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Review

Synaptic biology of barrel cortex circuit assembly

Ilaria Vitali, Denis Jabaudon*

Department of Basic Neurosciences, University of Geneva, Switzerland

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ABSTRACT

Mature neuronal circuits arise from the coordinated interplay of cell-intrinsic differentiation programs, target-derived signals and activity-dependent processes. Typically, cell-intrinsic mechanisms predominate at early stages of differentiation, while input-dependent processes modulate circuit formation at later stages of development. The whisker barrel cortex of rodents is particularly well suited to study this latter phase. During the first few days after birth, thalamocortical axons (TCA) from the somatosensory ventral posteromedial nucleus (VPM) form synapses onto layer 4 (L4) neurons, which aggregate to form barrels, whose spatial organization corresponds to the distribution of the whiskers on the snout. Besides specific genetic programs, which control TCA and L4 neuron specification, the establishment of the barrel pattern also depends on the information resulting from whisker activation. The plasticity of this system during the first few days after birth is critical for barrel formation: damage to the sensory periphery impairs TCA patterning, while lesions after this period have less pronounced effects. Here, we will review the role and position of L4 neurons within cortical columnar circuits and synaptogenesis during barrel formation.

Contents

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; dLGN, dorsal lateral geniculate nucleus; FS, fast spiking; IN, interneurons; ION, infraorbital nerve; KO, knockout mouse; L4, layer 4; LTD, long term depression; LTP, long term potentiation; M1, primary motor cortex; NMDAR, N-methyl-D-aspartate receptor; PMBSF, posteromedial barrel subfield; PoM, posteromedial nucleus; RGC, retinal ganglionic cell; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SPN, star pyramidal neurons; SSN, spiny stellate neurons; TCA, thalamocortical axons; TTX, tetrodotoxin; V1, primary visual cortex; VPM, ventral posteromedial nucleus.

* Corresponding author at: University of Geneva, Centre Medical Universitaire, 1, rue Michel-Servet, 1211 Geneva, Switzerland. Tel.: +41 022 379 53 87.
E-mail address: denis.jabaudon@unige.ch (D. Jabaudon).

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1. Introduction

In 1970 Woolsey and Van del Loos first used the term "barrel field" to describe vibrissae on the rodents' snout being topographically represented in the contralateral primary somatosensory cortex (S1) by distinct cytoarchitectonic units in L4 [1]. The macroanatomy of a barrel is relatively simple: clusters of somata of excitatory locally connecting L4 neurons, mostly spiny stellate neurons (SSN), surround a hollow center mainly composed of thalamocortical and intracortical axons, dendrites of SSN and somata of some L4 neurons [2]. In mice, cell density in the barrel hollows is lower than in the barrel borders, although this varies across species [3]. Barrels are separated by septae, a domain with lower cell density which are less prominent in mice than in rats [4].

The tangential barrel field in S1 can be divided in subfields. The posteromedial barrel subfield (PMBSF) has the largest and most elliptical-shaped barrels, whose topographical organization corresponds to that of the major facial whiskers, also called mystacial vibrissae. These whiskers are organized in 5 rows of 4–7 large whiskers that run almost parallel to the bridge of the nose [1]. This organization led Woolsey and Van der Loos to formulate the "one-barrel-one-vibrissa" hypothesis: each barrel in the PMBSF corresponds to a single mystacial vibrissa on the contralateral side of the animal. Within S1, PMBSF-surrounding representations in S1 are devoted to processing information from the rostral nose, the lower jaw and the fore- and hind-limbs.

In the 1950s, Vernon Mountcastle introduced the expression "cortical column", which implies that information is processed vertically across layers in the somatosensory cortex [5], matching the anatomical and functional "one-barrel-one-vibrissa" hypothesis of Woolsey and Van der Loos. A whisker-related barrel column is a cylindrical structure extending vertically through the six layers of the barrel cortex and its border is defined by spatially aligned L4 neuron dendrites and thalamic afferents. Septal columns refer to vertically aligned neurons above and below the septae in L4, they surround the barrel columns and separate them from each other.

Here, we will review the anatomical, cellular and functional features of barrel cortex development, with particular emphasis on the synaptic processes leading to cortical column circuit assembly.

2. Role of L4 stellate neurons in barrel column circuits

A key question in cortical connectivity is whether area-specific cortical circuits develop following a common canonical framework or whether they each have their idiosyncratic developmental programs of connectivity (Fig. 1). Similarities between visual and somatosensory circuits suggest that a canonical circuit exists [6–8]. In barrel column microcircuits, L4 SSN are the main recipient of peripheral sensory information coming from the ventral posteromedial nucleus (VPM), as is the case for L4 neurons in V1 which receive fibers from the dorsal lateral geniculate nucleus (dLGN) [9,10]. L4 SSN next connect with pyramidal L2/3 callosal neurons [11], which in turn send their axons to L5 pyramidal neurons [12] similar to what occurs with L4 neurons in V1 [13]. The strongest intracortical projection to L6 neurons comes from collaterals of L5B subcerebral projection neurons [14]. Both L5 and L6 neurons connect with the thalamus, although with distinct nuclear target specificities [15,16 see Section 2.2 for details on corticothalamic projections].

Strikingly, this overall connectivity is also present in V1 and in the primary auditory cortex, a main difference being that the radial distribution of individual TCAs is spatially more confined in S1 than in other areas (i.e. columnar organization is more precise) [132,133]. Whether a similar circuitry is also present in the motor cortex is more difficult to establish, since the presence of genuine

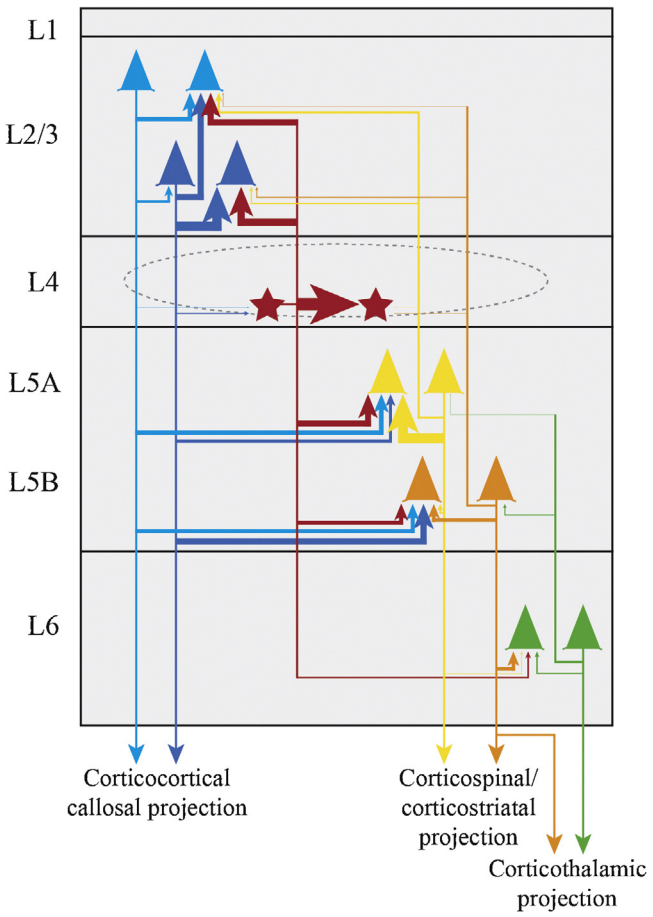

Fig. 1. Columnar microcircuitry in S1. Schematic representation of connection probabilities and information flow in a cortical barrel column. The thickness of each axonal collateral (i.e. horizontal lines and size of their corresponding arrowhead) corresponds to the probability of connection based on recorded unitary EPSPs between synaptically coupled cortical excitatory neurons of different layers (e.g. 24.3% for L4→L4 connections, 14.5% for L4→L3) [14].

L4 neurons is debated [20,21]. One reported specificity of the motor cortex is that motor thalamic input connects predominantly with L5B neurons, which in turn send their axon to L2/3 neurons [22]. Therefore, area-specific differences in the structure of input and intracortical circuits are still poorly characterized.

2.1. Columnar input to L4 neurons

In S1, the highest density of VPM axon collaterals is found in L4, which represents the major input layer of the barrel column [23,24]. VPM afferents from a single barreloid (*i.e.* the thalamic counterpart of a barrel) extend several collaterals toward L4 neurons of a single barrel [25]. In addition, L5B and L6A neurons are also innervated by VPM axons, while L2/3 neurons receive only sparse VPM input and L5A and L6B neurons almost none [23,26]. V1 and S1 differ in their afferent circuit organization: while dLGN TC synaptic responses in L4 and L6 neurons in V1 have distinct properties [27], these responses show similar latencies in S1 in response to VPM stimulation [28], suggesting area-specific differences in the weight and function of TCA-L4 and -L6 synapses in V1 and S1. Interestingly, VPM input is equally distributed onto L6 and L4 neurons at birth, and experience-dependent strengthening of input to L4 neurons occurs during the first postnatal week ([134], Cerebral Cortex). Most VPM axon boutons form synapses with L4 SSN, but these synaptic contacts represent only about 15% of the total number of synaptic contacts in L4 [29], suggesting that they are outnumbered by intracortical synaptic connections. This

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