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Development of the Thalamocortical Interactions: Past, Present and Future

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Abstract—For the past two decades, we have advanced in our understanding of the mechanisms implicated in the formation of brain circuits. The connection between the cortex and thalamus has deserved much attention, as thalamocortical connectivity is crucial for sensory processing and motor learning. Classical dye tracing studies in wild-type and knockout mice initially helped to characterize the developmental progression of this connectivity and revealed key transcription factors involved. With the recent advances in technical tools to specifically label subsets of projecting neurons, knock-down genes individually and/or modify their activity, the field has gained further understanding on the rules operating in thalamocortical circuit formation and plasticity. In this review, I will summarize the most relevant discoveries that have been made in this field, from development to early plasticity processes covering three major aspects: axon guidance, thalamic influence on sensory cortical specification, and the role of spontaneous thalamic activity. I will emphasize how the implementation of new tools has helped the field to progress and what I consider to be open questions and the perspective for the future.

Key words: thalamus, axon guidance, spontaneous activity, somatosensory system, cortical maps, calcium waves.

INTRODUCTION

The thalamocortical system has been widely used as a model to study basic axon guidance mechanisms, decipher the factors involved in the development of cortical maps, understand how sensory systems develop, and study the mechanisms involved in anatomical and functional circuit plasticity following sensory loss. The reason for this great interest is due to the unique anatomical and functional specificities of the thalamus. Anatomically, thalamocortical axons (TCAs) comprise a large ipsilateral projection, which develops embryonically crossing various anatomical boundaries. Thalamocortical neurons can be classified into two broad types, those that are specific and topographically organized, mainly projecting to layer 4 of primary cortical areas, and those that are multi-specific, less topographically structured and massively innervating layer 1 of extensive cortical regions. The functional role of TCAs is central to sensory processing and perception as they carry information received from the periphery to specialized cortical areas. During development, specific sensory thalamic projections help define functional cortical areas. More recently, the application of novel techniques in this field, such as the use of conditional mouse lines or *in utero* electroporation, has greatly contributed to our understanding on the role of TCAs in cortical development and sensory function (Fig. 1A).

Here, I will give an outline of the major discoveries made in the thalamocortical system, and then review the technical advances that have rapidly helped discern the role of intrinsic and extrinsic (mainly thalamic) mechanisms involved in the development of sensory cortical areas. The main themes covered are (i) axon guidance and the handshake hypothesis, (ii) the influence of sensory thalamic inputs to cortical specification, and (iii) the role of spontaneous thalamic neural activity.

AXON GUIDANCE TO THE CORTEX

At the end of the last century the ability to trace axons in fixed embryonic tissue offered by the carbocyanine dye technique was pioneering. Using these anterograde and retrograde tracers to label axons and cells, several authors described for the first time the timing and trajectory of thalamocortical connectivity and associated projections (McConnell et al., 1989; Blakemore and Molnar, 1990; Catalano et al., 1991; De Carlos and O'Leary, 1992; Ghosh and Shatz, 1992; Agmon et al.,

Abbreviations: A1, auditory area; dLGN, dorsolateral geniculate nucleus; DTB, diencephalic-telencephalic boundary; MGE, medial ganglionic eminence; PSPB, pallial subpallial boundary; S1, primary somatosensory cortex; TCAs, thalamocortical axons; V1, primary visual cortex; VPM, ventromedial posterior.

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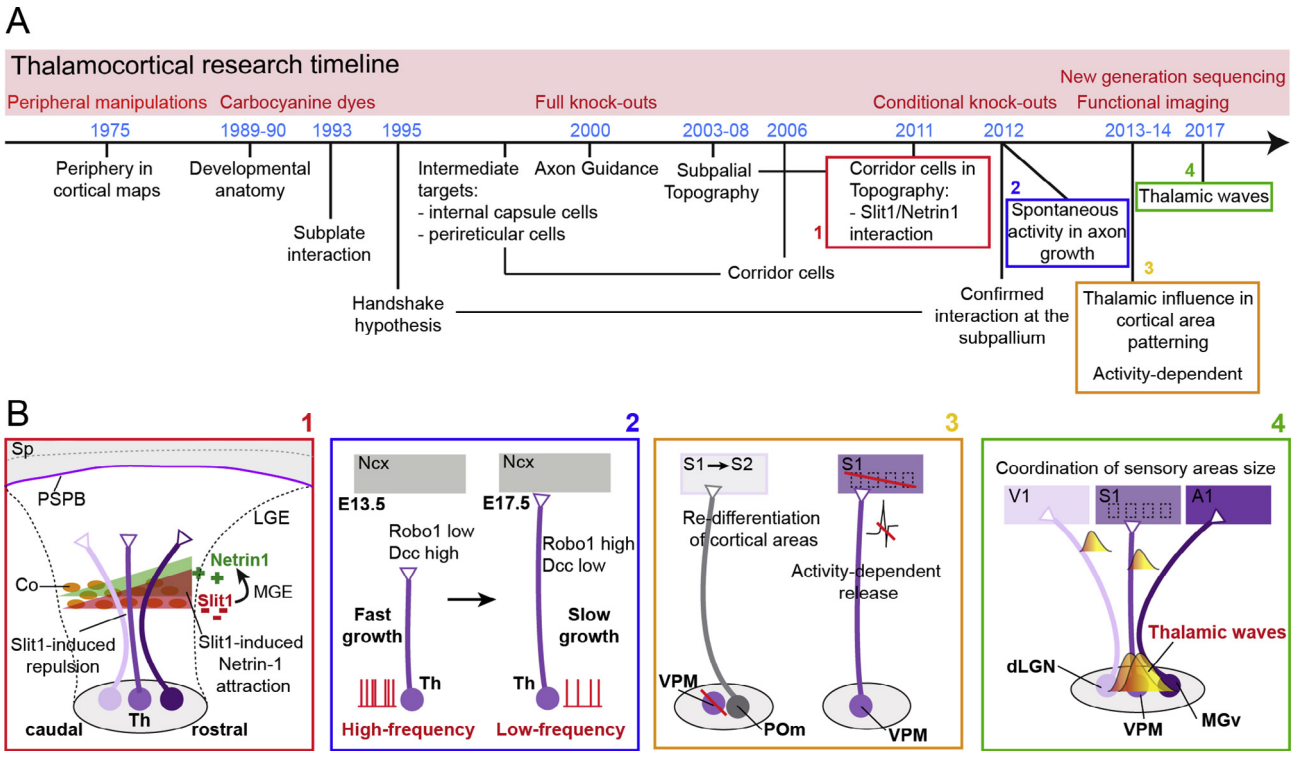

Fig. 1. Developmental timeline in the thalamocortical research. (A) Timeline representing the major discoveries in the field of thalamocortical development over the past 40 years. The major techniques used to achieve those findings are highlighted. (B) Schemas representing four key findings in the field that were made in the last few years. (1) The mechanism that allows rostral and intermediate TCAs to topographically arrange depends on interaction of guidance cues and receptors at the corridor cells. (2) The velocity of axonal growth in TCAs is controlled by activity-dependent gene expression. (3) The specification of a cortical area directly depends on the subtype of thalamic input that receives, being the higher-order mode the default signature. Moreover, this thalamic influence depends on neurotransmitter release from thalamic neurons. (4) Prenatal thalamic neurons are able to generate calcium waves of spontaneous activity among sensory nuclei that influence cortical areas size and plasticity.

1995; Molnar et al., 1998a; Molnar and Cordery, 1999). Briefly, thalamic axons exit the thalamus, traverse the pre-thalamus avoiding the hypothalamic region to cross the diencephalic-telencephalic boundary (DTB) to reach the subpallium. They then cross different anatomical territories, interact with other developing axons, and cross the pallial-subpallial boundary to enter the neocortex at around E15.5 in mice (reviewed in (Lopez-Bendito and Molnár, 2003; Molnar et al., 2012; Leyva-Díaz and Lopez Bendito, 2013; Garel and Lopez-Bendito, 2014)).

A new wave of discoveries was initiated in the late 90s following the first anatomical description of the TCA pathway. Using full knock-out mice for genes expressed at the origin, along the pathway or in the target structure, several transcription factors such as *Emx2*, *Pax6*, *Tbr1*, *Gbx2*, *Nkx2.1* or *Ebf1* (Bishop et al., 2000; Mallamaci et al., 2000; López-Bendito et al., 2002) were identified as being involved in thalamocortical pathfinding (Bishop et al., 2000; Mallamaci et al., 2000; López-Bendito et al., 2002). Moreover, axon guidance molecules were also implicated. To cross the DTB, TCAs need a Slit-mediated repulsion from the hypothalamus (Braisted et al., 1999; Bagri et al., 2002; López-Bendito et al., 2007). Once in the subpallium, TCAs are attracted toward the corridor, a dynamic region at the mantle of the medial ganglionic eminence (MGE) populated by GABAergic neurons originated from the lateral ganglionic eminence (LGE) (Lopez-Bendito et al., 2006). This cellular bridge provides a permissive environment for TCAs to cross the MGE and arrive at the cortex through the action of guidance molecules of the *Nrg1* family. The position of these corridor cells at the mantle of the MGE is controlled by the midline repellent Slit2 (Bielle et al., 2011a). It is believed that fine control of the location of these corridor cells during evolution contributed to the switch from an external TCA pathway to the internal path that is characteristic in mammals (Bielle et al., 2011a).

Other cells also provide guidance information to TCAs. Neurons located at the prethalamic, perireticular and internal capsule regions, with early projections to the thalamus, also influence TCAs' pathfinding at the DTB and subpallial levels (Mitrofanis and Guillery, 1993; Metin and Godement, 1996; Molnar et al., 1998a). In fact, in mutant mice with displaced internal capsule projecting cells, TCAs do not cross the DTB (López-Bendito et al., 2002). Our understanding of the role of striatal cells in the guidance of TCAs at the subpallium is gaining importance, as many of their projections are located in the vicinity of TCAs. Modification of the position of these striatal cells or their elimination leads directly to consistent TCAs' pathfinding errors (Uemura et al., 2007). They may influence TCAs' trajectory indirectly by modifying the position of corridor cells in a Frizzled-dependent manner (Morello et al., 2015).