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Visual System: Prostriata — A Visual Area Off the Beaten Path

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but since the Kai proteins of the cyanobacterial TTFL clockwork are not conserved in most archaea, a critical test of the potential universality of the PRX oscillator in prokaryotes was to check a representative archaeon, *Halobacterium*. Here, they also observed strong rhythmic PRX oscillations, providing compelling evidence that a PRX-oxidation oscillation is a conserved circadian feature across all phylogenetic domains.

The next step was to check whether known mutations of the TTFL system would affect the PRX oscillator. Fortunately, a considerable amount is known of these systems and appropriate models are available. Using mutations of the TTFL system, which disables the conventional circadian clock, the authors nonetheless observed oscillations of PRX oxidation in flies, plants, algae and cyanobacteria. This might suggest that the two systems run independently. Clock-disrupting mutations of the TTFL system did, however, alter phasing of the PRX oscillator, and when they checked more subtle TTFL mutants, which just changed period length (i.e., slowed down the clock), they also observed lengthening of the PRX cycle. So, it appears that the TTFL and PRX oscillators may in some way be coupled. Disabling the PRX oxidation rhythms (using mutations of 2-Cys PRX) in plants and bacteria revealed that the core TTFL clockwork continued to tick, but with different phases and amplitudes. Thus, a clock can run without either the TTFL or the PRX system, but for normal physiology, both need to operate.

The evolution of ∼24-hour cycles of PRX oxidation–reduction in all domains of life now suggests that cellular rhythms may employ common molecular elements. Critically, PRX proteins are involved in the removal of toxic metabolic byproducts (ROS), and so their appearance may have contributed a selective advantage at the beginning of aerobic life on earth (Figure 1). This is thought to have occurred around 2.5 billion years ago, with the development of photosynthetic bacteria and photo-dissociation of water. This in turn led to the extremely rapid accumulation of (toxic) atmospheric oxygen during what is termed the Great Oxidation Event (GOE). The GOE led to a catastrophic change in earth ecology, with the loss of many anaerobic life forms, while intriguingly the most ancient TTFL clockwork mechanism, found in cyanobacteria, is thought to have evolved at around this time. Thus, during the GOE, rhythms of oxygen consumption/generation and ROS production would be driven by the solar cycle, leading to the evolution of a metabolic clock, which persists in the absence of a conventional TTFL cycle.

The discovery of the PRX oscillation has now opened new avenues for research. It is likely that the PRX system is representative of the 'arms' of an inner rhythmic process, the most likely of which is an internal cycle within the cell of production of hydrogen peroxide, and investigations are already under way to explore this circuit. Importantly, these new discoveries help to explain what up till now has seemed a paradoxical feature of the 'conventional' TTFL molecular clockwork. Here, we see conserved oxygen-sensing PAS-domain proteins as a common feature in many eukaryotic TTFL clocks [7,8]. In animal clocks, the core TTFL drives a great complexity of outputs but included are many members of the nuclear hormone receptor family, key regulators of intermediary metabolism. One member, REVERB-alpha, in particular is of current interest as this hormone receptor has been shown to act as a key redox sensor for the cell and to drive rhythmic metabolic and immune responses [9,10]. Much of our own physiology therefore may reflect an ancient oxygen-sensitive clockwork.

Finally, a fascinating speculation is that the clock as we know it may have appeared at the time of the GOE. A prediction therefore is that methanogenic organisms should lack circadian oscillators of any sort. Perhaps someone can be persuaded to mount an expedition to explore the biology of hyperthermophilic archaea in deep-sea vents of the oceans?

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Recent work establishes that Prostriata, a little-studied area of the visual cortex neighboring V1, has distinct but hybrid visual properties which are suggestive of an unsuspected role in the rapid analysis and integration of peripheral visual stimuli.

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The cortical visual system in primates consists of a highly specialized primary area (area V1 or 17) and an extensive network of visual association areas. The primary area is unambiguously identified by multiple criteria, such
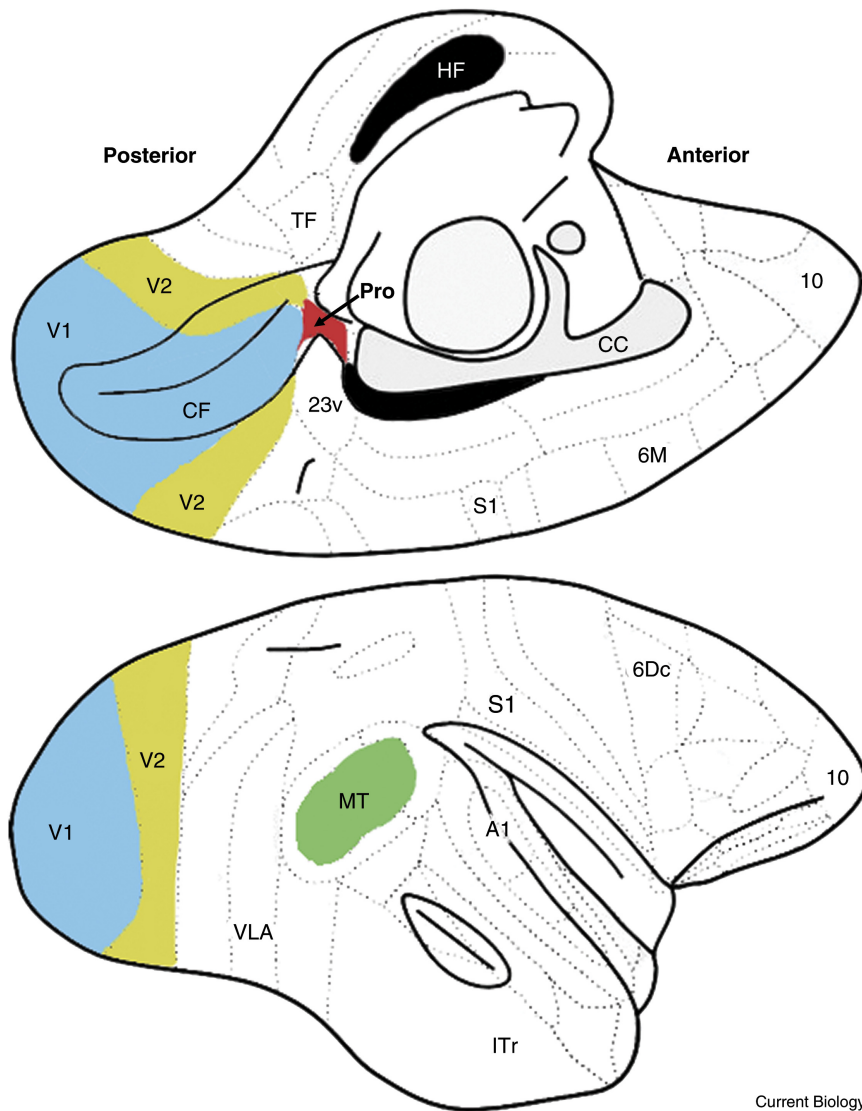
Figure 1. Area Prostriata (Pro) is a small area in the anterior calcarine fissure (CF).

Prostriata (in red) has hybrid features, compatible both with an early visual area such as V1 and with higher order association areas. The schematic shows medial and lateral views of the marmoset cerebral hemisphere. Dotted outlines indicate major cortical areas, a subset of which are labeled as in [7]. Areas V1, V2, and MT are in color. The hippocampal formation (HF; deep within the temporal lobe) and related areas (on the medial surface) are in black. (Adapted with permission from [7].)

architectonic-based brain mapping. The term comes from architectonics [4], where 'striata' refers to the elaborate sublamination of primary visual cortex and 'Pro' loosely means 'before', as in an earlier evolutionary stage of lamination and specialization. Prostriata can be classified as 'Prokoniocortex', a cortical type viewed as precursor to more specialized cortical areas with a well-developed, thalamo-recipient layer 4 ('konio' referring to small, densely packed cells, in layer 4). Prostriata has a thin layer 4 and an accentuated layer 2, features characteristic of limbic areas.

Early studies in the late 1960s reported short latency visual responses in Prostriata in squirrel monkeys. The more sophisticated investigation in marmoset by Yu *et al.* [2] confirms the short latency responses and further demonstrates a panel of response properties suggestive of an early visual area; that is, robust, non-adapting responses to simple stimuli, and responses that are broadly tuned to stimulus orientation and spatiotemporal frequency. Receptive fields, however, are large, and on the basis of this feature, Prostriata is more comparable to a higher-order area, such as inferotemporal cortex. The known connections of Prostriata are also suggestive of a higher-order area: labeled neurons occur in Prostriata, but not in adjoining V1, after injections of retrograde tracers in cingulate [5], auditory [6], orbitofrontal [7], and frontal polar [7] cortex.

The output projections from Prostriata provide one clue as to its functional significance. In particular, the projections to the cingulate motor area constitute an indirect but oligosynaptic pathway linking Prostriata to the upper spinal cord and facial nucleus [5]. A second clue is the specialization of this area for the peripheral visual field [2]. Together, these two features, as the authors remark, suggest a role in monitoring peripheral visual space for new, unexpected stimuli and in coordinated responses or shifts in attention.

A major unanswered question is: what are the inputs to Prostriata and especially what inputs might be a source of the specific visual properties? The short latency responses would be consistent with inputs from magnocellular neurons in

as direct and dense connections from visual thalamus, a complete representation of the visual hemifield, relatively simple receptive field properties, and a distinctively stratified arrangement of cell bodies (whence the term 'striate cortex'). In contrast, the association or 'extrastriate' areas are with few exceptions harder to delineate, and their identity and features are often the subject of vigorous debate [1]. Given that the network of extrastriate areas numbers well over 30, the report in this issue of *Current Biology* by Yu *et al.* [2] of

an additional visual area is not in itself surprising. What is surprising is that Prostriata, a limbic area by virtue of its simple lamination, is found to have specifically visual response properties (Figure 1). These mixed visuolimbic features raise broad implications for how we view the cortical visual system and, consequently, for how we see.

Prostriata was described as a distinct area in the late 1960s by Friedrich Sanides [3], a student of the Vogts, themselves mentors of Brodmann and pioneers in

the visual thalamus or possibly from the koniocellular population. Koniocellular neurons project directly to extrastriate area MT, where neurons also have short latency responses [8]. For Prostriata as well as for MT, such a direct pathway, bypassing V1, could be a substrate for the residual perception of moving stimuli after loss of V1 ('blindsight') [8]. Other sources of visual input could be visually responsive neurons in the medial pulvinar or other visually responsive thalamic nuclei. For example, a population of non-standard intrinsically photosensitive retinal ganglion cells has thalamic projections to the ventral lateral geniculate nucleus and intrageniculate leaflet, in addition to projections to the suprachiasmatic nucleus (involved in photic entrainment of the circadian clock) and the olivary pretectal nucleus (a crucial link in the circuitry of the pupillary light reflex) [9].

A long-standing and fruitful model of visual cortical organization proposes that extrastriate areas can be grouped into two segregated processing streams, deriving from differential projections from area V1. The dorsal and ventral streams are construed as involved with spatial or object submodalities, respectively [1]. In this framework, Prostriata would be most closely aligned with the dorsal stream and, in fact, it is interconnected with area MT, a dorsal stream area [10]. Alternatively, area Prostriata may be part of another distinct processing stream, concerned with visuomotor or visuolimbic attributes. Whether there are properly two or more processing streams, however, is subject to ongoing discussion [1,11], and the fact that Prostriata does not fit neatly into the current ideas of visual processing may be a signal of persisting shortcomings in the standard model.

The current model, emphasizing parallel streams and hierarchical progression from V1, has been faulted as not taking full account of the importance of context effects and intentionality, or the diversity of visual codings and the cross-species ubiquity of non-standard ganglion cells ("Vision without a million densely packed ganglion cells remains quite workable") [12]. In a remarkably cogent statement of the problem, Churchland *et al.* [13] set forth a contrast between what they termed 'pure vision' and 'interactive vision'. Pure vision was described,

albeit with some simplification, as epitomizing a hierarchical, modular, input–output theory. Interactive vision was taken to imply significant roles for systems ostensibly extrinsic to seeing the world-as-replica, such as motor and other sensory systems. Similar arguments have been made for the integration of movement with sensing, 'active touch', for purposes of acting effectively in the world [14].

To what degree can areas be viewed as organized in a strict hierarchy [15]? Is Prostriata 'equivalent' to V2, because it borders V1 (but has a topographic organization more similar to inferotemporal cortex), or equivalent to inferotemporal cortex (but with simpler response properties)? The issue relates in part to the question, what is an area? In an earlier article, Rosa and Tweedale [16] thoughtfully discuss the distinction between 'core areas', where borders are clear and probably genetically fixed, and areas with a more ambiguous identity, better described in terms of gradients. Moreover, physiological activity patterns cross area borders: a recent study [17] has shown that stimulation of a single whisker in rats evokes neuronal activation that radiates from a localized focus, deep into neighboring auditory, visual, and motor cortical territories.

Limbic areas have traditionally been viewed as sharply segregated from sensory areas, especially primary sensory. In rodents, however, there are direct connections from both areas 17 and 18b to part of retrosplenial cortex [18]. In primates, there are direct, cross-domain projections from parietal and temporal association cortices to CA1 of hippocampus [19]. In primates, the peripheral field representations of V1 and, somewhat more densely, V2 receive direct projections from auditory, parietal, and parahippocampal association areas [20]. Yu *et al.* [2] conclude that Prostriata may provide a pathway mediating relatively coarse but fast spatial information across multiple cortical systems, based on its physiological properties and connections. An open question is whether this is another parallel processing stream, an unappreciated fundamental aspect of vision, or both.

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