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BOOK REVIEW

A deep look at the thalamocortical continuum

Functional Connections of Cortical Areas: A New View from the Thalamus. By S. Murray Sherman & R.W. Guillery. 2013. The MIT Press, Cambridge, MA.

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The current state of neuroscience is both impressive and puzzling. On the one hand, neuroscience has become a field that is extremely rich in data at different scales (the Allen Brain Atlas and the Human Connectome Project are good examples). On the other hand, its fundamental theory has changed surprisingly little in the past few decades, despite some glaring discrepancies between textbook conceptualizations and actual experimental results.

This situation is not easily improvable because data do not automatically become theory. In fact, there are fundamental limits to how much number crunching can help us in this endeavor. To quote Henri Poicaré, "There is no disputing the fact that a selection must be made: however great our activity, facts outstrip us, and we can never overtake them; while the scientist is discovering one fact, millions and millions are produced in every cubic inch of his body. Trying to make science contain nature is like trying to make the part to contain the whole. But scientists believe that there is a hierarchy of facts, and that a judicious selection can be made. They are right, for otherwise there would be no science, and science does exist. (The) economy of thought, […] the constant tendency in science, is a source of beauty as well as a practical advantage." (Poincaré, 2001)

For readers seeking a fundamental understanding of the brain, *Functional Connections of Cortical Areas: A New View from the Thalamus* by S. Murray Sherman and R.W. Guillery is a landmark publication. The monograph builds on two previous books by the authors, *Exploring the Thalamus* and *Exploring the Thalamus and Its Role in Cortical Function*, but it can be read as a self-contained piece of work. Since the authors further refine their theory, cite new experimental findings, and consider the thalamus and cerebral cortex as a continuum, readers of the previous two books are strongly encouraged to add this volume to their professional library. I have used the last two books in my graduate neuroanatomy courses, where they have generated interest not only among experimental neurobiologists but also among computational neuroscientists investigating cognitive processes.

In a typical textbook presentation, the thalamus collects information from the external world and the body, and then relays it to the cerebral cortex. Specifically, signals from peripheral sensors are sent to a modality-specific thalamic nucleus, which then forwards them to the appropriate primary sensory cortex (e.g., signals travel from the retina to the lateral geniculate nucleus to V1). Once the information reaches the cerebral cortex, it flows to other cortical areas, including the multimodal association cortices. The signals eventually reach the cortical motor areas, which update the body's position in space. The exact computational transformations used at each of these points are often poorly understood, but this flowchart is assumed to generally well reflect how the brain interacts with its environment.

This model is so intuitive that it has changed little since the dawn of modern neuroscience. It is sensible from the engineering point of view, consistent with typical clinical observations, and conceptually simple. In particular, it has a clear causal direction, which suggests that the cortex may produce similar responses when exposed to similar sensory inputs (if the system is "well behaved" and not hypersensitive to minor changes in the stimulus). This approach greatly facilitates experimentation and has led to some spectacular progress: visual neuroscience, with its foundations dating back to David Hubel and Torsten Wiesel, is a prime example of how far it can take us.

But one can see some clouds gathering. This has been going on for decades, but we can no longer ignore them. Is the textbook model an optimal, or even acceptable, conceptual generalization? Does it capture the accumulated body of experimental evidence, or does it merely reflect the engineering sensibilities of the era in which neuroscience took root?

We now know that the flow of sensory information is as much "top-down" as it is "bottom-up," even in invertebrate nervous systems (Mischiati et al., 2015). The brain relies on its species-specific models of reality that allow perception to operate on shockingly narrow bandwidths, in direct contrast to human-made cameras and scanners (Raichle, 2010). These models include the knowledge of the organism's possible actions. Curiously, some of these ideas can be traced back to Kenneth Craik (1914–1945) and Edgar Adrian (1889–1977) and are as old as the textbook model. Current state-of-the-art experimental approaches provide neuron-level evidence that the early stages of sensory processing (e.g., the receptive field characteristics in sensory cortices) can indeed be strongly influenced by "top-down" signals (Cooke et al., 2014).

Further, some thalamic nuclei are neatly associated with specific sensory modalities, but some are not (e.g., the mediodorsal and pulvinar nuclei). Their function is assumed to be "association," leaving the student with the impression that the thalamus is functionally dual. A similar approach is taken to the multimodal cortical "association" areas that are supposed to bridge sensory inputs and motor outputs. While remarkable progress has been made in the understanding of their functional mappings, it is unclear if their thalamic connectivity is fundamentally similar to that of the unimodal sensory cortices.

Also, it is obvious that the brain is not an input–output machine but a vast system of dynamic loops. In some subsystems, one can ignore this fact and survive, but the textbook model cannot even begin to capture such core processes as sleep and mind wandering (there is no question they need better names instead of their current introspective labels). What is the "input" and "output" there?

And so we have a peculiar situation. The textbook model is elegant, but it fails to incorporate a large amount of experimental data and illuminate a number of complex neuroprocesses. If one starts with the data and tries to build a new theory, another problem arises: an extraordinary human insight is needed to see what small set of fundamental principles may lead to everything else. In particular, one has to detect common themes in vast amounts of data that are inherently uneven in their reliability and generalizability. This requires years of experience and a measure of intellectual solitude. With the exception of very specific verifications, "omics" projects, large consortia, or computer grids cannot advance theory. *Functional Connections of Cortical Areas* is a shining example of how much we can still benefit from this art.

With regard to the thalamic inputs, the authors see no fundamental difference between signals that are generated by the external world and signals that arise in the cerebral cortex itself. Instead of their origin, these inputs are divided based on their neurophysiological effects on thalamic neurons. They fall into one of the two crisp categories, drivers and modulators, that can be robustly distinguished based on their postsynaptic receptors, paired-pulse effects, the size of excitatory postsynaptic potentials, and other characteristics. The glutamatergic driver inputs from the cortex to the thalamus originate in cortical layer V and resemble the classic driver inputs that carry spatiotemporally precise information from the external world (e.g., the retinogeniculate projection) or the body (e.g., the posterior column-medial lemniscus pathway). The glutamatergic modulator inputs from the cortex to the thalamus originate in cortical layer VI and resemble other classic modulatory projections, such as serotonergic and cholinergic afferents. On the way to the thalamus, all driver inputs send direct collaterals to higher or lower motor centers. They appear to produce no collaterals to the thalamic reticular nucleus, which is classically contacted by modulating corticothalamic projections. For example, both the retinogeniculate axons and the corticothalamic axons from the visual cortex send branches to the superior colliculus and the pretectum, which have known motor functions. Likewise, the mammillothalamic axons (a part of the Papez circuit) send branches to the medial pontine reticular nucleus that is involved in the control of gaze. Importantly, the above set of principles applies to the entire thalamus and all cortical areas. This leads to a number of novel insights.

The brain becomes less corticocentric, and the distinctions among sensory perception, "higher cognitive functions," and motor output become less obvious. Each cortical area, no matter where it is in the currently presumed hierarchy, is similar to a peripheral sensor: it produces a driver signal that reaches both the thalamus and a motor center. The thalamus then advances this signal to another cortical area that can generate its own driver input, again with a motor copy. More abstractly, the thalamus receives inputs from the actual physical world and its virtual model in the cortex. These inputs map back into the physical world (through their motor collaterals) and into its virtual model (through thalamocortical projections). The difference between the "first-order" ("relay") and "second-order" ("association") thalamic nuclei is merely that the former receive driver inputs from peripheral sensors, whereas the latter receive driver inputs from the cerebral cortex. If the authors' hypothesis is correct, the brain may be considerably less hierarchical than how we usually see it.

This provides a solid neuroanatomical foundation for the current approaches in cognitive neuroscience that emphasize large-scale networks (Menon, 2011) and suggest that the brain uses surprisingly little information from the external world (Raichle, 2010). However, it also serves a warning: no serious progress can be made in the understanding of cortical function if only direct corticocortical projections are considered (because all cortical areas communicate with each other through the thalamus). Also, all cortical areas produce motor signals, ignoring which may lead to a warped picture of an area assumed to be safely upstream from the classic motor areas. The "sensory" areas are not linked to the "motor" areas by vast swaths of "association areas": instead, all of them are motor, to a significant functional extent. This may sound unusual, but it is easy to find examples where "sensory" and "motor" appear to be two sides of the same process. Eye saccades lie at the core of visual perception and can affect such global perceptual entities as space and time (Burr et al., 2010). All cortical activity maps onto the basal nuclei and the cerebellar cortex that then channel this information to the classic motor areas (by way of the thalamus). Some marsupials have a fused sensorimotor area, with no distinct motor area, and the cortex in the expected location of the primary motor cortex does not project to the spinal cord.

A careful reader will notice that "an input to the thalamus with a motor branch" can be interpreted as "a motor command with a thalamic branch." From this point of view, retinogeniculate projections can be seen as "efference copies" of motor-related signals addressed to the superior colliculus and the pretectum. The authors note that the entire set of "efference copies" (or driver inputs) gives the forebrain "a full view of how the organism relates to the world and what the organism and the world are likely to do next." It also allows us to "distinguish our own actions from those of others."

Considering the sheer number of connections in the brain, selectively focusing on some of them always carries risks. However, the proposed hypothesis makes specific predictions that can be falsified by future experiments. For example, a large class of primate retinal ganglion cells (P-cells) is not known to send collaterals to the superior colliculus or the pretectum, but the authors are not convinced ("the evidence is not adequate for an entirely definitive conclusion"). They continue, "There is evidence that *some* axons of the parvocellular component branch, and, given the difficulty of the techniques that were used, […] it is not unreasonable to conclude that primates may be like the other mammals that have been studied." To recall Poincaré, the entire science is built on clever selections—or a small set of facts from which the rest can be inferred. Theories live or die by such inferences.

Functional Connections of Cortical Areas towers above many other attempts at synthesis. The authors are leading authorities in the field, with nearly half a century of experience in both classic and highly original approaches to the brain. The monograph includes a sweeping review of the literature dating back to Ramón y Cajal, which makes it a fascinating reading independent of the proposed hypothesis. The authors conveniently list unsolved problems in a separate section ("Outstanding Questions") that is likely to inspire new researchers in the field. The organization of the book is exemplary: the argument is built step-by-step, in small sections, with each piece eventually summarized and returned to the big picture.

The monograph could have been strengthened with modern microscopy images. As an owner of the Swansons' translation of *Histology of the Nervous System*, I understand the authors' temptation to use Cajal's drawings. Some of them remain unsurpassable despite the enormous progress in microscopy techniques. However, a reader casually flipping through the book may get the impression that it is a historical review, even though it is meant to take us in the exact opposite direction, the future. The authors' summary of their general ideas in the first two figures is likely to minimize this potential misunderstanding. Generally, classic drawings and modern images can work together: *Arthropod Brains* by Nicholas Strausfeld is a brilliant example of it.

I find it curious that the authors have not discussed alpha-like cortical oscillations that are thought to depend on interactions between the thalamus and the cerebral cortex, but this may have been the consequence of the authors' general decision. As they write in the closing pages, "It may seem strange that in the book so far we have said almost nothing about the mind, limiting ourselves (at most) to brief references to cognitive or perceptual functions. This has been a book about nerve cells and their interconnections, and our central aim has been the provision of some ground rules […]." The monograph indeed focuses on the fundamental structure and leaves readers to decide how it may affect dynamic neurophysiological processes or cognition.

Overall, *Functional Connections of Cortical Areas* is an outstanding piece of work. The authors present compelling evidence that the big picture may be vastly different from how we usually see it and suggest a conceptual path that is both elegant and rich in its implications.

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