Dynamic Interplay between Nature and Nurture in Brain Wiring

College de France Lectures May 2011
Carla J. Shatz, Professor of Biology and Neurobiology and Director of Bio-X,
Stanford University, Stanford CA 94305 USA

In this series of three lectures, I will consider examples of how neural activity, initially spontaneously-generated and at later ages driven by sensory experience, contributes to the shaping and tuning of neural circuits during critical periods of brain development. The lectures focus on the development of the mammalian visual system and specifically consider the connections from retina to lateral geniculate nucleus to primary visual cortex. These connections begin to form early in life- in utero in many species and well before the onset of vision. Initially, a basic wiring plan from eye to brain is established using strictly determined axon guidance cues. This period is followed by a prolonged phase of activity-dependent development in which initially diffuse synaptic connections are fine-tuned to yield finally the highly precise circuits present in the adult brain. This tuning process is thought to occur throughout the brain during development, endowing it with a vast capacity to adapt to the environment and also underlying the brain's ability to learn throughout life.

In the visual system, retinal ganglion cells from each eye connect to LGN neurons in adjacent eye-specific layers. LGN neurons representing each eye, in turn, connect to neurons in layer 4 of primary visual cortex to form the alternating system of ocular dominance (OD) columns. But during development, eye inputs are intermixed; the adult LGN layering or cortical OD columns then form as connections remodel. Remodeling requires ganglion cell signaling: blocking action potentials prevents eye-specific layering (Shatz and Stryker, 1988; Sretavan et al, 1988) and also alters the patterning of OD columns. The first lecture, "Brain Waves and Synapse Remodeling in the Developing Visual System", will present the discovery that the retina generates its own spontaneous activity long before vision starts. Ganglion cells in the eye fire synchronously in "waves" that sweep across retinal domains. (Meister et al, 1991; Wong et al,1993; Feller et al, 1996). Moreover, these retinal waves are needed for ganglion cell axons to segregate into eye-specific layers in the LGN: blocking them prevents segregation, while altering the spatio-temporal pattern of waves perturbs segregation (Penn et al., 1998; Stellwagen and Shatz, 2001). It is as if the eye is running "test patterns" on the brain to check for correct connections weeks before the onset of vision. Thus, the brain internally generates highly coordinated patterns of neural activity early in development even before sensory input.

The second lecture, "A Transient Scaffold for Circuit Construction: Subplate Neurons and the Cerebral Cortex", considers the concept that the development of connections between thalamus and cortex involves an intermediate step in which an entire neural circuit in the subplate is first constructed, then functions synaptically, and finally is dismantled, leaving little trace in the adult brain. Prior to the formation of adult connections between LGN axons and layer 4 neurons of visual cortex, there is a protracted period of development in which thalamic axons interact with a transient set of neurons called subplate neurons. Subplate neurons are the first postmitotic neurons of the neocortex and their axons pioneer the pathway from cortex towards thalamus (McConnell et al, 1989). Subplate neurons then serve as temporary targets for ingrowing thalamocortical connections and finally they are eliminated by cell death. Ablation studies, in which subplate neurons are deleted at various times in fetal development and consequences for formation of connections between thalamus and cortex are examined, have indicated a crucial role for subplate neurons in proper patterning and functioning of cerebral cortex. Early deletion of subplate neurons causes a complete failure of LGN axons to invade visual cortex, implying that subplate neurons are required for normal target selection and ingrowth (Ghosh et al.,1990). Deletion of subplate neurons at later ages prevents segregation

of LGN axons into OD columns (Ghosh and Shatz, 1992 and alters the expression of plasticity genes, such as BDNF, known to be required for synaptic plasticity during the formation of OD columns (Lein et al, 1999). More recent experiments show that subplate neurons are essential for the functional strengthening of synaptic connections needed to establish the columnar organization of cerebral cortex (Kanold et al, 2003) as well as to regulate the proper sign of synaptic plasticity following monocular eye closure (Kanold and Shatz, 2006). These experiments indicate that subplate neurons play crucial roles in directing distinct steps early in the formation of connections between thalamus and cortex. It is now hypothesized that insults to the fetal brain leading to the destruction of subplate neurons may be responsible for postnatal problems in children such as cerebral palsy, autism and other learning disabilities.

The final lecture, "Releasing the Brake on Synaptic Plasticity: Immune System Genes Moonlighting in the Brain", will present the idea that there are signaling pathways that oppose or "brake" synaptic plasticity, in addition to well-known molecular pathways such as MAP Kinase signaling and CREB mediated transcription that enable activity-dependent plasticity. One such "brake" was uncovered in an unbiased PCR-based differential screen searching for genes in the LGN regulated by the endogenous activity driven by retinal waves. Unexpectedly, members of the MHC Class I gene family (the HLA genes in humans) were found to be expressed in neurons and regulated by neural activity and visual experience (Corriveau et al, 1998; Goddard et al, 2007). The discovery was especially surprising because it was thought previously that neurons do not express MHC Class I under normal conditions due to the brain's "immune-privilege" (reviewed in Boulanger and Shatz, 2004). To assess requirements for MHCI in the CNS, the LGN was examined in mice lacking MHCI: eye-specific layers do not form, and synapse regression fails to occur. What's more, contrary to the usual situation following gene knockout in which synaptic plasticity is abolished, in the MHCI mutant mice, there is *greater* synaptic strengthening than normal. In particular, OD plasticity is enhanced in visual cortex (Datwani et al, 2009) and in adult hippocampus LTP is 150% larger than wild type and LTD is absent (Huh et al, 2000). These observations suggest that MHCI molecules might act as *negative* regulators of synaptic plasticity- rather like a "molecular brake".

In the immune system, certain MHCI family members function in cell-mediated immunity by interacting with a variety of receptors on immune cells, the most famous of which is T-cell receptor (TCR). Similar receptors on neurons could interact with neuronal MHCI and carry out activity-dependent synaptic processes. In a systematic search for receptors known to bind MHC Class I (MHCI) proteins in the innate immune system, we found that mRNA for PirB, an Ig-like transmembrane receptor, is highly expressed in neurons in many regions of mouse CNS, particularly in cerebral cortex, olfactory bulb and cerebellum. We generated mutant mice lacking PirB function and discovered that the extent of OD plasticity in visual cortex is *increased* (Syken et al., 2006). Thus, PirB, like its MHCI ligands, appears to function to limit the extent of synaptic plasticity in the CNS. Together, experiments imply that this family of immune molecules, thought previously to function only in the immune system, may also work at neuronal synapses to limit how much- or perhaps how quickly- synapse strength changes in response to new experience (Shatz, 2009). These molecules may be crucial for controlling circuit excitability and stability in developing as well as adult brain, and changes in their function may contribute to developmental disorders such as Autism and Schizophrenia.

Experiments described here have been funded by NIH Grants EY02858, MH071666, the Mathers Charitable Foundation and the Ellison Medical Foundation.