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IN AND OUT FROM THE CORTEX: DEVELOPMENT OF MAJOR FOREBRAIN CONNECTIONS

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Abstract—In this review we discuss recent advances in the understanding of the development of forebrain projections attending to their origin, fate determination, and axon guidance. Major forebrain connections include callosal, corticospinal, corticothalamic and thalamocortical projections. Although distinct transcriptional programs specify these subpopulations of projecting neurons, the mechanisms involved in their axonal development are similar. Guidance by short- and long-range molecular cues, interaction with intermediate target populations and activity-dependent mechanisms contribute to their development. Moreover, some of these connections interact with each other showing that the development of these axonal tracts is a well-orchestrated event. Finally, we will recapitulate recent discoveries that challenge the field of neural wiring that show that these forebrain connections can be changed once formed. The field of reprogramming has arrived to postmitotic cortical neurons and has showed us that forebrain connectivity is not immutable and might be changed by manipulations in the transcriptional program of matured cells.

Key words: axon guidance, fate determination, callosal projection neurons, corticospinal tract, corticothalamic axons, thalamocortical axons.

Contents

INTRODUCTION

The function of the cerebral cortex relies on several stereotypical long-distance projections, which originate from excitatory projection neurons that represent the largest portion of all cortical neurons. These neurons are born from neural progenitors in the dorsal telencephalon and are classified into numerous subtypes based: (i) on their location within different cortical layers and areas, (ii) their axonal projections to distinct intracortical, subcortical, and subcerebral targets; and (iii) the combinatorial expression of different neuron-type specific genes.

Four broad axonal tracts exist within the forebrain: the corpus callosum (CC), the corticospinal tract (CST), the corticothalamic projection and the thalamocortical projection (Fig. 1). Cortical projection neurons can be classified into two broad classes: corticocortical neurons and corticofugal neurons. The corticocortical neurons can be subdivided into ipsilateral and callosal projection neurons (CPN), which project axons to ipsilateral and contralateral cortices, respectively. The cell bodies of these neurons are in layers II through VI, interconnecting cortical neurons in complex networks.

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Abbreviations: A1, auditory cortex; CC, corpus callosum; CP, cortical plate; CPN, callosal projection neurons; CSMN, corticospinal motor neurons; CST, corticospinal tract; CTA, corticothalamic axons; Ctip2, COUP-TF interacting protein 2; DCC, deleted in colorectal carcinoma; DF, dorsal funiculus; dLGN, dorsal lateral geniculate nucleus; DTB, diencephalon-telencephalon boundary; E, embryonic day; IC, internal capsule; IGF-1, Insulin-like growth factor-1; IZ, intermediate zone; MGN, medial geniculate nucleus; NCAM, neural cell adhesion molecule; Npn-1, Neuropilin-1; PRN, perireticular thalamic nucleus; PSPB, pallial–subpallial boundary; RTN, reticular thalamic nucleus; Satb2, Special AT-rich sequence-binding protein 2; SVZ, subventricular zone; TCA, thalamocortical axons; TF, transcription factor; V1, visual cortex; VB, ventrobasal nucleus; vTel, ventral telencephalon; VZ, ventricular zone.

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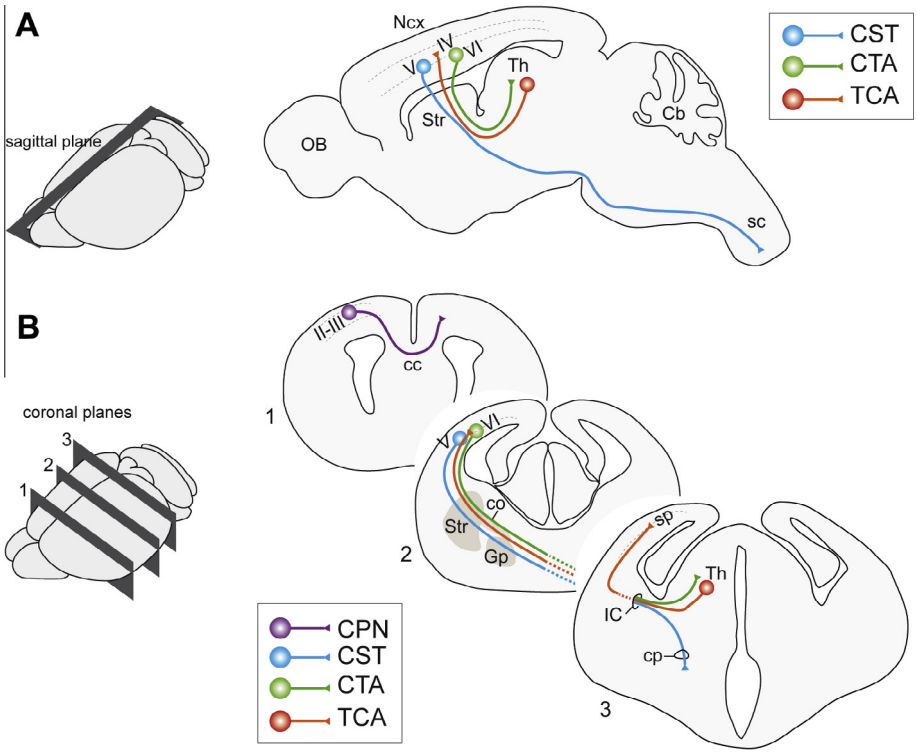

Fig. 1. Major forebrain axonal tracts. Schematic representation of CPN (in purple), CST (in blue), CTA (in green) and TCA (in red) projections in a sagittal section (A) and in serial coronal sections (B). This figure is partially adapted from (A) Fame et al. (2011) and (B) López-Bendito et al. (2007). *Abbreviations:* OB, olfactory bulb; Str, striatum; co, corridor; Gp, globus pallidus; Th, thalamus; Cb, cerebellum; Ncx, neocortex; sp, subplate; cc, corpus callosum; IC, internal capsule; cp, cerebral peduncle; sc, spinal cord. Copyright Elsevier.

The cortex receives its major sensory input from the thalamus via the thalamocortical projection, which is reciprocally connected with the cortex via the corticothalamic projection. Corticofugal neurons are further divided into two groups: corticothalamic neurons, which reside in layer VI and extend their axons into the thalamus; and subcerebral projection neurons, which are confined to layer V and project axons away from the cortex into basal ganglia, diencephalon, midbrain, hindbrain and spinal cord. In this review we will highlight new discoveries regarding the development of these major forebrain tracts with an emphasis on the fate determinants that specify the different projection neuron subtypes and on the axon guidance mechanisms that assist in the formation of these connections, providing a comprehensive frame to understand their development.

CORTICOCORTICAL CALLOSAL PROJECTION

Origin and function

The majority of inputs onto cortical neurons arise from other cortical neurons, either in the same hemisphere (ipsilateral corticocortical connections) or in the opposite hemisphere (callosal connections). The two hemispheres of the cerebral cortex communicate through the largest fiber tract in the mammalian brain, the CC, which plays an essential role in high-level associative connectivity. The CC is not the only fiber tract that connects the two hemispheres, the anterior commissure and the hippocampal commissure also cross the forebrain midline, but it is the only one devoted to integrate the information from the two cortical sides. Regarding its origin, the CC is formed by the axons of a diverse population of neocortical pyramidal neurons called CPN whose cell bodies principally reside in cortical layers II/III (approximately 80% in rodents), layer V (approximately 20% in rodents) and, to a lesser extent, layer VI (Koester and O'Leary, 1994; Rash and Richards, 2001; Richards et al., 2004; Mitchell and Macklis, 2005; Lindwall et al., 2007; Petreanu et al., 2007; Donahoo and Richards, 2009; Molyneaux et al., 2009; Fame et al., 2011). Agenesis of the CC in humans is associated with a large number of different neurological syndromes with a diverse range of symptoms, including language dysfunction, abnormalities in social interaction, attention deficits, and poor personal insight (Yorke and Caviness, 1975; Paul et al., 2007).

The formation of the CC requires several critical developmental events. First, the formation of the midline which is crucial acting as a substrate for pioneering callosal axons formed by distinct midline cellular populations including the midline zipper glia, the glial wedge, the indusium griseum glia, and the subcallosal sling (Silver, 1993; Silver et al., 1993; Shu et al., 2003a). Second, the generation of callosal pyramidal neurons and their axons. Neocortical projection neurons arise primarily from apical and early basal intermediate progenitors in the pallial ventricular zone (VZ) and later from an intermediate population of basal progenitors in the subventricular zone (SVZ), a type of transit-

amplifying progenitor generated from radial glia progenitors (Tarabykin et al., 2001; Noctor et al., 2004; Richards et al., 2004; Mitchell and Macklis, 2005; Lindwall et al., 2007; Donahoo and Richards, 2009; Kowalczyk et al., 2009; Molyneaux et al., 2009; Fame et al., 2011). As development proceeds, the six-layered neocortex progressively forms in an inside–out fashion where superficial neocortical layers arise primarily from later-born intermediate basal progenitors of the SVZ. CPN are not a homogenous population of projection neurons. While deep-layer CPN have long-distance dual projecting axons, superficial-layer CPN participate in local circuitry within cortical columns (reviewed in Fame et al., 2011). Moreover, superficially located CPN also extend collaterals within the contralateral cortex, as their axons project radially into the neocortex after crossing through the CC (Paul et al., 2007; Petreanu et al., 2007). Thus, in addition to their role in integrating two homotopic regions of the neocortical hemispheres, CPN are responsible for association and integration among different neuronal types in ipsilateral and contralateral cortical hemispheres.

Finally, callosal axons are guided medially to the midline where the midline cellular populations secrete extracellular cues that assist in the turning and channeling of CPN axons across this structure. Moreover, an important mechanism used by CPN is to grow within the path formed by pioneering axons which originate from the cingulate cortex and reach the midline betweeen embryonic day (E) 14 and E15 (Silver, 1993; Silver et al., 1993; Koester and O'Leary, 1994; Rash and Richards, 2001; Shu et al., 2003a). Axons from the CPN of the neocortex then grow along the pathway defined by the pioneers, expanding the CC by E17 (Fig. 2). After crossing of the midline, callosal axons arrive to their targets in the contralateral hemisphere and innervate them in a homotopic manner; thus, the location of a CPN within the cortex defines the target of its axon (Yorke and Caviness, 1975; Tarabykin et al., 2001; Noctor et al., 2004; Richards et al., 2004; Mitchell and Macklis, 2005; Lindwall et al., 2007; Donahoo and Richards, 2009; Kowalczyk et al., 2009; Molyneaux et al., 2009).

Fate determination

Gene expression patterns in the SVZ are correlated with those of neurons in layers II-IV. As most CPN lie in superficial cortical layers, the first identified transcription factors (TFs) controlling CPN generation and development were identified as laminar-specific genes. The POU domain TFs *Brn-1* and *Brn-2* were identified as expressed in superficial cortical layers and regulate the generation of upper layer neurons (McEvilly et al., 2002; Sugitani et al., 2002). *Brn-1* or *Brn-2* single mutants show phenotypes in limited areas of the brain, however, in double mutants superficial-layer pyramidal neurons are not generated (Sugitani et al., 2002), suggesting a cell-autonomous role for *Brn* genes in upper layer neurogenesis. Besides, TFs cut-like homeobox 1 and 2, *Cux1* and *Cux2*, are expressed in SVZ cells and in their progeny in layers II–IV (Iulianella et al., 2003; Nieto et al., 2004; Zimmer et al., 2004). The analysis of *Cux2* knockout animals has revealed that *Cux2* function is necessary for SVZ formation, as is promoting the exit of SVZ cells from the cell cycle (Cubelos et al., 2008).

Special AT-rich sequence-binding protein 2 (Satb2) was the first key regulator of CPN specification identified. Satb2 is a DNA-binding TF expressed by a subset of neurons throughout the cortical layers, with a prominent expression in layers II–IV (Szemes et al., 2006; Alcamo et al., 2008; Britanova et al., 2008). The ectopic expression of *Satb2* in neurons markedly reduces the fraction of cells that express COUP-TF interacting protein 2 (Ctip2), a TF critical for corticospinal motor neurons (CSMN) axon outgrowth and fasciculation (Arlotta et al., 2005; Molyneaux et al., 2005; Chen et al., 2005a, 2005b), and alters the projections of deep layer neurons; whereas, in the absence of *Satb2*, CPN extend axons toward subcortical targets (Alcamo et al., 2008; Britanova et al., 2008). Indeed, it has been demonstrated that Satb2 promotes CPN identity in the cortex by repressing Ctip2 (Alcamo et al., 2008; Britanova et al., 2008; Gyorgy et al., 2008). It is not clear whether this repression is mutual, although the expression of Satb2 is significantly upregulated in the deep layers of *Fezf2* mutants (Chen

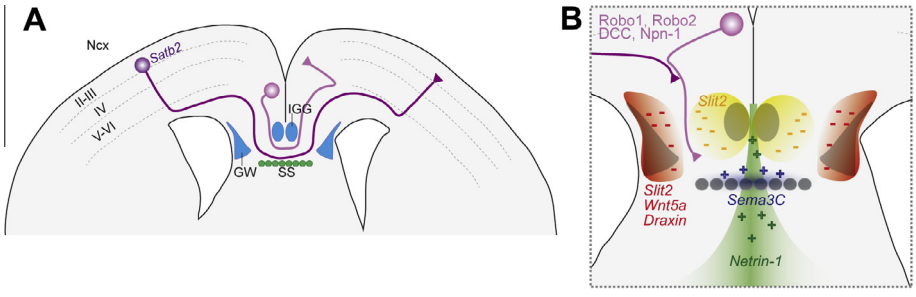

Fig. 2. Callosal axons guidance at the midline. (A) Schematic representation of the corticocortical callosal projection in a coronal section showing the midline glial structures, the callosal pioneering axons derived from the cingulate cortex (in pink), and the neocortical callosal axons that make up the bulk of the projection (in purple). (B) High-magnification scheme showing the guidance cue gradients present in the forebrain midline and the guidance receptors expressed by callosal axons. This figure is partially adapted from (A) Donahoo and Richards (2009). *Abbreviations:* Ncx, neocortex; GW, glial wedge; IGG, indusium griseum glia; SS, subcallosal sling. Copyright Elsevier.

et al., 2008), suggesting that Fezf2 can repress *Satb2* expression in subcortical projection neurons (see Fig. 5).

Identification of Satb2 as a molecular regulator of CPN identity across all layers significantly advanced the characterization of CPN at a molecular level; however, little is known about the molecular development and heterogeneity of CPN subpopulations. The purification of specific neuronal populations, followed by comparative gene expression analysis, has led to the identification of genes expressed by each population at distinct stages in development and has enriched for critical subtype-specific molecular controls by comparing gene expression between very closely related cortical projection neuron populations (Catapano et al., 2004; Arlotta et al., 2005; Molyneaux et al., 2005; Pinto et al., 2009). The work by Molyneaux and colleagues (2009) define the first set of genes that identify and molecularly subcategorize distinct populations of CPN during embryonic and postnatal development. Identification of CPN genes has been done based on their laminar and sublaminar specific distributions across different stages of maturation (Molyneaux et al., 2009). Genes expressed highly at early stages of CPN development (before E18.5 in the mouse, such as *Inhba*, *Btg1*, *Frmd4b*, *Epha3* and *Ptn*) likely act during neuronal subtype specification, differentiation, migration or initial axonal extension. Genes whose expression sharply rises and falls (mid-stages of CPN development, such as *Cpne4*, *Tmtc4*, *Nnmt*, *Cav1*, *Nectin*-3 and *Chn2*) might function at the time when CPN have already crossed the midline and are extending toward their specific targets. Finally, genes expressed specifically late in CPN development (e.g. *Plexin-D1*, *Gfra2*, *TcrB* and *Dkk3*) might function in the final stages of CPN maturation and refinement in adult connectivity. Moreover, this work also identifies differential subtype-specific laminar gene expression: a subset of genes appears specific to all CPN (e.g., *Hspb3* and *Lpl* in layers II/III and V–VI), whereas others discriminate between CPN of the deep layers and those of the upper layers (e.g., *Nectin-3*, *Plexin-D1*, and *Dkk3*). Furthermore, now we know that there are several genes that finely subdivide CPN within individual layers (Molyneaux et al., 2009).

Axon guidance control

As aforementioned, there is a wide diversity of developmental processes regulating the midline crossing of callosal axons and in the last decade several studies started to elucidate the mechanisms involved in CPN axon guidance (Fig. 2B).

CPN send axons away from the cortex when they are still migrating toward the cortical plate (CP) guided in part by guidance factors such as Semaphorin (Sema) 3A which repels axons away from the cortical marginal zone (Polleux et al., 1998). At the intermediate zone (IZ) callosal axons turn toward the midline, rather than projecting laterally as corticofugal axons do. This key decision point is regulated by the action of Sema3A that is expressed in a gradient from lateral-high to medial-low within the cortex (Zhao et al., 2011).

The CPN axons approach the midline in a steep ventral trajectory through the cingulate cortex and then abruptly turn to cross the midline at the corticoseptal boundary (Fig. 2). Once they arrive at the midline, axons are guided by midline glial structures (as the glial wedge and the indusium griseum), by neurons in the subcallosal sling (Niquille et al., 2009), and by short-range guidance molecules of the Eph/ephrin family (Mendes et al., 2006). The glial wedge is a bilaterally symmetrical glial structure that releases a cocktail of repulsive molecules such as Slit2, Draxin, and Wnt5a preventing the ventral growth of CPN axons into the septum (Shu and Richards, 2001; Bagri et al., 2002; Marillat et al., 2002; Shu et al., 2003b; Keeble et al., 2006; López-Bendito et al., 2007; Islam et al., 2009). The indusium griseum is an area of neurons and glia positioned dorsal to the CC that express Slit2 and act as a dorsal repulsive barrier for CPN axons (Shu et al., 2003b). At least some guidance roles of the subcallosal sling are mediated by Sema3C attraction through the Neuropilin-1 (Npn-1) receptor on CPN (Niquille et al., 2009; Piper et al., 2009; Fothergill et al., 2013). Npn-1 is expressed by cingulate pioneering axons and has been shown to be involved in CC formation (Gu et al., 2003; Hatanaka et al., 2009; Fothergill et al., 2013). As discussed above, axons from neurons of the cingulate cortex begin the process of midline crossing and might act as pioneers for neocortical CPN, which begin to cross one day later (Silver et al., 1982; Koester and O'Leary, 1994; Ozaki and Wahlsten, 1998; Rash and Richards, 2001; Piper et al., 2009). The pioneering axons are hypothesized to guide neocortical axons by providing a structural framework for callosal axons to follow by direct axon-axon contact, that could be also mediated by Npn-1 (Norris and Kalil, 1991; Hatanaka et al., 2009). Further, it has been shown a guidance cue integration mechanism that allows callosal axons to navigate toward the midline. Netrin-1 (Serafini et al., 1996) initially attracts callosal pioneering axons derived from the cingulate cortex, but is not attractive for the neocortical callosal axons that make up the bulk of the projection. Instead, Netrin-1 attenuates Slit-Robo repulsion in pre-crossing callosal axons to allow them to cross the midline of the developing brain (Fothergill et al., 2013).

When callosal fibers fail to cross the midline, they often remain ipsilateral and form longitudinal axon fascicles (known as Probst bundles). Probst bundles (Probst, 1901) are likely to be a product of callosal axon misguidance caused by disruption of the midline structures or their secreted molecules. Upon encountering the contralateral glial wedge, CPN axons must turn dorsally to enter the contralateral cingulate cortex and to extend into the contralateral neocortex toward their homotopic targets. The mechanisms regulating the precise targeting of CPN axons to contralateral homotopic regions are still unknown, although it has been proposed that callosal axons follow the trajectory of radial glia in the contralateral

hemisphere as they extend their axons to appropriate targets (Norris and Kalil, 1991). The final pattern and maintenance of CPN projections is likely to be sculpted by activity-dependent mechanisms (Koralek and Killackey, 1990).

CORTICOSPINAL PROJECTION

Origin and function

Among the different subcerebral axonal tracts, the CST constitutes one of the longest longitudinal projections in the vertebrate central nervous system (CNS) and the major output from the motor cortex, which connects the cerebral cortex to the spinal cord. These axons are extended by large pyramidal neurons located in deep layer V of the sensorimotor area of the neocortex and are known as CSMN. CSMN are the most well studied subtype of subcerebral projection neurons where their anatomical and morphological development has been extensively characterized (Jones et al., 1982; Terashima, 1995). They maintain primary projections to the spinal cord, with secondary collaterals to the striatum, red nucleus, caudal pons and medulla. CSMN extend their axons via the internal capsule (IC), remain ipsilateral with respect to the midline and descend in the ventral region of the cerebral peduncle, through midbrain and hindbrain until they reach the caudal-most part of the hindbrain, where most of these axons cross the midline dorsally to the contralateral side, forming the pyramidal decussation (Fig. 3). CSMN axons further project caudally within the marginal zone of the spinal cord, in a region containing the dorsal funiculus (DF) in rodents, and innervate neurons located within the spinal gray matter (Stanfield, 1992). In addition to the projections found in DF, a small number of CST axons do not decussate in the medulla, but continue downward in the ventral funiculus, close to the midline, and then decussate just prior to innervation of the gray matter in the spinal cord (Schreyer and Jones, 1982; Joosten et al., 1992; Brösamle and Schwab, 1997, 2000; Gianino et al., 1999). The complete trajectory reaches a maximum level of gray matter innervation by P14 in mice, after which time the connectivity is gradually refined and cemented over the following weeks. When fully developed, the CST allows the execution of precise movements of different muscle groups. The CSMN are of great clinical interest because they form the basis of voluntary movement in humans, they deteriorate in degenerative motor neuron diseases including amyotrophic lateral sclerosis (ALS), and disruption of the axons contributes to the loss of motor function after spinal cord injury.

Fate determination

The identification of a large number of subcerebral and CSMN-specific genes has enabled an expanding effort to decipher the programmes controlling CSMN development (Arlotta et al., 2005; Molyneaux et al.,

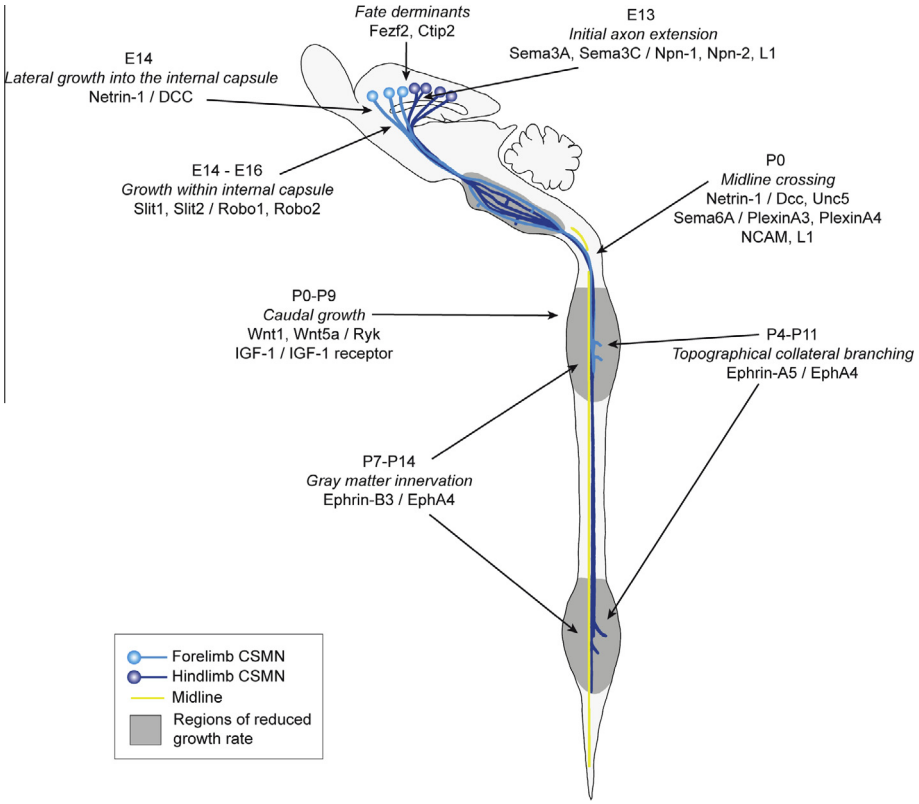

Fig. 3. Key events in corticospinal tract guidance. Schematic representation of the rodent corticospinal projection (in blue) from the motor cortex to the spinal cord gray matter, indicating the major guidance events at the different developmental stages and showing the regions of reduced growth rate where axons branch. This figure is adapted from Canty and Murphy (2008). Copyright Elsevier.

2007; Leone et al., 2008; Belgard et al., 2011). The expression patterns of these genes indicate that the fate specification and differentiation of subcerebral projection neurons in general, and CSMN in particular, are probably directed by a combinatorial code of TFs and other molecules. These include TFs (e.g., *Ctip2*, *Sox5*, *Fezf2*); cell surface proteins (e.g., *Encephalopsin*, *Itm2a*, *Daf1*); calcium signaling proteins (e.g., *Pcp4*, *S100a10*); cell adhesion proteins (e.g., *Cdh22*, *Cdh13*, *Cntn6*), axon guidance molecules (e.g., *Neto1*, *Netrin-G1*) and lincRNAs. All these factors are expressed in a pattern that together uniquely identifies CSMN. For example, *Diap3*, *Igfbp4* and *Crim1* are genes that are restricted in a small number of CSMN in the sensorimotor cortex, suggesting that they distinguish CSMN from other subcerebral projection neurons of layer V; while other genes are expressed across the full extent of layer V such as *Ctip2*, *encephalopsin*, *Fezf2*, *Clim1*, *Pcp4* and *S100a10* suggestive of expression to the majority of subcerebral projection neurons. Most importantly, beyond their roles as CSMN markers, some of these genes have been shown to control central steps of development of CSMN, including the timing of birth, fate specification and axonal connectivity (Arlotta et al., 2005).

Fezf2 is a key zinc-finger TF expressed in all subcerebral projection neurons from early stages of development through adulthood, which has been shown to be essential for CSMN early specification *in vivo* (Molyneaux et al., 2005; Chen et al., 2005a, 2005b). In *Fezf2* null-mutant mice, the entire population of subcerebral projection neurons is not specified, and the axons from CSMN fail to extend into the CST and adopt the phenotypes of CPN (Molyneaux et al., 2005; Chen et al., 2005a, 2005b). Therefore, Fezf2 appears to repress *Satb2* (directly or indirectly) thereby repressing callosal identity (Fig. 5). A second set of genes has been identified that controls later aspects of subcerebral projection neuron development, possibly acting downstream of *Fezf2*. The zinc-finger TF *Ctip2* is a crucial regulator of subcerebral axon extension and of the refinement of collaterals as CSMN mature (Arlotta et al., 2005; Chen et al., 2008). In *Ctip2* mutant mice, subcerebral projection neuron axons exhibit defects in fasciculation, outgrowth and pathfinding, with decreased numbers of axons reaching the brainstem (Arlotta et al., 2005). Similarly, the SRY-box gene *Sox5* is normally expressed by subcortically projecting neurons in layers V, VI and the subplate, and its expression is largely excluded from CPN. The ectopic expression of *Sox5* in upper layer neurons prevented them from extending axons across the CC and stimulated the extension of corticofugal axons, suggesting that *Sox5* actively promotes the differentiation of subcortical projection neurons (Lai et al., 2008). *Sox5* has been demonstrated to control the timing of generation, migration and connectivity of the CSMN population (Kwan et al., 2008; Lai et al., 2008), as *Sox5* mutants extend axons along novel trajectories and apparently fail to form a coherent CST in caudal regions. Another key TF known to have a role in the target choice of subcerebral projection neurons is *Otx1*. This protein shows a clear correlation in expression between early VZ progenitors and deep layer neurons (Frantz et al., 1994; Weimann et al., 1999). The study of mice lacking *Otx1* indicates that this gene has a later role in subcerebral projection neuron development than *Fezf2* and *Ctip2*, possibly in controlling the refinement and pruning of axonal collaterals.

Axon guidance control

In rodents, spinal cord innervation of the CST commences relatively late in development and occurs almost entirely postnatally. The topographic organization of the motor cortex develops concurrently with axonal outgrowth through the spinal cord and does not achieve its final configuration until at least 3 weeks after birth. Interestingly, despite the eventual topographic organization of the cell bodies in the motor cortex, there is no apparent grouping of functionally similar axons during their descent through the brain and brainstem. It is not until they reach the level of the spinal cord that the axons segregate into topographically specific projections.

Similar to the callosal projection, the forefront of the developing CST is composed of a small number of pioneering axons, while the majority of axons follow in tightly fasciculated bundles. The tract remains fasciculated for almost the entire developmental period and it is not until the axons have passed through the brain and have entered the spinal cord that they defasciculate from each other and spread out, at the precise level where they will connect with their respective targets in the spinal gray matter.

The guidance of CST has been extensively reviewed (Canty and Murphy, 2008; Sakai and Kaprielian, 2012). After axon specification, axons navigate into subcortical regions, with those neurons born first sending the leading axons out of the cortex. It is at this point that the CST axons begin their prolonged journey descending through the subcortical structures and into the spinal cord in search of their target cells. The trajectory of the CST axons results from a combination of various guidance factors acting at different choice points along its journey (Fig. 3). These decisions are strongly influenced by an array of transcriptional regulators (Polleux et al., 2007). Early axonal guidance cues are likely to be common for all corticofugal projecting axons as they course laterally toward the IC into the oncoming traffic of the thalamocortical projection. The coordinated expression of chemoattractive Sema3C and the chemorepellent Sema3A, via interaction with Npn-1 and Npn-2 receptors on the axons, is thought to contribute to the initial ventrally directed growth of axons from the CP into the IZ at E12.5 (Bagnard et al., 1998). In addition, Sema3A signaling might involve the cell adhesion molecule L1 as part of the receptor complex with Npn-1, during early cortical growth (Castellani et al., 2000; Castellani, 2002). Diffusible Netrin-1, coming from the underlying ganglionic eminences provides a chemoattractive gradient for early subcortically projecting axons in the IZ (Métin et al.,

1997; Richards et al., 1997). After the lateral turn away from the midline, the axons extend through the IZ toward the pallial–subpallial boundary (PSPB). Once inside the IC, the CST separate from the corticothalamic projection and enter the cerebral peduncle. Slit1 and Slit2 are involved in the maintenance of the dorsoventral positioning of the corticofugal axons within the IC and in the prevention of axonal growth toward and across the midline (Bagri et al., 2002). Both, Robo1 and Robo2 Slit-receptors are expressed in developing cortical axons and a massive number of axons abnormally cross the forebrain midline in *Robo1*;*Robo2* double mutants (López-Bendito et al., 2007). The axons then pass through the midbrain and track to the ventral pons in a more loosely fasciculated bundle. By birth, they reach the caudal region of the medulla where the majority of axons (80–85%) decussate at the junction with the spinal cord (Jones et al., 1982; Schreyer and Jones, 1982; de Kort et al., 1984). A number of molecules have been implicated in the decision to cross the midline. Netrin-1 signaling through deleted in colorectal carcinoma (DCC) and Unc5 (Finger et al., 2002), in combination with the cell adhesion molecules L1 (Joosten, 1990; Joosten et al., 1990; Cohen and Greenberg, 2008) and neural cell adhesion molecule (NCAM) (Rolf et al., 2002), are crucial for correct guidance of the CST through the medulla and midline crossing. Furthermore, the findings from the mutants for these different molecules suggest that Netrin-1 is acting to direct CST growth mainly at the level of the pioneer axons, whereas NCAM and L1 are acting on the following axons to regulate their interactions with each other and with the pioneer axons (Canty and Murphy, 2008). More recently, different reports suggest that Sema6A-PlexinA3/A4-mediated repulsion normally drives CSMN axons toward the midline where they undergo decussation (Faulkner et al., 2008; Rünker et al., 2008). After crossing the midline within the caudal hindbrain, rodent CSMN axons project caudally in the DF of the spinal cord (Stanfield, 1992). The presence of insulin-like growth factor-1 (IGF-1) and a decreasing gradient of Wnt1 and Wnt5a (Liu et al., 2005; Ozdinler and Macklis, 2006) in the neonatal gray matter immediately surrounding the DF helps to direct all CST axons, which express the IGF-1 Receptor and the Ryk receptor, down toward the lumbar levels of the spinal cord.

Following its descent, each CST axon must exit the DF at a discrete location along the spinal cord in order to make topographically specific connections with its target neuron in the dorsal horn. Decreasing levels of EphA4 within the DF immediately surrounding the descending axons allows topographically proper exit of ephrin-A5-not-expressing forelimb axons into the cervical enlargement and prevents the ephrin-A5-expressing hindlimb axons from exiting until they reach the lumbar enlargement several days later. Following branching in the DF, the collaterals of the CST enter the gray matter of the spinal cord. The initial stages of innervation and restriction to medial regions of the cord are partially controlled by EphA4, and this guidance molecule is also required to the final guidance of the CST axons to their terminal field in the dorsal horn (Dottori et al., 1998; Coonan et al., 2001). Finally, repulsive interactions between the EphA4 receptor expressed by the CSMN axons and the transmembrane ephrin-B3 ligands expressed at the ventral midline prevents decussated CSMN axons from re-crossing back to the ipsilateral side (Dottori et al., 1998; Yokoyama et al., 2001; Kullander et al., 2001a, 2001b).

CORTICOTHALAMIC PROJECTION

Origin and function

All cortical areas receive thalamic input and send projections to the thalamus (Caviness and Frost, 1980). These reciprocal connections are formed by corticothalamic axons (CTA) and thalamocortical axons (TCA), representing a highly integrated processing unit that dynamically regulates thalamic transmission of peripherally derived data for cortical processing (Sherman and Guillery, 1998) (Fig. 4). Both TCA and CTA contribute to the IC, the large axonal highway navigating through the subpallium, which also comprises output subcerebral axons *en route* toward the cerebral peduncle and pyramidal tract. CTA are generated by corticofugal pyramidal neurons located in cortical layer VI, with a smaller population in layer V (Auladell et al., 2000; Price et al., 2006; Molyneaux et al., 2007).

The cortical innervation of thalamic nuclei depends on the laminar identity of the cortical neurons (Grant et al., 2012). Layer VI corticothalamic neurons project to the first-order thalamic nuclei from which they receive input, continuing modality specificity: from primary visual cortex (V1) they project to the dorsal lateral geniculate nucleus (dLGN); from primary somatosensory cortex (S1) to the ventrobasal nucleus (VB); and from auditory cortex (A1) to the medial geniculate nucleus (MGN) (Guillery, 1967; Jones and Powell, 1968; Diamond et al., 1969; Hoogland et al., 1987). Layer VI CTA form numerous glutamatergic synapses on the distal dendrites of the relay cells, modulating their activity and thus gating pathways that transmit peripheral information (Guillery, 1995; Sherman and Guillery, 1998; Rouiller and Welker, 2000; Jones, 2002). Layer VI CTA also send collateral projections to the reticular thalamic nucleus (RTN), generating an inhibitory circuit that modifies thalamic relay cell activity (Guillery, 1995; Jones, 2002). On the other hand, the higher order thalamic nuclei (pulvinar group, mediodorsal thalamic group and lateral posterior nucleus) receive most of their inputs from collaterals of layer V corticobulbar and corticospinal neurons (Sherman and Guillery, 2002). These collaterals form synapses in large glutamatergic terminals on the matrix cells (Sherman and Guillery, 1998). In turn, the higher order thalamic nuclei project excitatory fibers to the upper and lower layers of a different cortical area than the one they received input from, distributing corticocortical information and integrating different cortical areas into a global network

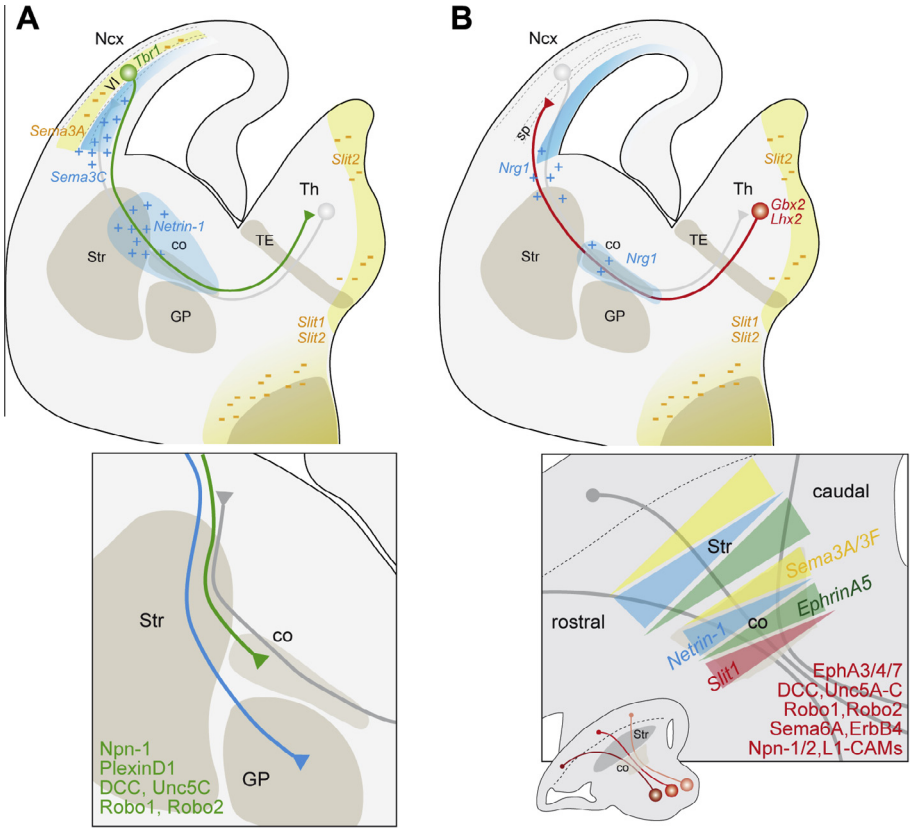

Fig. 4. CTA and TCA guidance in the developing brain. (A) Schematic representation of the corticothalamic projection trajectory (in green) in a developing coronal brain section showing the key gradients for their guidance and the close anatomical relation with TCA (in gray). The inset shows the different trajectory of subcerebral axons (which grow through the GP; in blue) and the corticothalamic axons (which grow through the corridor; in green) in the subpallium, indicating the guidance receptors expressed by CTA. (B) Schematic representation of the thalamocortical projection trajectory (in red) in a developing coronal brain section showing repellent Slit gradients at the midline and hypothalamus, growth promoting Nrg1 gradients at the corridor and the angle region of the pallium, and the close anatomical relation with CTA (in gray). The inset shows a high-magnification schema from the vTel region in a 45° corridor section (Bielle et al., 2011b), indicating the guidance receptors expressed by TCA. The intricate display of overlapping gradients in the developing vTel leads to the initial topographical sorting of the thalamocortical projection at the corridor. *Abbreviations:* Ncx, neocortex; sp, subplate; Str, striatum; co, corridor; GP, globus pallidus; TE, thalamic eminence; Th, thalamus.

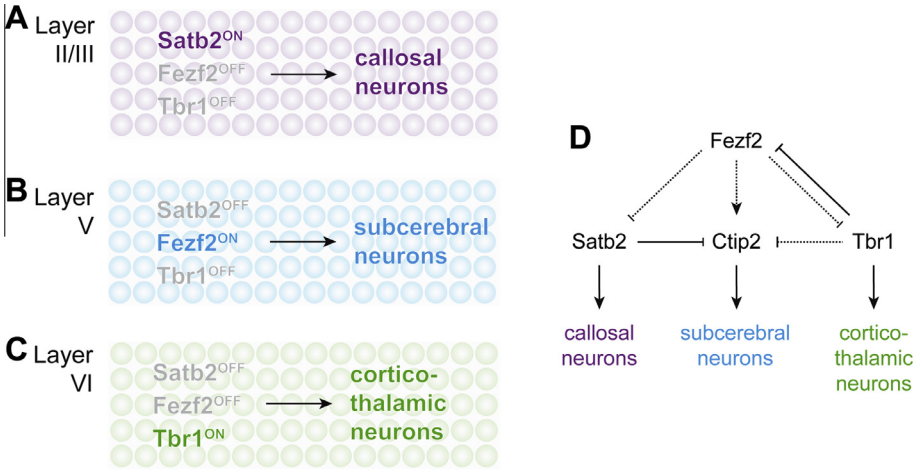

Fig. 5. Transcription factors interaction regulates cortical neuron fate specification. Schemes showing the key transcription factors for neuron fate specification in the different cortical layers. *Satb2* expression in layer II/III is key for CPN specification (A); while *Fezf2* expression in layer V is essential for the specification of CSMN (B); finally, *Tbr1* expression in layer VI cortical neurons has a critical role regulating fate divergence toward corticothalamic instead of subcerebral projection neurons (C). (D) Schema showing the interactions between different key transcription factors for neuron identity specification. The dashed arrow from *Fezf2* to *Ctip2* indicates an indirect positive regulation; while the dashed bar-end lines between *Fezf2* and *Satb2*, *Fezf2* and *Tbr1*, and *Tbr1* and *Ctip2* represent that direct inhibition has not been established. This figure is partially adapted from (D) McKenna et al. (2011). Copyright Elsevier.

for the widespread synchronization of cortical and thalamic cell populations.

Fate determination

Similar to layer V subcerebral projection neurons, the corticofugal fate of layer VI corticothalamic neurons seems to be partially determined by the expression of *Fezf2*, *Ctip2* and *Sox5* TFs. As reviewed above, both *Fezf2* and *Ctip2* are expressed by subcortically projecting neurons in layer V and in the corticothalamic projection neurons of layer VI (Arlotta et al., 2005; Molyneaux et al., 2005; Chen et al., 2005a). In the absence of *Fezf2*, subcortical projection neurons in layers V and VI alter their normal fates and adopt the connections, physiological properties and gene expression patterns typical of CPN (Chen et al., 2008). *Fezf2* is transiently expressed in all subtypes of newly postmigratory early-born neurons, but is subsequently downregulated in layer VI and subplate neurons, establishing its layer V-enriched postnatal pattern. Two different groups have reported that *Sox5* regulates the identity and differentiation of corticofugal neurons (Kwan et al., 2008; Lai et al., 2008). *Sox5* is normally expressed in three different deep cortical layer neurons (layer V subcerebral, layer VI corticothalamic and subplate neurons) and seems to control the timing of layer V neuron generation by suppressing *Ctip2* expression in subplate and layer VI neurons (Lai et al., 2008). Indeed, Lai and colleagues hypothesized that varying levels of *Sox5* act in combination with distinct levels of *Tbr1* and *Ctip2* to control the specific identities of subplate and deep layer neurons.

Furthermore, T-box brain gene 1 (*Tbr1*) seems to have a key role in the molecular mechanisms regulating fate divergence of layer VI corticothalamic and layer V subcerebral projection neurons. Tbr1 is expressed in the preplate and layer VI during early corticogenesis, and CTA are absent in *Tbr1* mutant mice (Bulfone et al., 1999; Hevner et al., 2001). Instead, in *Tbr1* mutants, corticospinal axons ectopically originate from layer VI neurons in a *Fezf2*-dependent manner. Consistently, misexpression of *Tbr1* in layer V neurons suppresses *Fezf2* expression and prevents them from extending axons into the brainstem and the spinal cord (Han et al., 2011; McKenna et al., 2011). These studies also demonstrated that Tbr1 directly binds the *Fezf2* locus and represses its activity in layer VI corticothalamic projection neurons to restrict the origin of the CST to layer V (Han et al., 2011; McKenna et al., 2011). Thus, *Tbr1* promotes the identity of layer VI corticothalamic neurons and represses layer V subcerebral fates, likely through reducing the expression of Fezf2 and Ctip2 (Fig. 5). In the *Fezf2* mutant mice, *Tbr1* expression was increased in layer V neurons, which projected axons into the thalamus, the normal target for layer VI neurons (Hevner et al., 2001; Han et al., 2011; McKenna et al., 2011). These results suggest that *Fezf2* blocks corticothalamic fate in layer V by reducing *Tbr1* expression in subcerebral neurons. Therefore, *Tbr1* and *Fezf2* participate in central transcriptional mechanisms that regulate fate specification of layer VI corticothalamic and layer V subcerebral neocortical projection neurons (Fig. 5).

Axon guidance control

Recent advances have identified major families of well-known guidance cues in the CTA growth (Fig. 4A). After the preplate, the earliest postmitotic cortical neurons migrate along radial glia to the nascent preplate around E10, and before they have even left the IZ the cells begin to extend neurites (Noctor et al., 2004; Lickiss et al., 2012). As it occurs with other corticofugal axons, CTA are repelled from Sema3A expressed by the CP neurons and attracted toward the Sema3C expressed in the IZ (Bagnard et al., 1998, 2001; Skaliora et al., 1998). The expression of Sema3A and Sema5B in the VZ prevents cortical axons overshooting into the cortical germinal zone (Bagnard et al., 1998; Lett et al., 2009). The lateral-to-medial gradient of Sema3C in the IZ attracts CTA toward the lateral cortex (Bagnard et al., 1998, 2000).

CTA extend through the IZ until they reach the lateral IC between E13 and E15.5 (Auladell et al., 2000; Jacobs et al., 2007), where they briefly pause in a first waiting period until dorsally derived axons have grown the extra distance (De Carlos and O'Leary, 1992; Molnár and Cordery, 1999). At E15.5 CTA resume extension, crossing the PSPB and entering the IC. The PSPB is a key decision point where early corticofugal projections turn sharply from their original ventrolateral trajectory to a medial one to enter the subpallium (Agmon et al., 1995; Molnár and Cordery, 1999). Pioneer CTA are generated by corticofugal pyramidal neurons located in the subplate and deep layer VIb. These pioneer axons seem to provide structural guidance to the bulk of layer VI CTA.

Netrin-1 expression in the IC and ventral telencephalon (vTel) attracts DCC-expressing CTA (Oeschger et al., 2012). This attraction appears responsible for CTA reorientation toward the vTel (Métin et al., 1997; Richards et al., 1997). Alternatively, Sema5B-mediated repulsion may also guide the turning due to its expression in the lateral cortex flanking the route of axons that cross the PSPB (Skaliora et al., 1998; Lett et al., 2009). Besides, Sema5B expression in the germinal zones of the ganglionic eminences and the globus pallidus further ensures that CTA remain within the IC (Skaliora et al., 1998; Lett et al., 2009). Slit/Robo guidance family also ensures the restraint of CTA within the IC, and upon reaching the diencephalon–telencephalon boundary (DTB) direct them dorsally toward the thalamus rather than crossing the midline (Bagri et al., 2002; López-Bendito et al., 2007; Braisted et al., 2009). Slit1 and Slit2 are expressed in overlapping domains including the ganglionic eminences, prethalamus, hypothalamus, and the germinal zone of the thalamus (Bagri et al., 2002); while Robo1 and Robo2 are expressed in complementary patterns in the CP, IZ, and thalamus (López-Bendito et al., 2007). In *Slit2* mutants, *Slit1*;*Slit2* double mutants, and *Robo1*;*Robo2* double mutants the corticothalamic projection, among other major projections, is severely defective (Bagri et al., 2002; López-Bendito et al.,

2007). Recently, the work by Deck et al. (2013) has shown that pioneer CTA and subcerebral projecting axons follow distinct trajectories within the subpallium (Fig. 4A): CTA navigate together with TCA in the permissive corridor (López-Bendito et al., 2006; see TCA guidance below) whereas subcerebral projecting axons grow through the globus pallidus before joining the cerebral peduncle (Deck et al., 2013).

Once at the DTB, CTA enter the prethalamus, where they encounter the cells of the perireticular thalamic nucleus (PRN) and RTN at E16. Here, CTA pause in a second waiting period until E17.5 (Molnár and Cordery, 1999; Jacobs et al., 2007). During development, PRN and RTN may act as accumulation compartments for growing CTA rearrangements, in a similar way to the accumulation of TCA in the subplate. However, research into the corticofugal rearrangements and transient circuits at the thalamus is less established than those between TCA and subplate neurons (Kostovic and Rakic, 1990; Allendoerfer and Shatz, 1994; Kanold and Luhmann, 2010).

After the second waiting period at the RTN, CTA invade the thalamus, a process that takes several days with most thalamic nuclei being innervated postnatally in rats, mice, and hamsters (Miller et al., 1993; Molnár et al., 1998a; Molnár and Cordery, 1999; Jacobs et al., 2007). Candidate guidance cues that direct axons from specific cortical regions to the thalamic nuclei that they connect to in adulthood are beginning to be identified. Ephs and ephrins, semaphorins, slits and netrin pathways are differentially expressed between the LGN and MGN (Horng et al., 2009). Therefore, distinct guidance cue expression may contribute to the specific neural connectivity between thalamic nuclei (reviewed in Price, 2012).

While the spatial control of axon guidance and network formation is well described, much less is known about the temporal regulation. Molecular control of temporal dynamics such as the waiting periods is harder to elucidate. New discoveries are beginning to suggest some mechanisms: Robo1 is expressed by corticothalamic neurons and it appears to act as a brake for axonal growth as *Robo1* mutants CTA reach their targets a day earlier than normally (Andrews et al., 2006; Mire et al., 2012). Moreover, CTA waiting period at the striatum is required for their ''encounter'' with TCA and is regulated by temporal modifications in cortical neuron properties (Deck et al., 2013). This study indicates that the temporal regulation of PlexinD1/Sema3E signaling controls a major checkpoint and thereby participates in the pathfinding of reciprocal projections between the thalamus and the neocortex (Deck et al., 2013; see interaction between forebrain axonal tracts below).

THALAMOCORTICAL PROJECTION

Origin and function

The thalamus is a central brain region that develops in the diencephalic part of the forebrain and is the major sensory relay station of the CNS, receiving most of sensory inputs (except olfaction) and connecting reciprocally with the overlying cortex. In mammals, this structure is composed of dozens of morphologically and functionally distinct nuclei (Jones, 2007), some of which project topographically to specific areas of the cortex, relaying sensory input from the periphery and playing a critical role in sensory functions (Jones, 2001; Clascá et al., 2009; Sherman and Guillery, 2011). Ascending projections from thalamic nuclei are primarily directed to modality-matched cortical areas, i.e., dLGN projects to primary visual cortex (V1). Thus, TCA constitute one of the most prominent higher-level processing connections in the mammalian brain. Most of the thalamic axons terminate in layer IV of the neocortex, although there are some terminations in layers I, II/III and VI (Caviness and Frost, 1980). Collaterals from these TCA synapse onto the GABAergic neurons residing in the RTN. These RTN neurons project back to the thalamus, connecting with thalamic relay cells thus closing an inhibitory feedback loop which is involved in modulating the activity of thalamic relay cells (Jones, 2002; Cruikshank et al., 2010). Layer VI neurons of each area send corticofugal projections back to the corresponding thalamic nucleus, and layer V sends projections to additional nuclei (López-Bendito and Molnár, 2003; see CTA above). The reciprocal connections have area and lamina specificity, they are remarkably similar for all cortical areas, and are highly conserved between species.

Around the second and third week of gestation (E12–E18 in mice), the neocortex and thalamus start to link with each other through specific and reciprocal connections (Fig. 4). Thalamocortical and corticothalamic projections have to cross several regions and emerging morphogenetic boundary zones, as the DTB and PSPB, to reach their ultimate target cells. TCA follow a highly stereotyped pathway from their origin in the thalamus to their final target, the cerebral cortex (López-Bendito and Molnár, 2003; Garel and Rubenstein, 2004). They run rostrally toward the telencephalon, make a sharp turn dorsally at the DTB to enter the mantle region of the medial ganglionic eminence (where they enter the IC by E13 in the mouse), and then advance through the striatum to finally reach the developing cortex. In mammals, thalamic fibers arrive at the appropriate cortical regions before their ultimate target neurons are born (Rakic, 1976; Lund and Mustari, 1977; Shatz and Luskin, 1986), and they have to wait at the subplate for 2 or 3 days (E16–E19 in rodents) before they can continue their growth and establish their final innervation pattern within the CP. Shortly before birth, most of the thalamic axons start to detach from the subplate and grow into the CP, forming branches and synapses in the appropriate layer.

Fate determination

The thalamus develops from neural progenitor cells located within the p2 domain of the alar plate of the caudal diencephalon between E10.5 and E16.5 (Angevine, 1970; Puelles and Rubenstein, 1993, 2003). Although recent studies have identified molecules that may influence the patterning of the diencephalon, it has

remained largely unknown how the distinct postmitotic thalamic nuclei emerge from discrete developmental units (Scholpp and Lumsden, 2010). Like in the neocortex and other brain regions, gradients of morphogenetic signal molecules secreted by signaling centers between tissue compartments organize the patterning and growth of specific tissues. The zona limitans intrathalamica (ZLI) expresses members of the Sonic hedgehog (Shh) family, which together with other secreted factors such as Wnts (Salinas and Nusse, 1992; Murray et al., 2007; Quinlan et al., 2009) and fibroblast growth factors (Miyake et al., 2005; Gimeno and Martinez, 2007; Kataoka and Shimogori, 2008), has been demonstrated to act as a local organizer for thalamic development. Several studies in various model organisms have shown that Shh is the main requirement for cell fate specification during thalamic development (Vue et al., 2007, 2009; Scholpp et al., 2009). Elimination of Shh activity in both chick and zebrafish results in the loss of genetic fate determinants and cell identity in both the prethalamus and the thalamus (Kiecker and Lumsden, 2004, 2005; Scholpp et al., 2006). Moreover, Shh is involved in the induction of specific sets of TFs through which Shh specify thalamic neuronal subtype identity during thalamic development (Scholpp and Lumsden, 2010). This induction occurs in a Shh concentration-dependent manner: induction of *Nkx2.2*, *Olig2*, *Sox14*, *Tal1* and *Gad1* in the rostral thalamus seems to require high levels of Shh, whereas low Shh signaling induces *Gbx2*, *Dbx1*, *Olig3*, and *Lhx2* in the caudal thalamus (Barth and Wilson, 1995; Hashimoto-Torii et al., 2003; Kiecker and Lumsden, 2004; Scholpp et al., 2006; Szabó et al., 2009; Vue et al., 2009).

However, it remains unclear how distinct pools of thalamocortical projecting neurons are topographically specified, and which TFs regulate the growth of their axons (López-Bendito and Molnár, 2003; Shimogori and Grove, 2005; Price et al., 2006). Numerous TFs are expressed in distinct but often overlapping patterns in the thalamus, suggesting that they cooperate to control the specification and differentiation of thalamic nuclei and cell types. One component of Shh-mediated nucleus formation is mediated via the activity of the TF *Gbx2*, which is expressed broadly and early in the thalamus (Bulfone et al., 1993), and later it is required for the differentiation of a subset of nuclei and the development of TCA projections (Miyashita-Lin et al., 1999). Furthermore, a recent study has demonstrated that *Gbx2* plays a non-cell-autonomous role in controlling the segregation of postmitotic thalamic neurons from the neighboring brain structures that do not express *Gbx2* (Chen et al., 2009). Pax6 was one of the first TFs shown to mediate a cell-autonomous role in thalamocortical pathfinding. The development of the thalamus is compromised in *Pax6* mutant embryos, and the thalamus exhibits abnormalities of differentiation and of the projection of axons (Pratt et al., 2000, 2002; Jones et al., 2002). Another key piece of work on the transcriptional control of TCA pathfinding came from the study of *Neurogenin2* (*Ngn2*) knockout mice, which are characterized by a targeting shift in the TCA projections that occurs initially in the vTel (Seibt et al., 2003), demonstrating that Ngn2 cell-autonomously specifies the projection of thalamic neurons to frontal cortical areas. Furthermore, *Lhx2*, a TF member of the LIM-HD family, is strongly expressed during thalamic development (Rétaux et al., 1999; Nakagawa and O'Leary, 2001). Severe thalamocortical pathfinding defects have been described in *Lhx2* mutant mice (Lakhina et al., 2007), implicating this TF in the guidance of these axons. Disruption of *Lhx2* regulatory activity only in thalamic neurons leads to axonal pathfinding defects in TCA, with fewer axons ultimately reaching their cortical targets (Marcos-Mondéjar et al., 2012). The exact TF repertoires that specify each thalamic nuclei and their axon projection remains to be determined.

Axon guidance control

The functional complexity of the thalamocortical projection is the consequence of an extremely elaborate process of axon guidance, orderly linking the various thalamic nuclei with specific cortical regions (reviewed in Molnár et al., 2012). Numerous anatomical studies have demonstrated that the topography of thalamocortical projections is extremely organized so that rostromedial thalamic neurons project to more-rostral cortical areas than caudolateral nuclei, which tend to project to more-caudal cortical areas (Caviness and Frost, 1980; Adams et al., 1997).

The molecular mechanisms that guide the first axons out from the thalamus into the prethalamus are poorly understood and it is though to depend on prethalamic and ventral telencephalic projections to the thalamus. As thalamic axons traverse the prethalamus, they grow toward the hypothalamus before they turn laterally into the IC (Fig. 4B). Several studies have shown that thalamic axons, which express Robo1 and Robo2 receptors, are deviated away from the Slit-expressing hypothalamus and midline via Slit-mediated repulsion (Braisted et al., 1999, 2009; Bagri et al., 2002; López-Bendito et al., 2007; Bielle et al., 2011a, 2011b).

In contrast to the hypothalamus, the subpallium attracts TCA and corticofugal axons, and constitutes a main intermediate target for these projections (Métin and Godement, 1996; Braisted et al., 1999, 2000; Garel and Rubenstein, 2004). As TCA travel internally through the subpallium, they diverge rostrocaudally along a fan-like structure, allowing distinct TCA to navigate toward different cortical areas. Although the final topography of this projection involves regionalized guidance activities within its final target, the cerebral cortex (Mann et al., 1998; Shimogori and Grove, 2005), analyses of several mutant mice in which the development of the subpallium or thalamus has been affected have revealed that its initial topography is essentially controlled by information contained within the vTel (Garel, 2002; Garel et al., 2003; Seibt et al., 2003; Shimogori and Grove, 2005). Recent studies show a detailed analysis of the patterns of *Netrin-1* expression in the vTel, where *Netrin-1* mRNA is expressed in an almost linear rostral-high to

caudal-low gradient (Bonnin et al., 2007; Powell et al., 2008). This gradient seems to play a dual role in attracting rostral but repelling caudal TCA (Powell et al., 2008), through the different expression of the Netrin-1 receptors DCC and Unc5A-C on TCA, and modulated by serotonin (Bonnin et al., 2007). Ephrins and their receptors also play a crucial role in guiding TCA to their proper targets in the developing cortex. Ephrin-A5 is expressed in a caudal-high to rostral-low gradient in the vTel and, in a complementary fashion, several EphA receptors are expressed in rostromedial-high to caudolateral-low gradients in the thalamus (Dufour et al., 2003; Egea et al., 2005; Torii and Levitt, 2005). Mice deficient in *EphA4*, *EphA7*, or both *ephrin-A5* and *EphA4*, show a fully penetrant topographic caudal shift of TCA, where rostral motor axons misproject to S1 (Dufour et al., 2003, 2006; Seibt et al., 2003). Immunoglobulin-class axon guidance molecules [L1-CAMs: L1, close homolog of L1 (CHL1), and neuron-glial related cell adhesion molecule (NrCAM)], in cooperation with Npn-1 and Npn-2, also regulate the pathfinding of TCA by mediating repellent responses to gradients of Sema3A/3F and ephrin-A5 in the vTel (Bagnard et al., 2001; Gu et al., 2003; Maness and Schachner, 2006; Wright et al., 2007; Demyanenko et al., 2011a, 2011b). The remarkable capability of TCA to reorganize themselves after a major prenatal derailment was shown in *Sema6A* mutant mice (Leighton et al., 2001; Little et al., 2009). In the later study, Little and colleagues show how misrouted dLGN axons are able to find their way to the visual cortex via alternative routes at postnatal stages and re-establish a normal pattern of thalamocortical connectivity (Little et al., 2009).

Moreover, the development of the thalamocortical projection has been shown to depend on the early tangential migration of a population of neurons derived from the lateral ganglionic eminence, called corridor cells, which establishes a permissive environment in the mantle of the medial ganglionic eminence through which TCA navigate (López-Bendito et al., 2006). This work also demonstrates that two different products of the *Neuregulin-1* gene, CRD-NRG1 and Ig-NRG1, mediate the guidance of TCA through the vTel (Fig. 4B). Recently, these corridor cells were implicated in the initial topography of the thalamocortical projection as they express gradients of guidance cues that exert specific chemotactic responses in these axons (Bielle et al., 2011a, 2011b). While most of these gradients are also present in the striatum and may have a redundant function (Fig. 4B), *Slit1* expression is exclusive to the corridor cells and has a dual function in TCA pathfinding: (i) prevents VB axons to invade rostral cortical areas by exerting a repulsive activity, and (ii) modulates Netrin-1 responsiveness in rostral axons to enable attraction toward rostral cortical areas (Bielle et al., 2011b).

Finally, the mechanisms that allow TCA to be guided beyond the subpallium and into the pallium remain unclear, although a recent study indicates that descending corticofugal axons might be important for guiding TCA across the PSPB (Chen et al., 2012; see interaction between forebrain axonal tracts below).

INTERACTION BETWEEN FOREBRAIN AXONAL TRACTS

The handshake hypothesis

The 'handshake hypothesis' was formulated by Blakemore and Molnár (1990) as a way to explain how ascending TCA navigate to their appropriate cortical targets with help from reciprocal descending cortical axons (Molnár and Blakemore, 1995). It was based on *in vivo* observations demonstrating an intimate anatomical relationship between developing thalamic and early cortical axons (Molnár et al., 1998a, 1998b) and on *in vitro* findings that cortical explants from different regions accept innervations from any region of the thalamus (Molnár and Blakemore, 1991). This hypothesis accounted for the fact that the earliest corticofugal projections and the thalamic projections encounter at the time of crossing the PSPB, raising the possibility that these two sets of axons guide each other.

However, the relationship between early corticofugal and thalamic projections has remained under debate for more than 20 years, as findings in the field were somehow contradictory. First, it was suggested that these two sets of axons fasciculate with each other in the IC and IZ (Molnár and Blakemore, 1995; Molnár et al., 1998a, 1998b); but other studies demonstrated that they run in separate compartments (Miller et al., 1993) or interdigitate only in a restricted portion of their path (Bicknese et al., 1994). In addition, *in vitro* studies revealed that thalamic and cortical axons repel each other (Bagnard et al., 2001).

The analysis of mutant mice lacking TFs affecting thalamic or cortical axon pathfinding did not help to get a definitive conclusion as the phenotypes varied among the mutants studied. Loss of *Emx2* or *Tbr1* produces errors in the pathfinding of both thalamic and corticofugal axons (Hevner et al., 2002; López-Bendito et al., 2002). However, the most severe phenotypes were observed in *Gbx2*, *Mash1* and *Pax6* mutant mice, with a complete loss of thalamic innervation (Stoykova et al., 1996; Tuttle et al., 1999; Hevner et al., 2002; Jones et al., 2002). Thalamic pathfinding errors also affect the reciprocal corticofugal projections in *Pax6* and *Gbx2* mutants, while normal corticofugal development was described in *Mash1* mutant mice.

Still, these analyses remain inconclusive as on one hand the lack of the TFs affected more than a single brain region, and the phenotype was only prenatally analyzed as all of these mice die at birth. Thus, during these years the handshake hypothesis has remained influential because of its appealing simplicity, while being challenging to test experimentally.

Recent research has shed some light into this issue by carefully looking at the timing of development of these axons at the subpallium, where they meet. The PSPB, first established as a gene expression boundary, extend along a graduated overlapping gene-expression domain

separating the developing cortex from the striatum. It is primarily generated and maintained by opposing gradients of *Pax6* expression in the cortex and *Gsh2* expression in the striatum (Carney et al., 2009). The early corticofugal projections reach and cross the PSPB before the thalamic projections. As reviewed above, pioneer CTA exit the cortex and, between E13.5 and E14.5, pause in the adjacent lateral part of the subpallium. In contrast to the waiting behavior of cortical axons, between E13.5 and E14.5, TCA progress through the subpallium to reach the lateral striatum. Thus, pioneer CTA enter the subpallium at least a day before TCA and halt their progression during a waiting period that allows TCA to reach their location. By the age at which thalamic axons approach the cortex, the PSPB has developed a striking radial glial fascicle that runs across the trajectory of TCA and has a high density of cells that migrate across the path of TCA (Chapouton et al., 2001; Carney et al., 2006, 2009). It has been suggested that these features make this region relatively hostile to the passage of thalamic axons and that descending corticofugal axons from the cortex interact with ascending thalamic axons and assist them across this region (Molnár et al., 1998a, 1998b; Molnár and Butler, 2002). The navigation of TCA through the subpallium is known to be independent of CTA and relies on the presence of guidepost corridor neurons (López-Bendito et al., 2006). For the latest guidance of TCA into the cortex, the work by Chen and colleagues reports than descending corticofugal axons are important for guiding TCA across the PSPB (Chen et al., 2012). The authors have used conditional mutagenesis to abolish corticofugal axonal development without disrupting thalamus, subpallium or the PSPB, and they found that thalamic axons still traversed the subpallium in topographic order but did not cross the PSPB. This study provides the clearest evidence to date for the importance of cortical efferents in guiding thalamocortical afferents across the PSPB and into the pallium (Chen et al., 2012).

In a complementary study, the work by Deck and colleagues indicates that the waiting period at the lateral subpaullium is also important for CTA to meet with TCA, as thalamic axons are required to guide pioneer CTA into the corridor and toward the thalamus (Deck et al., 2013). In this work the authors found that pioneer CTA and subcerebral axons follow distinct trajectories within the subpallium. While CTA navigate together with TCA in the permissive corridor, subcerebral axons grow in the globus pallidus before joining the cerebral peduncle. They use a genetic manipulation to ablate TCA and show that CTA follow a default subcerebral-like trajectory within the cerebral peduncles, indicating that TCA are required to guide CTA into the corridor (Deck et al., 2013). These observations revealed that subpallial corridor cells are not sufficient to guide CTA; instead, they indicate that TCA within the corridor are required to open a corticothalamic path. The guidance function of TCA relies on a pause in the progression of corticofugal axons, given that pioneer CTA reached the lateral subpallium at least a day before TCA. At the molecular level, PlexinD1/Sema3E signaling is required to prevent premature subpallial progression of pioneer CTA before TCA have reached the proper position, thereby ensuring that pioneer CTA follow their normal trajectory (Deck et al., 2013). Remarkably, this work reveals that the formation of reciprocal connections between the thalamus and cortex relies on a timing of sequential events: the migration of conserved subpallial guidepost cells defines the trajectory of TCA (López-Bendito et al., 2006; Bielle et al., 2011a, 2011b), which in turn guide reciprocal CTA (Deck et al., 2013).

In sum, it has come a long way since the handshake hypothesis was first postulated, and thanks to the use of new tools and genetic strategies it has become more evident that corticothalamic and thalamocortical axons interact with each other, although this interaction occurs in a particular stage and region of the subpallium.

CONCLUDING REMARKS

As reviewed here, the transcriptional regulation underlying the formation of forebrain axonal tracts has drastically advanced in the last years. The studies on the roles of *Tbr1*, *Fezf2*, *Ctip2* and *Satb2* TFs during cortical development have showed that a genetic mechanism controls the identity of cortical projection toward a callosal, subcerebral or corticothalamic fate (McKenna et al., 2011) (Fig. 5). Now the challenge is to know whether these fate determination and connectivity patterns for a given neuron are immutable or can be changed through postnatal life. Some recent pioneer work has started to test this possibility by the use of master TFs. *Fezf2* can instruct the birth of new neuronal subtypes from neural progenitors of the developing cortex and striatum, *in vivo*. The ectopic expression of *Fezf2* in cortical progenitors fated to become upper layer neurons is sufficient to change their fate to subcerebral projection neurons (Molyneaux et al., 2005; Chen et al., 2005b; Lodato et al., 2011). Moreover, overexpression of *Fezf2* is also sufficient to switch lateral ganglionic eminence progenitors into corticofugal projection neurons *in vivo* (Rouaux and Arlotta, 2010), demonstrating the powerful master role played by *Fezf2*. But can functional connected cells be reprogrammed to adopt a new connecting behavior? With the exception of the adult neurogenic niches, neurons are largely made during embryonic development, they are permanently postmitotic cells and do not normally change identity (Rouaux et al., 2012). However, two recent pieces of work had challenged this view (De la Rossa et al., 2013; Rouaux and Arlotta, 2013). The work by Rouaux and Arlotta show that embryonic and early postnatal layer II/III CPN can be postmitotically lineage reprogrammed into layer V/VI corticofugal projection neurons following expression of the TF encoded by *Fezf2* (Rouaux and Arlotta, 2013) The reprogrammed callosal neurons acquire molecular properties of corticofugal projection neurons and change their axonal connectivity from interhemispheric, intracortical projections to corticofugal projections directed below the cortex. Similarly, De la Rossa and colleagues report that the molecular identity,

morphology, physiology and functional input–output connectivity of layer IV mouse spiny neurons can be specifically reprogrammed during the first postnatal week by ectopic expression of also *Fezf2* (De la Rossa et al., 2013). These two pieces of work indicate that neocortical excitatory neurons can be postmitotically reprogrammed *in vivo* from one subtype into another opening news perspectives for brain repair. Future work will be necessary to understand the mechanisms by which these neurons are newly fated and to test whether other forebrain connections are also susceptible to be reprogrammed. Finding the master transcription factors that are key for the fate determination and connectivity of the other forebrain connections remains mandatory.

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