COMPETING FINANCIAL INTERESTS

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The thalamic paradox

László Acsády

Most thalamic research has focused on sensory transmission. Now three independent groups reveal the thalamus to be critical in behaviors linked to frontal cortex and the maintenance of persistent cortical activity during delays.

Before the nineteenth century, few if any scientists attributed major functions to the cortex. Cortex was mainly regarded as a rind around the more important parts of the brain. According to the leading theories of the era, the highest sensory functions were located in the thalamus and the highest motor functions in the striatum¹. This view changed abruptly at the end of the nineteenth century as a result of the famous experiments by Fritsch and Hitzig, who discovered that electrical activation of the cortex induces movements². The importance of cortex was soon demonstrated in all major cognitive functions, and cortical computations continue to fascinate us today, perhaps more than ever. However, in this corticocentric view of the brain, the thalamus was relegated to subserving an elementary function: namely, providing accurate topographical sensory information to the cortex. All other higher-order processing was (and is) attributed mainly to hierarchically organized cortico-cortical connections (Fig. 1). This view prevails even though all cortical regions are known to have strong bidirectional connections with the thalamus³. In addition, it is also clear that only a minority of the thalamus receives subcortical sensory inputs⁴. Thus, largely because of a historical bias, the role of the thalamus in cognitive functions has not been explored in depth, and as a consequence there is a substantial gap in our knowledge concerning the nonsensory functions of the thalamus. I call this chasm between the basic anatomical data and the lack of cognitive studies the thalamic paradox.

This is now about to change. As with the cortex in the nineteenth century, critical experiments were needed to launch a new way of thinking about thalamus in the twenty-first century. The simultaneous publication of two papers in *Nature*^{5,6} and one in *Nature Neuroscience*⁷ about interactions between thalamus and frontal cortex in different behavioral situations in mouse marks the beginning of a new era in thalamic research. Whereas we may have thought sensory transmission to be the rule in thalamocortical function, now it seems equally likely that it is the exception, a highly specialized form of thalamocortical activity. As shown in these three landmark papers, the rules of operation are qualitatively distinct in other parts of thalamic circuits.

The new data unequivocally demonstrate the importance of thalamus in frontocortical functions. In addition, they show the conceptual differences in thalamocortical interactions in sensory and frontal territories. In sensory transmission, there is a clear one-way drive of cortical activity by the thalamus to accurately transfer transient sensory events to the cortex8. According to the new studies, however, in the frontal cortex, there is a continuous reverberation of activity between the cortex and thalamus. The data show a mutual interdependence of cortical and thalamic activity that persistently maintains information in the cortex. The three papers tell the same story of sustained interactions, and yet there are significant differences among them. This indicates that, depending on the task and the actual circuit in question, the thalamocortical interplay in frontal cortex may take many different forms and support cortical functions in various ways.

All three papers revolve around persistence of frontal cortical activity during behavior. Persistent activity is widely regarded as the neuronal correlate of the internal representation of an environmental variable⁹, decisionmaking¹⁰, preparation of a motor act¹¹ or working memory¹²; in brief, something we need to keep in mind before we act. Persistent activity frequently manifests as a sequential activation of well-defined cell populations (called synfire chains) that tiles the period during decision-making and is known to require recurrent synaptic connectivity.

The behavioral and decision variables in the three studies were different, yet the three papers together make a very strong case that the thalamus acts to maintain persistent activity in the frontal cortex. Guo et al.5 asked mice to lick left or right depending on the location of an object they sensed with their whiskers (directional licking task). Bolkan et al.7 asked mice to remember which way they turned in a T-maze and to choose the opposite arm after a delay (spatial, delayed nonmatch-to-sample task). Finally, Schmitt et al.⁶ asked mice to keep in mind a rule (attend to vision or attend to audition) during a delay period (two-alternative forced-choice task). In all three cases, precisely timed optogenetic inhibition of the relevant thalamic territories perturbed both the sequential cortical activity that tiled the delay period as well as task performance. This clearly demonstrates that frontal cortex and corticocortical connections alone are not sufficient to perform persistent delay activity.

So, what was actually represented in the thalamus during the delay periods while the mice were deciding what to choose, and what was the impact of the thalamus on cortical activity? This is where the three studies diverge. The strongest interdependence of cortical and thalamic activity was observed by Guo *et al.*⁵. Thalamocortical neurons displayed directional responses (lick left, lick right) that tiled the delay period (~1 s) between sample and choice. Notably, this activity was identical to that of cortical pyramidal cells. Blocking thalamic activity resulted in a marked drop in cortical firing and the loss of directional specificity. Likewise, blocking cortical activity abolished thalamic

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Figure 1 Changing view of thalamus. Left: according to the classical view, the thalamus has one entry point to cortical computation: providing accurate topographical representation of sensory inputs to primary sensory cortices (cortex 1), while higher-order computations take place via cortico-cortical connections. Right: in reality, all cortical regions receive thalamic inputs. Many thalamic regions receive nonsensory excitatory (blue) and inhibitory (red) inputs and project widely, linking several cortical regions (thalamus 2). Other thalamic nuclei are entirely devoid of subcortical glutamatergic inputs (thalamus 3) and are dedicated to transferring cortical information back to the cortex. Notably, both thalamus 2 and thalamus 3, are well suited to supporting reveberating thalamocortical activity. Guo *et al.*⁵ studied thalamus 2, whereas Bolkan *et al.*⁷ and Schmitt *et al.*⁶ likely invoked both thalamus 2 and thalamus 3. Not all connection types are shown; at right, some important ones (for example, thalamostriatal) have been omitted for clarity.

firing. Thus, it seems the same behaviorspecific information was distributed and reverberating between cortex and thalamus. This strongly suggests the presence of recurrent excitation in these thalamocortical loops and mutual interdependence of cortical and thalamic firing in establishing selective persistent activity, something not observed between sensory thalamus and sensory cortex.

In contrast to those in Guo et al.⁵, the cortical and thalamic neurons in the mice studied by Bolkan et al.7 did not display behavioral (that is, spatial) specificity (turn left, turn right) during the delay period (60 s in this case). Still, thalamic activity was instrumental for delay period activity and for the correct response. Notably, blocking thalamic activity affected task performance and cortical firing rates only during the delay period, not during the sample or the choice, but the effect was not as dramatic as that observed by Guo et al.⁵. The authors clearly demonstrate double dissociation in the role of thalamic versus hippocampal inputs on frontal cortex in the delay and samples phases of the task, respectively.

Schmitt *et al.*⁶ found that cortical pyramidal cells displayed robust, rule-specific firing (attend to light or attend to sound) that was curiously absent from the thalamus during the delay-selective, sequential activity. This indicates that cortical neurons with different categorical firing converge on thalamic cells, which results in noncategorical thalamic firing. This is the first clear demonstration that the output of a so-called thalamocortical 'relay' neuron is not representing its input but is a novel signal generated in the thalamus. In this study, the impact of thalamic activity on cortical firing was modest, again in sharp contrast with the findings of Guo *et al.*⁵. The authors in fact concluded that the role of the thalamus here is not to make cortical cells fire but to promote synaptic interactions among cortical cell ensembles, which allows the unfolding of synfire chains necessary to represent the actual rule (that is, attend to light or sound). Bolstering this claim, augmenting thalamic activity led to better categorical representation in the cortex and augmented behavioral performance, a result demonstrated by Bolkan *et al.*⁷ as well.

The significant differences in the three papers in categorical representations by thalamic cells and in thalamic impact on cortex is clearly puzzling. It seems to deepen rather than resolve the paradox. How can we explain these discrepancies? Clearly, task type matters. The cognitive demand is different in the three studies. In Guo et al.5, the delay period can be regarded as motor preparation. The situation is similar in Bolkan et al.⁷, but here the motor act needed to be stored for a longer period. However, in Schmitt et al.⁶ the animal kept in mind a rule (attend to light or sound), not a motor act, which is the most complex cognitive task of the three. So, one idea might be that more difficult tasks may require less-specific categorical representations in the thalamus and that, in these cases, the thalamus does not directly drive cortical activity but rather promotes the unfolding of cortical firing sequences. The problem clearly begs for more experiments.

The other significant difference among the studies is the actual thalamocortical circuit involved. Guo et al.5 studied lateral motorcortical territories that are in contact with thalamic nuclei receiving inputs from the basal ganglia or cerebellum. Bolkan et al.7 and Schmitt et al.⁶, by contrast, scrutinized mediofrontal territories that innervate distinct sectors in the mediodorsal and intralaminar nuclei. Owing to the thalamic paradox itself, we know relatively little about the exact differences in the organization of these circuits, but available evidence indicates that there may be substantial diversity among frontal thalamocortical circuits with regards to excitatory⁴ and inhibitory¹³ inputs, as well as outputs¹⁴. This might account for the differences in taskspecific firing in thalamus and the distinct impacts of thalamus on cortex.

Future directions are clear. Far from resolving the thalamic paradox, these three studies in fact emphasize it. I predict that many scientists will realize that the nonsensory thalamus is an uncharted forebrain territory and that, with cutting-edge circuit-specific interrogation, we will soon see major breakthroughs in this field. Each cortical function has a thalamic story to tell and each thalamocortical circuit has a specialized connectivity to fulfill a distinct role in cortical computations that is yet to be revealed. Our historical ignorance of thalamic contributions to higher-order cortical activity will fade and these two interdependent systems will be studied together, as in these three exemplary studies.

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