Interhemispheric Olfactory Circuit and the Memory Beyond

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In mammals, olfactory sensory neurons project their axons exclusively to the ipsilateral olfactory bulb. It remains unclear how odor information interacts between the two hemispheres of the brain. In this issue of *Neuron*, Yan et al. describe the precise interbulbar connection through the anterior olfactory nucleus pars externa (AONpE), which links contralateral isotypic olfactory columns.

Since the discovery of odorant receptors (ORs) (Buck and Axel, 1991), there has been tremendous progress in understanding how odor information is represented in the olfactory bulb (OB), the first center for processing odor information. Airborne odorants are detected with ~1000 types of ORs expressed by olfactory sensory neurons (OSNs) in the olfactory epithelium (OE). Each OSN expresses only one functional OR gene in a monoallelic manner, following the one neuron-one receptor rule (reviewed by Serizawa et al., 2004). Furthermore, OSNs expressing a given type of OR converge their axons to a specific pair of glomeruli in each OB, referred to as the one glomerulus-one receptor rule (reviewed by Imai and Sakano, 2007). The result is a stereotyped, mirror-symmetric glomerular map (Figure 1). Thus, the odor information detected in the OE is converted to a topographic map of activated glomeruli (reviewed by Mori et al., 2006).

In the OB, each glomerulus with its underlying neurons forms a functional unit called the "olfactory column" for odor processing (reviewed by Wilson and Mainen, 2006). Local interneurons, such as periglomerular cells and granule cells, tune the odor-derived signals that are conveyed to second-order neurons, the mitral/tufted (M/T) cells. Each M/T cell receives direct inputs from a single glomerulus and sends branched axons to several distinct regions in the olfactory cortex (OC), as well as to other brain regions involved in multimodal sensory integration. A recent study demonstrated that activation of specific sets of glomeruli in the dorsal domain of the OB elicits stereotyped innate behaviors, suggesting the presence of a hardwired neural circuit in the mammalian main olfactory system (Kobayakawa et al., 2007). In contrast, discrimination and associative learning of odor information appear to be more complex and plastic. Fundamental questions regarding these processes remain mostly unanswered. It is yet to be elucidated how odors are recognized and discriminated and how olfactory memories are stored and retrieved. The first step toward answering these questions is to describe the neural circuitry for respective olfactory responses from both anatomical and functional aspects.

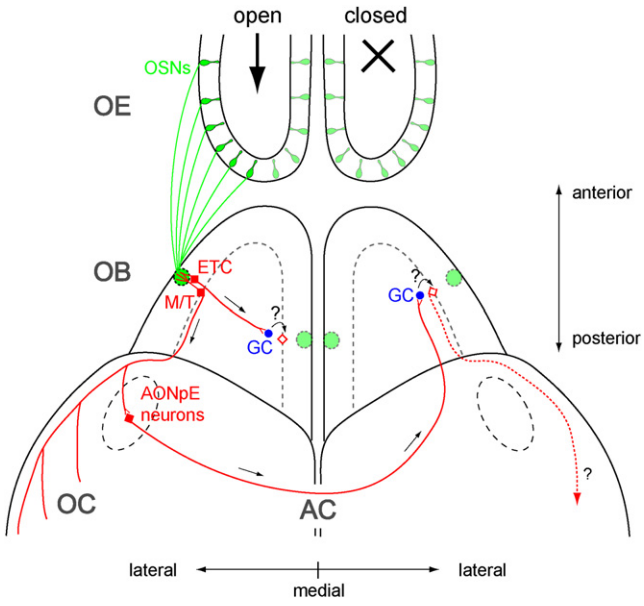

Figure 1. Intrabulbar (Lodovichi et al., 2003) and Interbulbar (Yan et al., 2008) Circuitries in the Mouse Olfactory System
A horizontal section of the mouse olfactory system is schematically shown. Information flow from one particular lateral glomerulus in the left OB is shown. Isofunctional glomeruli are shown in green. Excitatory and inhibitory neurons are shown in red and blue, respectively. External tufted cells project axons to the granule cells in the isofunctional olfactory columns, to form intrabulbar connections (Lodovichi et al., 2003). M/T cells project axons to the OC, including the AON. In the AONpE, M/T cells synapse to excitatory neurons, which in turn project axons to the granule cells in the isofunctional olfactory column in the contralateral OB. This disynaptic circuitry forms the interbulbar connection (Yan et al., 2008). AC, anterior commissure; ETC, external tufted cell; GC, granule cell.

In this issue of *Neuron*, Yan et al. (2008) address an important question for odor perception: how are the olfactory inputs from two nostrils coordinated in the brain? In contrast to retinal projection in binocular animals, mammalian OSNs project their axons solely to the ipsilateral OB: right nostril to the right OB and left nostril to the left OB. The same is true for second-order neurons: the M/T cells project their axons to the ipsilateral OC. Nonetheless, behavioral studies demonstrate that the olfactory memory learned by one nostril can be recalled by stimuli to either nostril (Kucharski and Hall, 1987), suggesting the existence of an interhemispheric connection

for olfactory learning and/or recall. Which neural circuit mediates the interhemispheric communication? And how?

The anterior olfactory nucleus (AON) is a region of the OC known to contain neurons that project to the contralateral OB. This contralateral projection passes through the anterior commissure, one of the fiber bundles connecting the two hemispheres of the brain. Notably, the anterior olfactory nucleus pars externa (AONpE) receives inputs from M/T cells in the ipsilateral OB and sends fibers exclusively to the granule cell layer in the contralateral OB. Among the AON subregions, only the AONpE exhibits topographic projection to the OB (Davis and Macrides, 1981). In the present study, Yan et al. (2008) analyzed whether or not connections through the AONpE link the OR-specific olfactory columns of opposite OBs. When fluorescent tracers were injected into a glomerulus for OR-M71, anterograde labeling was detected in a specific spot within the ipsilateral AONpE. Anterograde labeling from various glomerular locations revealed a conservation of topography between the OB and AONpE: relative locations of glomeruli in the OB along the anterior-posterior, dorsal-medial, and medial-lateral axes are all preserved in the AONpE. The projection of AONpE neurons to the contralateral OB also occurs in a topographically conserved manner: tracer injection to the granule cell layer resulted in retrograde labeling of a specific spot in the contralateral AONpE region. To examine the OR-specific neuronal connection through the AONpE, Yan et al. (2008) injected red tracers into the M71 glomerulus and green tracers into the granule cell layer beneath the contralateral M71 glomerulus. They found colocalization of red and green dyes in a restricted area in the AONpE. Thus, the two projections, one from OB to ipsilateral AONpE and the other from AONpE to contralateral OB, link the two corresponding OR-specific ''isofunctional'' olfactory columns with high precision (Figure 1).

The next question was, does this circuit regulate the neuronal activity of the contralateral OB? Using c-Fos expression as a measure of activity, Yan et al. (2008) analyzed the odor-evoked neuronal activity in the OB. Odorant stimuli induced c-Fos expression in the periglomerular cells and granule cells in the OB. When one nostril was occluded, c-Fos signals were dramatically reduced on the occluded side. Interestingly, however, significant levels of signal were detected in granule cells. The activities of the underlying granule cells were caused by excitatory inputs from the contralateral AONpE. When AONpE neurons on the contralateral (open) side were killed by isobutenic acid, c-Fos signals in granule cells on the occluded side were not observed. These results indicate that M/T cells activate the ipsilateral AONpE neurons, which in turn lead to the excitation of granule cells in the contralateral OB. This notion was also confirmed by electrophysiological recordings of granule cell activities.

In each OB, mirror-symmetrical maps are formed in the medial and lateral halves, and reciprocal projections within the OB link the isotypic olfactory columns (Lodovichi et al., 2003). Connectivity of the interbulbar circuitry appears to be analogous to the intrabulbar circuitry. It has been found that external tufted cells (excitatory neurons) project to granule cells within the isotypic olfactory column on the other side of the OB (Figure 1). However, it is still unknown how the activated granule cells modulate M/T cells, and how the intrabulbar association tunes olfactory signals as a whole. Because granule cells are GABAergic neurons, both intrabulbar and interbulbar connections appear to be inhibitory. These systems might be used to synchronize the odor-evoked neuronal activity and transmit the robust signals to the OC. Alternatively, interbulbar reciprocal connections may enhance the difference in inputs between the two nostrils, allowing the ''stereo'' sensation of odors. Indeed, there is a report demonstrating that bilateral sniffing is essential to sense the direction of the odor source in rat (Rajan et al., 2006).

Yan et al. (2008) assume a different scenario for the function of interbulbar connection. They examined the functional requirement of interbulbar circuitry for the exchange of olfactory information between hemispheres. It has been reported that unilateral olfactory learning can be recalled by stimulating either of the two nostrils, trained or untrained, and that transection of the anterior commissure impairs the memory recall by the untrained nostril (Kucharski and Hall, 1987). Yan et al. (2008) specifically eliminated the AONpE neurons by focal injection of isobutenic acid and assessed its impact on bilateral communication. They used a unilateral olfactory learning/recall paradigm in which both ANOpE-lesioned and sham-lesioned mice were trained to associate footshock with a particular odor through a single nostril and then tested for the olfactory memory either with the trained or untrained nostril. Sham-lesioned mice could avoid the odor with either nostril. Even when the AONpE was lesioned, the mice still successfully avoided the associated odor with the trained nostril, suggesting that olfactory learning and recall in the ipsilateral brain was not affected by the surgery. In contrast, the AONpE-lesioned mice did not avoid the odor with the untrained nostril. Because the AONpE neurons project exclusively to the contralateral OB and not to other brain regions (Davis and Macrides, 1981), these results indicate that the projection from AONpE to contralateral OB is essential for interhemispheric communication in the olfactory learning and/or recall. This finding is quite amazing; however, one must be cautious in interpreting the data of surgical lesions. In the vicinity of the AONpE, other subregions are closely packed, some of which also project to the contralateral hemisphere (Davis and Macrides, 1981). Therefore, one cannot exclude the possibility that the AONpE lesion may have also damaged other subregions, which might instead mediate the learning and/or memory recall between the two hemispheres. To address these issues, specific elimination or silencing of AONpE neurons using genetic methods (e.g., Kobayakawa et al., 2007) will be useful for future studies.

The present study by Yan et al. (2008) also raises some important questions. If the interbulbar circuitry indeed mediates the learning and/or recall, does the activation of granule cells in the contralateral OB elicit the memory? In order to learn or to recall the olfactory memory in the brain, regulation of M/T cells appears to be essential, because they are the only projection neurons in the OB. Yan et al. (2008) indeed find that the neuronal activities of some M/T cells are changed (either excited or inhibited) by contralateral inputs.

However, it is puzzling that the activation of the underlying GABAergic granule cells leads to such changes. Future studies using genetic methods that label a specific subset of neurons or stimulate them by light-gated ion channels will help describe the local neural circuitry in detail.

Interbulbar circuit formation is an intriguing issue in developmental neurobiology. Recent studies have shed light on the molecular basis of olfactory map formation in the OB: OR-derived cAMP signals direct the axonal projection of OSNs by regulating the gene expression of axon guidance/sorting molecules (reviewed by Imai and Sakano, 2007). Spontaneous signaling from ORs, rather than odor-evoked activity, appears to be important in mammalian OSN projection, whereas the intrabulbar projection of external tufted cells is highly dependent on neuronal activity (Marks et al., 2006). Although the intrabulbar connection is monosynaptic, the interbulbar circuit described in the present study is disynaptic, which may require more complicated processing during development. The commissural fibers play an important role in exchanging higher-order information between hemispheres, and studies on the interbulbar circuitry will provide new insights into the molecular mechanisms of the precise wiring between hemispheres.

Another issue raised in the present study is the interhemispheric exchange of olfactory information. The reported failure of interhemispheric communication in the behavioral experiments on the AONpE-lesioned mice may be due to the inability to either "form" the memory or to "transfer" it to the contralateral hemisphere. Alternatively, it may be due to the deficit of the "recall" of memory stored in the contralateral hemisphere. These possibilities are not mutually exclusive and can be dissected and tested with genetic tools to silence the AON in a reversible manner. It is still not well understood where and how olfactory memory is stored and what kinds of neuronal activities lead to learning and recall of olfactory information. The interbulbar circuitry described in the present study will continue to serve as an excellent tool for the study of olfactory memory.

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Although adaptation is a ubiquitous property of neurons in the early visual pathway, the functional consequences in the natural visual environment are unknown. In this issue of *Neuron*, Mante et al. show, through a comprehensive set of in vivo experiments in the visual thalamus, that the basic functional mechanisms of adaptation that have been well studied with artificial probes capture the neuronal response in the natural environment and are predictable from properties of the visual scene that may be represented by local neural ensembles.

Nature does nothing uselessly.
—Aristotle, 384–322 BC

It is this compelling idea that has driven neuroscientists for decades to ponder the evolution, development, and function of the brain in the context of the natural environment within which we exist. Simply put, to understand the brain, we cannot ignore our surroundings. Although the key to the mysteries of the endless complexity of the anatomy and function may indeed lie at the interface between the individual and the world, scientific exploration of the brain from this perspective is a vexing task. The idea does not lend itself well to carefully controlled experiments that normally constitute scientific investigation. Nevertheless, confronting this issue may help us move from *what can the brain do?* to *what does the brain*