Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Looking for the roots of cortical sensory computation in three-layered cortices

Julien Fournier, Christian M Müller and Gilles Laurent

Despite considerable effort over a century and the benefit of remarkable technical advances in the past few decades, we are still far from understanding mammalian cerebral neocortex. With its six layers, modular architecture, canonical circuits, innumerable cell types, and computational complexity, isocortex remains a challenging mystery. In this review, we argue that identifying the structural and functional similarities between mammalian piriform cortex and reptilian dorsal cortex could help reveal common organizational and computational principles and by extension, some of the most primordial computations carried out in cortical networks.

Addresses
Max Planck Institute for Brain Research, Max-von-Laue-Str. 4, Frankfurt am Main 60438, Germany

Corresponding author: Laurent, Gilles (gilles.laurent@brain.mpg.de)

Current Opinion in Neurobiology 2014, **31**:119–126

This review comes from a themed issue on **Brain rhythms and dynamic coordination**

Edited by **György Buzsáki** and **Walter Freeman**

http://dx.doi.org/10.1016/j.conb.2014.09.006

Introduction

Despite considerable effort over a century and the benefit of remarkable technical advances in the past few decades, we are still far from understanding mammalian cerebral cortex. With its six layers, modular architecture, canonical circuits [1], innumerable cell types [2], and computational complexity [3], isocortex remains a challenging mystery. Isocortex most likely evolved from simpler layered circuits in the forebrain of ancestral amniotes, structures that we still find in mammals today, as paleo-cortices and archi-cortices (piriform and hippocampal formations, respectively), together with a few 'transitional' areas with n ($3 \leq n < 6$) layers [4].

Among three-layered cortices in mammals, piriform cortex (PCx) is a good model system to investigate the function, dynamics and computational properties of cortical circuits. Understanding piriform cortex function, however, is made difficult by the complexity of the sensory space it subserves and the current lack of common metrics to describe the relevant psychophysical dimensions of olfactory perception [5].

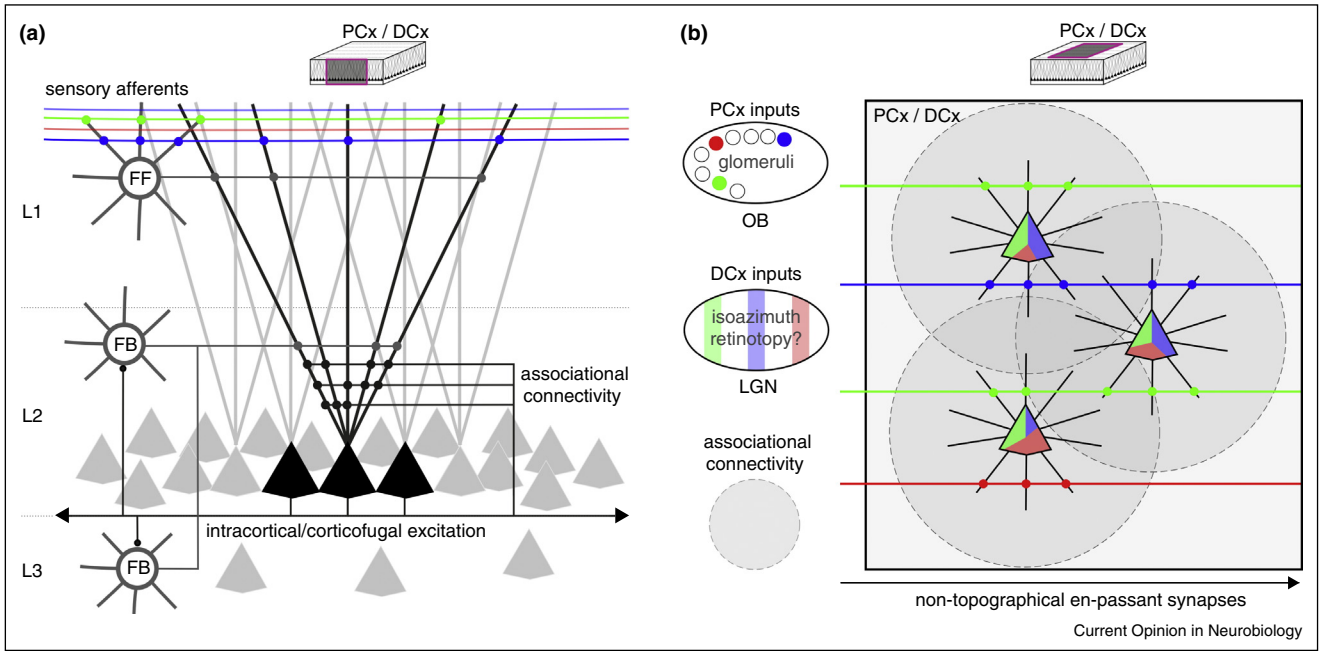
Simple cortices are not limited to the olfactory system. In reptiles, the entire cerebral cortex is composed of only three layers and some of these cortices are primary sensory areas. The visual cortex of turtles (dorsal cortex, DCx) and the mammalian piriform cortex (PCx) hold very similar positions along their respective sensory pathways. They are just one processing station — the lateral geniculate nucleus (LGN), or the olfactory bulb (OB) — removed from their respective sense organ. Our current understanding of sensory processing in turtle visual cortex is still limited, but one notable advantage of this system is that its sensory input space is more easily defined.

Hodology and transcription factor expression during development suggest that the three layers of reptilian cortex may be homologous to layers 1, 5, and 6 of the mammalian isocortex [6]. In this review, we argue that identifying the structural and functional similarities between PCx and DCx could help reveal common organizational and computational principles and by extension, some of the most primordial computations carried out in cortical networks.

Vertical connectivity

The architecture of PCx and DCx is archetypal of a three-layered paleocortex. Layer 1 contains mainly dendrites of layer 2 principal cells, a few scattered interneurons and afferent and local axons. Layer 2 contains the densely packed somata of pyramidal cells, whose apical dendrites run radially toward the pial surface. Layer 3 contains basal dendrites of pyramidal cells, corticofugal and local axons, some interneurons and a few deep pyramidal neurons in PCx [7,8]. Incoming afferents to PCx run through the lateral olfactory tract (LOT) [9•]; those to DCx through the lateral forebrain bundle (LFB) [10]. These input fibers fan out below the pial surface and make en-passant synapses on cortical neurons within the distal 50–100 μm of layer 1 [11,12]. Afferent synapses impinge on both layer-1 interneurons and on distal dendrites of layer-2 pyramidal cells; interneurons provide both feed-forward and feedback inhibition to pyramidal cells which themselves provide recurrent excitation to other pyramidal neurons [12,13•,14•,15,16]. In both PCx and DCx, superficial layer-1 interneurons tend to receive a higher density of afferent input than pyramidal cells do [12,14•,17•] which, combined with a strong feed-back inhibition via layer-2/3 interneurons [14•,15,17•] may explain the observed strong inhibition evoked by sensory stimulation

Figure 1



Connectivity in mammalian piriform cortex (PCx) and turtle dorsal cortex (DCx). **(a)** Transverse view (see inset) of the basic microcircuits. Sensory afferents from the lateral olfactory tract (in PCx) or lateral forebrain bundle (in DCx) make en-passant synapses in superficial layer 1 on distal segments of layer-2 pyramidal cell dendrites and on superficial inhibitory interneurons. Layer-2 pyramidal neurons receive recurrent excitation from other pyramidal cells (associational connectivity), feed-forward inhibition from superficial interneurons (FF), and feed-back inhibition from layer-2/3 interneurons (FB). **(b)** Top view (see inset) of PCx and DCx connectivity. Afferents from the olfactory bulb (OB) project to PCx without apparent topographical order. In DCx, there may be a coarse topography of lateral geniculate nucleus (LGN) projections that preserves visual isoazimuth neighborhoods [10,40]. In both cases, recurrent excitation through local (gray) and long-range (not shown) associational connections contributes to broadening the stimulus selectivity of pyramidal cells and may mask any local anisotropy in the spatial distribution of the primary sensory afferents (see color tiles).

and the sparseness of pyramidal cell firing. To a first degree, PCx and DCx thus have a similar microcircuit layout: both exhibit distal dendritic excitation from sensory afferents, strong feed-forward inhibition, recurrent excitation through the so-called associational intracortical connections, and feed-back inhibition [18,19•] (Figure 1a).

Different cell types have been identified in PCx. Most segregate into specific sublayers of the piriform microcircuit. Excitatory neurons in layer 2 can be subdivided in semilunar (upper layer 2) and superficial pyramidal neurons (lower layer 2) while those in layer 3 comprise a few deep pyramidal cells and scattered multipolar spiny glutamatergic neurons [20–22]. Although they are embedded in the same basic connectivity scheme, semilunar and superficial pyramidal cells receive different ratios of afferent to associational inputs, and may thus belong to distinct functional subcircuits [13•] (but see [23•]), consistent with morphological differences between their dendritic trees and their laminar position [24]. Although data on subpopulations of principal cells in DCx are few, analysis of Golgi-stained material also revealed different morphological classes of spiny neurons at different laminar and sublaminar positions in reptilian cortex [25,26•]. PCx and DCx pyramidal neurons are also similar with respect to their dendritic electrophysiological properties, suggesting comparable integrative properties at the subcellular level [27•,28]. Different subtypes of inhibitory interneurons have been identified in PCx, based on molecular markers, the morphology of their dendritic arbor and the distribution of their axonal projections (reviewed in [29]). These subclasses seem to correlate with the type of inhibition they subserve, that is, primarily feedback or feed-forward. Horizontal and neurogliaform interneurons in layer 1 receive afferent inputs from the LOT and mediate fast feed-forward inhibition targeting apical dendrites of layer-2 pyramidal cells. Bitufted, fast-spiking and regular spiking interneurons from layers 2 and 3 receive very little direct afferent input from the LOT but provide strong feedback inhibition onto the somata and basal dendrites of pyramidal cells [14•,17•]. Similarly, different populations of inhibitory interneurons in turtle DCx subserve mainly feed-forward (subpial cells [16]) or feedback [16,30] inhibition. Axonal reconstructions of DCx interneurons [31] and immunocytochemical labeling [32,33] suggest the existence of morphologically and physiologically identifiable classes of inhibitory interneurons. It remains to be

shown that those groupings also share functional similarities with those in PCx. Given the anatomical similarity of input projections to PCx and DCx, one may speculate that the inhibitory circuit topology of these two cortices could also be similar.

Horizontal connectivity

In PCx, afferents from mitral/tufted (MT) cells appear to project throughout the cortex without any clear topographical relationship to their glomeruli of origin [9•,34•,35,36,37•] (Figure 1b). Although this does not rule out the possibility of some fine-scale topographical mapping of OB projections (e.g. mitral versus tufted cell projections [38•]), it is now accepted that the glomerular clustering of olfactory receptor cells axons in OB is entirely discarded at the level of PCx [39]. In DCx, early tracing studies from Ulinski and colleagues suggested that the visual field is projected onto the rostro-caudal axis of DCx in the form of iso-azimuth lamellae covering the naso-temporal dimension of the visual field [10,40] (Figure 1b). Such a mapping of projections still awaits physiological confirmation and fine thalamo-cortical projection tracing. If confirmed, this topographical mapping would differ from the topology of mammalian olfactory projections to PCx, at least along one cortical dimension.

In both PCx and DCx, the density of sensory afferents varies over the cortical surface: high rostrally and laterally, it decreases progressively as one moves away from the entry point of the LOT (PCx) or the LFB (DCx). Hence, the balance between afferent and associational connectivity decreases along the rostro-caudal and latero-medial (or ventro-dorsal) axes [10,18,39,41,42]. PCx is subdivided into anterior (aPCx) and posterior (pPCx) regions, which differ not only in the density of afferent versus associational fibers [18] but also in the properties of odor-evoked responses [43,44]. PCx microcircuits may also contain fine-grain connectivity gradients: *in vitro* recordings from aPCx reveal that inhibition of pyramidal cells is asymmetric and stronger along the rostro-caudal axis of the anterior part of PCx, over distances as short as 200 μm [45•]. In turtle, DCx has been classically divided into two different regions (D2 and D1) along the latero-medial axis [8,26•]. This dichotomy rests mostly on cytoarchitectural features, related to the thickness of subcellular layer 3 — thick in D2 laterally, thin in D1, with a significant transition zone between the two. Recent molecular data suggest that this separation may be correlated with higher expression level of layer-4 markers in D2 [46•]. Confirmation of this division and of its potential functional significance needs additional work. Such gradients of connectivity across the cortical surface (in PCx and DCx) should be clearly described because any horizontal heterogeneity could influence the propagation and reverberation of activity across cortex, under the combined influences of spreading afferent input and widespread associational activity.

Given their reciprocal interconnections with high-order cortical areas and a lack of evident sensory topography, PCx and DCx are sometime described as associational rather than primary sensory cortices [18,19•]. The major partners of PCx are the orbitofrontal cortex [47,48], the lateral entorhinal cortex [49,50] and the agranular insular cortex [50]. Connectivity to these downstream targets differs between aPCx and pPCx, supporting the notion that they play different functions. Similarly, DCx is reciprocally connected to dorso-medial (DMCx) and medial (MCx) cortices [25,26•]. Those regions are, on the basis of hodology and position, often compared to parahippocampal and hippocampal cortices [26•,51,52,53]. Both PCx and DCx are thus directly connected to associational networks, likely involved in controlling or modulating behavior.

PCx and DCx are further interconnected with other cortical-like areas, which also receive parallel sensory afferents from the OB or the LGN respectively. For PCx, these include the anterior olfactory nucleus (AON) [54,55], the olfactory tubercle (OT) [54], and the amygdala [50,56]. AON might be a first stage of odorant-feature processing, in turn used by PCx to detect complex odorant combinations [18,57,58]. DCx's AON-equivalent could be the pallial thickening (PT), for it receives direct thalamic afferent input and projects to DCx [10,59]. If AON and PT also share functional characteristics, these similarities may point to common elementary processing streams of three-layered sensory cortices.

Coding and sensory representation

To a first degree, functional investigations of olfactory tuning on PCx neurons confirm anatomical results: the discretization of the olfactory bulb into glomerular domains disappears in PCx. Instead, odorants activate ensemble of PCx neurons, scattered over the cortical surface, with no apparent spatial clustering [35,60•,61,62•]. Both the dispersion of afferent bulbar inputs and a widespread network of associational connections likely contribute to the spatial spread and heterogeneity of PCx-neuron response selectivity [23•,63,64•]. This lack of visible organization of population responses is similar to that observed in the insect mushroom body, a structure directly postsynaptic to the antennal lobe, itself analogous to the olfactory bulb [65]. It may thus be a deep feature of this early encoding stage for odors [66].

A similar situation seems to hold true for DCx, although studies of RF mapping in turtle DCx are few [67]. In all such experiments, most cells were activated indiscriminately wherever a stimulus (typically a small dot) was flashed in the visual field, unlike thalamic neurons which exhibit spatially restricted RFs [68]. Voltage-sensitive-dye (VSD) recordings of DCx responses to stimulation of four visual quadrants yielded similar

activity patterns across the cortical surface, consistent with the absence of clear retinotopic mapping of visual space along the surface of DCx [69]. Although VSD experiments reveal no functional evidence for the anatomical lamellae of thalamo-cortical projections [10], they do not necessarily disprove the older tracing studies. For example, widespread associational connections could easily mask the topography of thalamocortical projections.

If true, the absence of cortical retinotopy in DCx suggests a few remarks. (i) That three-layered reptilian visual cortex is not organized along the same principles as mammalian primary visual isocortex. (ii) That projections to a sensory three-layered cortex lack the functional, developmental or molecular substrates for spatial or functional segregation. Some have indeed argued that this diffuse organization represents the primordial structure of sensory cortex, prior to the evolution of isocortex in the synapsid and later, mammalian lineage [6]. (iii) That the computational properties of turtle primary visual cortex are more similar in essence to those of high-order cortices (e.g. parahippocampal, retrosplenial or infero-temporal), and that the true response properties of DCx neurons have yet to be discovered.

Until recently, functional experiments in PCx relied on sampling neuronal responses to limited sets of odors. Although these studies spanned stimulus sets large enough to identify the dispersion of RF selectivity across the cortical surface, they did not allow an evaluation of the actual 'size' of these RFs along the many dimensions of odor space. Recent studies examined how PCx process patterns of activity in the bulb by direct stimulation of ensembles of glomeruli using photo-uncaging of glutamate [64•] or optogenetic stimulation [70•]. These studies indicate that individual PCx neurons respond selectively to distinct combinations of active glomeruli [64•] and are sensitive to the temporal sequence of activation [70•]. A more exhaustive exploration of this sensory space might allow one to better estimate the selectivity of PCx RFs, thereby facilitating comparisons with DCx. Although both PCx and DCx clearly exhibit no mapping of the first-order physical dimensions of their respective sensory space, they may both represent sensory features in some abstract and related feature spaces [39]. Mazurskaya [67] observed that, although DCx visual neurons respond unselectively to any flash of light, they may respond to pairs of flashes with sublinear or supralinear summation depending on the relative timing and spatial separation of the two stimuli, suggesting selectivity to high-order spatiotemporal correlations in the visual field. It could be that DCx neurons are selective to high-order correlations, and process spatiotemporal sequences of distributed visual cues in a manner similar to how PCx processes spatio-temporal activation of specific glomeruli.

Cortical dynamics and oscillations

As observed in many sensory systems, PCx and DCx exhibit various types of oscillations. In PCx, these oscillations are usually split into 3 frequency bands: slow respiratory theta rhythm (1–15 Hz); beta (15–35 Hz); and gamma (40–100 Hz) [71]. Although gamma has long been a focus of research in mammalian cortex, beta oscillations have, over recent years, grown in importance in olfactory studies. Interestingly, 20-Hz oscillations are a prominent feature of population activity also in some insect species [66]. Sensory-evoked LFP responses in DCx and PCx both exhibit a noticeable increase in beta-frequency oscillations following sensory stimulation in both anaesthetized and awake cortical states [72,73•,74–76]. It is currently difficult to assess whether beta oscillations in PCx and DCx share more than just a frequency and if they contribute to information processing in similar ways. The similarity, however, may be linked to common underlying mechanisms of generation. Except for the fact that beta oscillations in OB precede those in PCx and hippocampus [72,74,77] but require intact feedback between PCx and OB [78], we know little about the mechanistic origin and role of beta. Beta power in PCx appears correlated with behavioral context; it increases during learning of a discrimination task [73•,79] and is correlated with pattern completion [73•]. In DCx, visually evoked beta oscillations appear to be coherent across the surface of DCx, with a rostrocaudal phase-lag consistent with the propagation of waves [75,80]. It was suggested that some components of these waves may encode spatial information about the stimulus [69,81]. However, physiological data are still missing, and whether cortical waves in DCx are reliable enough to represent efficiently the spatiotemporal position of visual cues (or any other feature) remains conjectural.

Beta coherence has been investigated across different areas of PCx. Available data suggest rather short delays over long cortical distances between paired recording sites [62•,72,77,82]. Nevertheless, the issue as to whether (and how) these oscillations propagate through the piriform network remains largely unexplored. Coherent beta oscillations between different olfactory areas have been observed, especially during odor learning and memory retrieval [79,83]. Theoretical work showed that beta frequencies are better suited than gamma oscillations to carry information over long distances [84]. This suggests that beta could contribute to synchronizing the activity of PCx with downstream targets. Assuming similarly distributed codes for PCx and DCx, beta oscillations might serve to support the formation of cell assemblies across their respective networks, synchronizing neurons by stimulus selectivity rather than position. Such role would probably require phase-locking of odor-evoked spiking to beta oscillations, to enable a concerted influence on downstream targets. Poo and Isaacson [62•] showed that PCx neurons responses are phase-locked to

beta oscillations as a result of a phase shift between excitatory and inhibitory synaptic drives. The preferred phase of firing was apparently cell-specific rather than stimulus-specific. More work is needed to elucidate whether or not cells with similar odor selectivity tend to have similar phase relationship to the beta oscillation cycle.

Conclusion

Piriform cortex and turtle dorsal cortex are good model systems to investigate sensory processing in cortical circuits; given their simple architecture, the mapping of elementary computations on specific circuit elements should be easier than with isocortex. Unfortunately, however, we have no clear understanding of the exact functional operations performed by these two cortices. PCx and DCx seem to process sensory inputs more like high-order cortical areas than primary sensory neocortex. According to this view, if we assume that the three-layered cortex of extant amniotes conserved functional features of the cortex of early amniotes (some 300 MYA), we would conclude that computations performed by high-order cortical areas are ancestral rather than evolved and that many operations found at initial stages of neocortical processing (first-order feature detection, local contrast enhancement,...) appeared later in evolution, possibly linked to the additions of new layers (2/3,4), specific to mammalian neocortex. Despite obvious differences between visual and olfactory signals, sensory coding in PCx and DCx might follow a similar functional logic, focused on behaviorally relevant features. Haberly [18] postulated that PCx may function as a combinatorial/associative array, performing recognition of OB activity patterns encoded in specific cortical cell assemblies that may contribute, after reinforcement, to memory formation and recall of relevant sensory experiences. Experimental evidence shows that functional connectivity in PCx is modified during associative learning [44,73•,78,79,85,86]. Similarly, lesion experiments in turtles suggest a role for dorsal and medial cortices in spatial learning and memory formation [52,87,88]. Visual processing in DCx might thus be closer to that in mammalian parahippocampal [89] or retrosplenial cortices [90]. Haberly [18] proposed that the topology and plasticity of PCx afferent and auto-associational connections are well suited to perform contextual learning of high-dimensional stimulus features. Plasticity has not yet been explored in DCx. But if DCx reveals experience-dependent changes in its functional connectivity, it would be an additional argument for considering PCx and DCx as equivalent networks, optimized for object recognition in a sensory landscape (made of odors or visual cues) whose relevant perceptual dimensions are dynamically shaped by sensory experience.

Conflict of interest statement

Nothing declared.

Acknowledgements

This work was supported by the Max Planck Society, the European Research Council and the Human Frontier Science Program (JF). We thank Stephan Junek, Robert Naumann and Mike Hemberger for their comments on the manuscript.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Douglas RJ, Martin R: **Canonical cortical circuits**. In *Handbook of Brain Microcircuits.* Edited by Shepherd GM, Grillner S. New York: Oxford University Press; 2010:15-21.

2. Markram H: **Microcircuitry of the neocortex**. In *Handbook of Brain Microcircuits.* Edited by Shepherd GM, Grillner S. Oxford University Press; 2010:22-30.

3. Frégnac Y, Rudolph M, Davison AP, Destexhe A: **Complexity in neuronal networks**. In *Biological Networks.* Edited by Kepes F. World Scientific; 2006:291-338.

4. Brodman K, Garey LJ: *Brodmann's Localization in the Cerebral Cortex*. Springer-Verlag; 2006.

5. Arzi A, Sobel N: **Olfactory perception as a compass for olfactory neural maps**. *Trends Cogn Sci* 2011, **15**:537-545.

6. Aboitiz F, Zamorano F: **Neural progenitors, patterning and ecology in neocortical origins**. *Front Neuroanat* 2013, **7**:1-15.

7. Neville KR, Haberly LB: **Olfactory cortex**. In *The Synaptic Organization of the Brain.* Edited by Shepherd GM. Oxford, New York: UP; 2004:415-454.

8. Ulinski PS: **The cerebral cortex of reptiles**. *Cereb Cortex* 1990, **8A**:139-216.

9. • Sosulski DL, Bloom ML, Cutforth T, Axel R, Datta SR: **Distinct representations of olfactory information in different cortical centres**. *Nature* 2011, **472**:213-216.

Using dye electroporation of mitral and tufted cells in mice olfactory bulb, the authors traced axonal projections from individual glomeruli to PCx and cortical amygdala. They show that glomeruli project diffusely to PCx without spatial preference while in the cortical amygdala, glomeruli projections are patchy and reveal stereotyped spatial segregation.

10. Mulligan KA, Ulinski PS: **Organization of geniculocortical projections in turtles: isoazimuth lamellae in the visual cortex**. *J Comp Neurol* 1990, **296**:531-547.

11. Haberly L, Behan M: **Structure of the piriform cortex of the opossum. III. Ultrastructural characterization of synaptic terminals of association and olfactory bulb afferent fibers**. *J Comp Neurol* 1983, **219**:448-460.

12. Smith LM, Ebner FF, Colonnier M: **The thalamocortical projection in *Pseudemys turtles*: a quantitative electron microscopic study**. *J Comp Neurol* 1980, **461**:445-461.

13. • Suzuki N, Bekkers JM: **Two layers of synaptic processing by principal neurons in piriform cortex**. *J Neurosci* 2011, **31**: 2156-2166.

14. • Suzuki N, Bekkers JM: **Microcircuits mediating feedforward and feedback synaptic inhibition in the piriform cortex**. *J Neurosci* 2012, **32**:919-931.

In this paper and the one above, the authors identified elementary circuit motifs in PCx using *in vitro* patch-clamp recordings from acute slices. In particular, they show that semilunar and superficial pyramidal cells receive distinct balances of afferent versus associational synaptic inputs and that feed-forward and feed-back inhibition in PCx originate from different inhibitory cell types segregating in distinct layers.

15. Kriegstein R, Connors BW: **Cellular physiology of the turtle visual cortex: synaptic properties and intrinsic circuitry**. *J Neurosci* 1986, **6**:178-191.

16. Mancilla JG, Fowler M, Ulinski PS: **Responses of regular spiking and fast spiking cells in turtle visual cortex to light flashes**. *Vis Neurosci* 1998, **15**:979-993.

17. • Stokes CCA, Isaacson JS: **From dendrite to soma: dynamic routing of inhibition by complementary interneuron microcircuits in olfactory cortex**. *Neuron* 2010, **67**:452-465.
The authors investigated *in vitro* the connectivity and temporal dynamics of inhibition in PCx. They show that layer-1 interneurons receive stronger afferent input from the LOT than layer-2 pyramidal cell do and provide early onset feed-forward inhibition to distal dendrites of pyramidal cells. On the other hand, layer-3 interneurons are activated exclusively by recurrent excitation from pyramidal cells and are responsible for a late onset feed-back inhibition onto a large fraction of local pyramidal cells.

18. Haberly LB: **Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry**. *Chem Senses* 2001, **26**:551-576.

19. • Shepherd GM: **The microcircuit concept applied to cortical evolution: from three-layer to six-layer cortex**. *Front Neuroanat* 2011, **5**:1-15.
The author reviews evidences for basic circuit motifs common to cortical circuits by comparing six-layer neocortex and three-layer olfactory, hippocampal and turtle cortices.

20. Haberly LB: **Structure of the piriform cortex of the opossum. I. Description of neuron types with Golgi methods**. *J Comp Neurol* 1983, **213**:163-187.

21. Suzuki N, Bekkers JM: **Neural coding by two classes of principal cells in the mouse piriform cortex**. *J Neurosci* 2006, **26**:11938-11947.

22. Bekkers JM, Suzuki N: **Neurons and circuits for odor processing in the piriform cortex**. *Trends Neurosci* 2013, **36**:429-438.

23. • Poo C, Isaacson JS: **A major role for intracortical circuits in the strength and tuning of odor-evoked excitation in olfactory cortex**. *Neuron* 2011, **72**:41-48.
Using whole-cell voltage-clamp recording *in vivo* and local application of a $GABA_b$ receptor blocker, the authors investigated the effect of silencing intracortical recurrent excitatory inputs on the selectivity of PCx neurons to odors. They show that the tuning of PCx pyramidal cells to odor is primarily determined by the strength of intracortical associational inputs rather than by the degree of convergence of olfactory bulb inputs.

24. Wiegand HF, Beed P, Bendels MHK, Leibold C, Schmitz D, Johenning FW: **Complementary sensory and associative microcircuitry in primary olfactory cortex**. *J Neurosci* 2011, **31**:12149-12158.

25. Ulinski PS: **Intrinsic organization of snake medial cortex: an electron microscopic and Golgi study**. *J Morphol* 1977, **152**:247-279.

26. • Desan PH: **Organization of cerebral cortex in turtle**. In *The forebrain of reptiles*. Edited by Schwerdtfeger WK, Smeets WJA. Basel: Karger; 1985:1-11.
In this book chapter, a digest of his doctoral thesis (The organization of the cerebral cortex of the pond turtle, Pseudemys scripta elegans. (Ph.D. thesis) Cambridge, MA: Harvard University; 1984), Desan described the main morphological cell types present in turtle dorsal cortex and identified the principal afferent and efferent connections of the cerebral cortex of turtles using retrograde and anterograde tracers.

27. • Larkum ME, Watanabe S, Lasser-ross N, Rhodes P, Ross WN, Ledergerber D, Larkum ME: **Dendritic properties of turtle pyramidal neurons**. *J Neurophysiol* 2008, **99**:683-694.
In this study, the authors performed whole-cell, dendritic and axonal patch-clamp recordings to characterize the electrophysiological properties of turtle cortex pyramidal neurons.

28. Bathellier B, Margrie TW, Larkum ME: **Properties of piriform cortex pyramidal cell dendrites: implications for olfactory circuit design**. *J Neurosci* 2009, **29**:12641-12652.

29. Suzuki N, Bekkers JM: **inhibitory interneurons in the piriform cortex**. *Clin Exp Pharmacol Physiol* 2007, **34**:1064-1069.

30. Connors BW, Kriegstein AFL: **Cellular physiology of the turtle visual cortex: distinctive properties of pyramidal and stellate neurons**. *J Neurosci* 1986, **6**:164-177.

31. Colombe JB, Sylvester J, Block J: **Subpial and stellate cells: two populations of interneurons in turtle visual cortex**. *J Comp Neurol* 2004, **471**:333-351.

32. Reiner A: **A comparison of the neurotransmitter-specific and neuropeptide-specific neuronal cell types present in turtle cortex to those present in mammalian isocortex: implications for the evolution of isocortex**. *Brain Behav Evol* 1991, **38**:53-91.

33. Reiner A: **Neurotransmitter organization and connections of turtle cortex: implications for the evolution of mammalian isocortex**. *Comp Biochem Physiol* 1993, **104**:735-748.

34. • Miyamichi K, Amat F, Moussavi F, Wang C, Wickersham I, Wall NR, Taniguchi H, Tasic B, Huang ZJ, He Z *et al.*: **Cortical representations of olfactory input by trans-synaptic tracing**. *Nature* 2011, **472**:191-196.
Using transynaptic-virus-dependent retrograde labelling, the authors traced the projections from mitral and tufted cells to the piriform cortex and cortical amygdala. They showed that afferent inputs to individual PCx neurons originate from multiple glomeruli that are distributed across the olfactory bulb and that mitral cells from the same glomerulus project independently to PCx neurons.

35. Illig KR, Haberly LB: **Odor-evoked activity is spatially distributed in piriform cortex**. *J Comp Neurol* 2003, **457**:361-373.

36. Apicella A, Yuan Q, Scanziani M, Isaacson JS: **Pyramidal cells in piriform cortex receive convergent input from distinct olfactory bulb glomeruli**. *J Neurosci* 2010, **30**:14255-14260.

37. • Ghosh S, Larson SD, Hefzi H, Marnoy Z, Cutforth T, Dokka K, Baldwin KK: **Sensory maps in the olfactory cortex defined by long-range viral tracing of single neurons**. *Nature* 2011, **472**:217-220.
Using a viral-based anterograde tracing technique, these authors compared axonal projections of single mitral cells to different cortical regions. In particular, they demonstrate that the axonal arborizations of mitral cells originating from the same glomerulus have no more overlap in PCx than those originating from different glomeruli.

38. • Igarashi KM, Ieki N, An M, Yamaguchi Y, Nagayama S, Kobayakawa K, Kobayakawa R, Tanifuji M, Sakano H, Chen WR *et al.*: **Parallel mitral and tufted cell pathways route distinct odor information to different targets in the olfactory cortex**. *J Neurosci* 2012, **32**:7970-7985.
This study compares mitral and tufted cells odor-evoked response profiles and show evidences that these two cell types target distinct, non-overlapping cortical subregions.

39. Wilson DA, Sullivan RM: **Cortical processing of odor objects**. *Neuron* 2011, **72**:506-519.

40. Ulinski PS, Nautiyal J: **Organization of retinogeniculate projections in turtles of the genera pseudemys and chrysemys**. *J Comp Neurol* 1988, **276**:92-112.

41. Hagiwara A, Pal SK, Sato TF, Wienisch M, Murthy VN, Shepherd GM: **Optophysiological analysis of associational circuits in the olfactory cortex**. *Front Neural Circ* 2012, **6**.

42. Cosans CE, Ulinski PS: **Spatial organization of axons in turtle visual cortex: intralamellar and interlamellar projections**. *J Comp Neurol* 1990, **296**:548-558.

43. Litaudon P, Amat C, Bertrand B, Vigouroux M, Buonviso N: **Piriform cortex functional heterogeneity revealed by cellular responses to odours**. *Eur J Neurosci* 2003, **17**:2457-2461.

44. Kadohisa M, Wilson DA: **Separate encoding of identity and similarity of complex familiar odors in piriform cortex**. *Proc Natl Acad Sci U S A* 2006, **103**:15206-15211.

45. • Luna VM, Pettit DL: **Asymmetric rostro-caudal inhibition in the primary olfactory cortex**. *Nat Neurosci* 2010, **13**:533-535.
Using whole-cell patch-clamp and focal uncaging of glutamate on interneurons in PCx slices, the authors showed that inhibition onto layer-2 pyramidal neurons is asymmetrical and stronger along the rostro-caudal axis of PCx.

46. • Dugas-Ford J, Rowell JJ, Ragsdale CW: **Cell-type homologies and the origins of the neocortex**. *Proc Natl Acad Sci U S A* 2012, **109**:16974-16979.
The authors investigated the distribution of molecular markers of mammalian layer-4 and layer-5 neocortical neurons in turtle and avian cortices. In particular, they found that in turtle DCx, layer-4 and layer-5 neocortical markers segregate horizontally along the rostro-caudal axis and are expressed by distinct cell ensembles.

47. Ekstrand JJ, Domroese ME, Johnson DMG, Feig SL, Knodel SM, Behan M, Haberly LB: **A new subdivision of anterior piriform cortex and associated deep nucleus with novel features of interest for olfaction and epilepsy**. *J Comp Neurol* 2001, **434**:289-307.

48. Illig KR: **Projections from orbitofrontal cortex to anterior piriform cortex in the rat suggest a role in olfactory information processing**. *J Comp Neurol* 2006, **488**:224-231.

49. Kerr KM, Agster KL, Furtak SC, Burwell RD: **Functional neuroanatomy of the parahippocampal region: the lateral and medial entorhinal areas**. *Hippocampus* 2007, **17**:697-708.

50. Johnson DMG, Illig KR, Behan M, Haberly LB: **New features of connectivity in piriform cortex visualized by intracellular injection of pyramidal cells suggest that ''primary'' olfactory cortex functions like ''association'' cortex in other sensory systems**. *J Neurosci* 2000, **20**:6974-6982.

51. Northcutt RG: **Evolution of the telencephalon in nonmammals**. *Annu Rev Neurosci* 1981, **4**:301-350.

52. López JC, Vargas JP, Gómez Y, Salas C: **Spatial and non-spatial learning in turtles: the role of medial cortex**. *Behav Brain Res* 2003, **143**:109-120.

53. Aboitiz F, Morales D, Montiel J: **The evolutionary origin of the mammalian isocortex: towards an integrated developmental and functional approach**. *Behav Brain Sci* 2003, **26**:535-552.

54. Haberly LB, Price JL: **Association and commissural fiber systems of the olfactory cortex of the rat**. *J Comp Neurol* 1978, **178**:711-740.

55. Illig KR, Eudy JD: **Contralateral projections of the rat anterior olfactory nucleus**. *J Comp Neurol* 2009, **512**:115-123.

56. Luna VM, Morozov A: **Input-specific excitation of olfactory cortex microcircuits**. *Front Neural Circ* 2012, **6**:1-7.

57. Lei H, Mooney R, Katz LC: **Synaptic integration of olfactory information in mouse anterior olfactory nucleus**. *J Neurosci* 2006, **26**:12023-12032.

58. Kay RB, Meyer EA, Illig KR, Brunjes PC: **Spatial distribution of neural activity in the anterior olfactory nucleus evoked by odor and electrical stimulation**. *J Comp Neurol* 2011, **519**:277-289.

59. Heller SB, Ulinski PS: **Morphology of geniculocortical axons in turtles of the genera Pseudemys and Chrysemys**. *Anat Embryol (Berl)* 1987, **175**:505-515.

60. • Stettler DD, Axel R: **Representations of odor in the piriform cortex**. *Neuron* 2009, **63**:854-864.
Using optical imaging of odor-evoked responses, this study demonstrates that different odorants activate distinct ensembles of cortical neurons that are distributed across PCx, without any apparent spatial segregation relative to the similarity between odorants.

61. Rennaker RL, Chen CF, Ruyle AM, Sloan AM, Wilson DA: **Spatial and temporal distribution of odorant-evoked activity in the piriform cortex**. *J Neurosci* 2007, **27**:1534-1542.

62. • Poo C, Isaacson JS: **Odor representations in olfactory cortex: ''sparse'' coding, global inhibition, and oscillations**. *Neuron* 2009, **62**:850-861.
These authors performed *in vivo* whole-cell recordings of PCx neurons. They show that inhibition to layer-2 cells is broadly tuned to odors while excitation is more selective and that the timing of action potentials is controlled by out-of-phase excitatory and inhibitory inputs oscillating in the beta frequency range.

63. Franks KM, Isaacson JS: **Strong single-fiber sensory inputs to olfactory cortex: implications for olfactory coding**. *Neuron* 2006, **49**:357-363.

64. • Davison IG, Ehlers MD: **Neural circuit mechanisms for pattern detection and feature combination in olfactory cortex**. *Neuron* 2011, **70**:82-94.
The authors recorded extracellularly and intracellularly responses of PCx neurons to glomerular activation by photo-uncaging of glutamate in the olfactory bulb. They show that PCx neurons receive weak subthreshold inputs from individual glomeruli distributed across the olfactory bulb but respond above spike threshold to specific combinations of glomeruli activation.

65. Perez-Orive J, Mazor O, Turner GC, Cassenaer S, Wilson RI, Laurent G: **Oscillations and sparsening of odor representations in the mushroom body**. *Science* 2002, **297**:359-365.

66. Laurent G: **Olfactory network dynamics and the coding of multidimensional signals**. *Nat Rev Neurosci* 2002, **3**:884-895.

67. Mazurskaya PZ: **Organization of receptive fields in the forebrain of *Emys orbicularis***. *Neurosci Behav Physiol* 1973, **6**:311-318.

68. Boiko VP: **Responses to visual stimuli in thalamic neurons of the turtle *Emys orbicularis***. *Zh Evol Biokhim Fiziol* 1980, **14**: 57-63.

69. Senseman D, Robbins K: **Modal behavior of cortical neural networks during visual processing**. *J Neurosci* 1999, **19**:1-7.

70. • Haddad R, Lanjuin A, Madisen L, Zeng H, Murthy VN, Uchida N: **Olfactory cortical neurons read out a relative time code in the olfactory bulb**. *Nat Neurosci* 2013, **16**:949-957.
This study investigates the response of PCx neurons to photo-stimulation of glomeruli and shows that PCx neurons are sensitive to the relative timing of activation of pairs of glomeruli, regardless of their spatial separation in the olfactory bulb.

71. Kay LM, Beshel J, Brea J, Martin C, Kopell N, Rojas-Líbano D: **Olfactory oscillations: the what, how and what for**. *Trends Neurosci* 2009, **32**:207-214.

72. Kay LM, Beshel J: **A beta oscillation network in the rat olfactory system during a 2-alternative choice odor discrimination task**. *J Neurophysiol* 2010, **104**:829-839.

73. • Chapuis J, Wilson DA: **Bidirectional plasticity of cortical pattern recognition and behavioral sensory acuity**. *Nat Neurosci* 2012, **15**:155-161.
In this study, the authors show that the ability of adult rats to discriminate between odors depends on the past behavioral experience and correlates with functional changes in the encoding properties of PCx neuronal ensembles. It suggests that the capacity of the PCx network to perform pattern completion or pattern separation is adjustable to the animal's experience.

74. Neville KR, Haberly LB: **Beta and gamma oscillations in the olfactory system of the urethane-anesthetized rat**. *J Neurophysiol* 2003, **90**:3921-3930.

75. Prechtl JC, Cohen LB, Persaran B, Mitra PP, Kleinfeld D: **Visual stimuli induce waves of electrical activity in turtle cortex**. *Proc Natl Acad Sci U S A* 1997, **94**:7621-7626.

76. Flanigan WF: **Sleep and wakefulness in chelonian reptiles. II. The red-footed tortoise, *Geochelone carbonaria***. *Arch Ital Biol* 1974, **112**:253-277.

77. Gourévitch B, Kay LM, Martin C, Beshel J, Goure B: **Directional coupling from the olfactory bulb to the hippocampus during a go/no-go odor discrimination task**. *J Neurophysiol* 2010, **103**:2633-2641.

78. Martin C, Gervais R, Messaoudi B, Ravel N: **Learning-induced oscillatory activities correlated to odour recognition: a network activity**. *Eur J Neurosci* 2006, **23**:1801-1810.

79. Martin C, Gervais R, Chabaud P, Messaoudi B, Ravel N: **Learning-induced modulation of oscillatory activities in the mammalian olfactory system: the role of the centrifugal fibres**. *J Physiol Paris* 2004, **98**:467-478.

80. Prechtl JC, Bullock TH, Kleinfeld D: **Direct evidence for local oscillatory current sources and intracortical phase gradients in turtle visual cortex**. *Proc Natl Acad Sci U S A* 2000, **97**: 877-882.

81. Nenadic Z, Ghosh BK, Ulinski PS: **Modeling and estimation problems in the turtle visual cortex**. *IEEE Trans Biomed Eng* 2002, **49**:753-762.

82. Freeman WJ: **Distribution in time and space of prepyriform electrical activity**. *J Neurophysiol* 1959, **22**:644-665.

83. Martin C, Beshel J, Kay LM: **An olfacto-hippocampal network is dynamically involved in odor-discrimination learning**. *J Neurophysiol* 2007, **98**:2196-2205.

84. Kopell N, Ermentrout GB, Whittington MA, Traub RD: **Gamma rhythms and beta rhythms have different synchronization properties**. *Proc Natl Acad Sci U S A* 2000, **97**:1867-1872.

85. Choi GB, Stettler DD, Kallman BR, Bhaskar ST, Fleischmann A, Axel R: **Driving opposing behaviors with ensembles of piriform neurons**. *Cell* 2011, **146**:1004-1015.

86. Cohen Y, Reuveni I, Barkai E, Maroun M: **Olfactory learning-induced long-lasting enhancement of descending and ascending synaptic transmission to the piriform cortex**. *J Neurosci* 2008, **28**:6664-6669.

87. Grisham W, Powers AS: **Function of the dorsal and medial cortex of turtles in learning**. *Behav Neurosci* 1989, **103**:991-997.

88. Blau A, Powers AS: **Discrimination learning in turtles after lesions of the dorsal cortex or basal forebrain**. *Psychobiology* 1989, **17**:445-449.

89. Moser EI, Roudi Y, Witter MP, Kentros C, Bonhoeffer T, Moser M: **Grid cells and cortical representation**. *Nat Rev Neurosci* 2014, **15**:466-481.

90. Vann SD, Aggleton JP, Maguire EA: **What does the retrosplenial cortex do?** *Nat Rev Neurosci* 2009, **10**:792-802.