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NEUROSCIENCE

An Olfactory Critical Period

A critical period of plasticity allows neuronal circuitry of the mammalian olfactory system to develop.

Claire E. Cheetham and Leonardo Belluscio

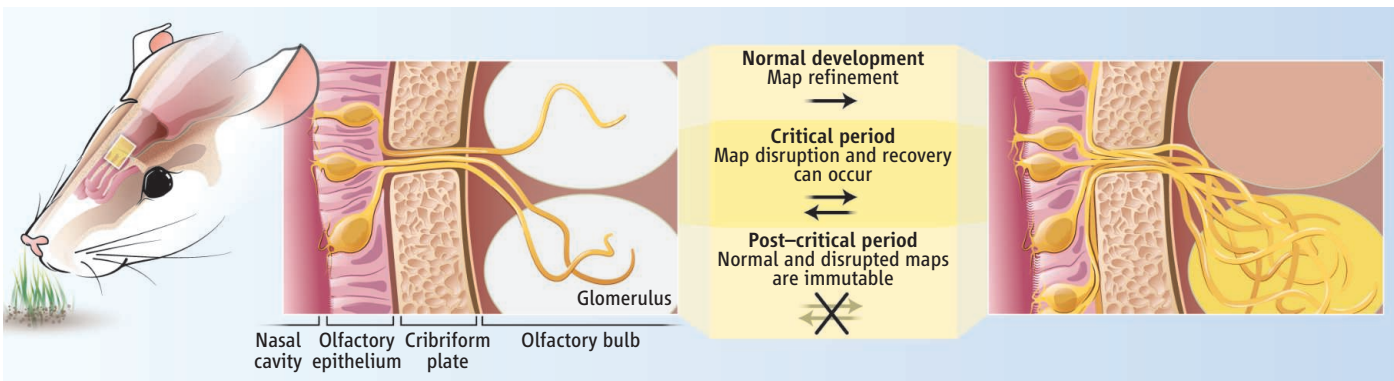
During development of the mammalian nervous system, initially imprecise neuronal connections are refined to generate mature, accurately wired circuits that support perception, cognition, and behavior. This developmental refinement typically depends on neuronal activity; hence, most sensory systems exhibit "critical periods" of heightened sensitivity to sensory experience. By contrast, the olfactory system retains high levels of plasticity throughout life, and there is mixed evidence as to the existence of critical periods. On pages 197 and 194 of this issue, Tsai and Barnea (*1*) and Ma *et al*. (*2*), respectively, support the existence of an unconventional, experience-independent, critical period for the mammalian olfactory system.

Mammals detect odors when the molecular constituents of an odor bind to odorant receptors expressed by olfactory sensory neurons (OSNs) in the nasal epithelium. The axons of these OSNs project directly to the olfactory bulb, where they form spherical structures called glomeruli (see the figure). Each OSN expresses just one type of olfactory receptor, and the axons of OSNs that express the same receptor project to the same glomerulus (convergence), producing a highly organized glomerular map. In the mouse, this map forms and refines during late embryonic and early postnatal life; the timing of maturation of individual glomeruli depends in part on odorant receptor identity. Because OSNs undergo continuous, lifelong turnover, maintaining the organization of the glomerular map poses a particular challenge.

Tsai and Barnea and Ma *et al*. both used a genetic approach in mice to induce the expression of different proteins in OSNs that disrupted the glomerular map. As a result, OSN axons expressing a particular odorant receptor innervated multiple glomeruli rather than just one specific glomerulus into adulthood. Tsai and Barnea investigated the time window during which establishment of the map could be disrupted by allowing it to develop normally through embryogenesis and then switching on expression of the transgene (encoding the disruptive protein) postnatally. They found that transgene expression rarely disrupted glomerular convergence even when expression was switched on at or shortly after birth, and never disrupted it when expression began after the first postnatal week. This implies that if a normal map forms initially, it can be reestablished even after the first postnatal week following ablation of the vast majority of OSNs (regenerating OSN axons can still converge on the appropriate glomeruli). Hence, glomerular map organization becomes immutable in early postnatal life, although the timing of development of individual glomeruli (*3*) may influence precisely when this occurs.

Ma *et al*. took a complementary approach by disrupting initial map formation and assessing the ability of the map to recover when transgene expression was then switched off. Glomerular maps could recover to a completely normal state when transgene expression ended at or shortly after birth. However, when expression continued beyond postnatal day 5, the map persisted in its disrupted state even several weeks later. Notably, similar developmental profiles were seen for three different methods of map disruption, and for OSN axons expressing three different odorant receptors, suggesting a uniform early postnatal time period beyond which glomerular maps cannot recover. Tsai and Barnea also found that disrupted maps could not recover in adult mice; even when OSNs were chemically ablated at the same time that transgene expression was switched off, the regenerating OSN axons still formed a disrupted map. Together, the studies of Tsai and Barnea and Ma *et al*. illustrate an abrupt developmental decline in glomerular map plasticity in early postnatal life. This provides an attractive model by which glomerular stability can be maintained in the face of the constant plasticity that results both from OSN turnover and the ongoing influx of newborn interneurons into the olfactory bulb. However, this perinatal period of heightened plasticity, unlike classical critical periods, does not depend on sensory input.

What factors, then, are required for accurate glomerular map formation? It may be that neuronal activity per se, rather than sensory input, is essential. Indeed, the main manipulation used by Ma *et al*. to disrupt map formation was suppression of OSN activity. However, studies using different forms of activity



The glomerular map. The olfactory system of the mouse requires neurons expressing the same odorant receptor to converge on the same structure (glomerulus) in the olfactory bulb. This convergence can be disrupted and then recover during a critical period, but map organization is immutable after critical period closure.

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manipulations have provided mixed results (*4*, *5*), leaving the role of neuronal activity still unclear. Odorant receptor expression is another likely candidate, as both Tsai and Barnea and Ma *et al*. show that widespread expression of a transgene that encodes an odorant receptor disrupts convergence of other axons that express the same receptor. By comparison, if widespread receptor expression begins in immature OSNs, then greater map alterations are observed and convergence is also disrupted in axons that express a different odorant receptor (*6*). This suggests that the scale of disruption may also affect map regeneration. In support of this, the P2 glomerulus could form de novo even after the first postnatal week following ablation of OSNs expressing the P2 receptor (*7*). However, as Ma *et al*. show, the P2 glomerulus could not recover after postnatal day 3 following more widespread disruption.

Recovery capacity may also vary between odorant receptors. Following map disruption by broadly expressing the amyloid precursor protein (APP) in OSNs, P2 glomeruli failed to recover after the APP-encoding transgene was switched off whereas M71 glomeruli could form again (*8*), further suggesting that the method of disruption may play a role. Another factor to consider is time and the concomitant OSN turnover. It remains possible that some recovery can occur after the perinatal critical period, but is much slower.

Many factors are likely to interact during glomerular map formation and maintenance, highlighting the need for further investigation. Nevertheless, the studies by Tsai and Barnea and Ma *et al*. suggest that regeneration differs fundamentally from initial olfactory circuit formation, relying on some form of positional cue that arose during prior map formation. This has important implications when considering the regeneration potential of the adult brain.

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BOTANY

Patterning Cues from the Altruistic Sibling

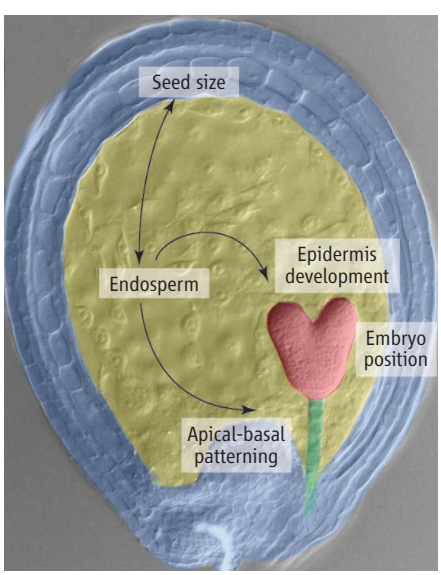
The endosperm acts as a signaling hub to orchestrate developmental processes in the *Arabidopsis* seed.

Martin Bayer

Double fertilization is a key feature of flowering plants. One sperm cell from the pollen grain fertilizes the egg cell to form the embryo while the other sperm fuses with a second female gamete, called the central cell. The second fertilization event gives rise to the endosperm, long thought to be mainly a nourishing tissue supporting the developing embryo or the germinating seedling (*1*). In this issue, Costa and co-workers report on page 168 that in *Arabidopsis thaliana* the endosperm also provides crucial signals for the apical-basal patterning process of the embryo (*2*).

In *Arabidopsis*, the fertilized egg cell or zygote elongates and divides asymmetrically to give rise to a smaller apical cell and a larger basal cell. While the smaller cell develops into the embryo proper, providing most of the later seedling, the larger basal cell forms a filamentous structure called the suspensor (*3*). The suspensor positions the embryo within the seed and serves as a conduit for nutrients and hormones (*4*).

Generally, three developmental pathways have so far been implicated in the apical-basal patterning of the early *Arabidopsis* embryo: (i) a mitogen-activated protein kinase (MAPK) pathway including the MAPK kinase kinase (MAPKKK) YODA (YDA), which promotes suspensor identity; (ii) a transcriptional network of WUSCHEL-RELATED HOMEOBOX (WOX) transcription factors, which is important for both apical and basal cell identity; and (iii) auxin signaling, which confers apical cell identity after the first zygotic cell division and is later involved in embryonic root formation (*3*). Because these three pathways in principle act in the embryo, it might not be surprising that little attention has been paid to the role of the endosperm in this process.



Endosperm as coordinator of seed development. Embryo proper (red), suspensor (green), endosperm (yellow), and maternal seed coat (blue) are false-colored for illustration.

Costa *et al*. now report that the endosperm has a profound influence on the patterning process of the embryo. They describe a small group of cysteine-rich peptides, termed EMBRYO SURROUNDING FACTOR 1 (ESF1). *ESF1.1* to *ESF1.3* are reported to be exclusively expressed in the central cell and the endosperm and to promote suspensor formation in the adjoining embryo in a non–cell-autonomous fashion. Genetic data tentatively place the ESF1 peptides upstream of the MAPKKK YDA, making these prime candidate ligands of a yet unknown receptor complex that positively regulates YDA activity. In addition, the authors report changes in auxin response as well as in the expression pattern of WOX genes in the embryo upon down-regulation of *ESF1* expression in the endosperm. These changes in apical-basal patterning in the embryo could be the result of altered YDA signaling, or they may reflect additional YDA-independent functions of the ESF1 peptides. Under certain in vitro conditions, microspore-derived embryos can reproduce the early division pattern of zygotic embryos in culture without surrounding endosperm (*5*). It will

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