of synergies will further our understanding as to how the brain controls the hand. In answering this question, the paper has provided an important step in the right direction.

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There and Back Again: The Corticobulbar Loop

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http://dx.doi.org/10.1016/j.neuron.2012.12.006

Feedback is a ubiquitous anatomical feature of sensory processing in vertebrates. In this issue of *Neuron*, two papers (Boyd et al., 2012, and Markopoulos et al., 2012) analyze the features of feedback from olfactory cortex to olfactory bulb.

The simplest view of sensory processing is a series of feedforward stages each extracting successively more complex features of incoming stimuli. A somewhat more sophisticated view incorporates parallel or divergent feedforward streams that are customized for processing of different stimulus features—such as the "what" versus "where" pathways of the visual system. However, even this view neglects a prominent anatomical attribute of all sensory pathways–extensive feedback connections that transmit activity from higher-order areas to more primary structures. Moreover, in many cases, feedback connections outnumber the feedforward connections between these same areas. The function served by these retrograde signals for the most part is unknown. How does the brain use feedback signals, which could be thought of as an "echo" of the output returning to its source?

Understanding the functional role of feedback connections requires answering two key questions. What patterns of activity are generated in the downstream areas? And what are the functional and anatomical properties of the feedback projections? Recent work from a number of groups has made strides toward addressing these two questions and provided a greater understanding of the role of feedback in olfaction. Electrophysiological and imaging studies have provided detailed analyses of how odors are represented in olfactory cortex (Miura et al., 2012; Poo and Isaacson, 2009; Stettler and Axel, 2009; Wilson and Sullivan, 2011). In this issue of *Neuron*, two papers (Boyd et al., 2012, and Markopoulos et al., 2012) use optogenetics to reveal specific features of the feedback connections from olfactory cortex to olfactory bulb, providing an important step in understanding the functional role of feedback in this sensory pathway (Figure 1).

Olfactory processing begins when odorant molecules bind to olfactory receptor proteins on the membrane of sensory neurons in the nose. Each sensory neuron expresses one of about one thousand different olfactory receptor genes found in the rodent genome. The axons of olfactory receptor neurons (ORNs) converge in structures called glomeruli that tile the surface of the olfactory bulb. In each glomerulus, the axons of ORNs expressing the same receptor form excitatory synapses with the dendritic tufts of excitatory mitral and tufted cells. Mitral and tufted cells send a primary apical dendrite to a single glomerulus; therefore, all the afferent input to these cells is provided by a single type of olfactory sensory neuron. Several classes of inhibitory neurons within olfactory bulb

regulate the activity of mitral and tufted cells. These include periglomerular (PG) neurons and superficial short axon (sSA) cells that have somas located in the glomerular layer (GL) as well as granule cells (GC) and deep short axon (dSA) cells that are located in the granule and internal plexiform layers. Lateral interactions between mitral and tufted cells associated with different glomeruli are mediated by connections between mitral/tufted cells and granule cells as well as short axon cells. Mitral and tufted cell axons form the lateral olfactory tract (LOT), which relays olfactory bulb output directly to pyramidal cells in the olfactory cortices. Pyramidal neurons in olfactory cortical areas close the loop by sending axon collaterals back to the olfactory bulb (Johnson et al., 2000; Luskin and Price, 1983; Figure 1). These feedback projections are the focus of the two papers in this issue of *Neuron*.

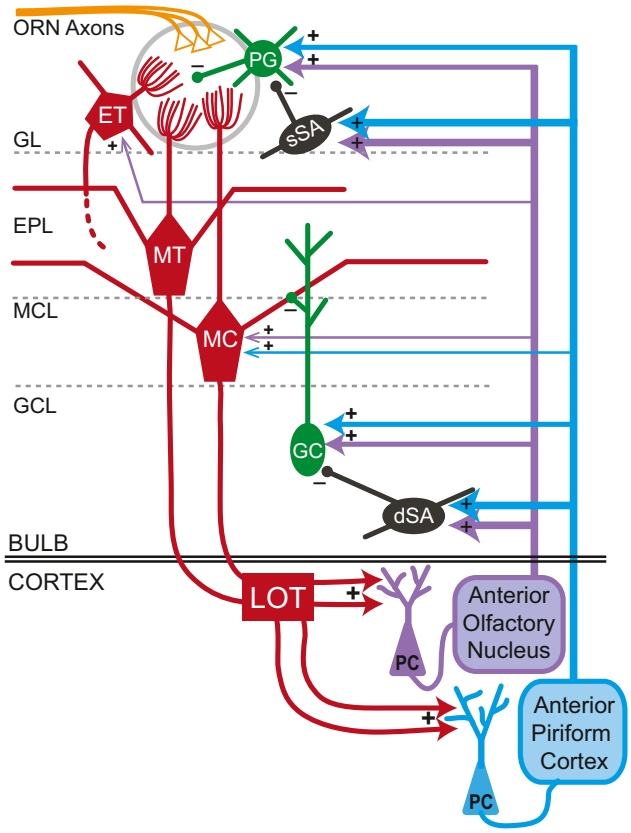

Figure 1. Cortical Feedback to the Olfactory Bulb
The pyramidal cells (PC) in anterior olfactory nucleus (purple) and anterior piriform cortex (blue) receive odor information from mitral cells (MC) and middle tufted cells (MT) of the olfactory bulb via the lateral olfactory tract (LOT). The PCs project axons back to the bulb (blue/purple lines) and the strength of connection is shown schematically by line thickness. PCs synapse predominantly with inhibitory interneurons in the granule cell layer (GCL) and the glomerular layer (GL). The strongest drive is to deep and superficial short axon cells (d/s SA) followed by granule cells (GC) and periglomerular cells (PG). There is weak excitatory input to MC and ET cells. In the glomerular layer (GL), PG cells inhibit external tufted (ET) cells. GC cells inhibit MT and MC cells at dendrodendritic synapses in the external plexiform layer (EPL). Other abbreviations: mitral cell layer (MCL), olfactory receptor neuron (ORN).

Inhibitory Feedback Dominates

Two papers in this issue describe experiments in which optogenetic approaches are used to produce selective activation of feedback cortical projections to the olfactory bulb. Two divisions of primary olfactory cortex are targeted: the anterior olfactory nucleus (AON) (Markopoulos et al., 2012) and the anterior piriform cortex (APC) (Boyd et al., 2012). These two areas have similar cellular and circuit properties with pyramidal cells mediating extensive feed-forward, recurrent, and feedback projections within and between brain areas. In both studies, adenoassociated viral vectors (AAVs) were used to express the light-activated ion channel, channelrhodopsin (ChR2), along with fluorescent reporter proteins in cortical neurons. Markopoulos et al. (2012) injected virus into the AON that nonspecifically infected cortical neurons; Boyd et al. (2012) used a conjunctive approach that limited ChR2 expression to pyramidal neurons of the APC. Both approaches generated similar patterns of fluorescently labeled axons in the ipsilateral olfactory bulb. Specifically, they observed bright fluorescence in the glomerular and granule cell layers, and minimal expression in the mitral cell and external plexiform layers, consistent with previous anatomical work on centrifugal inputs to the olfactory bulb (Luskin and Price, 1983). These data suggest that pyramidal cell axons provide strong feedback at two stages of bulbar processing; influencing circuits both in the input glomerular layer and in the deeper granule cell layer. A second feature of this feedback is that neurons from the AON, but not the APC, provided a similar, though weaker, pattern of input to the contralateral bulb. This suggests that AON feedback plays an additional role in bilateral processing between the two olfactory bulbs (Yan et al., 2008).

But what synaptic connections are made by these pathways? Optical activation of ChR2$^+$ terminals within the olfactory bulb reveals four key features of cortical feedback. First, the dominant effect of light-activated cortical feedback is inhibition that is sufficient to suppress the firing rates of mitral cells both in vitro and during odor presentation in vivo. Both groups report that this inhibition is mediated through a disynaptic path in which axons of cortical projection neurons excite granule cells, which in turn, inhibit mitral cells. This inhibition can be quite strong and is observed at short latencies from the light pulse. Second, PG neurons receive excitatory cortical input and act as a major source of the IPSPs recorded in external tufted cells during light activation. PG cells may also provide an additional source of cortically driven disynaptic inhibition to mitral cells but this is only observed in one of the studies. Markopoulos et al. (2012) show that local application of the $GABA_A$ antagonist, gabazine, to the apical dendritic tuft of a recorded mitral cell reduced light-evoked IPSP amplitude by ~30%. However, Boyd et al. (2012) show that selective light activation of single glomeruli evokes IPSPs in associated external tufted cells, but not associated mitral cells. Nonetheless, these studies confirm that there are two levels of inhibitory feedback from the cortex to olfactory bulb. The first is through a PC → PG → ET circuit and the second a PC → GC → MC/MT circuit.

A third feature of cortical feedback is that superficial and deep short axon cells (SAC) also receive excitatory input from the pyramidal cells. This input is stronger than that seen in GCs or PGs, likely due to a larger number of convergent axons synapsing onto short axon cells. Since deep SACs are a main source of inhibition onto GC and PG cells, cortical feedback also has the capacity to disinhibit mitral and tufted cells. Alternatively, a delay between cortical excitation in GC or PG cells and SAC mediated inhibition could create a narrow temporal window for cortically driven feedback inhibition. The fourth feature of cortical feedback is a weak (~10 pA), direct excitation of mitral cells. Although reported by both groups, Boyd et al. (2012) suggest that these excitatory currents may be due to nonsynaptic sources and they were not observed to elicit action potentials. In contrast, Markopoulos et al. (2012) find that these small currents can trigger reliable and precisely timed action potentials when mitral cells are firing at low rates but not when neurons are at rest or strongly driven. The reasons for these differences remain unclear, though the greater specificity of infection in the Boyd paper or the differences in cortical areas targeted seem likely reasons for this difference. In any case, these latter two features (disinhibition and direct excitation) suggest that cortical feedback may under some circumstances enhance the firing of weak to moderately active mitral/tufted cells. However, the in vivo data presented in both papers suggest that under most conditions these excitatory circuit mechanisms are overwhelmed by dominant cortical inhibitory feedback.

Given their physiological properties, a question remains as to how these feedback connections influence the coding of odor stimuli by olfactory bulb neurons. Odor-evoked responses in olfactory cortical neurons are thought to be sparser, less locked to respiration and tightly controlled by local cortical inhibition (Miura et al., 2012; Poo and Isaacson, 2009; Wilson and Sullivan, 2011) than mitral/tufted cell responses. A longstanding hypothesis on the role of piriform cortex has been that it functions to reconstruct patterns of stored activity in the face of degraded or noisy stimuli (Haberly and Bower, 1989). This view has received some support recently from detailed studies of local cortical circuitry (Franks et al., 2011) and odor-evoked activity (Chapuis and Wilson, 2012). The feedback of a completed or reconstructed pattern of activity to the olfactory bulb may provide a useful signal for plasticity in the bulb. Indeed cortical inputs to granule cells are one of the few places in which synaptic plasticity has been observed in the olfactory bulb (Gao and Strowbridge, 2009; Nissant et al., 2009). However, such a mechanism would seem to require that the feedback be provided specifically to those bulbar neurons that were initially activated by the current or stored odor. This provides motivation for future studies that analyze the topography of the cortical feedback projections to the bulb. In addition, any analysis of the role of feedback also must consider that the bulb-cortex interactions will be dynamic. If cortical feedback changes activity in the bulb, this will in turn change activity in the cortex which will alter activity in the bulb etc. Previous work indicating that beta oscillations in the bulb depend on cortical feedback (Neville and Haberly, 2003) are consistent with this view in which the echoes of cortical activity reverberate throughout early stages of olfactory processing.

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