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Critical period for the whisker-barrel system

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A remarkable feature of the sensory maps in the neocortex is the patterning of pre- and post-synaptic elements which replicate a specific feature of the sensory periphery. Ocular dominance columns in both the feline and the primate visual cortex and whisker-specific neural modules, the “barrels” in the rodent somatosensory cortex are perhaps the most notable examples. In common laboratory rodents, such as the mouse and the rat, thalamocortical axon arbors form synaptic terminal aggregations, around which layer IV stellate neurons arrange their cell bodies to form “barrels,” and they orient their dendritic trees to embrace the presynaptic afferents. The spatial arrangement of barrels replicates the patterned distribution of whiskers on the snout (Woolsey and Van der Loos, 1970). Barrel patterns are established during the first few days after birth and depend on the information flow from the sensory periphery and the subcortical somatosensory structures (see reviews O’Leary et al., 1994; Woolsey, 1990). The instructive role of the sensory periphery in shaping neural patterns has been shown by whisker follicle or infraorbital nerve lesions in neonatal rodents, and in mice bred for aberrant numbers of whiskers (Ohsaki et al., 2002; Ohsaki and Nakamura, 2006; O’Leary et al., 1994; Welker and Van der Loos, 1986; Woolsey, 1990). When the sensory periphery is damaged during the first few days after birth, thalamocortical terminals fail to develop their normal patterning. Consequently, layer IV stellate cells do not form barrels (O’Leary et al., 1994; Woolsey, 1990). In newborn rats and mice, if one row of whisker follicles is cauterized, the area of cortex devoted to the representation of those follicles fuse and shrink, and then the neighboring barrels expand (Belford and Killackey, 1980; Van der Loos and Woolsey, 1973). A developmental time window exists during which these structural alterations take place and it ends by postnatal day (P) 4; as a consequence, lesions after this period do not lead to major structural alterations in the barrel patterning of the cortex or whisker-specific neural patterns in subcortical structures (Belford and Killackey, 1980; Datwani et al., 2002b; Durham and Woolsey, 1984; Rebsam et al., 2005; Van der Loos and Woolsey, 1973; Woolsey and Wann, 1976). In the extant literature, this phenomenon is referred to as the critical period for structural plasticity along the rodent trigeminal pathway (reviewed in Erzurumlu, 2009).

Several studies have investigated the role of sensory activity on barrel patterning and plasticity during early postnatal development. Whisker plucking or various types of whisker trimming, such as whisker pairing (clipping of all whiskers but two), sparing of one row of whiskers and clipping all the others have been used to induce sensory deprivation in neonatal rodents. In contrast to peripheral lesion experiments, structural alterations which follow neonatal whisker trimming has not been as robust at the morphological level assessed with routine histochemical and cytological stains. Whisker plucking, daily trimming of

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whiskers or blockade of action potentials along the infraorbital nerve with tetrodotoxin does not alter whisker-specific pattern formation along the trigeminal pathway (Fox, 1992; Henderson et al., 1992; Simons and Land, 1987). Nevertheless, at the functional level, “experience-dependent plasticity” has been revealed in neonatal, juvenile, and adult barrel cortex (Armstrong-James et al., 1994; Finnerty et al., 1999; Fox, 1992, 1994, 2002; Isaac et al., 1997; Lebedev et al., 2000; Maier et al., 2003; Rema et al., 2003). Whisker trimming in young rats leads to long-lasting enlargement of barrel cell receptive fields and weaker inhibitory interactions between adjacent barrels, even after the whiskers have been allowed to grow back (Simons and Land, 1987). Severe impairments in the ability of discriminating between rough surfaces have also been found in rats that underwent bilateral whisker trimming from birth to 45 days of age (Carvell and Simons, 1996). While these whisker trimming/sensory deprivation studies have underscored the importance of early tactile experience, a developmental “critical” period with a specific closure time has yet to be defined.

In this issue of *Experimental Neurology*, Lee et al., (2009) describe a critical period for fine structural organization of the barrel cortex and functional (behavioral) development, which depends upon whisker-specific sensory experience during the first few days after birth. Interestingly, the end of this critical period coincides with that of the peripheral lesion-induced structural plasticity, postnatal day 3. Different from previous whisker trimming (sensory deprivation) approaches, the investigators trimmed all of the whiskers bilaterally on the day of birth for only three days. After P3 the whiskers were allowed to re-grow, and the juvenile rats were subjected to a variety of behavioral tests, and their barrel cortex was examined for dendritic complexity. These investigators found that P0-P3 whisker sensory deprivation leads to profound behavioral deficits later in life. P0-P3 whisker-trimmed adolescent rats displayed poor performance in a gap crossing test in which the animals had to detect a gap of increasing distance on a beam with their whiskers to cross to the darker side of a two-sided chamber. While the maximum crossable distance for control animals was 6–9 cm, the whisker-trimmed group could only detect and cross up to 4–5 cm distances. On the other hand, no difference in distance detection was observed between control rats and rats whose whiskers were trimmed only on P3. P0-P3 whisker trimmed rats also displayed increased locomotion in an open-field test and increased investigative and contact behaviors in a social interaction test with another rat. These results clearly reveal that a critical period exists for whisker sensation for normal development of a variety of behaviors, ranging from sensory discrimination to social interaction.

Lee et al. (2009) also examined structural features of the barrel cortex in rats that were whisker sensory-deprived during the critical period. As in numerous previous studies, barrel patterns were present and there was no notable change in the overall area of the barrel field in whisker-trimmed animals. However, the size of the individual barrels increased by 14.5% in P0-P3 whisker trimmed rats. This was particularly noteworthy for the caudal large whisker barrels. Detailed analyses of the dendritic fields of barrel cells revealed more primary dendrites, less branching, and wider dendritic spans. Dendritic spines were also affected; spine density increased and many spines displayed multiple heads. Since the investigators relied on Golgi staining of dendrites, these changes probably reflect rapid spine turnover *in vivo* and altered synaptic landscape which probably underlie the observed abnormal behaviors. The structural findings have similarities with those observed in mice with cortex-restricted genetic impairment of NMDA receptors (Datwani et al., 2002a; Iwasato et al., 2000; Lee et al., 2005).

Whisker follicles develop during the latter third of the gestation and rat pups are born with a full set of fine whiskers that are curved back and are immobile. The whiskers grow to their adult size during the first postnatal month and active “whisking” starts towards the end of

the second week of life before the opening of the eyes (Landers and Ziegler, 2006; Welker, 1964). Whisker stimulation during suckling and exploration behavior occurs and trigeminal ganglion cells are responsive to whisker stimulation (Shoykhet et al. 2003). Neonatal rats also show behavioral responses to whisker stimulation, and display tactile learning in a classical conditioning avoidance paradigm (Landers and Sullivan, 1999; Sullivan et al., 2003). In their natural environment, whisker-related tactile experience of rat pups is mostly limited to close contacts with their littermates and their mother as they huddle, suckle, or are groomed by their mother. Whisker trimming between postnatal days 3–5 disrupts nipple attachment and huddling behaviors (Sullivan et al., 2003). Sensory experience through the immobile whiskers is presumably similar between different postnatal days at least until the end of the first postnatal week. The results presented by Lee et al. (2009) are intriguing and raise the question about what specifically determines the end of the critical period for plasticity abruptly at P3. Clearly some activity- or sensory experience-dependent signaling mechanisms must be set into motion during the first few days after birth. The question arises whether these mechanisms operate similarly or differentially at subcortical and cortical levels.

We do not know which cellular and molecular mechanisms regulate critical and sensitive period plasticity, nor do we know where, along the whisker-to-barrel pathway, the duration of the plasticity is set. An earlier regional pharmacological blockade study in newborn rats suggested that NMDARs are involved in the barrel cortex sensitive period. Local application of NMDAR blocker APV over the barrel cortex extended the duration of the sensitive period following whisker lesions on different postnatal days (Schlaggar et al., 1993). However, later studies, particularly studies on cortex-specific *NR1* knockout mice, have shown that when cortical NMDARs are genetically impaired, whisker lesion-induced plasticity and its developmental duration do not change (Datwani et al., 2002b).

The issue of whether cortical or subcortical mechanisms regulate the sensitive period was addressed in an interesting experimental paradigm: Disruption of the serotonin (5-HT) degrading enzyme monoamine oxidase A (*MAOA*) gene in a transgenic mouse line leads to 7–9-fold increase in 5-HT levels. The presence of high levels of 5-HT during thalamocortical development leads to a permanent expansion of thalamocortical axon projection fields in the barrel cortex and subsequent lack of barrels (Cases et al., 1996). Intraperitoneal administration of parachlorophenylalanine (PCPA) in neonatal *MAOAKO* mice degrades excess serotonin and restores barrel patterns (Rebsam et al., 2005). Barrel development can be reinitiated until P11 by PCPA treatments in *MAOAKO* mice. When these investigators examined whisker lesion-induced cortical plasticity, they found that the parameters and timing of the plasticity (i.e., postnatal day 3) did not change, even though barrel formation was delayed by 3–4 days after the closure of the sensitive period. The finding that the emergence of whisker-specific patterning in the barrel cortex can be delayed several days after birth, without a concomitant extension of the sensitive period, indicates that this plasticity is neither influenced by cortical serotonin levels nor by the delay in cortical pattern formation. Thus the window of sensitive period plasticity might be set by molecular and cellular mechanisms operating at the subcortical trigeminal centers. The role of subcortical trigeminal areas in the critical period for whisker sensory experience remains to be tested.

Sensory experience in early postnatal life shapes the morphological and functional organization of brain circuits. Uniquely timed critical periods in postnatal life regulate competition between inputs, tune synaptic activity, balance between excitation and inhibition, and impart a blueprint of the sensory world upon the intrinsic molecular landscape of the brain (Hensch, 2004, 2005). Undoubtedly, the most illustrative example of the developmental critical period in sensory biology comes from visual neuroscience. Since

the classical studies of Hubel and Wiesel (1962), it has been well established that the occlusion of one eye (monocular deprivation) during a defined period in early life leads to irreversible loss of visual acuity (amblyopia) through the deprived eye. Amblyopia and anatomical remodeling within the primary visual cortex have been observed in a wide range of species, including humans (Daw 1995; Prusky and Douglas, 2003; Wiesel, 1982). Unbalanced visual experience following monocular deprivation leads to a rapid shift of neuronal responses in favor of the open eye (ocular dominance), pruning of dendritic spines, and rewiring of thalamocortical afferents (Antonini et al., 1999; Hensch, 2005; Wiesel and Hubel, 1963).

A critical period can be defined as a time during which the presence of specific external or internal condition is necessary for the normal development and that the absence of such condition leads to irreversible alterations in the organism (Erzurumlu and Killackey, 1982). The concept of a developmental critical period for the whisker-barrel pathway was inspired by that of ocular dominance plasticity (Belford and Killackey, 1980; Durham and Woolsey, 1984; Van der Loos and Woolsey, 1973). However, there are significant differences between the two systems in the sensory deprivation paradigm used by the experimenters. Monocular deprivation (occlusion of an eye by lid suture) blocks natural visual stimulation without any damage to the sensory epithelium, the retina. In contrast, whisker follicle lesions or infraorbital nerve cut damages the sensory apparatus. In this sense, the structural plasticity seen following whisker or nerve lesions indicates the vulnerability of the developing system to physical damage during its wiring rather than the critical nature of the sensory experience. In pioneering studies on the structural plasticity of the whisker-barrel pathway, Belford and Killackey (1980) used the term “sensitive period” instead of critical period. The concept of “sensitive period” refers to the period in development during which the system is highly vulnerable, and susceptible to the presence of harmful conditions, such as toxic insults or structural damage (reviewed in Erzurumlu and Killackey, 1982). In the literature that followed the earlier studies of the whisker-barrel pathway, the term critical period has been used to refer to any type of plasticity following neonatal damage to the whisker sensory apparatus or clipping of whiskers to induce sensory deprivation.

The current study by Lee et al., (2009) shows that whisker trimming without follicle damage has a critical period for the functional and fine structural organization of the system which coincides with the timing of the structural plasticity period. However, it is important to note that, whisker trimming (in this study and several others before it) only blocks tactile inputs that follow mechanical distortion of the whisker hair itself. It does not completely block activation of sensory receptors on the snout (and in the trimmed whisker follicles); because the pups huddle in their litter, crawl under the belly of the dam to suckle, or when they are groomed by the dam. Furthermore, Lee and colleagues did not investigate whether prolonged whisker clipping after P3 might have deleterious effects as well.

The onset of whisker-driven sensory activity is prenatal (Waite et al., 2000). Clearly, tactile information flowing through the whisker-barrel pathway during perinatal and early postnatal life is critical for the tuning of synaptic circuits and a normal behavioral repertoire. The cellular and molecular bases of signals that set the duration of whisker sensory critical period remain unknown. Recent studies in the visual system have revealed that GABAergic connections mediated by parvalbumin-positive neurons and selective re-expression of an embryonic homeoprotein, *Otx2*, regulate the timing of the critical period for ocular dominance in the mouse visual cortex (Sugiyama et al., 2008). It remains to be seen whether these players are also involved in the critical period plasticity of the whisker-barrel system. Hyperactivity, poor sensory discrimination, and impaired social interaction seen in early whisker sensory-deprived rats underscore the role of early sensory experience in the development of brain circuits and setting up behavioral traits later in life.

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