



TrkB Signaling Regulates AChR Clustering at the Neuromuscular Junction

that TrkB may be involved. It is worth noting that neuronal activity can markedly increase BDNF expression in hippocampal neurons. Furthermore, BDNF rapidly and substantially increases responsiveness of NMDA receptors, probably by enhancing tyrosine phosphorylation of the NMDA receptor subunits NR1 and NR2B in the postsynaptic density (Black, 1999). Thus, in addition to its traditional role in cell survival, TrkB may play an important role in activity-dependent regulation of both the responsiveness and stability of postsynaptic receptors. Such activity-dependent regulation of postsynaptic receptor properties may underlie the mechanisms for the induction of long-term potentiation, a correlate of learning and memory (Malenka and Nicoll, 1999).

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## Whisking Away Space in the Brain

Information about the world around us continuously bombards the brain. The salient features of this stream of input are reflected in the mosaic of maps that tile the neocortex. These maps are highly dynamic and can be sculpted by the very experiences they represent. Thus, a lost limb's cortical space is reallocated to other body regions, an open eye comes to dominate the visual response after a period of monocular occlusion, or a routinely encountered tone is overrepresented in auditory cortex (Buonomano and Merzenich, 1998). What these and myriad other examples collected over the past 40 years all have in common is that inputs with a competitive advantage will enlarge their territory within the limited confines of sensory neocortex. A report by Polley et al. (1999 [this issue of *Neuron*]) now challenges the view that bigger is better.

Polley and colleagues found that removing all but a single whisker on one side of a rat's face can induce either a lasting expansion or a *contraction* of its functional representation in the barrel cortex. The key variable appears to be how that whisker is used during the time the map is being reshaped. If the animals are simply returned to their "boring" home cage, an expansion occurs as expected. However, given brief opportunities to actively explore a "novel" environment, the single whisker representation contracts. Both expansion and contraction reverse upon regrowth of the deprived whiskers. These intriguing observations suggest a mechanism drawn from three emerging themes of cortical function.

The first is that the central concept of the receptive field is undergoing a profound change. In the traditional view, feedforward connections from the periphery—such as one whisker's input into a single cortical barrel—drive their primary targets to fire action potentials and thereby define the receptive field of those cells. Recent evidence reveals that the influence of any given input to cortex extends well beyond its primary zone of termination (Gilbert, 1998). In the visual system, for example, line segments outside the receptive field can influence the orientation tuning of a cell to a line segment within the receptive field. The substrate for these contextual influences lies in the rich plexus of lateral intracortical connections. The findings of Polley et al. (1999) hinge on the method of optical imaging of intrinsic signal responses, which is exquisitely sensitive to these sub-threshold interactions. Under their conditions, it is quite evident that the flow of activity upon striking a single whisker radiates across several barrels.

Second, the possibility that a spared whisker representation may then *contract* naturally draws attention to suppressive or inhibitory processes. Sensory deprivation can regulate short-term depression at individual

synapses (Finnerty et al., 1999), as well as the phenotype of subpopulations of interneurons (Carder et al., 1996). Indeed, recent work demonstrates that local inhibitory circuits drive competitive plasticity in the neocortex (Hensch et al., 1998). In the visual system, a lasting shrinkage of open eye representation can be obtained if intracortical inhibition is saturated during a period of monocular deprivation (Hata and Stryker, 1994). Could it be that the balance of excitation to inhibition in barrel cortex is tipped in favor of the latter during the brief exploratory bouts in a novel environment? The only way to find out will be to record chronically across multiple units and cortical layers during the actual behavior and plasticity process.

Finally, how such a shift in excitatory–inhibitory balance might be achieved is of interest. The brevity of the exploratory behavior required for bidirectional map changes is suggestive. Remarkably, just 4 min/week (of which only a fraction is spent actively scanning) in a novel environment over a month of deprivation is sufficient to shrink the spared whisker representation. Focal attention to a stimulus can enhance a cell's peak response (Gilbert, 1998) and has most often been linked with state-dependent activity of neuromodulatory systems (Weinberger, 1995). Increases in behaviorally relevant inputs require cholinergic input from the basal forebrain, whose stimulation can also modify cortical maps (Kilgard and Merzenich, 1998). It is tempting to speculate that the decreases reported by Polley et al. (1999) may be similarly regulated by diffuse systems that selectively modulate subsets of inhibitory interneurons (Kawaguchi and Shindou, 1998; Xiang et al., 1998). Would it be possible to replace the very brief behavioral exploration of a single whisker with exogenous neuromodulators to produce similar map changes in nondeprived animals?

Is there an advantage to shrinking cortical representations in the face of rich experience or is this just a by-product of competitive mechanisms? Perhaps a smaller, tighter representation is more efficient than a widely distributed one in certain cases. For example, in human mapping studies it has been observed that the dominant language occupies less territory than others in multilingual subjects (Ojemann, 1991). The results of Polley et al. (1999) offer an opportunity to understand how and under what behavioral conditions a particular direction for sensory map plasticity is favored.

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## Retinal Waves: Stirring Up a Storm

In many parts of the developing nervous system, neuronal connectivity becomes more precise as some inputs are eliminated while others are maintained. This process of synaptic refinement requires neurotransmission (Lichtman et al., 1998). The temporal properties of this activity, rather than its mere presence, are thought to be necessary to drive segregation of competing inputs. In particular, much modeling work built on the initial theory by Hebb suggests that synchronous inputs are costrengthened, whereas asynchronous firing of inputs results in weakening of one set of connections (see, e.g., Miller, 1996). This theory is supported by experimental findings in which coactivated inputs are potentiated, whereas inputs are depressed when they are silent during postsynaptic activity (Lichtman et al., 1998). Although the actual withdrawal of synaptic contact due to asynchronous firing has not yet been observed experimentally, this simple theory has provided much impetus for a search for endogenous patterned activity during the period of synaptic refinement in the developing nervous system.

Patterned spontaneous activity has now been observed in many developing circuits, including neurons in the spinal cord, hippocampus, auditory nuclei, and retina (reviewed by O'Donovan, 1999; Wong, 1999). Neurons in all of these systems spontaneously fire rhythmic bursts of action potentials that are temporally synchronized between neighboring cells. The prevalence of this activity pattern in developing networks has long prompted the question of what competitive events might be driven by this activity. This question has been addressed extensively in the visual system.

Synchronized spontaneous retinal activity takes the form of propagating waves with the degree of coincident firing between cells decreasing as a function of intercellular distance. Waves are generated prior to vision (but disappear upon photoreceptor maturation) and are thought to bear spatiotemporal cues that guide the refinement of retinal ganglion cell projections to visual targets in the brain. In particular, it has been suggested that waves underlie the activity-dependent segregation of eye input and the refinement of retinotopic maps at subcortical visual targets, such as the dorsal lateral geniculate nucleus (dLGN) (Wong, 1999).

While retinal activity is needed for the emergence of