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Cortical dendritic spine development and plasticity: insights from *in vivo* imaging

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Dendritic spines are the postsynaptic sites of most excitatory synapses in the cerebral cortex. Their morphology and density change throughout life, reflecting the maturation and reorganization of excitatory circuits. The development of *in vivo* two-photon microscopy has enabled the monitoring of the same dendritic spines over time during different developmental periods. In this review we focus on recent *in vivo* imaging studies in rodents that have revealed cell type-specific and region-specific structural dynamics of dendritic spines. We also discuss how the contributions of local inhibitory neurons and long-distance excitatory and neuromodulatory inputs to the cortex influence dendritic spine development and dynamics. Such studies will facilitate our understanding of how environmental factors and experiences affect cortical synapse development.

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Introduction

Building the complex architecture of the cerebral cortex is a protracted endeavor: the establishment and refinement of synaptic connections between neurons begins prenatally and continues well into postnatal life, and plasticity of such connections persists into adulthood. Rakic and colleagues [1] demonstrated that in various cortical regions of the macaque, synaptogenesis occurs during early postnatal development, following which synaptic density decreases through adolescence until it reaches the adult level and remains relatively stable thereafter. Other mammals, including rodents and humans, also exhibit this developmental pattern [2–4]. Such fixed-tissue studies continue to deepen our understanding of cortical synaptic development, but they provide only single snapshots of the developmental trajectories of synapses. At the turn of the 21st century, two-photon microscopy [5] and fluorescent labeling strategies [6,7] paved the way for observing synapses longitudinally in the living brain [8,9]. Since then, a wealth of *in vivo* imaging studies has revealed that cortical synapses are much more dynamic than can be inferred from fixed-tissue studies. Insight into how cortical synapses are formed, stabilized, and eliminated over the course of development informs how cortical circuits contribute to brain function and behavior across the lifespan. This knowledge also advances our understanding of the pathophysiology of neuropsychiatric disorders, such as autism spectrum disorder and schizophrenia, in which cortical synaptic development is thought to be disrupted [10]. Here, we review recent *in vivo* work on postnatal cortical development, and we discuss how local and long-range circuits affect the development and experience-dependent refinement of excitatory synaptic structures. Specifically, we focus on dendritic spines, the postsynaptic sites of most excitatory synapses in the mature cortex that may serve as structural proxies for excitatory synaptic connectivity [11].

Excitatory synapses are dynamic during development

The first two postnatal weeks in the rodent cortex are associated with a relatively increased presence of filopodia [7]: long, thin structures protruding from the dendritic shaft that differ from dendritic spines morphologically and functionally. *In vivo* imaging reveals that filopodia are highly dynamic. In adolescent mouse somatosensory cortex, most filopodia are short-lived, with fewer than 3% persisting for more than two days. Some surviving filopodia adopt a mushroom-like head and transform into stable dendritic spines, which suggests that they are structural precursors of dendritic spines [12]. Throughout adolescence, the percentage of filopodia among all protrusions (i.e. filopodia and spines) along the apical dendrites of cortical pyramidal neurons (PNs) decreases continuously, until they comprise only a small fraction of protrusions in the adult cortex. At the same time, the presence of dendritic spines with a mature morphology increases, and these spines tend to be highly stable [9,12,13]. Thus, cortical dendritic protrusions exhibit an increasingly mature morphology during postnatal development.

While dendritic spines tend to be more stable than filopodia, they are not static. During adolescence, spine elimination outpaces formation, leading to a net decrease in spine density [12,13]. In adulthood, spine elimination

and formation are balanced, and the overall turnover slows down [8,12,13]. In the mouse visual cortex, around 25% of spines are eliminated over one month during adolescence, while 96% are stable in the adult over the same time interval [8]. Interestingly, presynaptic axonal boutons from different thalamic and cortical neuron populations exhibit diverse dynamics [14,15]. Around 1–2 months of age, most axonal boutons in mouse somatosensory, visual, and auditory cortices are more stable than nearby spines [16]. Together, these studies illustrate that the dynamics of both presynaptic and postsynaptic components of excitatory synapses are developmentally regulated, which impacts excitatory synapse density.

Cell-type and region-specific development of spines

Many of the studies discussed above focus on cortical layer (L) 5 PNs using transgenic mouse lines in which the *Thy1* promoter drives the expression of cytoplasmic fluorescent proteins (e.g. YFP or GFP) in a subset of these neurons [[17••]]. Taking advantage of the different birthdates of PNs destined to reside in distinct cortical layers, recent studies have used *in utero* electroporation to express fluorescent proteins in cortical L2/3 PNs, allowing comparison of their spine dynamics with those of L5 PNs [17••,18] (Figure 1). Interestingly, spine density is higher on apical dendrites of L2/3 PNs than on L5 PNs, a difference that is apparent from the second postnatal week onward [17••]. Protrusion density along L2/3 PN dendrites in rodent somatosensory cortex rapidly increases during the first postnatal weeks, with spine dynamics (i.e. formation and elimination of spines) decreasing during this time [[17••],18]. However, during adolescence, spine density on L2/3 PN apical dendrites does not change; in contrast, L5 PN spine density decreases by approximately 20% between the second postnatal week and adulthood [12,17••,19]. This discrepancy between L2/3 and L5 PN spine pruning is attributable to differences in their dynamics. Specifically, L2/3 PN spine formation and elimination are comparable in adolescence, while spine elimination outpaces formation on L5 apical dendrites at the same age [17••,20]. By adulthood, spine elimination and formation rates are essentially equal for both neuronal types [17••,19,20]. Across adolescence and adulthood, apical dendritic spines on L2/3 PNs are more dynamic than those on L5 PNs, although turnover rates for both populations decrease with age [17••]. Future studies are needed to determine if such differences arise from intrinsic properties of these neurons or are due to their participation in distinct neuronal circuits.

Spine motility and dynamics also differ among cortical regions. One earlier study shows that spines on L5 PNs change their length rapidly at postnatal day (P) 28, and such changes are significantly larger in somatosensory and auditory cortices than in the visual cortex [16]. Observing spine dynamics in the frontal cortex using an implanted microprism, a recent study reports that spine formation over one day is higher in the prelimbic (PL) region of the medial prefrontal cortex (mPFC) than in frontal association area (FrA) at P30, while spine elimination rates are comparable. This difference in dynamics contributes to a transiently increased spine density in PL at P30 [21••]. Taken together, these studies illustrate the cell type-specific and regional differences in spine dynamics during postnatal development. Furthermore, since many neuropsychiatric disorders (e.g. autism and schizophrenia) are associated with abnormal spine phenotypes and can become symptomatic during early postnatal or adolescent development [10], it is worthwhile to investigate the cell type-specific and region-specific spine dynamics in the context of such disease models.

Circuit-specific cortical spine development and plasticity

Influence of local inhibitory circuits

Within the cortex, local inhibitory interneurons (INs) releasing gamma-aminobutyric acid (GABA) play an important role in the development and plasticity of dendritic spines. Recent work shows that GABA can facilitate spine formation on L2/3 PNs of 1–2 week-old mice [22], and the expression of α4βδ GABA receptors at dendritic spines is associated with spine pruning in hippocampal CA1 PNs during adolescence [23]. These studies highlight the diverse effects of GABA signaling on spine dynamics; future work is needed to resolve whether the influence of GABA on spines (i.e. participating in spine formation or elimination) is regulated by factors such as cell type, receptor subtype, or developmental stage. Similar to dendritic spines, cortical inhibitory synapses are dynamic, and their formation and elimination can be influenced by experience [24–26]. Furthermore, structural and functional changes in INs are associated with experience-dependent spine plasticity. A recent study shows that motor skill learning induces loss of axonal boutons of somatostatin-expressing (SOM) INs, and optogenetically activating SOM axonal boutons during motor training blocks the stabilization of newly formed spines [27]. Additionally, restraint stress, a paradigm that immobilizes the mouse in a tube for two hours daily, reduces the activity of parvalbumin-expressing (PV) INs, and pharmacogenetically increasing their activity prevents stress-induced spine elimination [28••]. Together, these studies provide evidence that experience-induced IN activity changes may be permissive for dendritic spine structural plasticity; although, how this relationship is developmentally regulated warrants further investigation.

Long-range cortical circuits

Thalamocortical (TC) projections transmit information from subcortical and peripheral structures to the cortex. In the somatosensory (barrel) cortex, TC axons travel to the cortex during late prenatal and perinatal development and are