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Somatosensory cortical plasticity: recruiting silenced barrels by active whiskers

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A unique feature of the mammalian neocortex is its areal specification, with allocations of neural tissue to primary sensory information processing, and dispersion of this information to the association areas, and motor cortex. The locations of the primary sensory cortices are similar in all mammals and set by gradients of differential gene expression during early development of the telencephalic vesicles (Lopez-Bendito and Molnar, 2003; Ragsdale and Grove, 2001). However, these intrinsically allocated cortical areas can shift or change their properties when thalamocortical inputs or sensory stimulation and distribution of receptors in the periphery are altered (Fox, 2002; Kaas, 2002; Kaas and Catania, 2002; Kossut, 1998; Pallas, 2001; Rauschecker, 2002). This plasticity allows the neocortex to adapt to changes in the environment, to loss of function in the sensory periphery or along the subcortical pathways that bring the sensory world to the neocortex. Plastic changes occur in the adult primate cortex following disuse or peripheral injury (Buonomano and Merzenich, 1998; Garraghty and Muja, 1995; Merzenich and Sameshima, 1993; Pons et al., 1991; Wall et al., 2002). Cortical plasticity has also been reported in humans with referred phantom sensations after spinal cord injury (Mackert et al., 2003; Moore et al., 2000). While some of these effects may be attributed to changes in subcortical somatosensory pathways and reflection of these changes in the somatosensory cortex (Florence and Kaas, 1995; Kaas, 2002; Wall et al., 2002), several lines of evidence indicate that alterations in intracortical pathways play a major role in functional plasticity. Interestingly, different forms of cortical plasticity are manifested during early stages of cortical development and throughout maturity.

The sensory periphery is mapped onto the neocortex across multiple synapses through subcortical structures; thus, a topographic map is set in the somatosensory, visual and auditory cortices. In most mammals, these maps are remarkably similar, but some variations also exist within closely related species (Kaas, 2002; Kaas and Catania, 2002). Another conspicuous feature of the sensory maps in the neocortex (and associated subcortical nuclei) is the patterning of pre- and postsynaptic inputs that replicate a specific feature of the sensory periphery. Ocular dominance columns in layer IVc of the primate visual cortex and “whisker barrels” in layer IV of the rodent somatosensory cortex are well-known examples. In layer IV of the primary somatosensory cortex of nocturnal rodents, thalamocortical axon arbors and their postsynaptic partners form discrete modules that replicate the patterned distribution of whiskers on the snout in a one-to-one fashion. These cellular modules are termed “barrels” (Woolsey and Van der Loos, 1970).

Patterned cortical maps (barrel fields) are established during a critical period in development and depend on an intact sensory periphery and subcortical somatosensory structures

(Killackey et al., 1995; O'Leary et al., 1994; Woolsey, 1990). Whisker and digit-related patterns are first established in the brainstem somatosensory nuclei, then in the VPM–VPL complex of the dorsal thalamus and finally in the neocortex (Belford and Killackey, 1980; Ma and Woolsey, 1984; Van der Loos, 1976; Woolsey and Van der Loos, 1970). The instructive role of the sensory periphery in sculpting central neural patterns has been demonstrated by whisker follicle or trigeminal nerve lesion studies performed in perinatal rodents, or in mice selectively bred for aberrant numbers of whiskers (Killackey et al., 1995; O'Leary et al., 1994; Welker and Van der Loos, 1986; Woolsey, 1990). Several lines of evidence indicate that somatosensory periphery-related neural maps and patterns are conveyed to target cells by the afferents at each synaptic relay station (Erzurumlu and Jhaveri, 1990, 1992a,b; Erzurumlu and Killackey, 1983; Senft and Woolsey, 1991). Current understanding is that topographically organized projections (somatotopic maps) along the somatosensory system are established via several axon guidance cues independent of neural activity (Erzurumlu et al., 1990; Fukuchi-Shimogori and Grove, 2001; Maier et al., 1999; Vanderhaeghen et al., 2000). On the other hand, patterning of neural connections within “somatotopic” maps is controlled by neural activity-mediated mechanisms (Erzurumlu and Kind, 2001).

The columnar and horizontal organization of the rodent primary somatosensory cortex can be visualized easily with routine anatomical methods and analyzed by electrophysiological recordings and imaging techniques. Within the S1 cortex of rodents, a large proportion of the body map is devoted to the representation of the whiskers (Dawson and Killackey, 1987; Riddle et al., 1992). Whisker-specific patterning of thalamocortical axon terminals and modular organization of layer IV granule cells around these patches (barrels) develop postnatally (Erzurumlu and Jhaveri, 1990). Morphological and functional organizations of the barrel fields are permanently altered if the whiskers or the infraorbital nerve innervating them are damaged before the first 4 days after birth (Belford and Killackey, 1980; Durham and Woolsey, 1984; Van der Loos and Woolsey, 1973; Woolsey and Wann, 1976). Thus, the structural organization of the barrel fields is highly sensitive to peripheral injury during a well-defined critical period in development. During the same period, receptive fields of barrel neurons are also highly plastic, and thalamocortical synapses show long-term potentiation, and silent synapses are converted to active ones (Isaac et al., 1997). Beyond this period, plasticity in layer IV decreases while plasticity in layers II and III becomes prominent (Glazewski et al., 2000). Peripheral injury after the critical period does not lead to structural alteration of the established barrel field but does affect intracortical connections (McCasland et al., 1992).

In recent years, increasing attention has been devoted to plasticity of the rodent barrel cortex well after the end of the critical period for structural plasticity. A variety of whisker deprivation paradigms, such as whisker pairing (clipping of all whiskers but two), sparing of one row of whiskers and clipping all the others (and numerous other combinations), have been used to induce plasticity in the barrel cortex (Armstrong-James et al., 1994; Finnerty et al., 1999; Fox, 1992, 1994, 2002; Lebedev et al., 2000; Rema et al., 2003). In such paradigms, there is no significant damage to the infraorbital nerve or its follicular branches, and plucked or trimmed whiskers regrow as part of the normal hair follicle cycle. On the other hand, such manipulations impart selective sensory experience and information flow to the barrel cortex. In general, selective whisker trimming leads to augmentation of responses in the barrels corresponding to intact whiskers and depression in the deprived barrels. As pointed out above, whisker trimming might affect the thalamocortical pathway during the sensitive period, but at later ages, it affects intracortical connections and their efficacy (McCasland et al., 1992). Interestingly, when the individual barrel corresponding to the spared whisker is ablated, plastic expansion of spared whisker representation in the cortex is prevented (Fox, 1994), indicating that the cortical plasticity is initiated from the spared

whisker's barrel. Lesions between the spared and neighboring barrels also block plasticity (Fox, 1994).

In this issue of *Experimental Neurology*, Maier et al. (2003) report that young adult hamsters that have undergone trimming of all whiskers except those in row C for brief (1 h) to long (2 weeks) periods of time display progressively more expansive cortical plasticity as detected by 2 deoxyglucose (2DG) metabolic labeling (see Fig. 1). Brief periods of sensory deprivation increase activity only in the barrels corresponding to intact whiskers. After longer periods of sensory deprivation, spared whiskers progressively activate more of the neighboring silenced barrels and eventually the entire barrel field. If the spared whiskers are trimmed shortly before 2DG injection, then 2DG labeling in the barrel cortex decreases, indicating that the higher metabolic activity seen in the entire whisker barrels was due to the activation of the spared whiskers and their cortical representation. The authors also find that following acute or chronic whisker trimming, parvalbumin-positive cortical GABAergic neurons are highly active, suggesting that cortical plasticity occurs in the presence of strong inhibition in intracortical circuitry. This finding stands in contrast to previous studies with selective whisker trimming for 3.5 days, which showed that stimulation of intact vibrissae led to a widened spatial distribution of barrel cortex activity, and a release from inhibition in deprived barrels suggesting that both inhibitory cortical circuitry and horizontal connections might underlie the cortical plasticity (Lebedev et al., 2000).

Maier et al. (1996) previously reported that whisker follicle ablation after the end of the sensitive and critical period in hamsters leads to a large-scale plasticity in the barrel cortex, even though the morphological organization of the thalamocortical axon terminals and barrels were not altered. Single unit recordings in the adult cortex also revealed that functional connections between spared whisker columns are potentiated after whisker pairing (repeated trimming of all but two whiskers) (Armstrong-James et al., 1994; Diamond et al., 1993, 1994). Similar findings were reported using 2DG autoradiography, physiological and optical recordings (Diamond et al., 1993, 1994; Kossut et al., 1988; Polley et al., 1999).

What are the underlying mechanisms of wide-spread cortical plasticity? Morphogenetic plasticity that occurs during critical period could be attributed to developmental arrest and/or aberrant maturation of thalamocortical axons, and consequently abnormal organization of their postsynaptic partners in the barrel cortex. Once the barrels are constructed and consolidated, plastic changes most likely occur through use or misuse of intracortical connections and modulation of cortical circuitry or sprouting new connections. Available evidence indicates that subcortical changes are not the prime candidates in mediating cortical plasticity in mature rodents (Fox et al., 2002). One study noted that deprived whisker responses are not depressed in the brain-stem trigeminal or ventroposteromedial thalamic nuclei, or in the thalamocortical pathway (Glazewski et al., 1998a,b). Response latency analyses in the cortex suggest that plastic changes occur intracortically via the horizontal connections (Glazewski et al., 1998a,b). It is highly likely that when multiple barrels are deprived of their sensory input for prolonged periods of time, horizontal inputs from active (non-deprived) barrels can now activate and potentiate the responses of their silenced neighbors much like that seen during potentiation and depression of cortical responses along layer IV to layers II and III projections (Allen et al., 2003; Feldman, 2000, 2001). Increasing evidence derived from anatomical and functional studies point to potentiation and sprouting of intracortical horizontal pathways in layers IV and II or III. These pathways might underlie the recruitment of silenced barrels by active ones in the study done by Maier et al. (2003). A direct test for this would be lesioning barrel septa separating row C barrels from their neighbors and determining whether such lesions block wide-spread activation of the cortical barrels by the spared whiskers. Presently, while

intracortical connections are prime suspects in mediating experience-dependent cortical plasticity following selective whisker-trimming paradigms, it is not clear whether these connections are from layer IV or supragranular layers II and III, or both. In one study, removal of supragranular layers in adult animals subjected to whisker pairing showed that plasticity was still present but reduced (Huang et al., 1998). Thus, it remains to be seen to what extent horizontal and vertical connections in different layers contribute to specific aspects of adult plasticity. Potentiation and weakening of synaptic connections in the adult barrel cortex have been shown following whisker-pairing paradigms (Armstrong-James et al., 1994; Diamond et al., 1994). Experience-dependent synaptic plasticity in the barrel cortex also depends on postsynaptic NMDA receptors (Rema et al., 1998; Urban et al., 2002). Recent imaging and recording studies indicate that experience-dependent cortical plasticity in the young rodent barrel cortex is accompanied by increased synapse turnover and remodeling of intrinsic cortical neural circuitry (Knott et al., 2002; Trachtenberg et al., 2002).

At the molecular level, calcium-dependent calmodulin kinase 2 (CamKII) and cyclic-AMP response binding protein (CREB), protein products of inducible transcription factors, have been implicated in mediating barrel cortex plasticity. For example, potentiation of spared whisker responses in layers II and III does not occur in mice that lack functional CamKII gene (Glazewski et al., 1996, 2000). In animals with one spared whisker, a substantial up-regulation of Cre-mediated gene transcription is noted in the corresponding barrel (Barth et al., 2000; Glazewski et al., 1999). In adult rats subjected to whisker clipping and allowed to explore enriched environments overnight, a significant increase in expression of transcription factors c-Fos, JunB, inducible cAMP early repressor and Krox24 has been noted in the barrels corresponding to intact whiskers (Staiger et al., 2000). Clearly, there is now ample evidence documenting that the adult barrel cortex undergoes plastic changes in response to altered sensory experience following selective whisker trimming and exposure to novel environments enriched with tactile cues. However, the underlying morphological, functional and molecular substrates of these changes are just beginning to emerge. A solid understanding of these underlying mechanisms will undoubtedly pave the pathway for evaluating human cortical plasticity and restorative measures following peripheral or central somatosensory pathway injuries.

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Fig. 1. Schematic representation of active barrels and intact whiskers (top), and progressive recruitment of inactive barrels by the active whiskers following trimming of all whiskers, except those in row A.