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Previews

The Many Layers of Specification and Plasticity in the Neocortex

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In this issue of *Neuron*, Li et al. (2013) show that transgenically eliminating thalamocortical neurotransmission disrupts the formation of barrel columns in the somatosensory cortex and cortical lamination, providing evidence for the importance of extrinsic activity-dependent factors in cortical development.

Which contributes more to the area of a rectangle, its length or its width? This was 20th century neuroscientist Donald Hebb's (perhaps apocryphal) response when asked to weigh the importance of nature versus nurture in the development of the nervous system. The story conveys the point that these two forces are inseparable. Contemporary developmental neurobiologists and psychologists would agree that the division of nature and nurture is artificial and simplistic and that there is a complex interplay of these two forces in the maturation of neural systems.

Despite agreement that the problem is complicated, there has been persistent interest in pinning down the forces that specify the anatomy and function of the cerebral cortex at different stages of development—studies that have alternatively shifted the focus from deterministic to environmental factors. Almost 20 years ago, tissue transplantation studies showed that certain patterns of gene expression that were specific to somatosensory cortex could be preserved even when this embryonic tissue was moved to the visual cortex (Cohen-Tannoudji et al., 1994), indicating that specification was established in embryonic development. A decade ago, a provocative study from Crowley and Katz (2000) suggested that larger-scale features of cortical organization such as ocular dominance columns could be established in the absence of sensory input from the periphery. More recently, the availability of gene expression atlases has enabled a search for identifying genes whose expression defines cortical areas (Morris et al., 2010). Defining patterns of gene expression that are linked to neural identity and function early in development are consistent with a deterministic process in circuit construction.

At the same time, it is incontrovertible that environment—more precisely, neural activity—shapes neural circuits under normal conditions as well as under artificial experimental conditions that can induce remarkable rewiring. Landmark studies from Pallas et al. (1990) in ferrets indicated that areal identity could be modulated by inputs—where visual inputs could transform auditory cortex into a visually responsive area. Sensory deprivation can induce remapping in neocortex, investigated perhaps most extensively as changes in ocular dominance in V1 (Levelt and Hübener, 2012). At the cellular level, neurotransmitter release can act as a trophic factor for guiding axons and establishing circuits, and neuron depolarization may be critical for initiating patterns of gene expression that are required for circuit formation and stabilization. Despite the diversity of approaches, all these studies share, at their core, a desire to know how neurons decide both who to be and what to do, a fascination that continues to the present day.

In this issue of *Neuron*, Li et al. (2013) use sophisticated genetic approaches to address the question of how afferent activity from the thalamus patterns neural anatomy and laminar organization of cortical columns in the mouse somatosensory system. In contrast to previous studies, wherein sensory input from the periphery has been modulated with sensory manipulation or pharmacological methods or neurotransmission has been directly modulated (Erzurumlu and Gaspar, 2012; Levelt and Hübener, 2012), Li et al. (2013) used a transgenic approach to virtually eliminate glutamatergic transmission specifically at thalamocortical synapses.

Although thalamocortical synapses are typically associated with presynaptic VGlut2, selective thalamic knockout of this transporter was not sufficient to suppress excitatory synaptic transmission because of compensation from VGlut1. Then, the authors created a thalamus-specific double knockout (ThVGdKO) of both glutamate transporters, leading to a nearly complete elimination of thalamocortical input, present from the first postnatal week onward. This complicated triple-transgenic approach was neatly verified by electrophysiological analysis, demonstrating the absence of both local field potentials and thalamic excitatory postsynaptic currents. Not surprisingly, given that other studies have shown a requirement for afferent activity in patterning barrel formation in layer 4, cytoarchitectonic barrels were absent in ThVGdKO mice.

However, unexpectedly, Li et al. (2013) observed changes in cortical lamination, specifically in layer 4, that showed a markedly reduced cell density in mutant animals. Although early lamination in the somatosensory cortex appears normal in ThVGdKO mice, it became profoundly disrupted by the beginning of the third postnatal week. This result itself is quite interesting—Crair and Malenka (1995) and others (Barth and Malenka, 2001) have shown that the first postnatal week is critical for the strengthening of thalamocortical to layer 4 neurons—and, yet, this period of plasticity can be dissociated from lamination.

Do these layer 4 neurons just disappear, or are they respecified? Using

gene expression patterns that have been established as markers for laminar identity, Li et al. (2013) found evidence that layer-4-associated transcripts were significantly altered in the ThVGdKO mice. For example, CUX1 expression marks superficial layers of the neocortex, including layer 4 (Nieto et al., 2004), where it can be observed during postmitotic differentiation and persists into adulthood. In ThVGdKO mice, CUX1 expression patterns were normal in the early postnatal period; i.e., before thalamocortical axons have established strong synaptic connections in layer 4. By the beginning of the third postnatal week, CUX1 expression in layer 4 was markedly reduced, and, unusually, scattered neurons in deep layers 5 and 6 showed CUX1 expression. Similarly, RORβ, another gene typically restricted to layer 4 in the neocortex (Schaeren-Wiemers et al., 1997), also showed scattered expression in deep layers at the 3 week time point—expression that was not overlapping with CUX1. Altered expression patterns of laminar markers in the absence of thalamic drive suggest caution in using such genes to define cytoarchitecture in experimentally manipulated conditions.

Not surprisingly, given that CUX1 is associated with dendritic elaboration (Cubelos et al., 2010), the typical spiny stellate morphology of layer 4 neurons was notably altered in ThVGdKO animals. In place of anatomically typical stellate cells were neurons of pyramidal morphology possessing an unusually long apical dendrite. Li et al. (2013) suggest that afferent activity drives programs of gene expression that are then required for normal morphology of layer 4 neurons. Consistent with this, the expression of activity-dependent transcription factors were severely altered in mutant mice. Notably, a recent study in primary visual cortex (V1) demonstrates that lack of thalamocortical axonal input to V1 was also accompanied by a diffusion of RORβ-expressing neurons across the areal boundaries of primary and higher-order visual cortex (Chou et al., 2013). Although Li et al. (2103) did not observe lamination deficits in other primary sensory areas, this was most likely because of incomplete knockout of the glutamate transporters due to the reduced expression of the Cre recombinase in those thalamic areas and not a fundamental difference in the rule of cortical patterning. These studies indicate that thalamocortical-mediated specification of primary cortex may be similar across different sensory areas and that RORβ represents a key element in the iterative process of molecular specification and activity refinement of cytoarchitectural patterning and cell identity.

Overall, a picture is emerging wherein cellular specification arises, in part, from patterning processes during proliferation and migration but is maintained by synaptic transmission and normal activity. At all stages there is interplay between electrical activity and cell identity that appears to be required for normal specification and development. In the present study, one might wonder whether the lack of columnar organization is a direct consequence of laminar disturbances. In this regard, it is relevant that markers of somatotopy and columnar organization are preserved in the reeler mutant, a mutation that is characterized as having substantial laminar disorganization (Wagener et al., 2010). Thus, circuit construction does not necessarily require precise lamination. Downstream from an initial requirement of thalamocortical neurotransmission, the development of these two properties appears to proceed in parallel, governed by distinct processes.

Multiple mysteries remain. Although layer 4 is the major thalamorecipient layer, layer 5 also receives substantial and independent thalamic input (Constantinople and Bruno, 2013) and appeared substantially less affected in mutant animals. Is layer 5 more resilient to changes in afferent drive? Or, perhaps, the time period in which this input is required was outside of the experimental windows examined. Can the change in layer 4 structure be ascribed simply to a decrease in excitatory drive and a reduction in firing across all cells, or does thalamic drive activate different cell types in layer 4 that amplify this activity? Inhibitory neurons in layer 4 receive much stronger thalamic drive than spiny stellate cells, and the developmental maturation of thalamic input to different cells types in layer 4 has not been well studied, although it is established that the development of thalamocortical input onto L4 inhibitory neurons requires sensory experience at this age.

Finally, there is a well-established role for serotonin in the development of primary sensory areas in the neocortex (Erzurumlu and Gaspar, 2012), as evidenced by the early expression of the serotonin transporter in the thalamus. Because serotonin transport was not affected in mutant mice, an important role for this neuromodulator in neocortical patterning prior to the second postnatal week remains. There is still room for instructional input from the thalamus at P6, when laminar defects appeared negligible in the ThVGdKO animals.

The study by Li et al. (2013) represents a significant advance in defining the role of thalamocortical neural transmission in early stages of cortical map formation. Previous work has suggested that laminar cell specification and coarse maps of sensory input might arise first through genetically encoded programs, and that activity plays a later role in refining circuits and sensory maps. Instead, it appears that cell specification is not yet complete by the time that activity begins to shape neocortical circuits. The influence of nature and nurture remain complementary and fully intertwined throughout development and, perhaps, even throughout the lifespan of the organism.

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Dopamine: Burning the Candle at Both Ends

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Dopamine neurons are well known for signaling reward-prediction errors. In this issue, Matsumoto and Takada (2013) show that some dopamine neurons also signal salient events during progression through a visual search task requiring working memory and sustained attention.

Imagine yourself on the hunt. This could be the hunt for the last vegetarian option at a department lunch or for a rare first edition of Darwin's "On the Expression of Emotions in Man and Animals" at a local flea market. Either way, the search is on, and all of your senses are bent toward that single goal. But what exactly is it that drives you? What in your brain is responsible for that sense of motivation, a drive perhaps independent of your relish at the attainment of the goal? What sets your expectations, registers the mismatch between anticipation and experience, and makes sure you don't waste time on a worthless search again? And what, above all, is facilitating the laser-like intensity with which your eyes—sifting, sorting, homing in—scan the world around you? The answer, of course, is complicated. It is complicated because it is biology. But there is also a simple answer, one that comes up over and over in studies of what drives us. That answer is dopamine.

For more than a decade, dopamine has been the darling of cognitive and systems neuroscience. Synthesized by only a few neurons (a mere 400,000) in the midbrain but projected broadly across the telencephalon, it has come to play an outsized role in our thinking about learning, memory, movement, and motivation. This stems in part from the key role it plays in maladies such as Parkinson's disease, addiction, and schizophrenia, but also from the emergence in the late 1990s of highly influential computational theories of its function (Berridge and Robinson, 1998; Schultz et al., 1997). Yet despite the highly structured connectivity patterns of midbrain dopamine neurons (Haber and Knutson, 2010), most theories have posited a single, unified role for their function.

The last few years, however, have witnessed a new wave of findings demonstrating previously neglected diversity in dopamine function, picking up on earlier observations that dopaminergic cells respond to salient events (Bromberg-Martin et al., 2010; Horvitz, 2000; Matsumoto and Hikosaka, 2009; Redgrave and Gurney, 2006) and perhaps even aversive outcomes (Fiorillo, 2013; Horvitz, 2000; Matsumoto and Hikosaka, 2009). These findings raise the possibility that dopamine release might subserve multiple functions, conveying different signals to different parts of the brain in order to meet a variety of behavioral demands. Yet a clear delineation of what functions these disparate signals perform has been lacking.

In this issue, Matsumoto and Takada (2013) set out to remedy this gap by studying the diversity of dopamine signaling across the midbrain during cognitive performance. To do this, they recorded single neurons from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) in monkeys performing a visual search task for fluid reward. On most trials, monkeys were first shown a cue indicating whether a large or small reward would be delivered for a correct response. This cue was followed by a sample stimulus (a slanted line). The monkeys were then shown an array of slanted lines (two, four, or six items), among which they had to search for a match to the sample stimulus. Monkeys indicated a match by visually fixating the matching target.

Previous work has shown that dopamine is necessary for maintaining working memory (Li and Mei, 1994; Sawaguchi and Goldman-Rakic, 1991, 1994; Watanabe et al., 1997; Williams and Goldman-Rakic, 1995), as well as for facilitating visual perception (Noudoost and Moore, 2011), and thus might be released in response to the display of the target