

vate p53 to a level that promotes the transcription of genes that are required for the localized activation of caspases in axons or dendrites subjected to extensive stimulation by excitatory neurotransmitters. This might lead to localized “synaptic cell death” and dendritic thinning. p53 is reportedly present in synapses where it has been suggested to mediate mitochondrial dysfunction and synaptic degeneration in response to DNA damage, oxidative stress, and excitotoxic insults (Gilman et al., 2003). Clearly, additional studies will be required to fully evaluate the role of p53 in HD and other neurological disorders, since other disease proteins may find the draw of p53’s dark side impossible to resist.

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Selected Reading

Bae, B.-I., Xu, H., Igarashi, S., Fujimuro, M., Agrawal, N., Taya, Y., Hayward, S.D., Moran, T.H., Montell, C., Ross, C.A., et al. (2005). *Neuron* 47, this issue, 29–41.

Beal, M.F., Brouillet, E., Jenkins, B.G., Ferrante, R.J., Kowall, N.W., Miller, J.M., Storey, E., Srivastava, R., Rosen, B.R., and Hyman, B.T. (1993). *J. Neurosci.* 13, 4181–4192.

Gilman, C.P., Chan, S.L., Guo, Z., Zhu, X., Greig, N., and Mattson, M.P. (2003). *Neuromolecular Med.* 3, 159–172.

Johnson, M.D., Kinoshita, Y., Xiang, H., Ghatan, S., and Morrison, R.S. (1999). *J. Neurosci.* 19, 2996–3006.

LaFerla, F.M., Hall, C.K., Ngo, L., and Jay, G. (1996). *J. Clin. Invest.* 98, 1626–1632.

Martin, L.J. (2000). *Neurobiol. Dis.* 7, 613–622.

Schuler, M., and Green, D.R. (2005). *Trends Genet.* 21, 182–187.

Shahbazian, M.D., Orr, H.T., and Zoghbi, H.Y. (2001). *Neurobiol. Dis.* 8, 974–981.

Steffan, J.S., Kazantsev, A., Spasic-Boskovic, O., Greenwald, M., Zhu, Y.Z., Gohler, H., Wanker, E.E., Bates, G.P., Housman, D.E., and Thompson, L.M. (2000). *Proc. Natl. Acad. Sci. USA* 97, 6763–6768.

Tabrizi, S.J., Cleeter, M.W., Xuereb, J., Taanman, J.W., Cooper, J.M., and Schapira, A.H. (1999). *Ann. Neurol.* 45, 25–32.

Vousden, K.H. (2000). *Cell* 103, 691–694.

Yuan, J., and Yankner, B.A. (2000). *Nature* 407, 802–809.

Zoghbi, H.Y., and Orr, H.T. (2000). *Annu. Rev. Neurosci.* 23, 217–247.

DOI 10.1016/j.neuron.2005.06.023

Sniffing Out NMDA Receptors in the Olfactory Cortex

Selective olfactory learning is essential for survival in most newborn mammals. Findings by Franks and Isaacson in this issue of *Neuron* suggest that early olfactory learning might be selective, in part because

olfactory experience downregulates NMDA receptors at primary inputs to the olfactory cortex.

Get a whiff of chocolate chip cookies baking in the oven, and the smell may conjure sudden fond memories of Grandma’s kitchen. Such strong odor associations are common, but we often take them for granted. However, for a newborn infant trying to locate mother’s nipple, the association between odor and experience becomes a powerful force forming the basis of a strong bond between infant and mother. Experience-dependent modifications in the olfactory bulb, the first relay between the nose and the higher olfactory areas of the brain, have been proposed to account for olfactory learning during early life (Wilson and Sullivan, 1994). In adults, on the other hand, the olfactory (piriform) cortex is thought to be a critical site for the formation of associative memories (Haberly and Bower, 1989). In this issue of *Neuron*, a new study by Franks and Isaacson (2005) challenges the view that modifications in the olfactory cortex do not contribute to early olfactory learning. The authors provide compelling evidence that early olfactory experiences have a profound impact on synaptic function and plasticity in the olfactory cortex, and it is tempting to speculate that these modifications might help establish strong and specific early olfactory memories.

To gain insights into the synaptic modifications that occur during development, the authors used an in vitro olfactory cortex preparation where they could take advantage of the laminar anatomical architecture of the rat olfactory cortex. Using this preparation, layer II pyramidal cells could be independently activated by stimulating either the mitral cell axons coursing along the lateral olfactory tract (LOT) or the feedback layer II associational fibers (Figure 1A). By carefully verifying that LOT afferents and associational inputs could be independently stimulated, the authors were able to localize pathway-specific synaptic modifications in the olfactory cortex across development and with experience.

Franks and Isaacson used electrophysiological approaches to first examine the relative contribution of AMPA and NMDA receptors at LOT and associational fiber synapses during the first few weeks of postnatal life. They noted that the AMPA/NMDA ratio was low at both sets of synapses during early life. Over the subsequent weeks, there was a dramatic increase in the AMPA/NMDA ratio at LOT but not associational inputs. A well-established observation is that an increase in the AMPA/NMDA ratio is associated with a decrease in the number of synapses that contain only NMDA receptors (Malenka and Nicoll, 1997). To address whether there was a change in the proportion of NMDA-only synapses, the authors used a minimal stimulation protocol. In this technique, the stimulation intensity of afferent inputs is adjusted to a minimal level such that a stimulus often fails to evoke a postsynaptic current in the recorded neuron. The reliability with which AMPA receptor-mediated and NMDA receptor-mediated currents can be evoked is indicative of whether NMDA-only synapses are present. Using this approach, the authors demonstrated that there is a developmental

loss of NMDA-only synapses at LOT inputs but not associational fiber inputs over the first postnatal weeks. The loss of NMDA-only synapses at primary olfactory inputs to the cortex is reminiscent of what has been observed in the somatosensory and visual systems (Isaac et al., 1997; Rumpel et al., 1998).

Does olfactory experience cause the loss of NMDA-only synapses? To address this question, the authors reduced the olfactory-driven activity of mitral cell inputs to the olfactory cortex by occluding the ipsilateral naris (nostril) at birth (Philpot et al., 1997). Because olfactory information largely flows in an ipsilateral manner from the nasal epithelium to the olfactory cortex, unilateral naris closure is an effective approach for limiting olfactory-driven activity. The authors found that olfactory deprivation significantly delayed the developmental increase in the AMPA/NMDA ratio and helped to maintain NMDA-only LOT synapses. The obvious conclusion from these studies, as has been observed in other systems (Malenka and Nicoll, 1997), is that there is an activity-dependent insertion of AMPA receptors during early development. However, the authors did not simply assume that a large-scale “AMPAfication” at LOT inputs could account for their findings. Instead, they further investigated whether the developmental change in the AMPA/NMDA ratio at LOT inputs could be a consequence of an increase in AMPA receptors, a decrease in NMDA receptors, or both.

To determine whether the developmental loss of NMDA-only synapses and the increase in the AMPA/NMDA ratio could be explained by an enhanced contribution of AMPA receptors, the authors performed voltage-clamp recordings in layer II pyramidal cells in the presence of strontium, a technique that allows quantal AMPA receptor-mediated currents to be evoked. Surprisingly, there was no change at LOT synapses in the size of the quantal AMPA receptor-mediated responses over development or with olfactory deprivation. These findings are intriguing and suggest that one of two possibilities could explain how the loss of NMDA-only synapses could occur in the absence of a change in the quantal AMPA receptor response. First, AMPA receptors could be inserted into NMDA-only synapses in packets that produce the same quantal response found at other synapses. Alternatively, there might be little change in AMPA receptor expression but, instead, a large reduction in the expression of NMDA receptors.

By comparing deprived and nondeprived olfactory cortices, Franks and Isaacson show that olfactory experience dramatically downregulates NMDA receptors while only modestly increasing AMPA receptor responses. The dramatic experience-dependent decrease in the synaptic NMDA receptor response could explain the increase in the AMPA/NMDA ratio. Moreover, as no developmental changes were observed at the associational inputs, the findings demonstrate that the synaptic expression of NMDA receptors can be regulated in a pathway-specific manner in addition to the cell-wide changes in NMDA receptor expression that have been observed previously in other systems (Perez-Otano and Ehlers, 2005; Turrigiano and Nelson, 2004). Future studies will need to distinguish between the possibilities that the loss of NMDA receptors might simply reflect an experience-dependent pruning back of NMDA-only

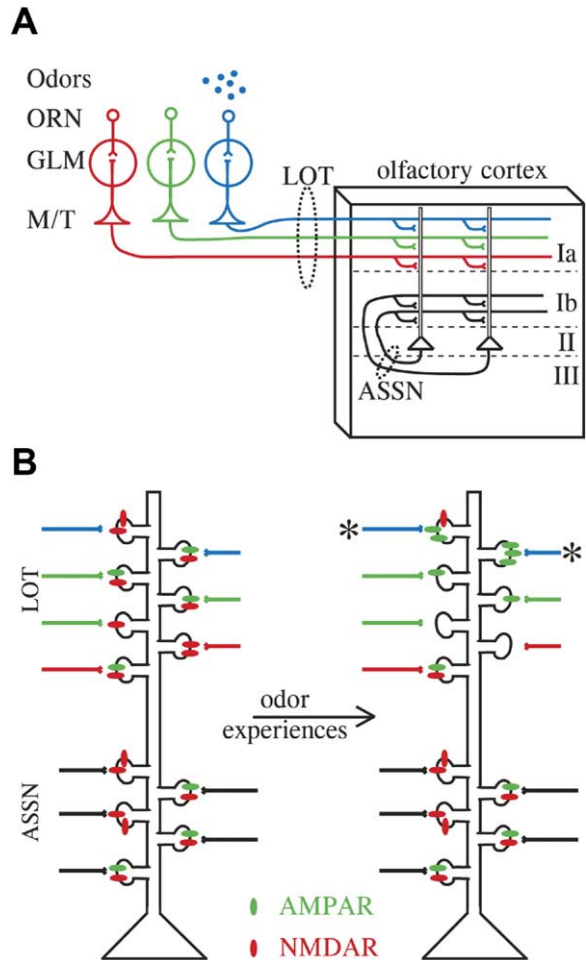


Figure 1. A Simplified Diagram of Olfactory System Circuitry and a Hypothetical Model of Synaptic Modifications Contributing to Early Olfactory Learning

(A) Basic wiring diagram of the olfactory system. ORN, olfactory receptor neuron; GLM, glomeruli; M/T, mitral/tufted cells; LOT, lateral olfactory tract; ASSN, associational fibers.

(B) Hypothetical model demonstrating how selective olfactory learning might arise from the insertion of AMPA receptors (AMPARs) at LOT inputs associated with maternal odors (indicated by asterisks) coupled with a wide-scale removal of NMDA receptors (NMDARs) (see text for details).

synapses or that NMDA receptor levels are lost across extant LOT synapses.

The olfactory cortex appears to be especially attuned to experience-dependent modifications during early life, as has been observed in other sensory cortices. The authors demonstrate that olfactory deprivation only modifies the AMPA/NMDA ratios at the LOT synapses if the deprivation begins during a sensitive period of early development. But what might be the consequences of the experience-dependent loss of NMDA receptors? The authors provide evidence that one straightforward consequence is that NMDA receptor-dependent strengthening at LOT synapses becomes more difficult to induce. Thus, the loss of NMDA receptors might help to stabilize LOT synaptic inputs such

that they are only modified in response to particularly salient events.

How might experience-dependent modifications at LOT synapses affect early olfactory learning? One attractive possibility is that a specific odor set, such as the odors associated with a mother, might cause a selective insertion of AMPA receptors at a small subset of LOT synapses when paired with a reward, such as a mother's milk (Figure 1B). These olfactory experiences may then set into motion a large-scale removal of NMDA receptors at LOT synapses but not at associational fiber synapses. The insertion of AMPA receptors at a limited set of synapses could account for the modest increase in AMPA receptor-mediated responses and could serve to increase the relative saliency of learned odors. The removal of NMDA receptors at LOT synapses could account for the large increase in the AMPA/NMDA ratio and might serve to limit subsequent NMDA receptor-mediated plasticity at these synapses. Coupled with plasticity in the olfactory bulb (Wilson and Sullivan, 1994), the aforementioned synaptic modifications could ensure that early olfactory experiences would strongly imprint a small odor set while limiting subsequent synaptic strengthenings associated with nonimprinted odors. Plasticity maintained at association fiber inputs, however, could still support olfactory learning throughout life (Haberly and Bower, 1989).

Although it is appealing to believe that early experience-dependent modifications across LOT synapses might increase the relative saliency of maternal and other learned odors, we must remember that there are simple, and no less important, alternative explanations for the synaptic changes observed at LOT inputs. For example, early odor experiences may serve to refine LOT inputs in a general manner rather than in a manner that increases the saliency for a small set of odors. Nevertheless, the findings by Franks and Isaacson further open the door to discovering the mechanisms whereby experience leaves its trace in olfactory cortex during early life. Many important questions stem from these findings. Do the observed LOT synaptic modifications contribute to early olfactory learning, or might they serve another purpose? What pattern of mitral cell activity initiates the downregulation of NMDA receptors at LOT synapses? What is the molecular signal that conveys the downregulation of NMDA receptors, and how is the pathway specificity of that signal achieved?

Future studies are needed to elucidate how or if the observed synaptic modifications in the olfactory cortex translate into olfactory learning and the encoding of memories, but an appealing hypothesis is that these modifications help establish strong olfactory memories in a small subset of LOT synapses. As a neuroscientist and a new parent, I cannot help but to wonder whether a synaptic trace is being left in my newborn daughter's olfactory cortex every time she breastfeeds.

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Selected Reading

- Franks, K.M., and Isaacson, J.S. (2005). *Neuron* 47, this issue, 101–114.
- Haberly, L.B., and Bower, J.M. (1989). *Trends Neurosci.* 12, 258–264.
- Isaac, J.T., Crair, M.C., Nicoll, R.A., and Malenka, R.C. (1997). *Neuron* 18, 269–280.
- Malenka, R.C., and Nicoll, R.A. (1997). *Neuron* 19, 473–476.
- Perez-Otano, I., and Ehlers, M.D. (2005). *Trends Neurosci.* 28, 229–238.
- Philpot, B.D., Foster, T.C., and Brunjes, P.C. (1997). *J. Neurobiol.* 33, 374–386.
- Rumpel, S., Hatt, H., and Gottmann, K. (1998). *J. Neurosci.* 18, 8863–8874.
- Turrigiano, G.G., and Nelson, S.B. (2004). *Nat. Rev. Neurosci.* 5, 97–107.
- Wilson, D.A., and Sullivan, R.M. (1994). *Behav. Neural Biol.* 61, 1–18.

DOI 10.1016/j.neuron.2005.06.021