

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

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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.

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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].

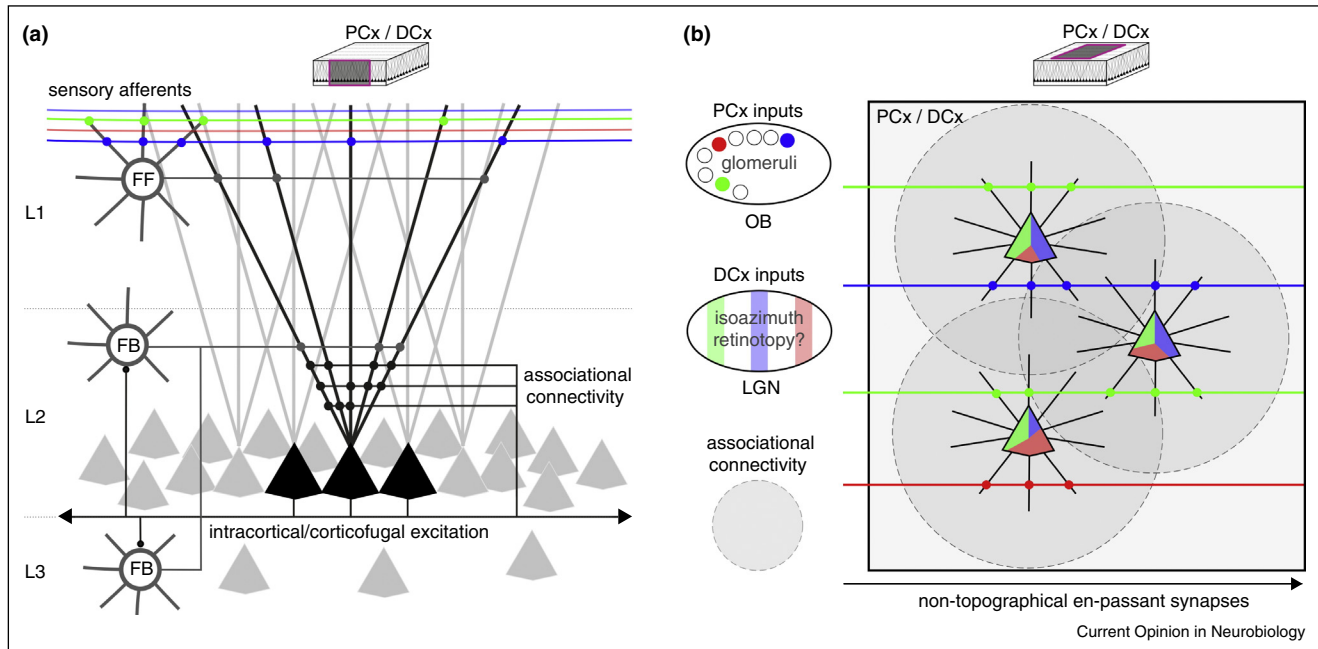
Simple cortices are not limited to the olfactory system. In reptiles, the entire cerebral cortex is composed of only three layers and some of these cortices are primary sensory areas. The visual cortex of turtles (dorsal cortex, DCx) and the mammalian piriform cortex (PCx) hold very similar positions 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 feed-back 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 thalamo-cortical 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 rostro-caudal 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.

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