FUNCTIONAL CONNECTIONS OF CORTICAL AREAS

A NEW VIEW FROM THE THALAMUS

S. Murray Sherman and
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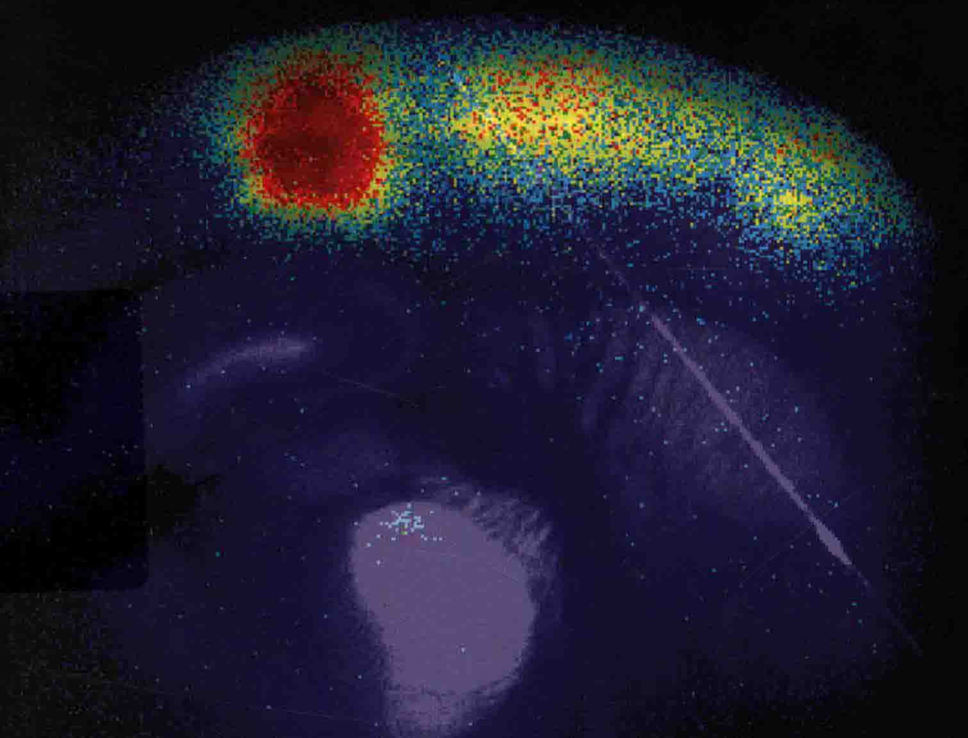

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The front cover shows a photograph of a section of the mouse brain containing the primary and secondary somatosensory cortex at the top and various subcortical structures below, including the posterior medial nucleus of the thalamus (which contains the tiny blue patch). The red and yellow zones in the cortex show regions of elevated neuronal activity as does the blue zone in the thalamus. In this experiment, layer 5 of primary somatosensory cortex was directly activated by delivery of glutamate (red patch on left in cortex), and this led to activity in the posterior medial nucleus, shown as the faint small patch of blue in the thalamus. This was followed by activity in the secondary somatosensory cortex (yellow patch immediately to the right of the red of the primary somatosensory cortex). Further to the right of this activity in the second somatosensory area the figure shows later, fainter activity in the third somatosensory area. This photograph is taken from figure 3a of Theyel et al. (2010b), where the dependence of the corticocortical transmission upon the thalamic relay is demonstrated. See chapter 5.1.2 for further details.

Functional Connections of Cortical Areas

Preface

This book follows two earlier books by the same two authors: the first one on the thalamus (Sherman and Guillery, 2001) and a second edition reaching somewhat beyond the thalamus to include more of the relationships to cortex (Sherman and Guillery, 2006). We decided that we now needed a distinct book, heading in a different direction but based on large parts of the same thalamocortical foundations. To some extent the title indicates this: we started with the ground rules that we had been able to define for the thalamus and followed their implications for the thalamic inputs to the connections of the cortical areas and their outputs. That is, we argued our way from the thalamus to the rest of the brain and arrived at new ways of thinking about the relationship of the brain to the world, to cognition, and to behavior. However, this is not a book about the brain and the mind. It is a collection of thoughts about neuroscience—the structure and functions of nerve cells and their interconnections. Our earlier thoughts about the thalamus, revisited and somewhat extended in the first three chapters, have led us now to look more closely at how the neural circuits of the brain relate to our actions and our perceptions, how not only people but also many other complex or even quite simple organisms relate to the world.

Two major points have become clear to us as we planned, wrote, and argued about the contents of this book. One, which runs through much of this book and is explored in detail in later chapters, was that a functional and structural analysis of the neural circuits that connect thalamus and cortex leads us beyond these neural centers to lower centers of the brain and through them to the body and the world. That is, not only the cortex as a whole but also each part of the cortex individually, each of the cortical areas that are often treated as distinct organs, is closely linked to the body and the world and relates closely to the way in which we act and think. Each receives inputs from the thalamus, and each has outputs to subcortical centers. This second view of cortical areas all having their own links to subcortical centers and to the body was a recognition that the view of cortex now dominating much contemporary research needs to be challenged. This currently widely accepted view is one that sees the cortex as a large collection of separate, functionally distinct areas that interact with each other in complex hierarchies and pass messages about the body and world to and fro among each other, eventually toward centers that can store memories or produce actions. In this view, the inputs from the body enter through the sensory areas, and the motor areas provide the outputs. The subcortical outputs from the sensory and intermediate areas do not play a part in this schema, nor do the thalamic inputs to higher cortical areas. There are several reasons why such a challenge is needed, and for us they arose directly out of our thoughts about the thalamus.

One element that is missing from this current view of corticocortical communication concerns the distinction between drivers and modulators. This distinction played a significant role in our earlier books, and it is revisited in chapter 4. It was crucial for understanding the thalamus and is proving equally relevant for understanding the functioning of the direct connections between cortical areas (Covic and Sherman, 2011; DePasquale and Sherman, 2011). Drivers carry messages for relay, whereas modulators modify the way in which the messages are relayed. The latter greatly outnumber the former in the thalamus and to a significant extent in the early stages of cortical processing. We have no relevant information about the proportions at higher levels. The nature of the message itself that is passed to the cortex and from one cortical area to another is important for understanding how the functions of any one cortical area are generated from their inputs, but this is unknown for most of cortex. For corticocortical communication, especially at higher levels, we know nothing about the distinctions between drivers and modulators, and we have very little information about the nature of the message. That is, we know about a great many of the connections in terms of their anatomical links, but we have no information about what they do.

A second element that plays essentially no role in most current views of cortical functions is the presence of transthalamic corticocortical connections, which were revealed once it was recognized that there are thalamic nuclei that relay messages from one cortical area to another. These were called higher order relays in our earlier books. These transthalamic links are pathways providing a route additional to the direct corticocortical pathways that dominate current thinking. They are reconsidered in chapter 5. They have two important features that the direct corticocortical pathways lack. One is that the messages have to pass through the thalamic gate, which can transmit a message with reasonable accuracy, block a message, or transmit it in a distorted form with a high signal-to-noise ratio for attracting attention. The condition of the thalamic gate that controls these different actions depends on a balance of excitatory and inhibitory inputs at the thalamic relay cell, and this can vary depending upon the particular relay and on many currently undefined conditions of the organism and the environment. We explore the functions of this gate to some extent but recognize that this is a key area where we need to learn more about how thalamocortical transmission for any one thalamic nucleus under any one set of particular conditions is controlled and how that control relates to action and perception.

Another feature present in the transthalamic pathway and missing from the direct corticocortical pathway, considered further in the next paragraph, is that the messages that come to the thalamus from the cortex are like the messages that travel along all thalamocortical pathways in that they transmit information to cortex about ongoing motor instructions in addition to the more generally recognized messages that they carry about activity at their origin in sensory receptors or other neural centers. We consider the actions of the thalamic gate and the motor copies that tell one cortical area about motor instructions being issued by another cortical area in chapters 5 and 6. They play a role in cortical processing that is almost entirely unexplored in the current literature.

A crucial feature that grew out of our earlier thoughts concerns the fact that the drivers that bring messages to the thalamus for relay to cortex all have branches that innervate motor centers. This raises an issue that puzzled us (and colleagues) for a long time and that is considered in chapter 6. Detailed consideration of the functional implications of these branching axons has led us to treat the driver afferents to the thalamus in a new light. We now suggest that these important inputs to the thalamus for relay to cortex should all be regarded as carrying copies of the motor instructions. Such a view allows recognition of the fact that these axons carry more than one type of message; not only do they bring to cortex information from peripheral centers or lower levels of the nervous system about the world and the body, but they also bring information about the motor instructions that these centers are currently generating and that will be executed after the afferent (sensory) messages have reached cortex. That is, they provide a view of future actions.

In chapters 7 and 8, we look at the way in which thalamus relates to cortex and cortex relates to the rest of the nervous system. We argue that, on the one hand, every cortical area receives inputs from the thalamus and that these inputs bring information about events in the world and in the rest of the nervous system to each area. On the other hand, every cortical area also has the capacity to influence the lower motor outputs through one or another of phylogenetically old centers relevant for the control of behavior. These include not only the spinal cord and the brain stem but also the basal ganglia, the tectum, and the cerebellum. That is, to understand the functions of any one cortical area, one needs to ask questions not only about the conditions under which the cells in that area become active or questions about how that area may be connected to other cortical areas. These are currently the two most common approaches: defining complex behavioral or perceptual situations, then showing which areas become more active in any one such situation, and subsequently exploring the corticocortical links of the active area. We argue that one also needs to ask about the nature of the thalamic inputs to that area and the motor outputs coming from that area. One needs to know which axons forming the connections are drivers and which are modulators, and when one has identified the drivers it will become of interest to define the nature of the message that is being transmitted. To understand the functions of the phylogenetically most recent, highest cortical centers concerned with cognitive functions, it will be necessary to learn how they are linked to the phylogenetically oldest parts of the nervous system that relate to the body and the world.[1]

These considerations raise a lot of unanswered questions about the thalamus, the cortex, and the rest of the brain. It is fashionable to ask, and we are often asked, what are the hypotheses that we are testing? We mention several in the course of the book, but the key consideration is about the questions we are asking about currently unexplored aspects of how thalamus and cortex relate to the rest of the brain. As in our previous books, we provide a short list of currently unanswered questions at the ends of chapters 3 to 8. These are not intended as questions that students should be able to answer in an exam but are questions that need to be answered if we wish to understand how the brain relates to the body and the world. It will be obvious to all that the questions we list represent but a fraction of the questions raised in the book and waiting to be attacked by the next generation of neuroscientists.

This book, as its two predecessors, is planned for individuals with a reasonable background in neuroscience at the undergraduate or graduate level. It should be of interest to anyone concerned with thinking about what the central nervous system may be doing. We have tried to let each chapter stand on its own so that it can be read independently of the other chapters. This has involved some repetition of subjects treated in one chapter in others. Chapter 9 provides an overview, but it has to be stressed that the detailed arguments supporting the views summarized in chapter 9 are in the earlier chapters. We

1. Evans (1982) has written, "Conscious experience results when 'the internal states which have a content by virtue of their phylogenetically more ancient connections with the motor system also serve as input to the concept-exercising and reasoning system." Here, a philosopher has anticipated one of the major conclusions of our book. We thank Andy Clark for citing this wonderfully percipient statement.

have avoided abbreviations as far as possible; they are a horrible feature of many current publications that often make comprehension difficult and usually do not save much ink. The few abbreviations that we use throughout the book are listed on page xvii at the beginning of the book.

We owe thanks to many colleagues who have discussed some of the issues we raise in the book or have read one or another of the chapters. These include Richard Boyd, Kevin Cheng, Christian Hansel, Jason MacLean, David Freedman, Peggy Mason, Kouichi Nakamura, Leslie Osborne, Luis Populin, Cliff Ragsdale, and Maria Wai. Robert Prior of MIT Press encouraged and advised us and helped us to learn what the publishers need. We thank the authors whose illustrations we have used for permission for their use, particularly Professor H. Ojima for sending us unlabeled high-definition versions of the images used in figure 3.7. Finally, we thank Marjorie Sherman for proofreading the entire manuscript.

Abbreviations

We have, as far as possible, avoided the use of abbreviations. Here, we list the ones that are commonly used by neuroscientists and widely recognized for complex names. They are the following:

A1 primary cortical auditory area A1

A2 secondary cortical auditory area A2

AMPA (*R*,*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

EPSP(C) excitatory postsynaptic potential (current)

GABA γ-aminobutyric acid

GAD glutamic acid decarboxylase

IPSP(C) inhibitory postsynaptic potential (current)

NMDA *N*-methyl-D-aspartate

PSP postsynaptic potential

S1 primary cortical somatosensory area S1

S2 secondary cortical somatosensory area S2

S3 cortical somatosensory area S3

V1 primary cortical visual area V1

V2 secondary cortical visual area V2

V4 cortical visual area V4

Brief Contents

Contents

1 An Introduction to Thalamocortical Pathways

1.1 An Overall View of the Thalamus and Cortex in Relation to the Rest of the Brain

In this chapter, we introduce some of the major functional and structural observations and interpretations that provide the basis of this book. These are more fully developed and related to each other in the last six chapters of the book. In the first three chapters, we introduce some basic facts and concepts about the structural and functional relations of thalamus and cortex and about neural and synaptic properties in general so that a reader with limited neuroscience knowledge can have enough information to follow the material in the last six chapters, in which we introduce a number of distinct observations of the thalamocortical pathways that lead to a view of thalamic and cortical functions substantially different from a currently widely accepted view prevalent in much current literature and in most textbooks. We summarize some of the major differences later in this chapter and in figures 1.1 and 1.2. These two figures illustrate only the main points in which the two views differ. Many details have been left out for the sake of clarity and simplicity. The figures show some of the major connections that thalamus and cortex establish with each other and with the rest of the brain. They are discussed in more detail later in this chapter and more fully in the rest of the book. However, these figures do not illustrate other major differences, which are more difficult to illustrate and which concern the functional properties of the pathways shown in the figures and the extent to which they differ from one another and can change depending on local conditions. These are briefly described in section 1.2 and fully considered in chapters 4 and 5. Nor do the figures illustrate the important connections that outputs of the cerebral cortex establish with the rest of the brain except to indicate that they involve very much more than the outputs of the motor cortex (see figure 1.2).

There is one other crucial point that is easily recognized when sensory or motor pathways near the periphery are under consideration but is often lost

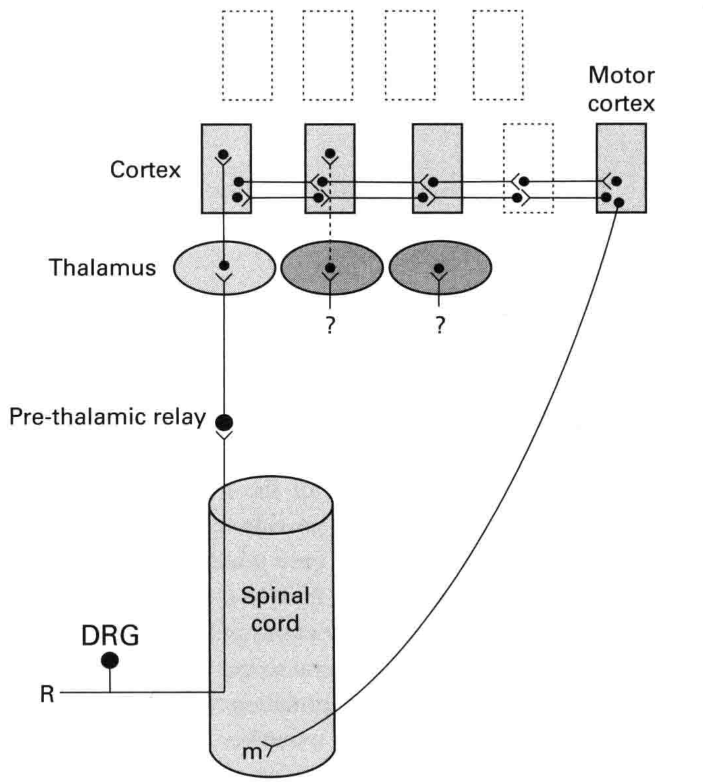

Figure 1.1
Schematic view of the major thalamic and cortical connections as seen in most current accounts. The sensory input from the spinal nerves shown here is representative of sensory inputs in general. Three thalamic nuclei are shown as ovals, and nine cortical areas are shown as rectangles. Only the thalamocortical and the corticofugal connections of the cortex are shown; cortical areas not shaded would have rich corticocortical connections, which are not illustrated here. Only the driver (Class 1) inputs, which transmit messages from the world and from other neural centers (see text), are shown in this figure and in figure 1.2. Modulatory connections, which do not transmit messages but modulate the way that messages are transmitted or processed, are not shown. In this schema, the information about events in the world once it reaches the cortex is thought to be processed through the several cortical areas, passing through a complex pattern of parallel and hierarchical feedforward and feedback connections, only some of which are shown in the figure, eventually reaching either areas for memory storage (not shown in the figure) or to the motor cortex for a motor output to lower centers and a contribution to the control of behavior. It is important to note that, on this view, once information reaches cortex through a primary thalamic relay, it is processed entirely within cortex through corticocortical connections without reference to any subcortical structures. There is a single entry point for each sensory modality for cortical processing (primary sensory cortex) and a single exit point (motor cortex). This view of thalamocortical connections can be found in most contemporary textbooks and is in contrast to the view on which this book is based, which is schematized in figure 1.2. DRG, dorsal root ganglion; m, lower motor center; R, receptor.