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# Regeneration and Rewiring the Olfactory Bulb

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During olfactory development axons from the sensory epithelium migrate to the olfactory bulb and gradually establish connections with targeted glomeruli (Key and St John, 2002). The spatial distribution of these connections form the basis of a topographical mapping of odorant receptors onto the olfactory bulb (Vassar *et al.*, 1994). The olfactory epithelium retains its capacity to undergo neurogenesis long after development and odorant receptors continue to establish new connections in the adult olfactory bulb. Remarkably, these newly rewired connections converge onto glomeruli in specific areas of the bulb maintaining a topographical mapping of odorant receptors. The preservation of this spatial mapping of odorant receptors onto the olfactory bulb plays an essential role in the processing of olfactory information while disruption of odorant maps results in impaired or altered olfactory function (Yee and Costanzo, 1998).

The olfactory system has become a popular model for the study of neural regeneration and the rewiring of axons following injury. Lesions to the neuroepithelium, nerve fibers and olfactory bulb all have disruptive effects on odorant receptor mapping. Regeneration and the restoration of olfactory receptor connections depend upon the degree and type of injury. For example, lesions to olfactory cells in the neuroepithelium are not reversible if the basal cell layer is destroyed. However, when spared, regeneration of the basal cells leads to a reconstitution of the sensory epithelium and a subsequent restoration of olfactory function (Iwema *et al.*, 2004).

Recovery following olfactory nerve transection also depends on the degree of injury. Extensive lesions involving damage to both the olfactory nerves and layers of the olfactory bulb are more likely to produce scar tissue and gliosis, introducing mechanical barriers to axon growth. Regenerating axons must penetrate or circumvent these obstacles if they are to successfully rewire the olfactory bulb. Early studies of olfactory nerve lesions used metal blade instruments. This often resulted in extensive damage to multiple layers of the olfactory bulb as well as the scraping of bone and dura along the cribriform plate. Very long recovery times were frequently needed to observe reconnected axons within the olfactory bulb, and connections were often formed in areas of injury extending well into the granule cell layer. Although new methods have been developed to selectively lesion the olfactory nerves with minimal or no damage to the olfactory bulb (Costanzo, 2000), regenerating nerve fibers still face the spatial challenges introduced by the disruption of axon sheath alignments at the cribriform plate. In spite of the many obstacles encountered when rewiring the olfactory bulb after injury, the olfactory system maintains its capacity to regenerate new axon processes and can reestablish functional connections with the olfactory bulb.

Figure 1 illustrates the changes that occur in the rewiring of the olfactory bulbs of P2-tau-LacZ mice following nerve transection. Although regenerated axons retain their ability to converge and reestablish connections with glomeruli, these rewired connections are distributed across a very wide area of the olfactory bulb (Figure 1A) and there is significant disruption to the normal P2 odorant mapping pattern observed in control mice (Figure 1B).

In addition to the wider spatial distribution of P2 labeled axons projecting to multiple glomeruli, histological observations of the olfactory bulb show that many glomeruli receive partial innervation by P2 axons. These findings suggest that after nerve transection, glomeruli in the olfactory bulb are no longer dominated by a single odorant subtype and that there is a competition among regenerating receptor axons to occupy synaptic sites within a glomerulus. This post lesion alteration in the rewiring of glomeruli may have significant functional consequences, especially for odor discrimination.

The inability of axons to accurately rewire the olfactory bulb and restore the spatial integrity of odorant receptor maps is more likely to occur following injury to the olfactory nerves and bulbs than to the neuroepithelium. When the olfactory nerves and bulbs are injured, regenerated axons must find new pathways or overcome barriers such as gliosis and the formation of scar tissue before they can reestablish connections with the bulb. In contrast, when injury is limited to the olfactory neuroepithelium, regenerating axons have access to intact nerve bundle sheaths that provide conduits to guide axons back to specific regions of the bulb.

Mechanisms that facilitate or inhibit the guidance of axons to specific targets in the olfactory bulb are topics of considerable interest. Axon–cell interactions, growth factors, the role of glia cells and axonal outgrowth and interaction with extracellular matrix molecules are all topics that need further investigation. These mechanisms are likely to play an important role in the rewiring of the

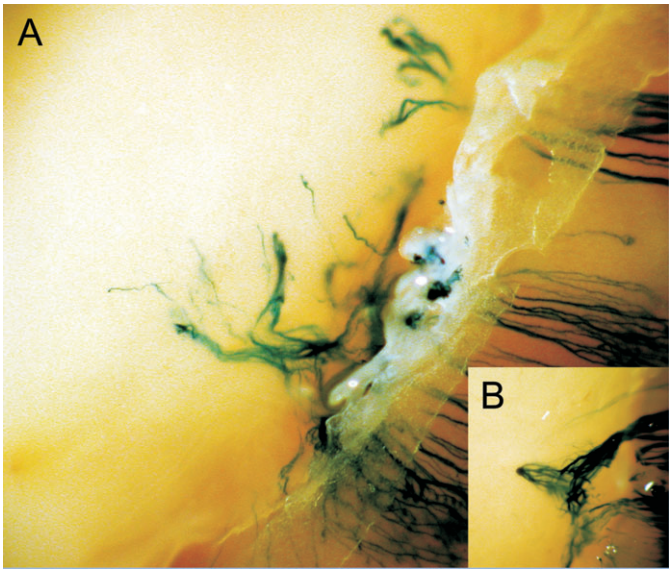


**Figure 1** Changes in P2 odorant receptor mapping after recovery from olfactory nerve transection. **(A)** 60 days following nerve transection regenerated P2 axons project to multiple glomeruli in different locations distributed across the olfactory bulb. **(B)** Typical P2 mapping onto a targeted glomerulus in the olfactory bulb of a control animal.

olfactory bulb. Future studies directed at understanding these mechanisms may help in the development of new strategies to improve recovery and restore olfactory function following injury.

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