

# You're Perfect, Now Change — Redefining the Role of Developmental Plasticity

## Minireview

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**The receptive field properties of neurons in the developing brain can in many cases be remarkably similar to those of adult neurons. This raises the question of why these same neurons need the capacity for such impressive developmental plasticity, most clearly demonstrated by the rewiring that occurs in response to sensory deprivation. The roles of developmental neuronal plasticity in the assimilation of neurons into a larger network, including temporal and cross-modal integration, are discussed.**

The vertebrate central nervous system is surprisingly precisely organized from the earliest ages at which accurate measurements can be made. In one of the earliest descriptions of the response properties of visual cortical neurons in young, visually inexperienced animals, Hubel and Wiesel pointed out that, while more sluggish to respond than adult cortex, the fundamental functional properties of these neurons were essentially adult-like (Hubel and Wiesel, 1963). This simple, yet profound, observation was somewhat eclipsed by their remarkable discovery that the immature visual cortex is also capable of dramatic physiological and anatomical plasticity in response to monocular deprivation of vision during a defined critical period. Appreciation of the degree of organization in the immature brain has been revived in recent years thanks to a number of insightful anatomical and physiological studies performed very early in postnatal development.

One of the most influential experimental models for the regulation of neuronal connectivity by patterned activity is the segregation of thalamocortical axons into ocular dominance bands in visual cortical layer 4. This had previously been thought to result from an initially exuberant thalamocortical projection that segregated into eye-specific bands as a result of activity-dependent competitive interactions during the critical period for ocular dominance plasticity described above. A careful re-examination of the early thalamocortical projection revealed that in fact the projection is already well-segregated long before the critical period (Crowley and Katz, 2000). This precocious arrangement of axonal inputs has also been observed in young kittens as early as P12 and in monkeys at birth. Optical imaging of intrinsic signals shows that physiological responses also cluster by eye preference as early as 2 weeks of age in cats, about 1 week prior to the onset of the critical period for monocular deprivation-induced plasticity (Crair et al., 1998). Although studies starting from even

younger developmental stages in altricial mammals like rats and ferrets show that properties such as orientation selectivity, receptive field size, and intracortical connectivity do develop measurably over time compared with their earliest states, the revelation that there is a high degree of order in the very immature visual cortex constituted an important step toward reversing the widely held bias that the immature brain is haphazardly wired at birth and later undergoes large-scale remodeling.

A comparably adult-like degree of organization has recently been reported for the immature somatosensory cortex. In the rat barrel cortex, *in vivo* whole-cell recordings from supragranular neurons at P8, shortly after these cells have completed their migration into the cortex, reveal adult-like receptive fields that are already highly selective for a single principal whisker (Bureau et al., 2004). Furthermore, the axonal inputs to these cells from layer 4 neurons show a surprisingly high degree of intra-barrel convergence within layer 2/3 at this stage, considering the fact that deprivation by whisker trimming for 5 days starting from this time leads to grossly expanded receptive fields that respond equally to stimulation of many whiskers (Foeller and Feldman, 2004).

The idea of adult-like initial formation of maps in very young animals is certainly not a novel concept, having its roots in the work of Sperry and colleagues in the retinotectal system, who proposed nearly a half-century ago that the ability of regenerating retinotectal axons in adult fish to reconstruct a functional retinotopic projection was evidence that normal development must be controlled by a precise set of mapping cues. Rough anatomical and electrophysiological mapping of the retinotectal projection in very young *Xenopus* tadpoles at the beginning of retinal innervation has provided support for this prediction (Holt and Harris, 1983). In rats, single-unit electrophysiological mapping studies of superior colliculus receptive field sizes found mature receptive field sizes around the time of eye opening, when visual stimuli are first able to drive retinal ganglion cell firing. However, it should be noted that this may already be too late, as the anatomical refinement of retinocollicular axon arbors is well underway by eye opening, having received patterned activity generated by spontaneous retinal waves of firing prior to that time (McLaughlin et al., 2003).

An article by Niell and Smith in this issue of *Neuron* addresses the very early development of receptive field properties in the optic tectum of zebrafish larvae starting from the period of initial ingrowth of retinotectal axons (Niell and Smith, 2005). They applied an innovative *in vivo* optical mapping approach in which the responses to visual stimuli of many dozens of cells can be studied nearly simultaneously. A large number of cells in the optic tectum of zebrafish were bulk labeled by allowing them to take up the fluorescent calcium indicator Oregon Green Bapta-1, which increases its fluorescence intensity in response to calcium flux during spiking activity at cell somata. Animals were then

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immobilized and presented with various visual stimuli projected onto a monitor in their visual field while two-photon optical scans were performed through the tectum.

Mapping responses in this manner in larvae ranging in age from 66 hr postfertilization, the earliest stage at which visual responses could be evoked, to mature 9 day postfertilization fish, they measured a number of receptive field parameters, including topographic organization, receptive field size, direction selectivity, and stimulus size preference. From 78 hr postfertilization onward, these features remained remarkably invariant, showing an increase in sensitivity but little change in selectivity, suggesting that receptive fields were essentially adult-like by this early stage. Moreover, dark rearing to deprive the visual system of patterned external drive had little effect on the development of these parameters. The proportions and classes of cells responsive to various stimuli types also remained consistent throughout development.

Together with the examples of precocious development described above, these experiments raise a number of fundamental questions about the function of developmental plasticity. Why, if the innate anatomical and physiological development of immature neurons so closely resembles that of the adult, is activity-dependent plasticity necessary at all? What is the role in receptive field and topographic map development of the intense morphological remodeling of axons, dendrites, and spines that have been observed in time-lapse imaging studies in these systems?

At least part of the answer is provided in a paper by Tao and Poo in this same issue (Tao and Poo, 2005). The future potential of the *in vivo* whole-tectum calcium imaging method of Niell and Smith for examining response properties of ensembles of neurons is impressive, particularly in zebrafish, in which it is possible to express calcium-sensitive fluorescent proteins in defined subsets of cells under genetic control. However, this approach is limited to detecting action potentials, perhaps even to detecting only bursts of action potentials, in the neurons being imaged. The study by Tao and Poo uses a similar visual field stimulation approach but combines it with electrophysiological whole-cell recordings from individual neurons to examine the development of receptive field properties in optic tectal neurons in *Xenopus* tadpoles. This method provides subthreshold sensitivity and, furthermore, by making recordings both at the reversal potential for glutamatergic currents as well as at the reversal potential for GABA and glycine, allows the respective contributions of both inhibitory and excitatory synaptic inputs to be assessed. These authors observed a modest but consistent reduction in both excitatory and inhibitory receptive field size during development from stage 44 to stage 48 in tadpoles. Significantly, there was also a progressive alignment and matching of excitatory and inhibitory receptive fields over this period. This process of receptive field refinement was impaired by either chronic bicuculline to block GABA<sub>A</sub> or diazepam to enhance GABA<sub>A</sub> currents—manipulations that perturb the precise timing of neuronal firing.

The observation that receptive field remodeling of excitatory and inhibitory inputs is both dynamic and progressive is quite consistent with the anatomical re-

arrangements that have been reported for retinotectal axons, tectal projection neurons, and interneuron dendrites in this system during identical developmental stages. As tadpoles grow, individual axon arbors gradually occupy a proportionally smaller fraction of the expanding tectal neuropil, consistent with the subtle sharpening of receptive field size observed by Tao and Poo in *Xenopus* and the increased sensitivity to smaller objects that Niell and Smith found in zebrafish (Sakaguchi and Murphey, 1985).

Moreover, it suggests that the normal role of developmental plasticity may not just be to produce and maintain precise receptive fields in any single domain like topography, which appears to be adequately encoded from the outset in immature cells, but also to match and align distinct assemblies of inputs onto a cell in a manner that enhances the function of that cell. There may be many transient encounters between pre- and postsynaptic partners that provide subthreshold inputs. Only a small fraction of these will be selected and strengthened enough to alter the receptive field as measured by the firing output of the cell, but in addition, there is a fine-tuning of more subtle properties of the cell like temporal response properties that may influence how the activity patterns of that neuron are integrated into the network.

The role of interaction between excitation and inhibition of neurons has been examined extensively in the regulation of ocular dominance plasticity in the visual cortex. In the developing visual system, the critical period for ocular dominance plasticity is delayed or absent in mice lacking the GAD65 isoform of the enzyme for GABA synthesis. It can be restored in these mutants and induced precociously in wild-type animals by pharmacological enhancement of GABAergic transmission by diazepam (Fagiolini and Hensch, 2000). This regulation of the critical period by GABAergic circuitry appears to be particularly dependent on the maturation of somatic targeting by parvalbumin-positive fast-spiking basket cells, which is itself regulated by visual experience (Chattopadhyaya et al., 2004). As this class of interneuron makes axosomatic synapses onto large numbers of excitatory pyramidal neurons in the cortical network, it is ideally situated to synchronize spike timing across many cells, thereby potentially enhancing the efficacy of each of their target neurons for engaging spike timing-dependent plasticity (Dan and Poo, 2004; Foeller and Feldman, 2004). Thus, by coordinating the temporal firing properties of cortical neurons, rather than stimulus selectivity, a modest change in the interaction between excitation and inhibition can lead to a profound modification of the network.

But isn't this all just a bit too circular? Maps and receptive fields are nearly adult-like from the outset, but plasticity is nonetheless required in order to permit further plasticity. There are three important considerations relevant to this point.

First, it is just as fallacious to assume that the earliest state of a neuron or network represents the state of the system in the absence of activity-dependent refinement as it is to infer that the disorganization of the network that is induced by activity blockade represents the maximal degree of precision that could be achieved if activity-dependent mechanisms did not exist. Activity-

dependent mechanisms may participate in the very earliest establishment of a projection.

Second, the maintenance of precision in a projection or circuit may itself be an important adaptive form of plasticity. This is the case for the retinotectal projection in amphibia and fish. The growth of the eyes and tectum continues throughout life in fish and frogs, but along different axes, with new cells being added in a ring at the peripheral margin of the retinal and in a band along the caudomedial edge of the tectum. This inevitably leads to a mismatch of topographic axes, forcing the retinal axons throughout the tectum to continually shift their termination zones caudally as the brain and eyes continue to grow. The absence of obvious disruption in topographic map organization and receptive field properties during this period suggests that this maintenance is in fact a highly effective form of map plasticity.

A similar degree of stability is present along the entire neuraxis of the somatosensory vibrissal system in mice. Trigeminal nerve axonal arbors in brainstem “barrelles” undergo only a small amount of growth after establishing their initial projection before birth, yet their arborizations are massively expanded in coverage area in NMDA receptor knockout animals, suggesting that arbor size is regulated by NMDA receptor activity (Lee et al., 2005). In contrast, in the cortical barrel fields of NR1 cortex-restricted conditional knockout mice, thalamocortical axon arbors in layer 4 are slightly smaller than in wild-type animals. In both cases, however, it is the higher-order, functional organization of afferents into barrelettes or barrels that is severely disrupted in the knockout mice. This becomes particularly clear when the orientations of postsynaptic dendritic arbors of cortical layer 4 cells are examined. Though they do not show dramatic overgrowth in knockout animals, the normal orientation of their dendrites toward the centers of barrels is entirely disrupted (Datwani et al., 2002). Thus, what appears to be only a small change over normal development at the level of single-cell morphogenesis is in fact a functional refinement of arbors that is essential for the formation of higher-order structures like barrels.

Third, one of the principal functions of neural circuitry in the brain is the integration of information from multiple sensory sources. While the inputs from each of these sources may be independently precisely organized, they may require further modification to efficiently map onto one another.

There are several striking examples of this in the optic tectum. In *Xenopus* frogs, which unlike tadpoles have binocular receptive fields, a map of visual space through the ipsilateral eye is provided to the optic tectum through the nucleus isthmi (Udin and Grant, 1999). This map maintains precise registration of its receptive fields with those of the retinotectal inputs from the contralateral eye, even as the eyes shift position on the head as the animal matures. Rotation of one eye leads to a complete remapping of this projection to realign newly overlapping receptive fields.

Cross-modal plasticity has been beautifully characterized in the optic tectum of barn owls. In these animals, the visual and auditory space maps within the superior colliculus are well aligned. Shifting the relative positions of either of these maps by prism rearing or

ear occlusion during an appropriate critical period in early life results in the reorganization of auditory projections to maintain close alignment with the map of visual space (Knudsen, 2002).

One interesting functional consequence of fine-tuning the interactions between excitation and inhibition in tectal neurons may be the modulation of the ability to induce rapid plasticity of neuronal selectivity. Engert et al. (2002) have demonstrated that direction selectivity of tectal neurons can be altered by repeated visual presentation of moving bar stimuli to a tadpole. This modification of neuronal selectivity is NMDA receptor dependent and therefore appears to share common mechanisms with long-term potentiation and long-term depression of retinotectal inputs. This plasticity of visual response selectivity might participate in normal development, or it could reflect a mechanism normally used by the brain of the tadpole to rapidly adapt to the environment without necessarily requiring gross rewiring of neural circuitry.

An interesting question raised by the work of Tao and Poo is whether the developmental refinement of the interaction between inhibition and excitation might enhance the receptivity of the retinotectal network to spike timing plasticity, analogous to the role of inhibition in ocular dominance plasticity in visual cortex. If so, it might be expected to facilitate this kind of experience-dependent rapid modification of receptive field properties. The experimental approach of Niell and Smith would provide a powerful system in which to ask this question, permitting the characterization of direction selectivity of many dozens of neurons before, immediately after, and then many hours after a conditioning protocol. In conjunction with the diazepam rearing protocol of Tao and Poo, which disrupts the developmental alignment of excitatory and inhibitory fields, this would provide a very elegant answer to the question of whether the developmental matching of inhibitory and excitatory receptive fields can modulate experience-dependent visual system plasticity in the optic tectum.

In conclusion, it is clear that for many areas in the brain the classic model of initial exuberance followed by the pruning of inputs, inspired by the developmental refinement of motoneuron axons at the neuromuscular junction, is not appropriate. There remain numerous examples of neural circuits that radically refine their connectivity and response properties during development; however, in many cases the initial connectivity and response properties of immature neurons starts out surprisingly adult-like. Given that these same neurons typically are capable of a tremendous degree of developmental plasticity of both form and function, the classic model should be revised rather than reviled. The ongoing refinement of neuronal connections may not result in obvious changes over time in axon arbor size or number of synaptic inputs to a cell, but instead produce a more efficiently matched set of inputs for that cell.

#### Selected Reading

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