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Unveiling the diversity of thalamocortical neuron subtypes

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Abstract

Our current understanding of thalamocortical (TC) circuits is largely based on studies investigating so-called 'specific' thalamic nuclei, which receive and transmit sensory-triggered input to specific cortical target areas. TC neurons in these nuclei have a striking point-to-point topography and a stereotyped laminar pattern of termination in the cortex, which has made them ideal models to study the organization, plasticity, and development of TC circuits. However, despite their experimental importance, neurons within these nuclei only represent a fraction of all thalamic neurons and do not reflect the diversity of the TC neuron population. Here we review the distinct subtypes of projection neurons that populate the thalamus, both within and across anatomically-defined nuclei, with regard to differences in their morphology, input/output connectivity and target specificity, as well as more recent findings on their neuron type-specific gene expression and development. We argue that a detailed understanding of the biology of TC neurons is critical to understand the role of the thalamus in normal and pathological perception, voluntary movement, cognition and attention.

Introduction

The gray matter of the dorsal thalamus can be subdivided into a number of cytoarchitectonically-defined nuclei, the basic layout of which is similar across mammalian species. Ascending input pathways to the thalamus distribute in general accordance with these cytoarchitectonically-defined nuclear borders. For example, neurons activated by input from skin mechanoreceptors are largely confined to the ventroposterior complex, whereas retinal input readily activates neurons in the dorsal lateral geniculate (DLG) nucleus. Thus, nuclei represent a key principle of thalamic organization and function (Sherman & Guillery, 2005; Jones, 2007).

Despite the central role of nuclear parcellation in the organization of thalamocortical (TC) connectivity, there is now ample evidence for the presence of distinct TC neuron types within cytoarchitectonically-defined nuclei (Jones, 1998, 2007; Rubio-Garrido *et al.*, 2009). Such diversity mainly involves differences in the tangential spread and lamina-specific termination of TC axons in the cerebral cortex, but also in the targeting of subcortical structures such as the striatum and amygdala. At least three broad TC cell types (Herkenham, 1986; Castro-Alamancos & Connors, 1997; Jones, 1998, 2007; Huang & Winer, 2000) can be identified based on such axonal differences (Table 1): intralaminar-type (IL-type), matrix-type (M-type) and core-type (C-type) neurons. Moreover, a further distinction can be made between M-type cells with widely ramified axons targeting multiple, distant cortical areas and M-type cells with an axon that arborizes within a single or few adjacent areas (Rubio-Garrido *et al.*, 2009) (Table 1). Remarkably, these axonally-diverse neuronal subtypes are found in most thalamic nuclei, albeit in markedly varying proportions, such that a given nucleus can be defined by a typical complement of TC neuron types (Fig. 1).

In addition to this hodological (i.e. connectivity-related) diversity, there is now ample evidence for diversity in the somatodendritic morphology of TC neurons (Jones, 2007). Although the intermingling of the distinct TC neuron types within the thalamus and the overlap of their axonal projections in the neocortex have long hampered the correlation between somatodendritic and axonal phenotypes (LeVay & Gilbert, 1976; Penny *et al.*, 1982; Avendaño *et al.*, 1985, 1990; Mitani *et al.*, 1987; Rausell *et al.*, 1992; Rubio-Garrido *et al.*, 2007), new labeling techniques now open the possibility of correlating, at the individual cell level, axonal architecture, somatodendritic shape and even gene expression. As examples, juxtacellular labeling (Pinault, 1996; Noceda *et al.*, 2011) and low-titer viral transfection (Kuramoto *et al.*, 2009) allow single-cell labeling of identified long-range projection neurons and open a new window for our appraisal of the diversity of TC neurons (Galazo *et al.*, 2008; Kichula & Huntley, 2008).

C-type neurons are the most widely studied type of TC neurons. Their highly topographic wiring and laminar target specificity are consistent with their role in the accurate and spatially precise 'bottom-up' transmission of inputs, either from ascending systems to primary cortical areas, or from primary areas to other areas higher in the hierarchy of cortical processing, via cortico-thalamo-cortical

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TABLE 1. General features of the main TC cell types based on observations in rodents, carnivores and primates

	IL-type	M-type (multiareal)	M-type (focal)	C-type
Laminar axonal arborization in neocortex	Mostly 6 and 5	1, 5a, 3; never 4	1, 3; never 4	4–2, 6; never 1
Area targeting in cortex	Single or adjacent areas	Multiareal, via subcortical axon branches	Single or adjacent areas	Single or adjacent areas, often highly topographic
Arborization pattern	No	Tangentially spread, multiple distant arbors	Tangential arborization (single or few arbors)	Dense branching, focal (single or few arbors)
Axon collaterals to striatum	Always present, extensive	Present in most (all?) cases	?	No
Relative soma size	Variable	Often smaller than other cells in the nucleus	Variable	Often larger than other cells in the nucleus
Dendritic tree complexity	Few, often long dendrites	Bushy dendrites, often less ramified	Bushy dendrites	Bushy dendrites
Calcium-binding protein expression	Most express Calbindin	Calbindin, never parvalbumin	Most express Calbindin, never parvalbumin	Parvalbumin in many primates (but not in rodents or carnivores)
General type of afferent input	Cortical layers 5 and 6 GPM/SNR	Cortical layers 5 and 6, non-lemniscal sensory GPM/SNR/ZI	Cortical layers 5 and 6, non-lemniscal sensory	Cortical layer 6, lemniscal sensory, deep cerebellar nuclei

connections (Sherman & Guillery, 2005, 2011). Such topographic wiring along with the robust responsiveness to peripheral stimulation, even under anesthesia, has historically made C-type neurons the focus of virtually all experimental and modeling studies on TC systems. In fact, C-type neuron anatomy and function are still widely believed to represent the thalamus as a whole, despite the evidence that such neurons are a minority outside the sensory relay nuclei (Jones, 2007; Rubio-Garrido *et al.*, 2009) (Fig. 1B). The wiring and functional properties of other TC neuron types remain at present poorly understood (Theyel *et al.*, 2010). The widespread divergence/convergence and specific laminar pattern of termination in the cortex of M-type cell axons are consistent with the view that they may support descending ('top-down') corticocortical interactions via the thalamus, and/or the synchronization of spatially distributed assemblies of cortical neurons in cognition and memory (Crick & Koch, 1998; Jones, 2001; Hawkins & Blakeslee, 2004; Rubio-Garrido *et al.*, 2009; Saalmann & Kastner, 2011; Viaene *et al.*, 2011). IL-type neurons, in turn, may be part of multisynaptic basal ganglia loops, but simultaneously provide innervation to the motor and limbic cortex (Parent & Parent, 2005).

In recent years, TC pathways have become major models for studies of axonal guidance, cortical specification and plasticity in development; careful consideration of TC neuron diversity is relevant for a thorough understanding of the cellular and molecular mechanisms controlling TC circuit formation. In the following sections, we will review emerging evidence for a broad diversity of TC neuron subtypes, with regard to their connectivity and morphology, but also in terms of their molecular identity and developmental biology.

Diversity in axonal branching and target specificity of thalamocortical neurons

The most consistent criterion for distinguishing distinct subtypes of TC neurons is their axonal distribution, including (i) the tangential spread of their axon in the cortex, (ii) the cortical laminar target specificity of these axons, and (iii) the presence or absence of axonal collaterals to subcortical structures.

Tangential spread of thalamocortical axons

Classical studies of TC connections based on lesion methods have suggested that the projections from each nucleus of the thalamus were circumscribed to specific regions of the cerebral cortex (for a historical review, see Jones, 2007). Subsequent electrophysiological and connectivity studies, conducted mainly in experimentally-accessible nuclei such as the such as the somatic Ventroposterior nucleus or visual Dorsal Lateral Geniculate nucleus, reinforced the notion of a rather strict point-to-point spatial correspondence between the neuron soma location in the thalamus and the axon distribution in the cortex. Overall, these observations led to the concept of thalamic nuclei being cytoarchitectonically-circumscribed regions receiving a specific set of afferent fibers and projecting topographically within the borders of a specific set of cortical fields.

However, early work by Lorente de No (1938) using Golgi stains had already suggested that, whereas some presumed TC axons enter the cortical gray matter at a single point to innervate a small cortical region, others branch in the subcortical white matter to enter the gray matter at several locations; he called these TC axons 'specific' and 'non-specific', respectively. Subsequent connection-tracing studies (Herkenham, 1979, 1986; Caviness & Frost, 1980; Macchi *et al.*, 1996; Rubio-Garrido *et al.*, 2009) indicated that, whereas some thalamic nuclei contain neurons whose axons target one or few adjacent cortical areas, other nuclei innervate wide regions of the cerebral hemisphere. Such extensive innervation may result from populations of neurons in a given thalamic nucleus projecting to different cortical regions (Spreafico *et al.*, 1987; Cappe *et al.*, 2009) or from neurons projecting to multiple cortical targets. Mounting evidence from rodents and primates suggests the latter scenario (Deschênes *et al.*, 1998; Rockland *et al.*, 1999; Gauriau & Bernard, 2004; Kuramoto *et al.*, 2009; Noseda *et al.*, 2011; Ohno *et al.*, 2011).

Laminar target specificity of thalamocortical axons

Marked differences exist in the targeting of TC axon terminals to the distinct neocortical laminae. Although the intracortical axonal arbors of TC neurons are complex and evidence from detailed single-axon reconstruction studies is still limited, each of the main TC cell types has a distinct laminar pattern of projection (Table 1, Fig. 1A). C-type neurons have a profuse arborization in cortical layers III–IV (and, to a lesser degree, upper layer VI), M-type neurons have a characteristic subpial arborization in layer I (and usually also in layer III or upper layer V) and, finally, IL-type neurons arborize in layers V and VI, with an occasional extension into supragranular layers (Killackey & Ebner, 1973; Jones & Burton, 1976; Herkenham, 1980, 1986; Frost & Caviness, 1980; Berendse & Groenewegen, 1991; Shinoda *et al.*,

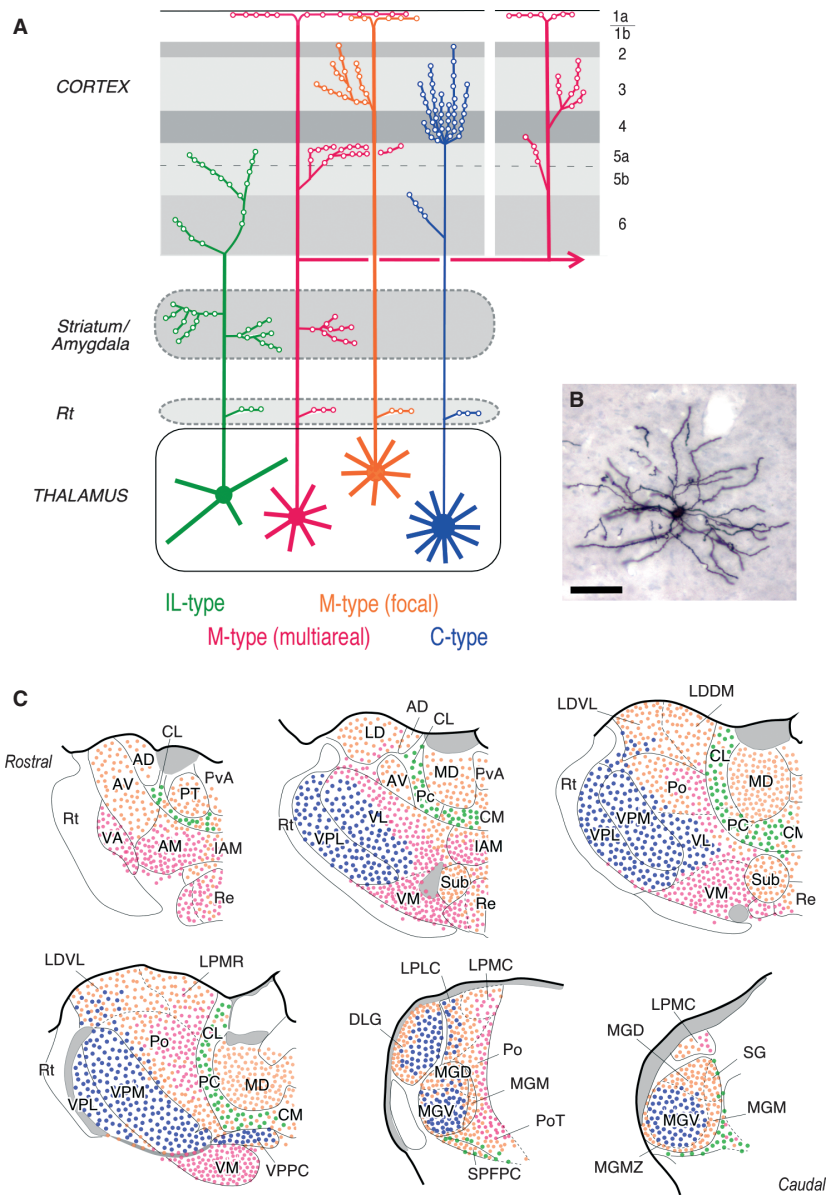

FIG. 1. (A) Schematic diagrams of the TC projection neuron types present in the rodent thalamus showing their typical somatodendritic axon morphology, including the distribution of axon terminals in the reticular prethalamic nucleus (Rt), striatum and cerebral cortex. (B) Somatodendritic appearance of a typical M-type TC neuron. The image, taken from a 40-μm-thick tissue section, shows the soma and many of the dendrites of a posterior nucleus neuron. Golgi-like labeling is the result of transfection with a Sindbis-Pal-Green Fluorescent Protein (GFP) vector and metal-enhanced immunohistochemistry. Bar: 100 μm. (C) Schematic cell somata distribution of TC cell types throughout the thalamus. General cell-type prevalence is represented by color dots (as in A) on six coronal section diagrams of the rat thalamus. AD, anterodorsal thalamic nucleus; AM, anteromedial thalamic nucleus; AV, anteroventral thalamic nucleus; CL, central lateral thalamic nucleus; CM, central medial thalamic nucleus; DLG, Dorsal Lateral Geniculate thalamic nucleus; IAM, interanteromedial thalamic nucleus; LD, lateral dorsal thalamic nucleus; LDDM, lateral dorsal thalamic nucleus, dorsomedial division; LDVL, lateral dorsal thalamic nucleus, ventrolateral division; LPLC, lateral posterior thalamic nucleus, caudal division; LPMC, lateral posteromedial thalamic nucleus, caudal division; LPMR, lateral posterior thalamic nucleus, rostral division; MD, mediodorsal thalamic nucleus; MGD, medial geniculate nucleus thalamic nucleus, dorsal division; MGM, medial geniculate thalamic nucleus, medial division; MGMZ, medial geniculate thalamic nucleus, marginal zone; MGV, medial geniculate thalamic nucleus, ventral division; PC, paracentral thalamic nucleus; Po, posterior thalamic nucleus; PoT, posterior thalamic nucleus, triangular division; PT, paratenial thalamic nucleus; PvA, Anterio paraventricular thalamic nucleus; Re, reuniens thalamic nucleus; Rt, reticular (pre)thalamic nucleus; SG, supragenicular thalamic nucleus; SPFPC, Subparascicular thalamic nucleud, parvocellular part; Sub, submedius thalamic nucleus; VA, ventral anterior thalamic nucleus; VL, ventral lateral thalamic nucleus; VM, ventromedial thalamic nucleus; VPL, ventroposterior lateral thalamic nucleus; VPM, ventroposterior medial thalamic nucleus; VPPC, parvocelular ventroposterior medial nucleus.

1993; Deschênes *et al.*, 1996, 1998; Jones, 2007; Kuramoto *et al.*, 2009; Ohno *et al.*, 2011).

These differences in laminar targets imply that the distinct TC neuron subtypes contact specific neurons and dendritic domains within the cortical microcircuit, and, consequently, may have different postsynaptic transduction mechanisms or computational value (Castro-Alamancos & Connors, 1997; Spratling, 2002; Llinás *et al.*, 2002; Larkum *et al.*, 2004; Petreanu *et al.*, 2009; Meyer *et al.*, 2010; Viaene *et al.*, 2011). For example, TC axons terminating mainly in layer IV may target spiny stellate neurons and apical dendrites of layer VI

neurons (Jones, 2007), whereas axons terminating in layer I may target the apical dendritic tuft of layer II, III and Vb pyramidal neurons (Kubota *et al.*, 2007). In the highly sublaminated visual cortex of primates or carnivores, laminar compartmentalization of TC afferents has been shown to be even more specific, with distinct C-type neuron varieties selectively arborizing in precise sublaminae of layers II–IV (Freund *et al.*, 1989; Boyd & Matsubara, 1996; Callaway, 2005).

Presence of subcortical collaterals

A third aspect of phenotypic diversity among TC cell axons is the presence or absence of collateral branches to non-cortical forebrain structures such as the striatum and amygdala (Fig. 1A). As all TC axons extend across the striatal gray matter on their way to the cortex, the question as to whether thalamostriatal projections represent axonal collaterals of TC neurons or in fact originate from a distinct, specific set of 'thalamostriatal' neurons remains controversial. The few single-axon reconstruction studies available to date indicate that most thalamostriatal projections arise from TC axon collaterals, but also reveal that specific subsets of TC neurons extend their axons across the striatum without branching (Deschênes *et al.*, 1996, 1998; Parent & Parent, 2005; Galazo *et al.*, 2008; Kuramoto *et al.*, 2009; Noceda *et al.*, 2011; Ohno *et al.*, 2011). In addition, specific subsets of TC neurons send collaterals to the amygdala in non-tonotopic auditory nuclei and adjacent multimodal nuclei (Namura *et al.*, 1997; Doron & Ledoux, 2000; Gauriau & Bernard, 2004). Moreover, whereas subcortical collaterals to the striatum or amygdala seem limited to M-type or IL-type neurons, the neurons in all thalamic nuclei extend collaterals to the reticular nucleus. Together, these data indicate that distinct subtypes of TC neurons extend axonal collaterals to specific subcortical targets, although the molecular mechanisms controlling this process are unknown.

Diversity in the somatodendritic morphology of thalamocortical neurons

The TC neuron morphology as revealed by Golgi stains or intracellular dye injections appears roughly similar throughout the thalamus, even in different species. TC neurons typically show a multipolar soma with numerous and highly branched dendrites with a radial or bipolar distribution, which give the cells a characteristic 'bushy' appearance (Fig. 1B). On closer inspection, however, consistent differences in soma size, dendrite length, thickness, and number have been noted, even within single thalamic nuclei (Jones, 2007). Two broad morphologies can be identified: neurons with a large soma, thick axon and abundant and profusely branched dendrites, and neurons with a smaller soma, thin axon and slender/sparse dendrites. As a striking example of these morphological differences, TC neurons in the DLG nucleus of carnivores and primates can be divided into different morphological cell types (Guillery, 1966; Hickey & Guillery, 1981; Saini & Garey, 1981; Garey & de Court, 1983), which have distinctive membrane conductances and relay specific retinal signals (Crunelli *et al.*, 1987; Boyd & Matsubara, 1996). However, major departures from the stereotypical 'bushy' morphology have been reported in TC neurons of the intralaminar (Deschenes *et al.*, 1996; Parent & Parent, 2005), ventromedial (Monconduit & Villanueva, 2005) and some non-tonotopic auditory nuclei (Smith *et al.*, 2006). Such TC neurons have much longer, less numerous and less ramified dendrites. In motor, sensory and associative thalamic nuclei of carnivores and primates, the neurons innervating layer I are significantly smaller than those in the same nucleus innervating only deeper cortical layers (LeVay & Gilbert, 1976; Carey *et al.*, 1979a,b; Penny *et al.*, 1982; Fitzpatrick *et al.*, 1983; Rausell & Avendaño, 1985; Mitani *et al.*, 1987; Avendaño *et al.*, 1990; Rausell *et al.*, 1992; Hendry & Yoshioka, 1994), and giant TC neurons with widespread cortical projection have been reported in the medial geniculate nucleus of carnivores and the pulvinar nucleus of monkeys (Huang & Winer, 2000; Imura & Rockland, 2007). Similarly, a recent single-cell virus-mediated labeling study in the rat ventral anterior nucleus (Kuramoto *et al.*, 2009) has revealed that the neurons projecting to superficial cortical layers of the motor cortex have significantly less profusely branched dendrites than neurons projecting to deeper cortical layers. Whether this correlation between laminar target specificity and cell morphology is the consequence of integration into a specific TC pathway, or reflects different aspects of neuron-type specific differentiation programs remains to be investigated.

Molecular and genetic diversity of thalamocortical neurons

Compared with the evidence for the hodological and morphological diversity of TC neurons, data on the neuron-type specific expression of gene transcripts or proteins are more limited. Although recent work has begun to shed light on adult and developmental gene expression in the distinct nuclei of mice and monkeys (Nakagawa & O'Leary, 2001; Migliore & Shepherd, 2005; Sugino *et al.*, 2006; Murray *et al.*, 2007; Horng *et al.*, 2009; Diez-Roux *et al.*, 2011; Yuge *et al.*, 2011; Suzuki-Hirano *et al.*, 2011; Otsuka & Kawaguchi, 2011), our current understanding of the molecular identity of the distinct subtypes of TC neurons largely rests on serendipitously-identified genes. This is in contrast with the state of research in the neocortex where, despite a tremendous cellular diversity, striking progress has been made over recent years in our understanding of the molecular identity and developmental controls over the distinct subtypes of projection neurons (Molyneaux *et al.*, 2007; Hattox & Nelson, 2007; Miller *et al.*, 2008; Fame *et al.*, 2011).

Calcium-binding proteins have historically been widely used as molecular 'markers' to identify distinct subtypes of TC neurons. In most nuclei of monkeys and rats, Calbindin 28K is expressed by the TC neurons projecting to layer I but not those innervating cortical layers III–IV (Rausell *et al.*, 1992; Hashikawa *et al.*, 1995; Rubio-Garrido *et al.*, 2007). In contrast, in many thalamic nuclei of primates, another calcium-binding protein, parvalbumin, is expressed in groups of TC neurons largely complementary to those expressing Calbindin 28K. Together, parvalbumin-expressing and Calbindin 28K-expressing cells are believed to encompass the whole population of TC neurons in macaque monkeys (Jones, 2007). Moreover, at least in the sensory relay nuclei of macaques, parvalbumin-expressing TC neurons innervate layers II–IV. However, this correlation cannot be extended to rodents, where virtually no cell in the dorsal thalamus expresses parvalbumin, or to carnivores, where parvalbumin is expressed not by TC cells but by the intrinsic interneurons. Finally, calcium-dependent calmodulin kinase 2a has been shown to be specifically expressed by neurons in some laminae of the monkey DLG (Hendry & Yoshioka, 1994; Jones, 2007), and the calmodulin-binding protein Purkinje Cell Protein 4 (PCP4) is expressed in discrete nuclei of the adult monkey (Murray *et al.*, 2007). Despite their widespread use as molecular markers for distinct classes of thalamic nuclei, the functional significance of the segregated distribution of these calcium-binding proteins remains unknown.

Beyond these 'classical' markers, a recent gene expression screen in the adult macaque thalamus has systematically compared gene

expression in select nuclei, identifying several genes with a nucleus-specific pattern of expression (Murray *et al.*, 2007). Similarly, early postnatal gene expression has been compared in the mouse DLG and medial geniculate nucleus (Horng *et al.*, 2009), a recent study has examined the expression of select hypothalamic genes in the embryonic and postnatal thalamus (Suzuki-Hirano *et al.*, 2011; Yuge *et al.*, 2011), and the Eurexpress consortium has identified several genes with mutually exclusive expression in the early (postconceptional day 14, 'E14') embryonic thalamus (Diez-Roux *et al.*, 2011). Candidate genes identified in these and other (Nakagawa & O'Leary, 2001) studies have a very broad ontology, and include transcription factors, extracellular matrix-related proteins, and synaptic/membrane gene products. Although these findings provide an important foundation for our future understanding of TC neuron diversity, the functional relevance of these candidate genes has generally not been examined (but see Horng *et al.*, 2009), and whether they are involved in the generation and specific differentiation of distinct subtypes of TC neurons remains unknown.

There is now ample evidence for parcellation of the embryonic thalamic neuroepithelium and mantle zone into distinct gene expression domains (Nakagawa & O'Leary, 2001; Bluske *et al.*, 2009; Diez-Roux *et al.*, 2011; other articles in this Special Issue). Although these distinct progenitor domains have been shown to give rise to excitatory projection neurons (dorsal thalamus) or inhibitory interneurons (prethalamus: reticular nucleus, ventral lateral geniculate nucleus and zona incerta), no marker or combination of markers has been shown to identify neurons destined to populate specific thalamic nuclei. Likewise, although the emergence of anatomically distinct nuclei during development is believed to result from transient anisotropic patterns of expression of regulatory genes and cell adhesion molecules (Nakagawa & O'Leary, 2001; Murray *et al.*, 2007; see other articles in this Special Issue), direct evidence for such processes is largely lacking. At later stages of development, however, some genes are progressively expressed within the thalamic nuclear boundaries (see references above), but the correspondence of these markers with the subtypes of TC neurons discussed here is unclear. Differences in gene expression such as those highlighted above are probably at the root of the distinctive morphology and connectivity of TC neuron subtypes. It is likely that the use of recombinant (e.g. Cre/lox) genetic techniques allowing fate mapping based on the combinatorial expression of multiple genes will in the future contribute to our understanding of the lineage relationships and molecular biographies of the distinct TC neuron subtypes.

Electrophysiological diversity of thalamocortical neurons

Studies in different mammal species have shown that TC neurons display roughly similar general membrane properties. These include a resting potential of around –60 mV (Turner *et al.*, 1997; Aguilar *et al.*, 2008; Li *et al.*, 2003; Bartlett & Smith, 1999; Smith *et al.*, 2006), input resistance of 55–80 Ω (Turner *et al.*, 1997; Smith *et al.*, 2006), and firing threshold of about −40 mV (Turner *et al.*, 1997). In addition, TC neurons have a low-threshold Ca^{2+} conductance that allows burst firing when the cell membrane potential is more negative than −65 mV (Deschênes *et al.*, 1982; Llinás & Jahnsen, 1982; Sherman, 2001). At more positive membrane potential levels, however, the neurons enter a tonic firing mode that is thought to be critical for the accurate transmission of peripheral information. Moreover, interactions between this and other membrane conductances allow TC cells to display different intrinsic rhythms, like the slow (0.5–4 Hz) (Nuñez *et al.*, 1992), very slow (0.05–0.2 Hz) (Leresche *et al.*, 1991) or spontaneous high-frequency (20–80 Hz) oscillations at membrane potentials of −45 mV (Pedroarena & Llinás, 1997).

As previously mentioned, virtually all of these studies were conducted in the lemniscal divisions of the main sensory relay nuclei. Although such nuclei turn out to be almost exclusively populated by C-type cells, some studies have described different functional response profiles. For example, in the visual and somatic relay nuclei, specific subsets of TC neurons were found to respond to brief peripheral stimuli with rapidly adapting (transient) discharges, whereas other neurons responded with slowly adapting (sustained) discharges (Yen *et al.*, 1985; Turner *et al.*, 1994, 1997). There are as yet virtually no studies in non-lemniscal nuclei correlating differences in membrane properties with TC cell somatodendritic and axon morphology (Smith *et al.*, 2006).

Overall, the situation is in contrast with cortical projection neurons, where recent studies have revealed striking electrophysiological differences between otherwise similar-looking pyramidal neurons of the same cortical layer (Christophe *et al.*, 2005; Molnar and Cheung 2006; Hattox & Nelson, 2007; Miller *et al.*, 2008). These cortical studies show that, in principle, beyond a basic similarity in electrotonic properties due to similar somatodendritic morphology, different electrophysiological properties may result from the specific combinatorial expression and/or subcellular localization of ion channel proteins. We think it thus quite possible that more detailed analysis of membrane conductances in TC neurons beyond the classical relay nuclei may in future reveal specific conductances and/or membrane dynamics that are associated with the various TC neuron types.

Developmental diversity of thalamocortical connectivity

In the past two decades, projection neurons of the thalamus have become key models to study developmental axonal guidance, activity-dependent pathfinding and plasticity, and cortical area specification (reviewed in Sur & Rubenstein, 2005; Price *et al.*, 2006). All of these studies, however, have focused on rodent thalamic nuclei that contain predominantly or exclusively C-type neurons, typically the VP and DLG nuclei. These studies have revealed that TC axon growth cones navigate rapidly across the prethalamus and medial and lateral ganglionic eminences to enter the pallium, where they fan in the intermediate zone in roughly straight trajectories until they reach the subplate (SP) underlying their cortical target area (López-Bendito & Molnár, 2003; López-Bendito *et al.*, 2006). Once in the SP, growth cones turn superficially and their advance slows markedly. Axons usually give off some short branches in the SP and the deep layers of the cortical plate (Fig. 2), where transient functional circuits are thought to be established (Kanold & Luhman, 2010). In carnivores and primates, the cortical neurogenesis and migration processes of which are much more protracted than in rodents, C-type neuron axon progression into the cortical plate virtually stalls in the SP for several weeks (the so-called 'waiting period') (Rakic, 1977; Shatz & Luskin, 1986). In rodents, carnivores and primates, ingrowth, arborization and synaptogenesis of C-type axons in the middle cortical layers is relatively slow-paced, and remarkably precise from the outset (Agmon *et al.*, 1995, Yamamoto *et al.*, 2000).

Although much less is known about the developmental connectivity of M-type thalamic neurons, the few studies investigating axonal pathfinding processes in these neurons have shown clear differences with C-type neurons (Galazo *et al.*, 2008; Kichula & Huntley, 2008) (Fig. 2). Although at early developmental stages the axons of M-type and C-type TC neurons cannot be distinguished, cortical invasion

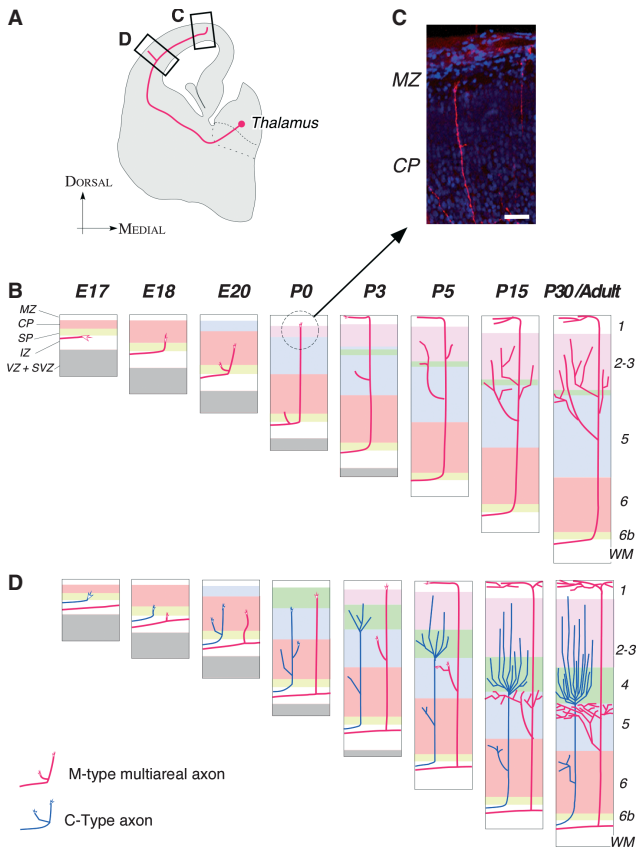

FIG. 2. Schematic developmental sequence of axon arborizations in a multiareal M-type TC axon (magenta lines) targeting two separate areas of the cerebral cortex. For comparison, the development of a typical C-type axon is shown by blue lines. (A) Sketch of the M-type cell extending its axon from the thalamus to the cerebral cortex on a coronal section of the rat embryo cerebral hemisphere around embryonic day (E) 20. Framed regions are those represented in B and D. Bar: 500 μm. (B) Arborization formed in a dorsal cortical region targeted by the main growth cone of the axon. Bar: 25 μm. (C) Fluorescently-labeled, growth cone-tipped axons radially extending to the marginal zone (MZ) (future layer 1) and waiting without extending tangentially in the MZ. (D) Growth of an idealized axonal arborization in a lateral cortical region. Note that this arborization develops from a collateral branch sprouted from the trunk of the primary axon. CP, cortical plate; IZ, Intermediate zone; P, postnatal day; SVZ, subventricular zone; VZ, ventricular zone; WM, white matter.

proceeds distinctly. In TC neurons that target multiple distant cortical areas, multiple arborizations develop from interstitial branches that sprout perpendicularly from axon trunks under the appropriate cortical regions (Galazo *et al.*, 2008). Cortical areas located more proximally on the axonal shaft are not necessarily innervated first; in posterior thalamic nucleus neurons, branches to the somatosensory cortex sprout later than branches to the motor cortex, despite the fact that the main axonal shaft of these neurons first has to extend under the presumptive somatosensory cortex to reach the dorsally situated motor cortex (Galazo *et al.*, 2008). Therefore, even within a single axon, mechanisms exist that regulate collateral sprouting in an area-dependent manner. Interestingly, branches to the striatum, although very proximal on the axonal shaft, sprout later than cortical branches, further suggesting tight site-specific control over axonal collateralization.

The layer-specific targeting of the M-type axon arbors is remarkably selective; they cross layer IV or VI without branching, but arborize from the outset in their appropriate target layers (I and Va) (Galazo *et al.*, 2008; Kichula & Huntley, 2008), suggesting that they respond to different guidance signals, or react to the same signals in a different manner, than C-type axons (Yamamoto *et al.*, 2000; Maruyama *et al.*, 2008). In the case of the tangential arborization in layer I in rodents, the radially-ascending growth cones pause for about 48 h upon arrival at the layer, then take a 90 ° turn and begin a fast subpial extension and branching (Portera-Cailliau *et al.*, 2005; Galazo *et al.*, 2008).

Although, in the fast-developing rodent brain, M-type and C-type axons have been observed to invade and arborize into the cortex on about the same day (Galazo *et al.*, 2008) (Fig. 2), it is worth noting that, in the slow-developing cortex of carnivores, the timing of cortical invasion and layer-specific arborization by M-type and C-type axons is strikingly different. In cats and ferrets, C-type axons wait for several weeks in the SP, as mentioned above, whereas M-type axons extend rapidly across the cortical plate to arborize and make functional synapses in layer I, weeks before C-type axons even begin entering their target layer (layer IV) (Shatz & Luskin, 1986; Kato, 1896, 1987; Clascá & Sur, 1996). As SP neurons are thought to play a critical role of transient scaffolding of TC circuits (Kanold & Luhmann, 2010), it is interesting to speculate that differences in the nature of interactions with SP neurons could contribute to the distinct connectivity of C-type and M-type TC neurons in the adult cortex.

It is currently unknown whether C-type and M-type TC neurons are equally affected by non-cell-autonomous processes such as cortex-derived signals or activity-dependent signals from the periphery. For example, whereas the genetic reassignment of cortical identity by the ectopic expression of the morphogen fibroblast growth factor 8 (FGF8) leads to a mirror-like duplication of S1 and corresponding branching of (otherwise unbranched) C-type ventroposterior medial thalamic nucleus axons to both areas (Shimogori & Grove, 2005), it is unknown how this affects M-type S1-projecting posterior thalamic nucleus axons.

Along the same line of thought, although several genes have been shown to play a critical role in the axonal guidance and connectivity of select C-type nuclei (e.g. 5 hydroxy-tryptamine transporter (5HTT) or adenylate cyclase 1 (AdCy1) in TC neurons of the ventroposterior complex) (for review see López-Bendito & Molnár, 2003), it is not known whether loss of these genes, when broadly expressed, also affects M-type neurons. Similarly, although input/activity-dependent processes have been shown to play a critical role in the assembly of C-type TC circuits, it is essentially unknown how peripheral input affects M-type TC neurons. For example, peripheral sensory deprivation in the trigeminal system induces rapid and dramatic changes in the TC arborization of C-type axons innervating the layer IV 'barrels' in the mystacial vibrissae representation of the rodent in S1 (Jensen and Killackey, 1987; Catalano *et al.*, 1991), but whether this affects S1-projecting M-type neurons in the posterior nucleus of the thalamus has not been examined.

Finally, beyond its basic importance in the understanding of TC circuits and physiology, a detailed understanding of the molecular mechanisms that account for the diversity of TC projection neurons will probably be critical to understand the neural basis and evolution of normal and pathological perception, voluntary movement, cognition and attention. Indeed, TC neuron dysfunction has been involved in a number of neurological disorders, most notably absence seizures (Beenhakker & Huguenard, 2009), but also in cognitive or neuropsychiatric conditions such as schizophrenia, Tourette's disease and chronic pain (Llinás *et al.*, 1999; Albin & Mink, 2006; Jones, 2010). As some of these disorders have been linked with genetic defects in human patients, it will be interesting in future studies to investigate whether genetically-based abnormal differentiation of specific TC

neuron subtypes is the basis of some of the clinical manifestations of these disorders.

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Abbreviations

C-type, core-type; DLG, dorsal lateral geniculate; IL-type, intralaminar-type; M-type, matrix-type; SP, subplate; TC, thalamocortical.

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