalamic nuclei that receive afferents from more than one source, but currently there is no evidence that the multiple inputs in such nuclei interact on single relay neurons to produce a significant change in the content of the input messages. The multiple pathways appear to run in parallel, with little or no interaction.

In this book we explore the way in which thalamic functions relate to cortical functions. Outputs of the thalamus that link it to other cerebral centers, particularly the striatum and the amygdala, represent a relatively small though important part of the thalamic relay. They play no role or only a very indirect role in influencing neocortical activity, and for this reason we will not explore them further. We shall argue that there is likely to be a basic thalamic ground plan that represents the way in which the thalamus transmits messages from its input to its output channels. It seems probable that this ground plan will apply to all thalamic relays, and possibly, when we understand how the thalamus relates to the cortex, the nature of the thalamic relay to other cerebral centers will help us understand the function of these currently even more mysterious pathways.

1.C. The Thalamus as a Part of the Diencephalon: The Dorsal Thalamus and the Ventral Thalamus

The term “thalamus” is commonly used to refer to the largest part of the mammalian diencephalon, the dorsal thalamus, and we generally use it in this sense in this book. However, there are several subdivisions of the diencephalon, and it is important to look briefly at all of them before focusing on just two subdivisions, the large dorsal thalamus and the smaller but closely related ventral thalamus.

Figure 1.6 shows relationships in the diencephalon at a relatively early stage of development. On the left is a view of a parasagittal section of the brain early in development, which shows that the most dorsal part of the diencephalon is the epithalamus. In the adult the epithalamus is

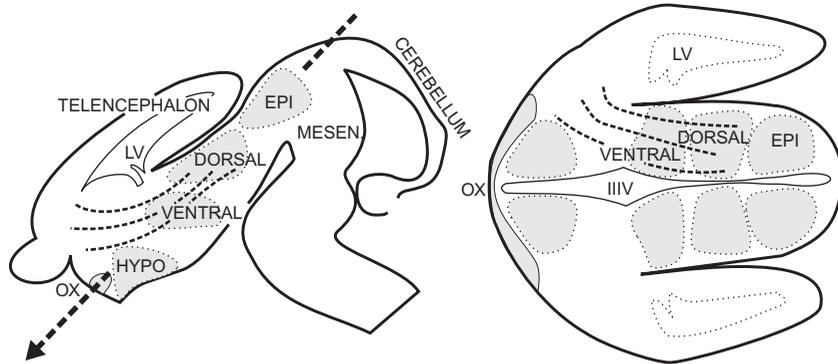


Figure 1.6

Schematic views of two sections through a 14-day postconception fetal mouse brain, based on photographs in Schambra et al. (1992). At left is a parasagittal section in which the position of the epithalamus, the dorsal thalamus, the ventral thalamus, and the hypothalamus within the diencephalon is shown (EPI, DORSAL, VENTRAL, HYPO). At right is a section cut transversely in the oblique plane (indicated by the arrow) that includes these four diencephalic parts and the optic chiasm (OX). The subthalamus is not included in these figures. The interrupted lines show the course of the fibers that link the dorsal thalamus to the telencephalon. LV, lateral ventricle; IIIIV, third ventricle.

made up of the habenular nuclei, a few other small, dorsally placed nuclei, and the related pineal body. These structures will not be of further concern to us, nor will two more ventral cell groups, the subthalamus, which is not shown in figure 1.6 and is involved with motor pathways, and the hypothalamus, which plays a vital role in neuroendocrine and visceral functions. In this book we are concerned solely with the dorsal thalamus and with a major derivative of the ventral thalamus, the thalamic reticular nucleus.³ These two are closely connected by the two-way links shown in figure 1.5, and it is reasonable to argue that neither can function adequately without the other. Figure 1.6 shows that originally, during development, the ventral thalamus lies ahead of (rostral to) the dorsal thalamus. The thick dotted lines in the schematic views in figure 1.6 stress an important relationship between the dorsal and the ventral

3. The ventral lateral geniculate nucleus is also developmentally a part of the ventral thalamus but will not play a significant role in this book. Although, like the thalamic reticular nucleus, it receives cortical afferents and does not send axons to cortex, it does not have the important connections with the dorsal thalamus that make the reticular nucleus a key part of the thalamocortical system as a whole.

thalamus, because they show that lines of communication between the dorsal thalamus and the telencephalon, which includes the cerebral cortex, must pass through the ventral thalamus. This is a key relationship and is maintained even when the ventral thalamic derivative, the thalamic reticular nucleus, moves into its adult position lateral to the dorsal thalamus, as shown in figures 1.2 and 1.3.

1.C.1. The Dorsal Thalamus

In most mammalian brains, and most strikingly in the primate brain, the dorsal thalamus is by far the largest part of the diencephalon. In size and complexity it is closely related to the development of the cerebral cortex. It can be defined as the part of the diencephalon that develops from the region between the epithalamus and the ventral thalamus. More significantly, it is the part of the diencephalon that has its major efferent connections with telencephalic structures, either striatal or neocortical. In mammals, the neocortical connections dominate, and all dorsal thalamic nuclei project to neocortex. Connections to the striatum are seen for only a few of the nuclei (primarily the intralaminar nuclei) in mammalian brains. All thalamic nuclei have relay cells, which send their axons to the telencephalon, and, with the curious exception of many nuclei in rats and mice,⁴ all have interneurons with locally ramifying axons.

1.C.1.a. The Afferents

We have seen that the first order nuclei of the dorsal thalamus receive a significant part of their afferent connections from ascending pathways. Some bring information about the environment to many of the major thalamic nuclei through sensory pathways, such as the visual, auditory, somatosensory, or taste pathways. Others bring information about activity in lower, subthalamic centers of the brain, such as the cerebellum for the ventral anterior and ventral lateral nuclei or the mamillary bodies for the anterior thalamic nuclei (figures 1.2 and 1.3). We shall argue that these afferents can be regarded as the driving inputs for their thalamic nuclei, determining the qualitative characteristics of the receptive fields

4. In a typical mammalian thalamic nucleus, roughly 15%–25% of the cells are interneurons, the remainder being relay cells. Thalamic nuclei in mice and rats appear to lack interneurons or to have only a few (Arcelli et al., 1997; but see Figure 12 of Li et al., 2003b, which shows a significant number of interneurons in the lateral posterior nucleus of a rat). The lateral geniculate nucleus of rats and mice has a normal share of interneurons, as do the thalamic nuclei of other rodent species that have been studied.

of the thalamic cells, where these can be defined. Other inputs, including all inhibitory inputs to first order nuclei, are best regarded as modulatory. These can change the way in which the message is transmitted and can affect quantitative aspects of the receptive field, but not its essential character or its qualitative structure.⁵ The modulators come from the brainstem, the thalamic reticular nucleus, the hypothalamus, the cerebral cortex itself, and the thalamic interneurons.

The thalamic nuclei not outlined in bold in figure 1.2 contain higher order circuits and appear to receive most or all of their driving afferents from the cerebral cortex itself, so that the qualitative aspects of their receptive field properties, insofar as they can be defined, depend directly on cortical, not ascending, inputs. This distinction is discussed further in later chapters, particularly chapter 8. Here it is to be noted that the higher order thalamic relays, in addition to the driving afferents that they receive from cortex, also receive modulatory afferents from cortex and from the other structures noted previously for the first order nuclei.

The distinction between corticothalamic axons that are drivers and those that are modulators can be made on the basis of the cortical layer from which they arise: current evidence suggests that corticothalamic afferents arising in cortical layer 5 are drivers, whereas those arising in layer 6 are modulators (Sherman & Guillery, 1996, 1998; see also chapter 3). In a few instances, discussed in more detail in chapter 9, this distinction between drivers and modulators can be demonstrated in functional terms by recording how inactivation of the cortical afferents affects the receptive field properties of thalamic cells, but so far these instances are regrettably rare. Silencing a cortical driver produces a loss of the receptive field, whereas after a modulator is silenced the receptive field survives. The difference between these two groups, the drivers and modulators, is seen not only in terms of their origin and their action on receptive field properties of dorsal thalamic cells, but also in terms of the structure of the terminals that are formed in the thalamus and the synaptic properties they display. This relationship is discussed in chapters 3 and 5.

5. To clarify the distinction between qualitative and quantitative receptive field properties, consider the receptive field of a relay cell of the lateral geniculate nucleus. Its classical visual properties, mainly the ocular input and the center/surround configuration, are what we would term the qualitative receptive field. Quantitative features include overall firing rate or pattern, size of the center or surround, relative strength of center or surround, etc. These quantitative features can be altered without changing the qualitative organization of the receptive field.

In summary, the thalamus can be regarded as a group of cells concerned, directly or indirectly, with passing on to the cerebral cortex information about almost everything that is happening in the central or peripheral nervous system. This includes passing information about one cortical area on to another. This relay of information is subject to a variety of modulatory inputs that modify the way the information is passed to the cortex without significantly altering the nature of that information, except where, as during slow wave sleep, it essentially prevents such information from reaching the cortex (see chapter 6).

We have seen that inhibitory inputs reach thalamic relay cells from the local interneurons and from cells in the thalamic reticular nucleus. In addition, there are some other, GABA⁶ immunoreactive, inhibitory afferents going to certain thalamic nuclei. The medial geniculate nucleus receives ascending GABAergic afferents from the inferior colliculus (Peruzzi et al., 1997), the lateral geniculate receives such afferents from the pretectum, there are GABAergic afferents from the zona incerta to higher order thalamic relays (Barthó et al., 2002; but see Power & Mitrofanis, 2002), and the globus pallidus and substantia nigra and zona incerta send GABAergic axons to the ventral anterior and the center median nucleus (Balercia et al., 1996; Ilinsky et al., 1997). The precise role of the GABAergic afferents is not well defined and is discussed further in chapter 7.

1.C.1.b. Topographic Maps

There is another basic feature of the organization of the dorsal thalamus that needs to be understood: most, possibly all, thalamocortical pathways are topographically organized. This organization is most easily seen in the visual, auditory, or somatosensory pathways, where the sensory surfaces (retina, cochlea, body surface) are represented or mapped in an orderly way in the thalamus and in the cortex, so that the pathways linking thalamus and cortex must carry these orderly maps. Even where it is not clear what is being mapped, or where the map appears not to be very accurate, as in many higher order circuits, we shall speak of mapped projections as having “local sign.”⁷ For example, there is

6. Gamma-aminobutyric acid (GABA) is the most common inhibitory neurotransmitter in the thalamus.

7. Mapped projections that represent a sensory or cortical surface have been widely described and discussed in the past. The implication is that such maps are representations that can be interpreted in terms of the detailed topography of their source, and the expectation has been that such maps, to be useful,

evidence for local sign for the whole of the pathways from the mammillary bodies through the anterior thalamus and to the cingulate cortex (Cowan & Powell, 1954), although it is not clear exactly what function is being mapped for most of this pathway.

Strictly speaking, a connection that shows no local sign can be regarded as a “diffuse” projection, but this term is often used rather loosely. Quite often the term is used (see Jones, 1998) to refer to a pathway that shows local sign but has significant overlap of terminal arbors or relatively large receptive fields. It is better to keep the term diffuse for a pathway that demonstrably lacks local sign. This means that the relationship between the cells of origin and the terminal arbors is essentially random in topographic terms, a relationship that is not easy to demonstrate. Mostly the term has been used where experiments based on relatively large lesions or injections of tracers fail to show topography for terminals or cells of origin, or where large receptive fields have been recorded and their topographic ordering has been difficult to discern. Any organization with large receptive fields and a crude local sign must be regarded as topographic rather than diffuse. It is probable that all driver afferents and many modulatory afferents have local sign. Some of the modulatory afferents coming from the brainstem will prove to be truly diffuse, but it is likely that others have local sign (Uhlrich et al., 1988).

A further distinction has to be made between an afferent system that is diffuse and relatively global, terminating throughout the thalamus, and one that is diffuse but has terminals that are limited to a single thalamic nucleus or a few specific terminal zones. Those that terminate throughout the thalamus can be regarded as global from the point of view of thalamic organization in general, whereas others that are limited to a few parts of the thalamus, possibly associated with one sensory modality, are to be seen as specific, although they may prove to be diffuse in the sense of lacking local sign within their specifically localized terminal sites.

It should be clear that within a diffuse projection any one afferent fiber may be limited to a small part of the total terminal zone of that

must have relatively small receptive fields. Large receptive fields have been represented as evidence for the lack of a map in a pathway. However, so long as receptive fields do not match the total projection, if they are arranged in a topographic order, then, no matter what their size, we shall treat them as a part of a projection that has local sign. We could refer to “crude maps” and “accurate maps,” but we stress the importance of “local sign” because there often is a reluctance to recognize a mapping in a pathway that simply allows a distinction between up and down, left and right.

projection without this revealing anything about the nature of the projection as a whole. It could be a part of a diffuse global pathway, or it could be a part of a mapped projection to a specific terminal region. In contrast, a single cell that sends axonal branches to different parts of a single established map should be regarded as a part of a diffusely organized projection. As the role of the modulatory pathways in the control of thalamic functions becomes defined, these perhaps arcane distinctions are likely to prove functionally highly significant.

The mapped projections between the thalamus and the cortex are of interest not only because they show how a group of thalamic cells relates to a group of cortical cells, but also because they impose important constraints on the pathways that link thalamus and cortex, and these constraints are likely to influence the connections made in the thalamic reticular nucleus as the fibers pass through it on the way to or from the cortex. If the thalamocortical and corticothalamic connections were both simple one-to-one relationships between a single thalamic nucleus and a corresponding single cortical field, then the topographic mapping of the pathways could be carried out by two simple sets of radiating connections, one coming from the thalamus and the other going to the thalamus, meeting each other on the way, as has been proposed by Molnár et al. (1998). The connections of the reticular nucleus lying on this pathway would then relate to this simple radiating pattern, with little interaction between adjacent sectors. However, the real-life situation is far more complex. Single thalamic nuclei can connect to several cortical areas, and vice versa, for both the driving and the modulatory connections. And many of the cortical maps are mirror reversals of each other, as are some of the thalamic maps. Figure 1.7 shows two adjacent cortical areas carrying mirror-reversed topographic maps (represented by 3, 2, 1 and 1, 2, 3 in the cortex) and connected to a single thalamic nucleus. In the cat, relationships in the visual pathways between areas 17 and 18 and the lateral geniculate nucleus show precisely this arrangement. In figure 1.7, the modulatory corticothalamic axons going from layer 6 of the cortex to the thalamus show that the mapping between thalamus and cortex requires complex crossing of the axon pathways. It should be clear that if all of the thalamocortical and corticothalamic pathways, which for any one modality often include several thalamic nuclei or subdivisions and several cortical areas, had been included in the figure, the result would show a complex system of crossing and interweaving axon pathways between the thalamus and the cortex. In the adult, some of this crossing occurs in the region of the thalamic reticular nucleus, as shown

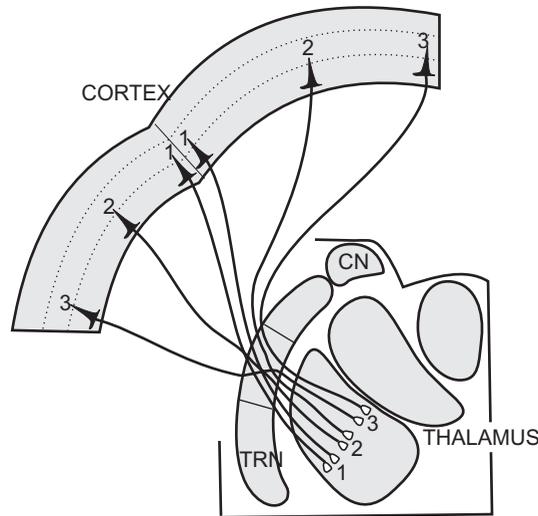


Figure 1.7

Schematic views of a coronal section through thalamus and cortex to show a single thalamic nucleus such as the lateral geniculate nucleus receiving corticothalamic afferents from two cortical areas. The topographic order of the projections is indicated by the numbers 1–3, and the two cortical representations are shown, as they often are, as mirror reversals of each other. The axons cross in the thalamic reticular nucleus, which is not labeled.

in the figure (Adams et al., 1997), and some occurs just below the cerebral cortex (Nelson & LeVay, 1985). The complex crossings are of interest because they establish a potential for connections in the reticular nucleus between the several maps present in the thalamocortical pathways of any one modality.

To summarize the main points presented so far, the dorsal thalamus can be subdivided into nuclei. Each nucleus sends its outputs to neocortex, and each nucleus receives different types of afferents, some classifiable as drivers, others as modulators. Many of these connections are mapped, and the multiplicity of maps leads to complex interconnections in the thalamic reticular nucleus, the major part of the ventral thalamus.

1.C.2. The Ventral Thalamus

The main part of the ventral thalamus lies directly on the pathways that link the dorsal thalamus to the telencephalon, either the striatum or the

neocortex. Figure 1.6 shows that axons do not pass in either direction between thalamus and telencephalon without going through the ventral thalamus. One important difference between the ventral and the dorsal thalamus is that the ventral thalamus sends no axons to the cortex. In mammals, the major part of the ventral thalamus forms the thalamic reticular nucleus, which was briefly introduced earlier. A smaller part forms the ventral lateral geniculate nucleus, which appears to have specialized roles related to eye movements but is of no further concern here.

As pointed out earlier and shown in figures 1.5 and 1.6, the thalamic reticular nucleus is strategically placed in the course of the axons that are going in both directions between the cerebral cortex and the thalamus. Although the positions of ventral relative to dorsal thalamus change as development proceeds, both sets of axons continue to relate to the ventral thalamic cells, and in the adult, many of them give off collateral branches to the cells of the reticular nucleus. The reticular cells in turn send axons back to the thalamus, roughly to the same region from which they receive inputs. The cortical and thalamic afferents to the reticular nucleus are predominantly excitatory (but see Cox & Sherman, 1999), and the axons that go back from the reticular nucleus to the thalamus are inhibitory (summarized in Jones, 1985). Through these connections the reticular nucleus can play a crucial role in the transmission of information through the thalamic relay to the cerebral cortex.

Although the reticular nucleus has a relatively homogeneous structure, it can be divided into sectors that connect to particular thalamic nuclei or groups of thalamic nuclei and the cortical area to which they connect. Thus, visual, somatosensory, auditory, and motor sectors can be identified, as well as a sector related to the cingulate cortex. Not only do the cells within each of the functionally distinct sectors of the reticular nucleus lie in a key position in terms of their connections, with pathways going in both directions between cortex and thalamus, they also lie in a region where many of these axons undergo some of the complex interweaving discussed earlier. Major changes in the topographic organization of thalamocortical interconnections occur in and just adjacent to the region of the thalamic reticular nucleus, and this pattern of interweaving axons gives the reticular nucleus its characteristic reticulated structure. This structure also contributes to important aspects of the function of the reticular nucleus, because we shall see that within any one sector of the nucleus, connections from more than one thalamic nucleus (first and higher order) and from more than one functionally related cortical area are established. Kölliker (1896), more than 100

years ago, recognized the crossing bundles and called the nucleus the *Gitterkern*, from the German word *Gitter*, for lattice. These axonal crossings and interweavings put the reticular nucleus in a position where the cells within any one sector can serve as a nexus, relating several different but functionally related thalamocortical and corticothalamic pathways to each other.

The thalamic reticular nucleus was for many years considered to have a diffuse organization and to lack the well-defined maps seen in the dorsal thalamus. More recent evidence has shown that in spite of the complex network that characterizes the nucleus, there are maps of peripheral sensory surfaces and of cortical areas within the reticular nucleus (Montero et al., 1977; Crabtree & Killackey, 1989; Conley et al., 1991; Crabtree, 1996). Understanding these maps and how they relate to each other and to the maps within the main thalamocortical pathways is likely to prove a key issue in future studies of the thalamic reticular nucleus.

There is one nucleus that is generally treated as part of the thalamic reticular nucleus and that has a distinct name and may have a distinct developmental origin. This is the perigeniculate nucleus, present in dogs, cats, ferrets, and other members of the order Carnivora. It lies between the reticular nucleus and the dorsal lateral geniculate nucleus, and many of the observations reported for reticular cells and connections have in fact been made in cats or ferrets on the perigeniculate nucleus. Perigeniculate cells show many of the same connections and functional properties as do reticular cells in rodents or primates, and throughout this book we treat the perigeniculate nucleus as a part of the reticular nucleus. However, there are some reasons for thinking that this generally accepted identity may be an oversimplification. This issue is considered in more detail in chapter 9.

1.D. The Overall Plan of the Next Ten Chapters

There are many (more than 30) individually identifiable nuclei in the thalamus, and it is probable that in any one species, each one has a more or less distinctive organization. Further, it is well established, and not surprising, that there are significant differences between species for any pair of homologous nuclei. For example, we noted that the perigeniculate nucleus characterizes members of the order Carnivora, and that some rodents lack interneurons. Some nuclei may receive their primary afferents from just one set or group of axons, whereas other nuclei

receive afferents from more than one functionally distinct set of primary afferent or driver pathways. Details of transmitters, receptors, and calcium-binding proteins differ to a significant extent from one nucleus to another, so that it may seem that a book on the thalamus must necessarily be a compendium of details about many individual nuclei. Even if such an account of the many differences among thalamic nuclei were to be limited to commonly used experimental animals, it would form a very heavy and singularly boring volume.

In the following chapters we present accounts of some of the major known structural and functional features of the thalamus. In the early chapters we introduce many of the relevant facts and start to look at interpretations, but our major interpretations are presented in detail in the later parts of the book. We have planned this book to be focused on questions about the functional organization of the thalamic relay in general, and we are especially interested in how this relay operates during normal, active behavioral states. As far as we can, we shall be looking for a common plan of thalamic organization that can serve as a basis for understanding any of the thalamic nuclei. Differences between nuclei can then be seen as opportunities for looking at the possible functional significance of one type of organization relative to another. Much of our discussion is focused on the visual relay through the lateral geniculate nucleus and will extend to other sensory relays, particularly the somatosensory and the auditory relays, as we look for common patterns and detailed differences. These nuclei are, at present, the best-studied thalamic nuclei, and details available for these sensory relays are often not available for the majority of thalamic nuclei.

The visual relay through the lateral geniculate nucleus has received very considerable attention over the years. In part this relates to the fact that we know a great deal about the organization of its input in the retina and about its cortical recipient area, the visual cortex (Hubel & Wiesel, 1977; Martin, 1985; Dowling, 1991; Rodieck, 1998; for more recent overviews see Callaway, 2004; Copenhagen, 2004; Ferster, 2004; Freeman, 2004; Nelson & Kolb, 2004; Sterling, 2004), so that it has been of particular interest to study the thalamic cell group that links these two. Not only has the intrinsic organization of the nucleus received detailed attention, but its reaction to varying, complex regimes of visual deprivation has taught us a great deal about the plasticity and development of thalamocortical connections (Wiesel & Hubel, 1963; Sherman & Spear, 1982; Shatz, 1994; Rittenhouse et al., 1999; Berardi et al., 2003; Heynen et al., 2003). In part the interest in the visual relay relates

to the intrinsic beauty of the lateral geniculate nucleus, most evident in primates and carnivores, where mapped inputs from the two eyes are brought into precise register in distinct but accurately aligned layers (Walls, 1953; Kaas et al., 1972a; Casagrande & Xu, 2004). We explore this arrangement in later chapters to a limited extent. Primarily, we use current knowledge of the visual relay in the thalamus to lead to general questions about thalamic organization, first in other sensory pathways and then in thalamic relays more generally.

In the next two chapters we first consider the nerve cells of the thalamus (chapter 2), distinguishing the relay neurons from the local interneurons and reticular cells and looking at the different ways in which distinct classes can be recognized within each of these major cell groups. Then in chapter 3 we look at the afferents that provide inputs to the thalamus, distinguishing them in terms of their structure, origin, and possible functional role as drivers or modulators. In chapter 4 we consider the intrinsic membrane properties of thalamic cells and outline the properties of the several distinctive conductances that determine how a thalamic nerve cell is likely to react to its inputs. In chapter 5 we consider the distinct actions of different types of synaptic input, focusing on the variety of transmitters and receptors that play a role in determining how activity in any one particular group of afferents is likely to influence the cells of the thalamus.

For each of these topics, only some of the available information can at present be readily related to the functional organization of the thalamus, which we consider in the later chapters. Many of the points presented raise key questions about the thalamus that are as yet unanswered. We have listed some of these questions at the end of each chapter, but the reader is likely to find a great many other that are interesting and deserve attention. In these four chapters (2–5) we present evidence in some detail to indicate the range of problems that still need to be considered before anyone can claim to understand the thalamus. As new investigators are attracted to the thalamus, as we hope they will be, they will be able to look at some of these problems anew, and where we see only puzzles and unanswered questions, they are likely to look at the problems from a fresh angle and have new insights. At present, only a limited part of the knowledge that we have about thalamic cells and their functional connections can be interpreted in functional terms.

In the second part of the book we introduce some of the features that are relevant to our view of what it is the thalamus may be doing. Chapter 6 explores the fact that the thalamic relay cells have two dis-

tinct response modes, which depend on the intrinsic properties and synaptic inputs discussed in chapters 4 and 5. One is the tonic mode, which allows an essentially linear transfer of information through the thalamus to the cortex, and the other is the burst mode, which does not convey an accurate representation of the afferent signal to cortex but instead has a high signal-to-noise ratio, so that it is well adapted for spotting new signals. Chapter 7 considers the two types of afferent to thalamic relay cells. The drivers serve to bring the information to the relay cells and the modulators determine the mode, burst or tonic, of the relay cell response. Distinguishing drivers from modulators is relatively simple in a few instances, but in many relays the distinction cannot be readily made, and we look at ways in which one may be able to classify afferents as either drivers or modulators. In chapter 8 the distinction between first order and higher order thalamic relays is explored. The former receive their driving afferents from ascending (subcortical) pathways; the latter receive their driving afferents from cortex and so serve as a relay in corticocortical communication, and insert essential thalamic functions into cortical communication. For any one ascending afferent to thalamus, as, for example, for any one sensory modality, there are several higher order circuits and several cortical areas. There are consequently many mapped pathways that relate to each other as they pass through the thalamus and the thalamic reticular nucleus. Chapter 9 considers some of the connectional relationships that are produced by a multiplicity of interconnected topographic maps in first and higher order thalamocortical circuits, showing how the functions of distinct cortical areas are brought into relation with each other in the thalamus and reticular nucleus. Chapter 10 presents evidence that many, possibly all, of the pathways that serve to innervate the thalamus are made up of axons that have branches innervating motor or premotor⁸ centers at levels below cortex and thalamus. That is, the pathways that are relayed in the thalamus, first order as well as higher order, carry not just the sensory messages represented by the classical model but also copies of motor commands that have already been sent out to the motor periphery before any messages can reach the cortex. The implication of these connections for understanding how action and perception may be intimately linked

8. *Premotor* is used here and in the rest of the book to refer to centers with significant connections to lower motor pathways, as opposed to ascending pathways that pass through the thalamus to the cortex. Examples include the pontine nuclei, the superior colliculus, the inferior olive, and some of the reticular nuclei of the brainstem.

is explored, and we conclude that this close link between action and perception, which has long puzzled philosophers, psychologists, and psychophysicists, may be understood to a significant extent in terms of the close, indeed inexorable, anatomical links that exist at the earliest stages of sensory processing but that have been largely ignored in the past. Chapter 11 presents an overview of some of our major conclusions, but we stress that this represents a relatively small slice of what is known about the thalamus. Many of the problems and issues raised as questions or currently unsolved problems in each of the chapters deserve close attention if we are to arrive at a more profound understanding of what it is that the thalamus does.