governed by fibroblast growth factor during embryogenesis. *Nat. Neurosci.* 2, 246–253

11 Raballo, R. *et al.* (2000) Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J. Neurosci.* 20, 5012–5023

12 Estivill-Torrus, G. *et al.* (2002) Pax6 is required to regulate the cell cycle and the rate of progression from symmetrical to asymmetrical division in mammalian cortical progenitors. *Development* 129, 455–466

13 Kingsbury, M.A. *et al.* (2003) Non-proliferative effects of lysophosphatidic acid enhance cortical growth and folding. *Nat. Neurosci.* 6, 1292–1299

14 Hecht, J.H. *et al.* (1996) Ventricular zone gene-1 (*vzg-1*) encodes a lysophosphatidic acid receptor expressed in neurogenic regions of the developing cerebral cortex. *J. Cell Biol.* 135, 1071–1083

15 Contos, J.J. and Chun, J. (2001) The mouse $lp_{A3}/Edg7$ lysophosphatidic acid receptor gene: genomic structure, chromosomal location, and expression pattern. *Gene* 267, 243–253

16 McGiffert, C. *et al.* (2002) Embryonic brain expression analysis of lysophospholipid receptor genes suggests roles for $s1p_1$ in neurogenesis and $s1p_{1-3}$ in angiogenesis. *FEBS Lett.* 531, 103–108

17 Contos, J.J. *et al.* (2000) Requirement for the lp_{A1} lysophosphatidic acid receptor gene in normal suckling behavior. *Proc. Natl. Acad. Sci. U. S. A.* 97, 13384–13389

18 Contos, J.J. *et al.* (2002) Characterization of lpa_2(*Edg*4) and lpa_1/lpa_2(*Edg*2/*Edg*4) lysophosphatidic acid receptor knockout mice: signalling deficits without obvious phenotypic abnormality attributable to lpa_2. *Mol. Cell. Biol.* 22, 6921–6929

19 Chenn, A. and Walsh, C.A. (2002) Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* 297, 365–369

The unexpected consequences of a noisy environment

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A recent study found that the functional organization of auditory cortex was disrupted when rats were exposed to a moderate level of continuous noise during early development. However, this detrimental effect on auditory cortex could be remedied later by stimulating the noise-reared rats with structured sounds. These findings suggest that the endpoint of the 'critical period' could be extended well into adult life, which has significant implications for our understanding of cortical plasticity.

In a modern society, we are constantly exposed to a noisy environment: for example, while driving a car during daily commuting; from the never-ending air conditioner in the office and at home; and from earth-shaking rock concerts. People usually give little thought to what these noises could do to our brains beyond the obvious hearing loss that one experiences after being exposed to loud sounds. Previous studies have shown that prolonged exposure to high-intensity noises results in damage to hair cells, the auditory receptors that convert the acoustic information into neural signals for the brain. Hair cells in infants and young children often suffer permanent damage due to prolonged and untreated middle ear infections. As one might expect from the work of Hubel and Wiesel on visual cortex development and its susceptibility to distorted visual inputs [1], the damage to hair cells and resulting interruption of auditory inputs should lead to alterations in the central auditory system, including cortex [2]. However, the nature of such plasticity in auditory cortex is not fully understood. What is even less well known but far more interesting is how auditory cortex responds to distorted acoustic inputs when peripheral receptors are intact. Recent studies showed that if one artificially manipulated acoustic inputs to the auditory system during early development, altered neural representations of sounds emerge in auditory cortex [3,4]. How far could auditory cortex be degraded if distorted acoustic inputs were prolonged, akin to the situation in which an infant suffers severe hearing loss owing to an untreated middle ear infection? Is such degradation a non-reversible process? A recent study by Chang and Merzenich [5] sheds light on these fundamentally important questions. Their results show that constant exposure to moderate levels of noise results in severe distortion of neuronal frequency tuning and disruption of tonotopic organization of auditory cortex, but that such alterations seem to be reversible later in life if structured auditory inputs are provided.

Tonotopic organization of mammalian auditory cortex

The auditory cortex of adult mammals is organized according to sound frequency. This organization, or 'tonotopic map', is most clear in the primary auditory cortex (A1), where individual neurons have well-defined frequency tuning properties. In immature animals, the tonotopic map is not as well organized as in adults and A1 neurons tend to have broad frequency tuning. As infants grow into juveniles and adults, a refined tonotopic map progressively emerges. In adult animals, the tonotopic map is reorganized in situations where permanent hearing loss is induced or if animals are extensively engaged in behavioral training [6–8]. Studies show that the tonotopic organization is much more susceptible to perturbations of acoustic inputs in infancy than in older animals, giving rise to the concept of a 'critical' or sensitive period of development, after which plasticity is more restricted

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[2,4]. In rats, the species used by Chang and Merzenich, the onset of hearing occurs at approximately postnatal day (P)12 and the critical period of A1 lasts to ~ P30. Exposure to pulsed tones during the critical period results in accelerated emergence of a refined tonotopic map and an expansion of A1 representations of the tone frequencies [3], whereas exposure to pulsed white noise leads to a distorted tonotopic map [4].

Delayed development of auditory cortex induced by continuous noise exposure

There are generally two approaches to studying auditory plasticity in developing animal models. One is to deprive an animal of acoustic inputs and the other is to alter the acoustic environment beyond what an animal would normally experience. The deprivation method, which was conveniently used in Hubel and Wiesel's studies of the visual cortex by suturing eyelids, turned out to be much more difficult to implement in the auditory system. This is because there is no easy way to close inputs to the auditory system reversibly. Blocking the ear canal with ear plugs does not completely shut off acoustic inputs (especially at low frequencies) and ablation of hair cells, an effective but irreversible method to induce hearing loss, makes it impossible to re-test the sensitivity of neurons to sounds afterwards. Chang and Merzenich's study took the approach of altering the acoustic environment, and exposed rats to continuous white noise, starting before the onset of hearing. The amount of noise these rats were exposed to far exceeded what they experienced in their normal housing environment and constantly excited auditory receptors across all frequencies. When these investigators mapped the auditory cortex of noise-reared adult rats at P50 or later, it looked like that of an immature rat with broadly tuned neurons and a less refined tonotopic map. In other words, the auditory cortex seemed to be 'retarded' by the noise exposure at a young age. Although this finding was obtained in a laboratory condition more extreme than one would typically experience in daily life, it has immediate implications for what could happen to human infants when, for example, a mother works or lives in a noisy environment throughout much of her pregnancy. In humans, the onset of hearing is at ~ 20 weeks before the birth. A poorly structured auditory cortex with broadly tuned neurons would be less capable of supporting fine frequency discrimination, among many other auditory perceptual capacities. It is not hard to imagine that a retarded, or severely developmentally delayed, auditory cortex is linked to a deteriorated speech and language processing ability.

Is the critical period plastic?

What arose from the second part of the Chang and Merzenich study was even more intriguing. Having described the infant-like auditory cortex in noise-reared adult rats, Chang and Merzenich asked whether the auditory cortex would stay abnormal forever. They took these animals off the continuous noise exposure after the animals reached adulthood (P50 or later) and then exposed them to a well structured, albeit simple, acoustic signal (a train of 7 kHz tones) for two weeks. Earlier studies in

Merzenich's laboratory showed that exposing infant rats to such highly structured acoustic signals during the critical period, but not during adulthood, resulted in an altered tonotopic map with overrepresentation of the stimulus frequencies [4]. The auditory cortex of these noise-reared adult rats behaved as if it were still during the critical period of immature rats. After a period of exposure to 7 kHz tones, the poorly defined tonotopic map became refined and broad tuning of A1 neurons became sharpened. Furthermore, there was an overrepresentation of the 7 kHz frequency in A1. This process took place during P50–P120 in the noise-reared adult rats, as opposed to during P12–P30 in normal infant rats, as if the 'critical period' had been reopened or extended in these animals. This novel finding poses questions about the very definition of the critical period and opens doors for many other studies. Interestingly, the delayed maturation of auditory cortex has also been noticed in studies of congenitally deaf cats whose auditory system was electrically stimulated by cochlear implants [9–11].

The findings of Chang and Merzenich raised several interesting questions pertaining to the nature of cortical plasticity. In the past several decades, the research on cortical plasticity has been largely pursued on two separate fronts. Through the work by Hubel and Wiesel and others [12], profound plastic changes in visual cortex were documented and the concept of a critical period during cortical development was formed. The work by Merzenich and others [13–16] since the early 1980s has showed us the other side of the coin – that the adult cortex is plastic as well. The two types of plasticity, during development and adulthood, undoubtedly take many different forms and are often difficult to directly compare. For example, behavioral training-induced cortical plasticity that has been demonstrated in various studies in adult animals [8] is much harder to investigate in infant animals. What is more interesting, but less explored, is how the two types of plasticity (developmental versus during adulthood) are fundamentally related. Most researchers have accepted the notion that developmental plasticity falls and adult plasticity rises as the brain matures. Fundamental questions that have not been adequately addressed are where this 'boundary' lies, if there is a true boundary, and how much these two seemingly different functionalities of the brain overlap in time. In light of the amazing ability of the brain to adapt itself to the ever-changing environment, for better or worse, one must wonder why this boundary cannot be plastic as well. The findings of Chang and Merzenich shed light on this very question and provide the first evidence in mammalian auditory cortex that the end of the critical period might not be as tightly sealed as previously thought. Under certain behavioral conditions, the critical period could remain open for a prolonged period. In visual cortex, there has been evidence that in dark-reared animals the duration of the critical period governing ocular dominance plasticity is prolonged [17,18].

Future directions

Obviously, many questions remain unanswered and await further studies that are likely to follow in coming years.

For example, could the auditory cortex recover after the 'retardation' and eventually function as it does in normal adults? What are the cellular and molecular bases that would allow the putative reopening or prolongation of the critical period? The end of the critical period in cortical development of normal animals has been shown to correlate with the changes in certain neurotransmitter receptor properties (e.g. NMDA receptors) as well as with the level of brain-derived neurotrophic factor (BDNF) [19–21]. It would be interesting to know whether behavioral manipulations used by Chang and Merzenich altered underlying molecular signaling mechanisms in auditory cortex. Studies of these questions will help us understand whether the extended cortical plasticity observed in noise-reared animals is an extension of the critical period that is observed in normally raised animals or whether it constitutes another form of cortical plasticity.

Nevertheless, the notion of a 'plastic critical period' has tremendous implications. Studies along this line could uncover unified mechanisms that link all types of cortical plasticity over the lifespan of an animal or human. Such findings should also have therapeutic implications for treating children with hearing loss at young ages. If the outcome of the Chang and Merzenich study and of studies of electrical stimulation in congenitally deaf cats [11] are of any indication, methods to help regain normal function of auditory cortex, and consequently speech and language processing ability, in effected children are some of the promising possibilities just over the horizon.

References
1 Hubel, D.H. and Wiesel, T.N. (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* 206, 419–436
2 Moore, D.R. (1985) Postnatal development of the mammalian central auditory system and the neural consequences of auditory deprivation. *Acta Otolaryngol. Suppl.* 421, 19–30
3 Zhang, L.I. *et al.* (2001) Persistent and specific influences of early acoustic environments on primary auditory cortex. *Nat. Neurosci.* 4, 1123–1130
4 Zhang, L.I. *et al.* (2002) Disruption of primary auditory cortex by synchronous auditory inputs during a critical period. *Proc. Natl. Acad. Sci. U. S. A.* 99, 2309–2314
5 Chang, E.F. and Merzenich, M.M. (2003) Environmental noise retards auditory cortical development. *Science* 300, 498–502
6 Irvine, D.R. *et al.* (2001) Injury- and use-related plasticity in adult auditory cortex. *Audiol. Neurootol.* 6, 192–195
7 King, A.J. and Moore, D.R. (1991) Plasticity of auditory maps in the brain. *Trends Neurosci.* 14, 31–37
8 Recanzone, G.H. *et al.* (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J. Neurosci.* 13, 87–103
9 Kral, A. *et al.* (2002) Hearing after congenital deafness: central auditory plasticity and sensory deprivation. *Cereb. Cortex* 12, 797–807
10 Kral, A. *et al.* (2001) Delayed maturation and sensitive periods in the auditory cortex. *Audiol. Neurootol.* 6, 346–362
11 Klinke, R. *et al.* (1999) Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. *Science* 285, 1729–1733
12 Wiesel, T.N. (1982) Postnatal development of the visual cortex and the influence of environment. *Nature* 299, 583–591
13 Merzenich, M.M. *et al.* (1983) Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience* 10, 639–665
14 Merzenich, M.M. *et al.* (1984) Somatosensory cortical map changes following digit amputation in adult monkeys. *J. Comp. Neurol.* 224, 591–605
15 Kaas, J.H. *et al.* (1990) Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. *Science* 248, 229–231
16 Pons, T.P. *et al.* (1991) Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 252, 1857–1860
17 Cynader, M. and Mitchell, D.E. (1980) Prolonged sensitivity to monocular deprivation in dark-reared cats. *J. Neurophysiol.* 43, 1026–1040
18 Mower, G.D. (1991) The effect of dark rearing on the time course of the critical period in cat visual cortex. *Brain Res. Dev. Brain Res.* 58, 151–158
19 Katz, L.C. (1999) What's critical for the critical period in visual cortex? *Cell* 99, 673–676
20 Berardi, N. *et al.* (2003) Molecular basis of plasticity in the visual cortex. *Trends Neurosci.* 26, 369–378
21 Bear, M.F. and Rittenhouse, C.D. (1999) Molecular basis for induction of ocular dominance plasticity. *J. Neurobiol.* 41, 83–91

Dissecting complex behaviours in the post-genomic era

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Identifying gene functions in behaviours has so far relied mainly on achievements in the field of molecular genetics. Further progress can be made by developing new approaches that allow refinement of behavioural phenotypes. The current availability of several thousand different mutant mice challenges behavioural neuroscientists to extend their views and methodologies, to dissect complex behaviours into behavioural phenotypes, and subsequently to define gene–behavioural

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