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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. © **2013 Published by Elsevier Ltd. on behalf of IBRO.**

Key words: axon guidance, fate determination, callosal projection neurons, corticospinal tract, corticospinal motor neurons, 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

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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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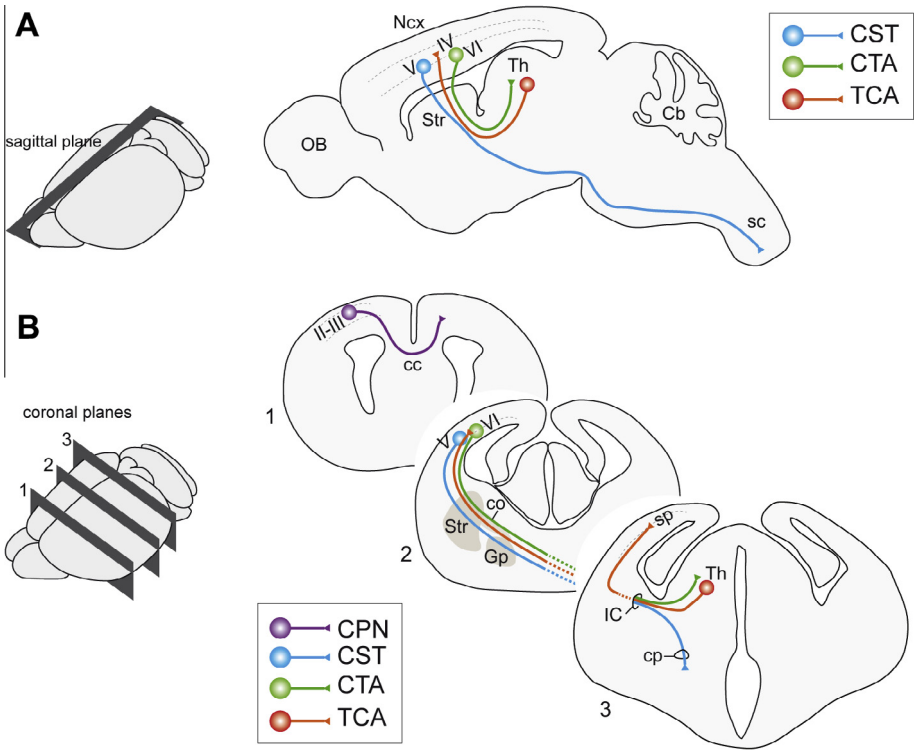

Fig. 1. Major forebrain axonal tracts. Schematic representation of CPN (in purple), CST (in blue), CTA (in green) and TCA (in red) projections in a sagittal section (A) and in serial coronal sections (B). This figure is partially adapted from (A) Fame et al. (2011) and (B) López-Bendito et al. (2007). *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.

these neurons are in layers II through VI, interconnecting cortical neurons in complex networks. 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