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Viewpoints

A Reconsideration of the Core and Matrix Classification of Thalamocortical Projections

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In 1998, Jones suggested a classification of thalamocortical projections into core and matrix divisions (Jones, 1998). In this classification, core projections are specific, topographical, innervate middle cortical layers, and serve to transmit specific information to the cortex for further analysis; matrix projections, in contrast, are diffuse, much less topographic, innervate upper layers, especially Layer 1, and serve a more global, modulatory function, such as affecting levels of arousal. This classification has proven especially influential in studies of thalamocortical relationships. Whereas it may be the case that a clear subset of thalamocortical connections fit the core motif, since they are specific, topographic, and innervate middle layers, we argue that there is no clear evidence for any single class that encompasses the remainder of thalamocortical connections as is claimed for matrix. Instead, there is great morphological variation in connections made by thalamocortical projections fitting neither a core nor matrix classification. We thus conclude that the core/matrix classification should be abandoned, because its application is not helpful in providing insights into thalamocortical interactions and can even be misleading. As one example of the latter, recent suggestions indicate that core projections are equivalent to first-order thalamic relays (i.e., those that relay subcortical information to the cortex) and matrix to higher-order relays (i.e., those that relay information from one cortical area to another), but available evidence does not support this relationship. All of this points to a need to replace the core/matrix grouping with a more complete classification of thalamocortical projections.

Key words: cortex; first-order; higher-order; thalamus

We have known for decades that thalamocortical projections represent a wide variety of forms and functions and that the classification and identification of the component motifs are a necessary early step in understanding this critically important set of connections (Halassa and Sherman, 2019). One of the earliest attempts claimed that thalamocortical pathways could be divided into specific and nonspecific or diffuse (Lorente de Nó, 1938; Jasper, 1949; Hanbery and Jasper, 1953). Specific projections were described as one from a single thalamic neuron that targets one or a few cortical areas topographically, whereas nonspecific ones target multiple areas broadly and diffusely near the cortical surface (e.g., Layer 1). Jasper (Jasper, 1949) included among the specific thalamocortical nuclei those involved in primary sensory relays (e.g., the lateral geniculate nucleus) as well as certain nuclei he referred to as “specific elaborative systems,” which included the pulvinar and medial dorsal nucleus.

The chief exemplars of the diffuse system were a number of intralaminar and midline thalamic nuclei. These nuclei have been identified with some variability in nomenclature and grouping

among authors, but it is beyond the scope of this account to go into the organization of this part of the thalamus in any detail. One such classification includes the following (Groenewegen and Berendse, 1994; Van der Werf et al., 2002; Vertes et al., 2015): the central medial, paracentral, central lateral, and parafascicular nuclei.

The function of specific thalamocortical projections always seemed fairly straightforward and noncontroversial: to relay peripheral information reliably, topographically, and precisely to the cortex. That of the diffuse projections has always been more difficult to pin down, but early suggestions tended to emphasize the ability to synchronize large areas of the cortex in their functioning for overall behavioral features, such as arousal (Lorente de Nó, 1938; Jasper, 1949; Hanbery and Jasper, 1953).

Core and matrix thalamocortical projections (Fig. 1)

These ideas from over 70 years ago were resurrected and further expanded by Jones (1998). He demonstrated an immunocytochemical division of relay cells in the thalamus of the macaque monkey: one set stained for calbindin and the other for parvalbumin. Because the calbindin-positive cells were distributed fairly evenly throughout the thalamus as a sort of background, he called this group “matrix.” Embedded among calbindin-positive cells were groups of parvalbumin-positive cells, which he called “core.” Both cell types were found in most nuclei, meaning these nuclei had both types of relay cell, but there was a pattern noted: for instance, the major sensory thalamic relays were dominated

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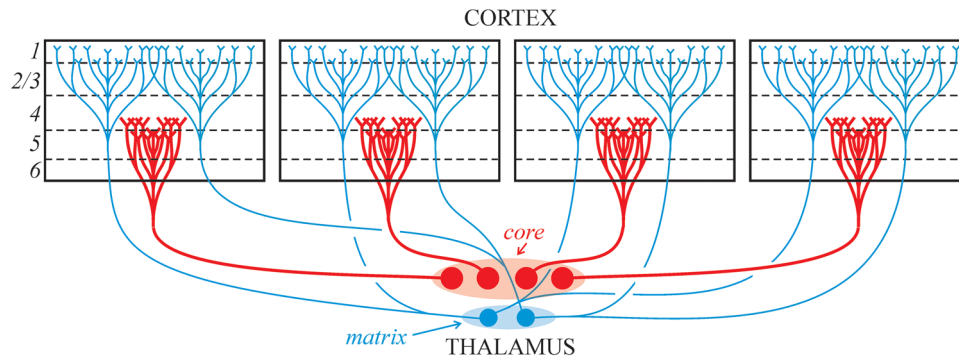


Figure 1. Examples of presumed core (red) and matrix (blue) thalamocortical projections. A core thalamocortical cell projects in a focused, highly topographical manner and primarily targets middle cortical layers, especially Layers 4 and 5, in one area. A matrix thalamocortical cell projects in a diffuse, less topographical manner and primarily targets upper cortical layers, especially Layer 1, in multiple areas.

by parvalbumin-positive cells and midline and intralaminar thalamic nuclei by calbindin-positive cells.

We note that many thalamic cells identified as matrix have extracortical projections, such as to the basal ganglia, amygdala, hippocampus, etc. (Vertes et al., 2015, 2022). However, in this account, we do not consider these extracortical pathways further, instead focusing on thalamocortical projections.

Jones also described differences between matrix and core thalamocortical projections (Hashikawa et al., 1991; Rausell and Jones, 1991; Rausell et al., 1992; Jones, 1998): matrix inputs target superficial cortical layers (such as Layer 1) in a diffuse manner, whereas the core projections target middle layers less diffusely, and matrix projections tend to involve axons that branch repeatedly to innervate a number of cortical areas, whereas core axons innervate one or a few areas.

Here, it is worth considering the descriptor “diffuse,” because it has potentially different meanings in the context of thalamocortical projections and these differences can be confusing as elaborated below. Many would define a diffuse thalamocortical projection as one in which individual axons branch extensively to innervate broad areas of the cortex nontopographically. Jones used a subtly different definition: he called the matrix projections diffuse, because retrograde label applied to superficial cortical layers labeled thalamic calbindin cells in many thalamic nuclei (Jones, 1998). Whereas this may be a reasonable use of “diffuse,” it should be noted that the pattern described by Jones could easily involve highly topographic projections from thalamic cells that converge onto one cortical region in upper layers. It is also possible that a thalamocortical axon can branch to innervate multiple cortical areas, what may be seen as a diffuse property, but the projections may all be topographic within their target zones. Thus, “diffuse” can mean nontopographic projections in one context but not in the other.

How are matrix thalamic cells defined and identified?

There appears to be some confusion or variability regarding how matrix thalamocortical projections are identified. The simplest criterion for identification applies only to monkeys: a thalamic cell that stains for calbindin is matrix. This is not very useful, because, as Jones points out (Jones, 1998), such staining for identification purposes is not clearly useful in mammals other than the monkey. Furthermore, such a staining pattern by itself does not provide any functional insights. Instead, the implicit identification of matrix thalamocortical cells seems to depend

on their projection patterns, namely, relatively nontopographic projections to multiple areas terminating in upper layers, mostly Layer 1, and avoiding deeper layers (Fig. 1).

However, a number of thalamocortical projections identified as matrix defy this classification. For instance, koniocellular cells of the lateral geniculate nucleus of monkeys, cells that stain for calbindin, are identified as matrix (Jones, 1998). These do project to upper layers, including Layer 1 of the primary visual cortex, but do so in an extremely topographic manner, and their axons do not branch to innervate other cortical areas (Ding and Casagrande, 1997; Casagrande et al., 2007). Whereas it is known that some koniocellular cells in the monkey project to extrastriate areas (Yoshida and Benevento, 1981; Sincich et al., 2004), it is as yet undetermined if these axons branch to innervate other areas as well. Other examples exist of topographic and specific thalamocortical innervation to Layer 1 (Odagiri et al., 2011). There are also thalamic relay cells that innervate Layer 1 (a matrix feature) but have axon collateral innervation of deeper layers, including Layer(s) 4 and/or 5 (core features; Usrey et al., 1992; Ohno et al., 2012).

How common are projections that terminate in Layer 1 and are diffusely distributed throughout much of the cortex? Clear examples outside of the intralaminar and midline thalamic nuclei are rare. These intralaminar and midline thalamic nuclei were the original focus of the so-called nonspecific thalamocortical projections (Lorente de N6, 1938; Jasper, 1949; Hanbery and Jasper, 1953), and so these nuclei may harbor cells that fit the criteria for matrix. However, a chief criterion is diffuseness of the projection, and modern neuroanatomical data suggest that such projections are not common. That is, the projections of these intralaminar and midline thalamic nuclei are typically specific and topographic (Groenewegen and Berendse, 1994; Van der Werf et al., 2002).

We suggest that many thalamic relays suggested to be matrix are topographic, specific, and often innervate deeper layers. Indeed, it is not clear how common the matrix pattern in Figure 1 is, and available data certainly do not support the idea that such a pattern represents a major type of thalamocortical projection. This raises the question: How valid and useful is the core/matrix classification for the thalamus?

Relationship to the first- and higher-order thalamus classification

In a different classification system, thalamic relays can be categorized based on the source of the information they relay to the

cortex: first-order relays receive such input from a subcortical source, whereas higher-order relays receive it from Layer 5 of the cortex (Guillery, 1995; Sherman and Guillery, 2013; Sherman, 2016; Usrey and Sherman, 2021). The lateral geniculate nucleus, which receives subcortical information from the retina, is a first-order exemplar, and one for higher-order is much of the pulvinar, which receives such input from Layer 5 of the visual cortex and projects to other visual cortical areas. This pattern is not limited to the visual system: for the somatosensory system, the ventral posterior nucleus is first-order, and the posterior medial nucleus is higher-order; for the auditory system, the ventral division of the medial geniculate nucleus is first-order, and the dorsal division is higher-order (details reviewed in Sherman and Guillery, 2013). This classification has been extended to most of the thalamus; for instance, the medial dorsal nucleus is identified as mostly a higher-order relay (Mitchell, 2015). Thus the question: How do the first-/higher-order classes relate to the core/matrix division?

There seems to be some confusion regarding the relationship of first- and higher-order relays to the core/matrix classification. For instance, some suggest that first-order relays are core and higher-order are matrix (Harris and Shepherd, 2015; La Terra et al., 2022; Aru et al., 2023; Munn et al., 2023). A likely problem with this, as noted above, is how one goes about identifying matrix elements. If a projection to Layer 1 indicates a matrix constituent, it is clear as indicated above that the lateral geniculate nucleus, by this definition, is partly matrix, which challenges the generalization that first-order relays are strictly core.

Perhaps more significant is the idea that higher-order relays are matrix. This idea is articulated in many recent publications, for example, that higher-order relays are "...nonspecific (diffuse projecting)..." (La Terra et al., 2022); that the "...thalamocortical network...includes both specific (a.k.a. 'core' or 'first-order'...) and nonspecific thalamocortical circuits (a.k.a. 'matrix' or 'higher-order'...)..." (Munn et al., 2023); or that "The thalamocortical network encompasses cortical areas, cortico-cortical connectivity, and higher-order thalamic nuclei with their diffuse projections to cortical areas..." (Aru et al., 2023). However, it is clear that many, if not most, higher-order nuclei are core based on topographic projections that target middle layers. Examples include higher-order thalamocortical projections of the visual thalamus (Niimi et al., 1974; Benevento and Rezak, 1976; Symonds et al., 1981; Dick et al., 1991; Lyon et al., 2003; Mundinano et al., 2019; Juavinett et al., 2020), of the somatosensory thalamus (Krubitzer and Kaas, 1992; Bureau et al., 2006; El-Boustani et al., 2020), of the auditory thalamus (Huang and Winer, 2000), and of the medial dorsal nucleus (Groenewegen, 1988; Mukherjee et al., 2020; reviewed in Usrey and Sherman, 2021).

We conclude that the idea that the core and matrix thalamus corresponds one to one onto the first- and higher-order moieties is wrong and misleading.

Concluding remarks

The real problem we see is establishing a clear definition for what is meant by the "matrix" thalamus. Is it a projection to cortical Layer 1? Is it diffuse, poorly topographic, or nonspecific thalamocortical innervation? Do all sets of requirements need to be met to identify the matrix thalamus, and if so, are there clear examples of such thalamocortical projections? We suggest that no clear criteria for the matrix thalamus exist that distinguishes it from the core thalamus. Instead, there is a wide variety of thalamocortical innervation patterns (Clascá et al., 2012; Halassa and

Sherman, 2019), some of which at one extreme of variation may resemble what is understood as matrix; others at another extreme, as core; and yet others as neither.

We suggest that the core/matrix idea has lived beyond its sell-by date and that it should be abandoned, because it now serves mainly to confuse and misrepresent. Instead, what is needed is a proper classification of thalamocortical projections. This is a daunting challenge: we are far from appreciating the range of variability and number of discrete motifs in thalamocortical processing. But the challenge must be recognized.

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