

Snakes as agents of evolutionary change in primate brains

Lynne A. Isbell*

Department of Anthropology, University of California, Davis, CA 95616, USA

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Abstract

Current hypotheses that use visually guided reaching and grasping to explain orbital convergence, visual specialization, and brain expansion in primates are open to question now that neurological evidence reveals no correlation between orbital convergence and the visual pathway in the brain that is associated with reaching and grasping. An alternative hypothesis proposed here posits that snakes were ultimately responsible for these defining primate characteristics. Snakes have a long, shared evolutionary existence with crown-group placental mammals and were likely to have been their first predators. Mammals are conservative in the structures of the brain that are involved in vigilance, fear, and learning and memory associated with fearful stimuli, e.g., predators. Some of these areas have expanded in primates and are more strongly connected to visual systems. However, primates vary in the extent of brain expansion. This variation is coincident with variation in evolutionary co-existence with the more recently evolved venomous snakes. Malagasy prosimians have never co-existed with venomous snakes, New World monkeys (platyrrhines) have had interrupted co-existence with venomous snakes, and Old World monkeys and apes (catarrhines) have had continuous co-existence with venomous snakes. The koniocellular visual pathway, arising from the retina and connecting to the lateral geniculate nucleus, the superior colliculus, and the pulvinar, has expanded along with the parvocellular pathway, a visual pathway that is involved with color and object recognition. I suggest that expansion of these pathways co-occurred, with the koniocellular pathway being crucially involved (among other tasks) in pre-attentional visual detection of fearful stimuli, including snakes, and the parvocellular pathway being involved (among other tasks) in protecting the brain from increasingly greater metabolic demands to evolve the neural capacity to detect such stimuli quickly. A diet that included fruits or nectar (though not to the exclusion of arthropods), which provided sugars as a neuroprotectant, may have been a required preadaptation for the expansion of such metabolically active brains. Taxonomic differences in evolutionary exposure to venomous snakes are associated with similar taxonomic differences in rates of evolution in cytochrome oxidase genes and in the metabolic activity of cytochrome oxidase proteins in at least some visual areas in the brains of primates. Raptors that specialize in eating snakes have larger eyes and greater binocularity than more generalized raptors, and provide non-mammalian models for snakes as a selective pressure on primate visual systems. These models, along with evidence from paleobiogeography, neuroscience, ecology, behavior, and immunology, suggest that the evolutionary arms race begun by constrictors early in mammalian evolution continued with venomous snakes. Whereas other mammals responded by evolving physiological resistance to snake venoms, anthropoids responded by enhancing their ability to detect snakes visually before the strike.

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Introduction

Primates possess a suite of characteristics including grasping hands, grasping feet, nails on at least the thumb or first toe, convergent orbits, enlarged brains, and visual specialization

(Dagosto, 1988; Cartmill, 1992; Rasmussen, 2002). Their visual specialization can be illustrated by their greater reliance than other mammals on vision for reaching and grasping. For example, humans with Parkinson's disease (PD) and green monkeys (*Cercopithecus aethiops sabaeus*) with experimentally induced PD are able to correct errors visually while reaching for small items (Pessiglione et al., 2003; Schettino et al., 2003, 2006). By contrast, although rodents, which are,

* Tel.: +1 530 754 9718; fax: +1 530 752 8885.

E-mail address: laisbell@ucdavis.edu

along with primates, members of the Euarchontoglires clade (Madsen et al., 2001; Waddell and Shelley, 2003; Reyes et al., 2004), can grasp and manipulate objects, including arthropods, using the tips of their digits (Whishaw et al., 1998; Iwaniuk and Whishaw, 2000; Whishaw, 2003), and they overlap with primates in their hand proportions (Hamrick, 2001), they do not employ visually guided reaching and grasping. Despite the similarity in the motor patterns of rodents' and primates' reaching and grasping (Cenci et al., 2002; Whishaw et al., 2002), rats with experimentally induced PD appear unable to correct errors in reaching and grasping through immediate visual feedback (Vergara-Aragon et al., 2003). In addition, rodents use their auditory, olfactory, and tactile senses, but apparently not vision, to locate and reach for food. Rats without vision are able to locate and reach for food as quickly as they did before being blinded, but rats without olfaction are slower (Whishaw, 2003). Greater reliance on vision for reaching and grasping in primates is reflected in their brains. Preuss (in press) noted that the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC), two areas involved in skilled hand movements and with extensive connections to visual areas, are larger in primates than in other mammals.

Locomotor niche, which, along with food acquisition, employs reaching and grasping, has also influenced primate brain evolution. This is illustrated by the finding that primate leapers and scurriers have the smallest brain proportions, followed by quadrupedal runners and jumpers, forelimb-dominated suspensory climbers and arm-swingers, and finally, bipedal walkers and runners, regardless of phylogenetic history. Thus, woolly monkeys (*Lagothrix*) and spider monkeys (*Ateles*) converge with hominoids in their brain proportions even though they have smaller brains overall (de Winter and Oxnard, 2001).

The selective pressures favoring these defining primate characteristics have long been debated (e.g., Napier and Walker, 1967; Cartmill, 1974; Sussman, 1991; Crompton, 1995; Rasmussen, 2002; Bloch and Boyer, 2002; Kirk et al., 2003), but there is still no consensus. Reasonably perhaps, current hypotheses focus on diet and substrate use as the key selective pressures.

The visual predation hypothesis proposes that stalking and grabbing arthropods at close range while on small-diameter branches favored the entire suite of primate characteristics (Cartmill, 1972, 1974, 1992). This hypothesis is supported by substantial comparative data. It is likely, for example, that many early primates were small and insectivorous to some degree, since many extant small mammals are insectivorous. Moreover, while many arboreal mammals do not have frontally directed orbits, some terrestrial mammals that do are visual predators (Cartmill, 1972, 1974). Recent research by Ravosa and Savakova (2004) supports the modified version of the visual predation hypothesis (Cartmill, 1992) that limits it to nocturnal visual predation, with a comparative study showing that nocturnal faunivorous mammals have more convergent orbits than their diurnal relatives and that early euprimates had orbital convergences similar to those of felids and extant nocturnal faunivorous primates.

It is also possible, however, that, like most modern primates, the first primates were not committed insectivores but were generalists, eating a variety of plant foods while also taking insects opportunistically (Richard, 1985; Rasmussen, 2002). Sussman (1991) hypothesized that orbital convergence and grasping evolved for detecting small fruits and flowers on fine, terminal branches of angiosperms that had just begun their radiation. In support of Sussman's hypothesis, morphological comparison with extant prosimians suggests that some early primates were frugivorous to some degree (Covert, 2002). There is also intriguing ecological evidence that early primates consumed nectar to a significant degree. As might be expected for animals with nectar as a large component of their diet, prosimians, the extant primates considered most similar in their visual systems and brain expansion to early euprimates, are heavily represented among mammals as plant pollinators (Carthew and Goldingay, 1997). Based on observations that visitors to flowers of the traveler's tree (*Ravenala madagascariensis*) are largely restricted to prosimians, and on characteristics of the flowers that limit pollen access to larger-bodied, non-volant animals, Kress and colleagues (Kress, 1993; Kress et al., 1994) provided evidence in support of Sussman and Raven's (1978) hypothesis that nectivorous prosimians could have been part of an early co-evolutionary plant-pollinator system. *Ravenala* is a basal genus of the Strelitziaceae in Madagascar that diversified in the late Cretaceous and early Tertiary (Kress, 1993; Kress et al., 1994).

A less food-based hypothesis is Crompton's (1995) leaping hypothesis, which argues that orbital convergence is important not only for short-range, or peripersonal, stereopsis, but also for "breaking through" camouflage. Orbital convergence would have been useful not only for capturing insects and finding small fruits, but also for aiming for small branches while leaping in a complex three-dimensional environment. Leaping appears to have been common in early euprimates but not plesiadapiforms, and is common in extant prosimians (Napier and Walker, 1967; Dagosto, 1988; Crompton, 1995; Covert, 2002; Gebo, 2002).

Although they disagree on the targeted object, all hypotheses propose that reaching and grasping were involved in the evolution of orbital convergence in primates, and all attempt to explain the entire suite of primate characteristics as a unitary phenomenon. However, this traditional view that the suite of primate characteristics evolved together is now being reconsidered. In an analysis of postcranial bones of *Carpolestes*, a plesiadapiform mammal sometimes considered a primate (McKenna and Bell, 1997), Bloch and Boyer (2002) showed that it possessed manual and pedal grasping but not leaping ability, and a nail instead of a claw on its hallux. This information, coupled with the absence of a postorbital bar, suggested to them that grasping evolved before leaping and frontally directed orbits. By extension, their results suggest that generalized reaching and grasping occurred before *visually guided* reaching and grasping. This would mean that the defining primate characteristics occurred through mosaic evolution, contrary to what existing hypotheses suggest. Mosaic evolution also occurred in hominid evolution, with changes in

limb morphology occurring before changes in dentition and brain size (McHenry, 1994).

Renewed investigation of the grasping ability of rodents supports Bloch and Boyer's (2002) argument that reaching and grasping evolved early (Whishaw et al., 1998; Iwaniuk and Whishaw, 2000; Whishaw, 2003), but it also suggests that reaching and grasping evolved even earlier than Bloch and Boyer (2002) recognized. In a phylogenetic analysis, Iwaniuk and Whishaw (2000) concluded that skilled forelimb movements, which they defined as the ability to reach for objects with a forelimb, hold them in a hand or forepaw, and manipulate them with the digits, are even more ancient than the last common ancestor of rodents and primates. Nevertheless, although plesiadapiforms, rodents, and more distant relatives of primates apparently share with primates the ability to grasp with the forelimbs, it is unlikely that these taxa can shed light on two key characteristics of primates—orbital convergence and visually guided reaching and grasping—because they have not been demonstrated to have those characteristics.

Barton (2004) recently examined whether convergent orbits in primates are correlated with various aspects of the visual system and the brain, including the size of the primary visual area (V1), the number of neurons in the parvocellular (P) and magnocellular (M) layers of the lateral geniculate nucleus of the thalamus (LGN), the neocortex (since the neocortex is devoted mainly to vision), and larger brains overall. In primates, the LGN P layers are part of the ventral visual processing stream, whereas the LGN M layers are part of the dorsal visual processing stream. These two visual streams are specialized for different aspects of vision, with the ventral stream being more involved in perception and the dorsal stream, in action (Goodale and Milner, 1992; Goodale and Westwood, 2004). After controlling for body size, phylogeny, and activity period (nocturnal vs. diurnal), Barton (2004) found that orbital convergence is positively correlated with all but the number of neurons in the M layers of the LGN.

Barton (2004) interpreted the findings as unresponsive of the visual predation hypothesis, which emphasizes movement detection, reaching and grasping, and close-range stereopsis. (Movement detection and reaching and grasping are domains of the M-dominated dorsal stream.) Indeed, Cartmill (1992) recognized that visual predation per se could not explain orbital convergence since there are numerous examples of insectivorous animals with lateral eyes. He qualified his original hypothesis by suggesting that only visual predators that are nocturnal would need orbital convergence in order to see clearly what is in front of them. Barton (2004) did not dispute that seeing objects clearly in front is important to primates. However, because of the absence of a correlation between orbital convergence and the visual pathway involved with movement detection, he interpreted his findings as more supportive of a modified frugivory/nectivory hypothesis, wherein fine-grained, close-range stereopsis would be required for visually guided grasping and manual manipulation of plant foods (rather than moving arthropods or feeding on fine terminal branches). Cells that are responsive to binocular disparity, which is important for depth perception and stereopsis, have

been found not only in the dorsal stream, but also in the P-dominated ventral stream (Hinkle and Connor, 2001).

The one problem with Barton's (2004) interpretation is that a large body of neuroscientific evidence clearly shows that visual control of reaching and grasping occurs in the M-dominated dorsal stream, not the P-dominated ventral stream (e.g., Goodale and Milner, 1992; Culham et al., 2003; Goodale and Westwood, 2004). There is even evidence that, under normal viewing conditions, when many visual cues are available to animals, binocular information, which is facilitated by orbital convergence, is not as important in accurately reaching and grasping as previously thought, and this is particularly the case for reaching (Watt and Bradshaw, 2000). Since the degree of orbital convergence is *not* correlated with the visual pathway involved in reaching and grasping, Barton's (2004) findings must be reinterpreted as evidence against any hypothesis that uses visually guided reaching and grasping to explain the changes in orbital convergence that occurred in primates.

Barton's (2004) findings are, nonetheless, a significant breakthrough because they reveal that orbital convergence, visual specialization, and brain expansion required acute vision and close-range stereopsis for something other than visually guided reaching and grasping of food or substrates. Barton's (2004) results thus open the door for a new hypothesis to explain primate visual systems, including their orbital convergence, visual specializations, and brain expansion.

The précis of a new hypothesis for primate and anthropoid origins

What besides visually guided insectivory, feeding on fruits and nectar, moving on fine terminal branches, or leaping could favor better depth perception in near space and a better ability to “break” camouflage, both of which are improved with orbital convergence (Allman, 1999), particularly in the lower visual field (Barton, 2004)? In the introduction to their analysis of neuronal preferences for near distances in the P-dominated ventral visual stream of macaques (*Macaca*), Rosenbluth and Allman (2002) suggested that near vision might be useful for seeing objects such as snakes, which “tend to creep in the lower visual field.” Here I offer a new hypothesis that is consistent with Barton's (2004) findings and Rosenbluth and Allman's (2002) suggestion. It proposes that orbital convergence, visual specialization, and brain expansion in early primates evolved in response to the selective pressures brought on by constricting snakes, and that the visual systems and brains of anthropoids became modified further in response to the appearance of venomous snakes (viperids and elapids).

Mammals appear to have a common set of brain structures that help them avoid stimuli, such as predators, that are dangerous to their survival. This set of structures may help to form the neurological basis for what Öhman and Mineka (2003) have called the mammalian fear module. The fear module likely evolved in the earliest mammals in response to their first predators; those that did not respond to predators by detecting and executing appropriate motor behaviors to avoid them likely did not survive long. The main predators of

mammals are snakes (including constrictors and venomous snakes), raptors, and carnivorans (Cheney and Wrangham, 1987; Isbell, 1994; Kingdon, 1997).

My main goals in this paper are to 1) show, through documentation of the relative appearance of snakes, raptors, and carnivorans, that snakes were the first of the modern predators of crown-group placental mammals; 2) locate the main structures in the brain that comprise the fear module of mammals, as determined by their functions in alerting mammals to potential danger and enabling the animals to respond appropriately; 3) examine the ways in which primates have incorporated greater visual input into these structures; 4) present the evidence for constrictors as a selective pressure favoring initial changes in orbital convergence, visual specialization, and expanded brain size in the first primates and for venomous snakes as a selective pressure favoring further modifications that led to anthropoids; and 5) investigate variation in the visual systems of catarrhines, platyrrhines, and prosimians relative to their different periods of evolutionary co-existence with venomous snakes.

Taken together, these data will show that there are enough lines of evidence to warrant further examination of the hypothesis that predation pressure from snakes has been a major force in the evolution of primate visual systems.

The evolution of predators relative to mammals in general and primates in particular

Origin of mammals

Evidence from the fossil record indicates that crown-group placental mammals first arose in Laurasia at around 65 million years ago (Ma) (Archibald, 2003). Over the past decade, however, numerous studies in molecular systematics have converged on a much earlier date of between 100 and 105 Ma and a Gondwanan origin for crown-group placentals (Hedges et al., 1996; Kumar and Hedges, 1998; Stanhope et al., 1998; Madsen et al., 2001; Murphy et al., 2001a,b; Springer et al., 2003, 2004; Waddell and Shelley, 2003; Reyes et al., 2004). This earlier date of origin is statistically more likely given the difficulty of finding fossils of any kind, let alone the first of any animal lineage (Tavaré et al., 2002).

Origin of constrictors

Basal snakes with gapes large enough to eat mammals are thought to have evolved before 100 Ma (Greene and Burghardt, 1978; Greene, 1983; Rage and Escuillié, 2000; Lee and Scanlon, 2002; Scanlon, 2003; Vidal and David, 2004). Fossils of madtsoiids—basal snakes often as large as modern constrictors—have been found mainly in Gondwana, but also in southern Spain, probably via Africa (Rage, 1996; Scanlon and Lee, 2000; Rage et al., 2004). Constricting snakes are thought to have evolved shortly afterward (Greene and Burghardt, 1978; Greene, 1997). The existence in Madagascar of modern constrictors whose closest relatives are boas (*Boa*) in South America (Kluge, 1991; Vences et al., 2001) suggests

a Gondwanan origin for constrictors, but fossil constrictors dated to the Paleocene (65 Ma) have also been found in Laurasia (Rodríguez-Robles et al., 1999). Mammals and snakes have been found at the same locality in India dated to the Maastrihtian (late Cretaceous) (Khajuria and Prasad, 1998; Rage et al., 2004).

Origins of venomous snakes and anthropoid primates

From a basic venom system that evolved early in reptiles (Fry et al., 2006), by about 60 Ma at the latest, a subset of colubroid snakes in Africa or Asia evolved an extraordinarily potent venom delivery system (Cadle, 1988; Vidal and Hedges, 2002), an innovation that is suggested to have coincided with the appearance of birds and fast-moving, small mammals such as rodents and primates on those landmasses (Greene, 1983; Feduccia, 1995; Douady et al., 2002; Huchon et al., 2002; Gebo, 2004). The highly venomous snakes include viperids and elapids. Viperids are basal relative to other colubroids (colubrids and elapids) (Cadle, 1987, 1988; Gloyd and Conant, 1990; Knight and Mindell, 1994; Heise et al., 1995; Dowling et al., 1996; Keogh, 1998; Lenk et al., 2001; Slowinski and Lawson, 2002; Vidal and Hedges, 2002; but see Gravlund, 2001). Both viperids and anthropoid primates appear to have evolved in the Old World (Keogh, 1998; Lenk et al., 2001; Beard, 2002; Dagosto, 2002). Putative anthropoid fossils have been found in strata dated to the middle Eocene in Afro-Arabia and Asia (Ross, 2000; Beard, 2002; Kay et al., 2004; but see Ciochon and Gunnell, 2002).

Venomous snakes arrived in South America from North America via Asia (Parkinson, 1999) either between 10 and 23 Ma, based on molecular data for bushmasters (*Lachesis*) and lanceheads (*Bothrops*) (Zamudio and Greene, 1997; Wüster et al., 2002), or by about 3 Ma, based on the timing of the formation of the Panamanian land bridge over which North American fauna crossed into South America (Vanzolini and Heyer, 1985; Cadle, 1987; Crother et al., 1992; Greene, 1997). Platyrrhines, on the other hand, arrived in South America no more recently than 35 Ma (Arnason et al., 1998; Nei and Glazko, 2002; Schrago and Russo, 2003). Prevailing thought is that platyrrhines arrived in South America from Africa (Fleagle, 1999). If true, this would mean that exposure to venomous snakes was interrupted for platyrrhines when they dispersed to South America. Platyrrhines are estimated to have begun their radiation in the New World by about 26 Ma, with extant platyrrhine genera diverging 11–20 Ma (Schneider et al., 1993, 2001; Chaves et al., 1999; Cropp and Boinski, 2000). It is possible, therefore, that platyrrhines began their radiation in the absence of venomous snakes.

The other landmass where primates occur is Madagascar. In contrast to Africa, Asia, and South/Central America, Madagascar is devoid of viperids and elapids. Similarly, although some colubrids are venomous, no truly venomous colubrids exist on Madagascar (Glaw and Vences, 1994; Kardong, 2002; Vidal, 2002). Molecular evidence suggests that Malagasy lemuriforms diverged from other strepsirrhines at around 60–65 Ma (Yoder et al., 1996; Eizirik et al., 2004; Yoder and

Yang, 2004). Thus, the prosimians on Madagascar have never been exposed to venomous snakes that could pose a deadly threat to them.

Raptors and carnivorans

Molecular data suggest that the Accipitridae (hawks and eagles) and Falconidae (falcons) diverged by about 68–80 Ma in South America (Sibley and Ahlquist, 1990; Griffiths, 1999; Haring et al., 2001; Riesing et al., 2003). Eagles, the major raptorial predators of modern primates, would have diverged from the other accipitrids even later. Fossil evidence indicates the existence of raptorial birds somewhat later, by about 55 Ma (Feduccia, 1995). Raptors thus appear to have evolved after snakes and crown-group placental mammals. Similarly, since carnivorans are crown-group placental mammals themselves but are not members of the basal clades Afrotheria and Xenarthra, they would have evolved after snakes evolved and at some point after Afrotheria and Xenarthra evolved. Molecular evidence and the fossil record both indicate that carnivorans evolved in Laurasia about 55 Ma (Martin, 1989; Wayne et al., 1989; Madsen et al., 2001; Murphy et al., 2001a,b).

Öhman and Mineka (2003) have summarized extensive experimental data on human and non-human primate responses to snakes. Available fossil, molecular, and paleobiogeographical evidence presented here supports their claim that snakes were the first predators of crown-group placental mammals. Constricting snakes were followed by venomous snakes, and both were undoubtedly predators of small mammals, including primates. Öhman and Mineka (2003) proposed that snakes provided the main selective pressure for the evolution of what they have labeled the fear module in mammals. The fear module is a behavioral and neural system that is, importantly, automatically activated and independent of cortical control. Their studies focused on the behavioral aspects of the fear module. In the following section, I focus on documenting the effects of snakes on the neural components of the mammalian fear module and note where primates differ from other mammals. A discussion of neural structures is important for understanding why the brain uniquely expanded in primates and the context for evidence against currently existing hypotheses for orbital convergence and visual specialization.

Overview of the fear module

Existing data indicate that snakes were the first predators of crown-group mammals, including primates. Obviously, there would have been strong selection for neural structures involved in predator detection and avoidance. My main purpose in this section is to give the reader a sense of how neurological structures are involved in predator avoidance. I do not attempt a detailed neuroscientific description of any of these structures. Those interested in more thorough descriptions are directed to several excellent reviews (e.g., Kaas and Huerta, 1988; Chalupa, 1991; Garey et al., 1991; Henry and Vidyasagar, 1991; Stepienewska, 2004; Preuss, in press).

Table 1 summarizes some of the areas of the brain that are likely to be involved either directly or indirectly in the mammalian fear module, as suggested by their functions. Figure 1 shows some of the neural connections of these structures in primates.

The amygdala

The amygdaloid complex is located in the temporal lobe and has connections to many parts of the neocortex (Amaral and Price, 1984; McDonald, 1998). It is composed of several nuclei. The lateral nucleus of the amygdala responds to auditory stimuli and is also involved with vision, particularly gaze direction (Brothers et al., 1990; LeDoux, 2000). The lateral nucleus receives input from the locus coeruleus (LC), dorsal pulvinar, inferotemporal cortex (IT), and the superior temporal sulcus (STS), and it sends projections to the basolateral and central nuclei of the amygdala (Jones and Burton, 1976; Amaral et al., 1992; Aggleton and Saunders, 2000; LeDoux, 2000; Pitkänen, 2000). The central nucleus mediates motor expressions of fear, e.g., freezing (Kalin et al., 2004). It has connections with the LC, substantia nigra, periaqueductal gray, and the basolateral nucleus (Jones and Burton, 1976; Iwai and Yukie, 1987; Amaral et al., 1992; Aggleton and Saunders, 2000; Davis, 2000; Kalin et al., 2004). The central nucleus does not appear to have been modified substantially in primates; it is not larger in primates in comparison to insectivores relative to body size (Barton and Aggleton, 2000).

The basolateral nucleus (also known as the basal nucleus) is involved in learning about fearful stimuli, acquisition of fearful behavior, acquisition of spatial memory, and modulation of memory storage, particularly of emotionally arousing stimuli (Cahill and McGaugh, 1998; LeDoux, 2000; McGaugh et al., 2000; Berridge and Waterhouse, 2003). Expression of fearful behavior following chemical blockade of the nigrothal inhibitory neurotransmitter pathway can be modified by concurrent inhibition of the basolateral nucleus in pigtailed macaques (*M. nemestrina*), suggesting that the basolateral nucleus also mediates expression of fearful responses (Zarbarlian et al., 2003). The basolateral nucleus receives input from the LC, PPC, and DLPFC, and it sends projections to many areas, including V1, the middle temporal cortex (MT), and, within the amygdala, the central nucleus (Selemon and Goldman-Rakic, 1988; Aggleton and Saunders, 2000). The basolateral nucleus is enlarged in haplorhines, and its size is correlated with the size of the neocortex in primates but not insectivores (Barton and Aggleton, 2000; Barton et al., 2003).

Abundant evidence thus exists that the amygdaloid complex is involved in aversive learning and the fear response (Jones and Burton, 1976; Morris et al., 1997, 1998; Cahill and McGaugh, 1998; LeDoux, 2000; Kalin et al., 2001; Amaral, 2002). Amaral (2003) suggested that the amygdala also plays a major role in surveying and evaluating the environment for danger signals. One of the ways in which animals can detect danger in their environment is by monitoring the behavior or expressions of conspecifics. In macaques, development of fearful responses to snakes requires only exposure to

Table 1
Summary of the main neural structures involved in 1) the mammalian fear module and 2) visual pathways in primates and their functions

Structure or pathway	Functions
<i>Visual pathways and early visual areas</i>	
Koniocellular (K) pathway	Rapid responsiveness to motion; blue hues; luminance; auditory stimuli; attention and arousal; eye movements; connections with superficial layers of SC, inferior pulvinar
Parvocellular (P) pathway	Central vision; responsive to color, form
Magnocellular (M) pathway	Responsive to motion, contrast
V1	Responsive to simple visual stimuli, e.g., orientation, color, motion
V2	Responsive to simple and dual visual stimuli, e.g., color and orientation; color and disparity; stereopsis
V4	Responsive to complex visual stimuli, e.g., faces; attention to less physically prominent stimuli
<i>Basic components of the fear module</i>	
Amygdala	
Lateral	Responsive to auditory and visual stimuli; gaze direction; connections with LC, dorsal pulvinar, basolateral and central nuclei of amygdala, many cortical areas, including IT and STS
Central	Mediates motor expression of fear, e.g., freezing; connections with LC, dorsal pulvinar, substantia nigra, periaqueductal gray, basolateral nucleus
Basolateral	Learning about fearful stimuli; acquisition of fearful behavior; acquisition of spatial memory; modulation of memory storage, especially of emotionally arousing stimuli; mediates expression of fearful behavior; connections with V1, LC, IT, MT, STS, PPC, DLPFC, central nucleus
Locus coeruleus (LC)	Primary CNS source of norepinephrine; responsive to salient, usually aversive stimuli; heightened attention; vigilance; learning; enhanced memory, especially of aversive experiences; connections with SC, amygdala, dorsal pulvinar, V2, many cortical areas
Superior colliculus (SC)	
Superficial layers	Responsive to visual stimuli, especially luminance and movement; sends visual signals rapidly to deeper layers for orienting head and eyes; connections with retina, V1, V2, FEF, LGN, MT
Deeper layers	Covert shifts of attention; motor expressions of fearful behavior; connections with superficial layers of SC, dorsal pulvinar, substantia nigra, cuneiform nucleus, PAG, IT, FEF, PPC
Pulvinar	
Inferior (inferior and ventral lateral pulvinar)	Attention; selective visual processing; modulates activity in V2 in anthropoids; connections with retina, LC, superficial layers of SC, V1, V2, STS, MT
Dorsal (medial and dorsal lateral pulvinar)	Eye movements; gaze direction; orienting to salient stimuli; coordinates and integrates selective spatial attention; connections with deeper layers of SC, lateral nucleus of amygdala, periaqueductal gray, locus coeruleus, IT, PPC, STS, DLPFC, posterior cingulate cortex
Substantia nigra	Involved in head and eye orientation; expression of fearful behavior; attention to salient but unpredictable stimuli; inhibits expression of fearful behavior in SC; connections with SC
Periaqueductal gray (PAG)	Freezing; connections with central nucleus of the amygdala, V2, cuneiform nucleus
Cuneiform nucleus	Motor expressions of fear, e.g., freezing, darting, running; connections with PAG, deeper layers of SC
<i>Associated Areas</i>	
Superior temporal sulcus (STS)	Responsive to eyes, faces, gaze direction of others, complex visual stimuli; directed attention; connections with dorsal pulvinar, DLPFC
Inferotemporal cortex (IT)	Responsive to faces and other complex visual stimuli; object recognition; connections with dorsal pulvinar, deeper layers of SC, V4, DLPFC
Middle temporal cortex (MT)	Involved in search of salient stimuli; motion; visual tracking; connections with V1, V2, PPC
Posterior parietal cortex (PPC)	Eye movements; attention; defensive motor behaviors; spatial localization of objects; memory of objects in nearby space; reaching; directed limb movements; connections with dorsal pulvinar, basolateral amygdala, DLPFC, deeper layers of SC; non-primary visual areas
Dorsolateral prefrontal cortex (DLPFC)	Eye movements; attention; spatial localization of objects; memory of objects in nearby space; reaching; directed limb movements; connections with dorsal pulvinar, basolateral amygdala, PPC, IT, STS
Frontal eye field (part of DLPFC or prefrontal cortex)	Involved in search and scanning for salient stimuli; anticipatory activity before target appears; saccade-related activity; connections with superficial and deeper layers of SC
Posterior cingulate cortex	Eye movements; spatial attention; spatial memory; connections with dorsal pulvinar, DLPFC, PPC

videotaped conspecifics reacting fearfully toward snakes; fearful responses do not develop when conspecifics are observed expressing fear toward flowers (Cook and Mineka, 1989).

The amygdala also appears to be sensitive to cues given by others for the pre-conscious detection of fear-related stimuli (Morris et al., 1999; Dolan and Vuilleumier, 2003). Anthropoid primates (but perhaps not prosimians) can orient their eyes in the direction of the gaze of others (using head and eyes as cues) (Emery, 2000; Kawashima et al., 1999; Scerif et al., 2004; see also Vuilleumier, 2002). Eyes alone can be

strong cues for detecting danger in the environment—humans merely need to see fearful eyes to evoke a response in the amygdala (Morris et al., 2002). A change in the direction of another's gaze triggers automatic orientation toward the direction of the gaze (Driver et al., 1999; Langton et al., 2000). Humans with damaged amygdalas can detect happiness but not fear in faces (Amaral, 2003), apparently because of a lack of automatic visual focus on the eyes (Adolphs et al., 2005). Automaticity, by definition, occurs before conscious awareness (Dolan and Vuilleumier, 2003).

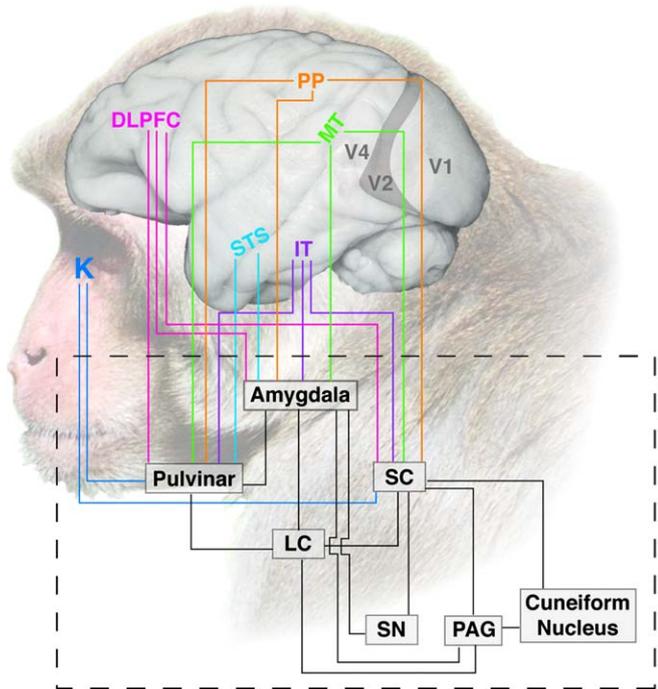


Fig. 1. Relevant connections between the K pathway, the structures of the fear module (located within the dashed box), and associated cortical areas in a macaque brain. Connections are mostly reciprocal and not exhaustive, e.g., they do not show connections with V1, V2, and V4. Koniocellular pathway to the lateral geniculate nucleus (LGN) is also not shown. Abbreviations for different structures: K, koniocellular pathway; LC, locus coeruleus; SC, superior colliculus; SN, substantia nigra; PAG, periaqueductal gray; DLPFC, dorsolateral prefrontal cortex; STS, superior temporal sulcus; IT, inferotemporal cortex; MT, middle temporal cortex; PP, posterior parietal cortex. Illustration by Kathy West.

The locus coeruleus (LC)

The LC is a structure in the midbrain whose neuronal activity is driven by salient and usually threatening or alarming stimuli (Berridge and Waterhouse, 2003). Lesions of the LC in rats result in a reduction in motor responses to threatening stimuli, e.g., freezing behavior (Neophytou et al., 2001). The LC is the primary source of norepinephrine in the mammalian brain, a neurotransmitter that is associated with heightened attention or vigilance, learning, and enhanced memory, particularly of aversive experiences (Foote et al., 1991; Aston-Jones et al., 1991, 1994, 1997; Lecas, 2004). Norepinephrine in the amygdala is necessary for the expression of fear (Schulz et al., 2002). The LC has widespread connections with the central nervous system, including the superior colliculus (SC), lateral posterior pulvinar (LP-pulvinar) complex, amygdala, early parts of the visual system (especially the LGN in non-anthropoid mammals), the second visual area (V2), and the neocortex (Morrison and Foote, 1986; Wilson et al., 1995; Berridge and Waterhouse, 2003).

The superior colliculus (SC)

The SC is separated into superficial and deeper layers (Kaas and Huerta, 1988). Cells in the superficial layers are highly

involved in vision, including detection of moving stimuli and changes in luminance (Kadoya et al., 1971). In hedgehog tenrecs (*Echinos telfairi*), which are often considered good representatives of basal placental mammals (Eisenberg, 1981), as well as in other mammals, cells in the superficial layers of the SC receive input from the retina and project to the W/K layers of the LGN and the inferior part of the LP-pulvinar complex (Glendenning et al., 1975; Benevento and Rezak, 1976; Harting et al., 1980, 1991; Huerta and Harting, 1983, 1984; Lachica and Casagrande, 1993; Künzle, 1996; Stepniewska et al., 1999, 2000). The superficial layers receive input from many areas of the cortex, including V1, V2, and, in primates, MT (Kaas and Huerta, 1988).

Intrinsic connections from the superficial layers to the deeper layers appear to provide a rapid route for orienting movements of the head and eyes, including express saccades, which are eye movements with extremely short reaction times (Isa, 2002; Doubell et al., 2003). The deeper layers are involved in motor behaviors interpreted as defensive. Stimulation of the deeper layers in rodents elicits orienting, freezing, and darting, and lesions reduce these responses to visual stimuli that loom or that are on the periphery (Ellard and Goodale, 1988; Northmore et al., 1988; Sowards and Sowards, 2002; Brandão et al., 2003). Descending connections from the deeper layers of the SC project to the periaqueductal gray and cuneiform nucleus, areas that are also associated with most of these motor responses (Mitchell et al., 1988; Dean et al., 1989; Westby et al., 1990; Vianna and Brandão, 2003). The deeper layers are also involved in covert shifts of attention, in which attention is directed toward salient stimuli without making eye movements (Ignashchenkova et al., 2004). In primates, the deeper layers have connections with the dorsal pulvinar and frontal eye fields (Fries, 1984; Helminski and Segraves, 2003; Stepniewska, 2004). Stimulation of the frontal eye fields influences preparatory neuronal activity in the deeper layers before saccades occur and neuronal activity at saccade initiation (Helminski and Segraves, 2003).

The deeper layers of the SC also have connections with the substantia nigra, in the ventral midbrain. The tectonigral connection provides a short latency signal that allows mammals to interrupt ongoing activities and orient to salient but unpredicted stimuli (Comoli et al., 2003). Chemical blockade of the nigrotectal pathway in macaques results in abnormal eye movements and head turning, and expression of fearful behavior, including exaggerated startle, cowering, and attack of inanimate objects (Zarbarlian et al., 2003). In humans, functional magnetic resonance imaging (fMRI) reveals that fearful facial expressions activate the SC (Vuilleumier et al., 2003). In long-tailed macaques (*M. fascicularis*), neurons in the SC respond only when the monkeys gaze at objects that are salient to them, including snakes (Arendes, 1994).

In their review of the evolution of innate predator recognition, Sowards and Sowards (2002) specified the SC as an important structure in mammals for detecting and avoiding predators. However, Sowards and Sowards (2002) also made a distinction between the function of the SC in primates and other mammals. They proposed that, for most mammals, the

SC is active throughout life in detecting and avoiding predators. For primates, however, they proposed that, as individuals mature, the role of the SC as a visual structure for recognizing salient stimuli such as snakes is replaced by the geniculocortical visual system. Greater reliance on vision is one of the hallmarks of primates, and it has been accompanied by expansion of many areas of the brain, including the LGN (Barton, 2000, 2004). However, while it is likely that the mammalian fear module has been modified in primates to accommodate greater visual input, the evidence outlined above suggests that the primate SC is still very much involved in detecting danger throughout life.

The LP-pulvinar complex

The pulvinar, located in the thalamus, has been described as small or even unidentifiable in rodents and other small mammals but obvious in primates, especially in anthropoids (Walker, 1938; Jones, 1985; Chalupa, 1991; Stepniewska, 2004). The LP-pulvinar complex in non-primates is probably similar to the inferior pulvinar in primates (Preuss, *in press*). One of its main functions is to facilitate selective visual processing or attention by shifting attention to relevant stimuli and filtering out distracting or irrelevant visual information (Ungerleider and Christensen, 1979; LaBerge and Buchsbaum, 1990; Chalupa, 1991; Robinson and Petersen, 1992; Robinson, 1993; Morris et al., 1997; Grieve et al., 2000; Bender and Youakim, 2001). In anthropoids, it also appears to modulate or enhance neuronal activity in V2 (Levitt et al., 1995; Soares et al., 2001a). In humans, damage to the pulvinar results in slower processing of and reactions to visually detected threats (Ward et al., 2005).

The LP/inferior pulvinar receives connections from the retina, the LC, and the superficial layers of the SC (Stepniewska, 2004). Among primates, the inferior pulvinar and ventral parts of the traditional lateral pulvinar appear to be conservative, though there are hints that taxonomic differences may exist (Stepniewska and Kaas, 1997; Gray et al., 1999; Soares et al., 2001b). The primate inferior/ventral lateral pulvinar sends projections to many cortical areas, including V1 and, as will be discussed below, those parts of V2 that are associated with increased cytochrome oxidase metabolic activity in anthropoids (Ogren and Hendrickson, 1977; Wong-Riley, 1977; Curcio and Harting, 1978; Livingstone and Hubel, 1982; Wong-Riley and Carroll, 1984; Levitt et al., 1995; Adams et al., 2000; Sincich and Horton, 2002; Stepniewska, 2004).

The inferior/ventral lateral pulvinar also sends projections to the STS (Stepniewska, 2004). The STS does not appear to exist in non-primate mammals. Among primates, it is enlarged in catarrhines and possibly platyrrhines (Preuss, *in press*). Cells in the STS are responsive to eyes, faces, the direction of gaze in others, moving limbs, and other complex visual stimuli (Földiák et al., 2004; Preuss, *in press*).

Most of the expansion of the pulvinar in primates, particularly in anthropoids, has been in the dorsal pulvinar (the traditional medial pulvinar and dorsal part of the lateral pulvinar).

It may also be unique to primates (Preuss, *in press*). The dorsal pulvinar is involved in many of the same functions as the SC, including eye movements and orienting to salient stimuli. It is also involved in gaze direction and selective spatial attention (Robinson and Petersen, 1992; Preuss, *in press*). The dorsal pulvinar receives connections from the deeper layers of the SC (Stepniewska, 2004) and sends projections to the lateral nucleus of the amygdala (Aggleton and Saunders, 2000). It does not have connections to V1, but it does have connections with more cortical areas than the visual pulvinar, including V2, V4, IT, posterior cingulate cortex, PPC, and DLPFC (Trojanowski and Jacobson, 1974; Glendenning et al., 1975; Baleyrier and Mauguier, 1985, 1987; Selemon and Goldman-Rakic, 1988; Garey et al., 1991; Robinson and Petersen, 1992; Gutierrez et al., 2000; Stepniewska, 2004). The PPC and DLPFC are smaller or absent in non-primate mammals, larger in anthropoid primates than in prosimians, and larger in catarrhine primates than in platyrrhine primates (Elston, 2003; Fang et al., 2005; Stepniewska et al., 2005; Preuss, *in press*).

Some caveats

The main point of the preceding section was to provide enough information to show that there are indeed structures in the brain that are well suited to assist mammals in detecting and avoiding predators, that some of those structures are modified or enlarged in primates, and that some of those same structures are connected to parts of the neocortex that are also modified, enlarged, or even novel in primates. I have focused on some of the major parts of the fear module, but it is important to keep in mind that these structures are not the only ones that influence behavioral responses to predators. Other areas include the hypothalamus, cingulate cortex, intralaminar thalamic nuclei, and the parabigeminal nucleus, all of which have connections to one or more basic structures of the fear module. Indeed, nearly all of the basic structures of the fear module have connections with many areas of the brain that likely help to coordinate appropriate behaviors when animals perceive predators and other dangerous stimuli; I have only briefly mentioned some of these connections. Some areas, e.g., V2, MT, and the frontal eye fields, may be involved in detecting predators; other areas, e.g., V1, V4, the prefrontal cortex, and anterior cingulate cortex, may be involved in perceiving the predator and processing the information after the predator has been detected (see Shulman et al., 2001). Some areas, particularly the PPC and STS, are involved in spatial perception, spatial attention, and spatial memory. In primates, spatial abilities such as these must be useful for negotiating travel in the complicated three-dimensional environments of tropical forests and perhaps for finding food. They have not been thought of in the context of predator detection and avoidance yet, although one can envision how they could also be useful for this purpose. The involvement of the PPC in dangerous situations is supported by evidence that stimulation of subregions of the PPC in galagos (*Galago*) and macaques evokes eye, ear, and arm movements interpreted as defensive behaviors (Cooke and Graziano, 2003; Stepniewska et al., 2005).

Mammals can probably activate the fear module through multiple modalities. In the next section, I concentrate on vision because its modification is what distinguishes primates from other mammals. In particular, I review the visual systems of mammals, emphasizing where primates differ, and I identify some of the ways in which primates have incorporated their greater reliance on vision into the structures of the fear module.

Visual systems in mammals (including primates) and the role of the W/K pathway in detecting salient stimuli pre-consciously

The visual systems of mammals include two systems that originate from the retina. One progresses via the thalamic LGN. In non-primate mammals, projections from the LGN go to V1 but also bypass V1 to go directly to extrastriate areas (Henry and Vidyasagar, 1991). In primates, projections from the LGN go mainly to V1, through V2, and beyond to associational areas of the neocortex (hereafter called the LGN visual system). The greater importance of V1 to primates is revealed by lesions to that area. Non-primates with V1 lesions still apparently have visual capability, whereas prosimians appear to have attenuated visual capability, and anthropoids, severely reduced visual capability (Henry and Vidyasagar, 1991; Bullier et al., 1994).

The other mammalian visual system has two branches, one progressing via the SC in the midbrain to the LGN and the other progressing via the pulvinar (both branches hereafter called the SC-pulvinar visual system). Both branches connect to V1 and V2, but they also connect directly to other areas of the neocortex (Jones, 1985; Kaas and Huerta, 1988; Henry and Vidyasagar, 1991; Garey et al., 1991; Rhoades et al., 1991).

Although it is often stated that the SC-pulvinar visual system has become nearly residual in primates as a result of the great expansion of the LGN visual system (e.g., Henry and Vidyasagar, 1991), both visual systems are actually larger in primates than in other mammals relative to body size (Chalupa, 1991; Garey et al., 1991; Robinson and Petersen, 1992; Barton, 2000). Considering the functions of the neurons in these systems, it is likely that expansion of both visual systems occurred in primates as a result of selective pressures operating to 1) increase central vision; 2) improve discrimination of fine detail, contrast, color, and form; 3) recognize objects; and 4) attend more quickly to salient stimuli within the environment (Streng, 1978; Kaas and Huerta, 1988; Mollon, 1989; Previc, 1990; Robinson and Petersen, 1992; Barton, 1998).

Primates and other mammals have visual pathways that are labeled from the types of cells present in the retina. The magnocellular (M) pathway in primates (and its counterpart in non-primates, the Y pathway) appears to be conservative (Allman and McGuinness, 1988). Cells in the Y/M pathway are responsive to contrast and movement (Kaas and Huerta, 1988). In primates, the M pathway is a major part of the dorsal

visual processing stream, which includes visual areas V1 and V2, as well as MT (DeYoe and Van Essen, 1988). The dorsal stream appears to be specialized for visual control of reaching or grasping in near, or peripersonal, space, e.g., monitoring of hand movements during feeding or locomotion (Previc, 1990; Goodale and Milner, 1992; Ganel and Goodale, 2003; Goodale and Westwood, 2004), the latter presumably being an important ability for arboreal animals for whom a misstep or misgrab could mean a fatal fall to the forest floor. The dorsal stream has been described as providing “vision for action” (Goodale and Milner, 1992; Goodale and Westwood, 2004).

Expansion within the primate visual systems largely comes from the other two visual pathways, the parvocellular (P) pathway (somewhat similar to the X pathway in non-primates) and the koniocellular (K) pathway (known as the W pathway in non-primates). Central vision and visual discrimination are largely contained within the P pathway (Kaas and Huerta, 1988). The P pathway is a major part of the ventral visual processing stream, which includes visual areas V1, V2, and V4, as well as IT (Maunsell, 1987; Maunsell and Newsome, 1987; DeYoe and Van Essen, 1988). Early in the P pathway (LGN, V1, and V2), cells are particularly responsive to color; later in the P pathway (V4 and IT), cells are responsive to complex forms and object recognition (Hubel and Livingstone, 1987; Kaas and Huerta, 1988; Tanaka et al., 1991; Kobatake and Tanaka, 1994). The ventral stream incorporates the foveal visual field representation in V1 and appears to be specialized for scanning, scrutinizing, and recognizing objects (Previc, 1990; Rosenbluth and Allman, 2002). The ventral stream has been described as providing “vision for perception” (Goodale and Milner, 1992; Goodale and Westwood, 2004).

Less studied than the P and M pathways is the W/K pathway. In non-primates, the W pathway mainly goes from the retina to the SC, with a more minor projection to the LGN (Henry and Vidyasagar, 1991). Until recently, the impression was that the K pathway is almost nonexistent in primates (Henry and Vidyasagar, 1991; Hendry and Reid, 2000), but this was partly a result of greater research focus on the P and M pathways (Casagrande, 1994; Kaplan, 2004). Recent research reveals that the K pathway is not only present in primates, but it is also highly complex. The K pathway goes from the retina to layers in the LGN variously referred to as interlaminar cells or intercalated, K, or S layers (Hendry and Reid, 2000). From the LGN, some K neurons project directly to MT (Sincich et al., 2004). The K pathway also projects to the SC, and it is the only visual pathway known to connect the SC with the LGN (Casagrande, 1994; Preuss, in press). Finally, the vast majority of retinal ganglion cells that project to the inferior pulvinar are K cells (Cowey et al., 1994; Stepniewska, 2004). Thus, in both primates and non-primates, the W/K pathway is distinguished by being more involved than the other pathways in the SC-pulvinar visual system, and hence, more involved in structures of the fear module.

The K cells are also heterogeneous in their response properties. These include very rapid responsiveness and visual processing of motion, probably via direct projections from the LGN to MT (thus overlapping somewhat with the “vision

for action” functions of the M pathway) and responsiveness to luminance, hues of blue, and even auditory stimuli (Irvin et al., 1986; Casagrande, 1994; Morand et al., 2000; Rodman et al., 2001; Casagrande and Royal, 2003; Sincich et al., 2004). The K pathway is also suggested to contribute to aspects of spatial resolution and object recognition (Casagrande, 1994; Casagrande and Xu, 2004) (thus overlapping somewhat with the “vision for perception” functions of the P pathway). Finally, through its connections with the SC, the K pathway is thought to be involved with attention and arousal, as well as eye movements (Allman and McGuinness, 1988; Mollon, 1989; Lachica and Casagrande, 1992; Casagrande, 1994, 1999; Martin et al., 1997; Reid et al., 1997; Hendry and Reid, 2000; Shostak et al., 2002; Casagrande and Xu, 2004; Chatterjee and Callaway, 2003). Lesions to the SC result in severe deficits of response to visual stimuli such as targets embedded in distractors and brief flashes of light in the peripheral visual field (Bender and Butter, 1987), where K cells are more common (Curcio et al., 1991). Disruption of the P pathway also results in severe deficits but not necessarily total blindness, as revealed by studies of blindsight.

In humans, damage to V1, to which both P and M (as well as K) cells project from the LGN, results in a loss of conscious visual awareness, or blindsight. Individuals with blindsight often are still able to locate visual targets despite having no awareness of having seen the targets (Weiskrantz et al., 1974, 1995; Barbur et al., 1980, 1999; Blythe et al., 1987; Stoerig et al., 1997; for a similar phenomenon in macaques, see Cowey and Stoerig, 1997). Macaques with V1 lesions can also still move their heads away from stimuli that suddenly expand or loom at them (King and Cowey, 1992). Importantly, V1 lesions cause degeneration of most P but no K ganglion cells in the retina (Stoerig and Cowey, 1993; Cowey et al., 1994), either because retinal K cells also project to the SC and the pulvinar, which both project directly to extrastriate cortex, or because LGN K cells also send projections directly to extrastriate cortex such as MT (Yukie and Iwai, 1981; Bullier and Kennedy, 1983; Cowey and Stoerig, 1989; Stoerig and Cowey, 1993; Bullier et al., 1994; Rodman et al., 2001; Sincich et al., 2004). In either case, the K pathway appears to be a likely candidate for involvement in blindsight (see also Vakalopoulos, 2005).

When humans with snake phobia are shown pictures of snakes and neutral objects using backward masking (a technique that mimics blindsight by presenting the image of the stimulus so briefly that it cannot be perceived consciously), they develop physiological indicators of anxiety only to the snakes (Öhman and Soares, 1993, 1994). It may also be significant that when snake-phobic people are shown images of snakes, relative regional cerebral blood flow increases in V2 but not V1, the area that is inactivated by blindsight (Wik et al., 1993; Fredrikson et al., 1995). These findings suggest that V1 may be necessary for the *awareness* of snakes but not for the *detection* of snakes.

Öhman et al. (2001) suggested that our brains are wired for fast, pre-attentional visual detection of salient stimuli such as snakes. Indeed, humans (even those without snake phobia) are

able to detect pictures of snakes embedded in neutral backgrounds faster than objects that do not evoke fear (Öhman et al., 2001). Consistent with their argument is the fact that the SC, LC, pulvinar, and amygdala—main structures of the fear module—are all involved in the ability to detect fear-related stimuli pre-attentively (Morris et al., 1999; Dolan and Vuilleumier, 2003; Liddell et al., 2005), emphasizing the importance of the SC-pulvinar visual system in pre-attentive visual processing (Liddell et al., 2005). Whereas the P-dominated ventral stream is specialized for “vision for perception” (Goodale and Milner, 1992; Goodale and Westwood, 2004), the W/K pathway may be involved in a more diffuse stream of “vision for detection” just before perception occurs.

The K visual pathway appears to be an important contributor to the fear module because it provides the major retinal input to the SC and is the only visual pathway known to connect the SC with the LGN. Investigation into Parkinson’s disease (PD) also implicates the K pathway as an important visual connection to the fear module. Although PD is perhaps more commonly associated with motor deficits in movement, balance, and fine motor control, vision is also affected in ways that suggest K-pathway involvement. For example, retinal cells of PD sufferers often respond more slowly than those of non-sufferers to blue stimuli (Haug et al., 1995; Sartucci et al., 2003). (Recall that sensitivity to blue is associated with the K pathway.) The loss of sensitivity to blue has been linked to a loss of dopamine in the amacrine cells of the retina (Sartucci et al., 2003). Retinal S cones, which are responsible for the blue wavelength (Dacey and Lee, 1994), are more common in the peripheral retina compared to the fovea, from which they are nearly absent (Curcio et al., 1991; Calkins, 2001). Sufferers of PD have slower reaction times in the presence of distracting stimuli in their peripheral visual fields (McDowell and Harris, 1997).

The K pathway may provide a link between vision and the motor deficits of PD. In addition to the aforementioned deficits in reaching and grasping, another motor deficit of PD is freezing, in which the sufferer is unable to initiate movement. It often occurs at a doorway or another confined space and when there are distractors or obstacles in the path (McDowell and Harris, 1997; Nieuwboer et al., 2001). McDowell and Harris (1997) suggested that freezing could be caused by disinhibition of SC responses to distractors, particularly in peripheral vision, by the damaged substantia nigra (McDowell and Harris, 1997). Recall that freezing is also a natural response of mammals to stimuli that appear suddenly on the periphery, and that the substantia nigra normally inhibits freezing and other fearful behavior in mammals via its connections with the SC. The motor deficits have been associated with a loss of cells producing dopamine in the substantia nigra (Feldman et al., 1997). Intriguingly, there is even greater cell loss in the LC (Zarow et al., 2003), another structure of the fear module that is involved in motor responses to fearful stimuli.

Reminiscent of findings from lesion studies of the SC (Bender and Butter, 1987), sufferers of PD perform poorly compared to non-sufferers in tests designed to measure pre-attentive pop-out, the ability to detect stimuli visually that

are immediately salient despite being embedded in distractors. (Pre-attentive vision is stimulus-driven, automatic processing, as opposed to attentive vision, which is affected equally by the stimuli and voluntary processing.) Non-afflicted people quickly detect lines of different orientations against a background of vertical lines, and quickly detect the letter L among + signs. Those with PD, however, detect lines oriented only at much greater angles from the vertical lines and require more time to detect the letter L (Lieb et al., 1999). Lines of different orientations are examples of classic experimental stimuli used to investigate cell response properties of neurons in mammalian visual systems.

Cell response properties of mammalian visual systems mirror snake features

Recognition that snakes were the first predators of crown-group placental mammals puts classical cell response properties of mammalian visual neurons into evolutionary perspective. For example, since the SC, LGN, and visual areas V1 and V2 appear to exist in all placental mammals (Rosa and Krubitzer, 1999), cells in those areas might be expected to respond to highly periodic patterns, which are common in snakes but are otherwise infrequent in nature (Coss, 2003). Such pattern recognition appears to be innate in California ground squirrels (*Spermophilus beecheyi*) and wood rats (*Neotoma albigula*) because they react fearfully to snakes on the first day that they can see (Coss, 1991, 2003).

Many areas of the mammalian brain have been modified and expanded in primates, and many areas of the brain in primates have no counterpart in other mammals, including some visual areas (Preuss, in press). The fact that naïve macaques begin to react fearfully to snakes only after observing the fearful responses of conspecifics to snakes indicates that there is a certain amount of learning and neocortical involvement in primates' behavioral reactions to snakes (Cook and Mineka, 1989). Expansion of the K and P pathways in primates predicts that primates may also more reliably detect snakes pre-attentively and recognize them more quickly than other mammals.

What is the evidence that mammalian neurons selectively respond to visual characteristics of snakes as opposed to other stimuli? In the LGN and V1, cells respond to local features that help identify snakes, e.g., simple cues such as oriented lines, edges, and contours (Marrocco, 1972; Norton and Casagrande, 1982; Peterhans, 1997; Roe and Ts'o, 1997; Kaas, 2004). This evidence is not sufficient, however, since most of nature is made up of lines, edges, and contours. Cells in the pulvinar and V2, on the other hand, are capable of higher-order integration of spatial and form visual cues (Benevento and Port, 1995) that reflect more global features (Peterhans, 1997; Roe and Ts'o, 1997; Kaas, 2004), particularly of snakes. Thus, pulvinar cells of cats have been found to respond to moving diamond-shaped patterns (Casanova et al., 2001), which are strikingly reminiscent of scale patterns of snakes. In V2 of macaques, in addition to responding to short lines and corners, contours, occlusion, and movement of elongated objects (Peterhans, 1997), cells respond

selectively to small spots of color within larger receptive fields (spot cells) (Roe and Ts'o, 1997) and to synchronized movement of contrast borders and rows of spots against a background (coherent motion cells) (Peterhans and von der Heydt, 1993; Peterhans, 1997). The latter response has been described by humans as an oscillating rodlike object (Peterhans, 1997), a description one might use for a moving snake. Spot cells and coherent motion cells do not exist in V1 (Peterhans, 1997; Roe and Ts'o, 1997). Neurons in V2 are also more binocularly responsive than V1 neurons in macaques, allowing greater figure-ground separation (Peterhans and von der Heydt, 1993), an ability that would be helpful for detecting snakes lying close to the ground.

Indeed, the visual stimuli used in classic experiments on response properties of neurons, e.g., oriented lines, edges, contours, spots, coherent motion of multiple spots, and illusory contours, are also common features of snakes in natural environments. Such features include scale edges and angles, differences between spots of color or contrast, small spots of color against larger backgrounds of skin, the elongate shape of snakes, their movements, and their frequent occlusion by grass and other vegetation.

Primates have more cortical areas devoted to vision than other mammals, and some of these areas also appear to be responsive to attributes of snakes. For instance, cells in V4 and IT respond to patterns that resemble segments of geometric patterns on snakeskins [compare the snakeskin in Coss (2003: 109) with the checkerboard pattern shown in Figure 1 of Kastner et al. (2000)]. In V4, neuronal activity increases more for checkerboard patterns than uniform textures shown in the peripheral visual field (Kastner et al., 2000), where, recall, K cells are more abundant (Curcio et al., 1991). In IT, a diamond shape evokes a greater neuronal response than a circle, a triangle, or random dots (Okusa et al., 2000). Cells in IT also respond to backwardly masked patterns composed of simple oriented segments (Kovács et al., 1995a) and to shapes that are partially obscured (Kovács et al., 1995b).

Such higher visual areas may thus be well designed for snake detection, though not, of course, to the exclusion of other objects. Obviously, other natural stimuli have at least some of these attributes. Taken together, however, many of the response properties of cells with higher-order integration of spatial and form visual cues appear to describe the coherence of visual attributes of snakes as well or better than other stimuli that might be important to mammals, including insects, fruits, and faces, i.e., other proposed selective pressures for visual specialization in primates. Integration of evolutionary theory with new techniques to search for the full range of stimuli to which cells in sensory systems respond (e.g., Brothers et al., 1990; Földiák et al., 2004) promises to expand our understanding of the selective pressures that have acted on mammals in the past.

To summarize and reinforce the relevance of this section to the previous section on the neural structures of the fear module, substantial neuroscientific research provides evidence that in mammals, the amygdala, LC, SC, pulvinar, and the W/K visual pathway, particularly via its connection to the SC and

pulvinar, are involved in a danger detection system called the fear module that acts pre-consciously before action and perception occur. Snakes were the first predators of crown-group placental mammals, and neurons in the visual systems of mammals appear to respond preferentially to cues that are characteristic of snakes. Parts of the fear module have expanded in primates, and in anthropoid primates, the fear module has dense connections with cortical areas that have also expanded. Primates have also expanded their visual systems beyond those of other mammals to include large areas of the neocortex, and cells in those areas also respond preferentially to the highly periodic patterns that are characteristic of snakes but are otherwise infrequent in nature. The connections of the fear module to the neocortex may allow more flexibility in responding to dangerous situations that require the animal's immediate attention.

Viewed in this light, it should not be surprising that glucose metabolism, a sign of brain activity, increases in the DLPFC when rhesus macaques are exposed to snakes but not when they are exposed to neutral objects, and that glucose metabolism does not increase in the DLPFC when macaques with amygdaloid lesions are exposed to snakes (Roberts et al., 2002).

Obviously, this is not to say that the fear module and associated areas were not also useful for other purposes or were not modified for other purposes over time. For instance, although it is possible that the fear module and associated cortical areas enabled primates to use the gaze of conspecifics initially to locate snakes, it might have been a relatively small next step for them to use the gaze of others to advantage in social situations (e.g., Emery, 2000). The PPC provides a concrete example of a brain structure initially used for one function and subsequently also used for others. In non-human primates, the PPC is activated during reaching and grasping with the forelimbs, but in humans it is also activated when people name objects, especially tools that they use with their hands (Chao and Martin, 2000).

Venomous snakes and the anthropoid adaptive shift

As many tropical field workers can attest, snakes are often difficult to see, even with our convergent orbits and high visual acuity. Viperids in particular are highly cryptic, often obscured by vegetation, and, as sit-and-wait predators, do not readily flee upon the approach of humans. All of these conditions work against our ability to detect them, and yet not many tropical field workers have been bitten by venomous snakes. In my own experience, several times in the course of fieldwork, I froze just a step away from a puff adder (*Bitis arietans*) or a cobra (*Naja nigricollis*). This may be due less to blind luck than to 60 million years of directional selection operating on the K pathway for pre-attentive detection and the P pathway for perception and identification.

Any increase in the degree of orbital convergence would improve stereopsis in the lower visual field and would enable primates to detect and therefore avoid snakes more reliably. Even among primates, however, differences in visual

specialization and brain size exist. Expansion of the fear module and associated cortical areas, along with greater visual specialization, occurred with the anthropoids (Chalupa, 1991; Barton and Aggleton, 2000; Barton et al., 2003; Stepniewska, 2004; Preuss, in press), which had originated by the late Paleocene (Ross, 2000; Beard, 2002; Dagosto, 2002; Eizirik et al., 2004; Ross and Kay, 2004). If constricting snakes were a selective force in the evolution of the mammalian brain and in the initial evolution of orbital convergence, visual specialization, and brain expansion in early primates, then is it also possible that they were important for the more extreme expression of these traits in anthropoids? Perhaps the best answer is that, while it is possible, it is not likely. Given the energetic cost of developing a larger brain (Armstrong, 1983; Martin, 1996; Aiello et al., 2001), there would have been diminishing returns of continued expansion of the brain with the same predator. At some point, only an evolutionary innovation that would make the predator more deadly would have favored further visual specialization and brain expansion in the predator-prey evolutionary arms race. I suggest that this occurred with the arrival of highly venomous snakes. Viperids appear to have evolved in Asia or Africa around the time that bats, rodents, primates, and other small animals appeared on those same landmasses (Greene, 1983; Cadle, 1988; Feduccia, 1995; Douady et al., 2002; Huchon et al., 2002; Gebo, 2004).

In the next section, I review evidence for the hypothesis that venomous snakes were such an important selective pressure favoring greater visual specialization in primates that they were ultimately responsible for the emergence of anthropoids. Many of the more obvious differences between anthropoids and prosimians, e.g., in orbital convergence and visual acuity, have been well summarized by Ross (2000). Differences between catarrhines and platyrrhines are less obvious but do exist, particularly in the brain's soft tissue. Here I will concentrate on some of these lesser known neuroscientific differences. I will show in the next section that these differences are correlated with different evolutionary histories with venomous snakes. Whereas catarrhines have always co-existed with venomous snakes and were the only primates that clearly radiated under the constraints imposed on them by the presence of venomous snakes, platyrrhines may have begun their radiation well before venomous snakes arrived in South America. As a result, they may have been free, at least initially, of the selective pressure imposed upon their Old World ancestors by venomous snakes. Relaxed selection could account, at least in part, for the variability seen in platyrrhine visual systems, which until now has escaped explanation. Differential evolutionary exposure of primates to venomous snakes by major geographic area has not been recognized previously.

Differences in the visual systems of primates

Primates differ in the complexity of the LGN. Although all primates have two distinct M layers in the LGN (Kaas and Huerta, 1988), they vary in the number or complexity of P layers in the LGN, with differences being most pronounced at higher taxonomic levels, i.e., prosimians vs. anthropoids

and platyrrhines vs. catarrhines (Kaas and Huerta, 1988). Thus, prosimians have fewer P layers, and the P layers are not interdigitated with each other (Kaas and Huerta, 1988). Poorer central vision and visual discriminative ability of prosimians are also indicated by the absence of a retinal fovea or the presence of a poorly developed fovea, except in tarsiers (*Tarsius*), which have a fovea (Rohen and Castenholz, 1967; Stone and Johnston, 1981; Kirk and Kay, 2004). Among anthropoids, P layers are weakly interdigitated with each other in platyrrhines but are more extensively interdigitated in catarrhines, with some notable exceptions, e.g., gibbons (*Hyllobates*), for which curiously there is no interdigitation (Tigges and Tigges, 1987; Kaas and Huerta, 1988). As mentioned in the introduction, the number of cells in the P layers is correlated with the degree of orbital convergence and other aspects of the visual system and brain in primates (Barton, 2004).

Among mammals, only primates have been found with cytochrome oxidase-staining stripes in V2 (DeYoe and Van Essen, 1985; Krubitzer and Kaas, 1990; Fig. 2). Conveniently, staining for cytochrome oxidase (CO) reveals relative metabolic activity of cells in the brain (Wong-Riley and Carroll, 1984; Wong-Riley, 1994). Cytochrome oxidase staining identifies neurons that are chronically active and that generate metabolic energy via sustained glutamatergic excitatory synaptic activity (Nie and Wong-Riley, 1995, 1996). Thus, darker staining indicates greater metabolic activity (Horton, 1984; Allman and Zucker, 1990). Primates appear to differ in the extent, clarity, or uniformity of CO-staining in V2 stripes, which suggests the possibility of taxonomic differences in energy metabolism in at least that part of the brain. Stripes are, at best, only weakly CO-reactive in nocturnal prosimians (no diurnal prosimians have been examined yet) (Condo and Casagrande, 1990; Krubitzer and Kaas, 1990; Preuss et al., 1993; Collins et al., 2001). Cytochrome oxidase stripes are more obvious in anthropoids, even the often nocturnal owl monkey (*Aotus*) (Krubitzer and Kaas, 1990; Fernandez-Duque, 2003), indicating the great importance of phylogeny in maintaining the high metabolic activity of the stripes. The pulvinar provides the

major thalamic input into darkly staining CO stripes that are diagnostic of V2 (at least in anthropoids) (Livingstone and Hubel, 1982; Levitt et al., 1995; Fig. 2). Perhaps related to this is an apparent difference in the pulvinar connections to V2. In galagos, it is the dorsal pulvinar that projects to V2, whereas in anthropoids, it is the inferior pulvinar (Glendenning et al., 1975; Stepniewska, 2004).

Considering only anthropoids, platyrrhines apparently have greater individual and interspecific variation in their visual systems than catarrhines. For example, platyrrhines are noted more often as being variable in patterns of CO staining in V2. Cytochrome oxidase-staining stripes are often separated by pale non-CO-staining interstripes (Livingstone and Hubel, 1984). Marmoset (*Callithrix*) CO stripes are apparently similar in width, whereas squirrel monkey (*Saimiri*) and owl monkey CO stripes form thick and thin stripes (Livingstone and Hubel, 1982; Tootell et al., 1983; Wong-Riley and Carroll, 1984; Krubitzer and Kaas, 1990; Fig. 2). Marmosets also show less contrast between CO and non-CO stripes than squirrel monkeys and owl monkeys (Kaas and Huerta, 1988; Krubitzer and Kaas, 1990). In both macaques and humans, by contrast, what are conventionally called thin CO stripes based on their function cannot be reliably distinguished from thick CO stripes by width alone, and the two stripes often blend together without an intervening pale stripe (Hubel and Livingstone, 1987; Ts'o and Gilbert, 1988; Wong-Riley et al., 1993; Roe and Ts'o, 1995; Ts'o et al., 2001; Roe, 2004). Projections from thin stripes go to MT in squirrel monkeys and owl monkeys but to V4 in capuchins (*Cebus*) (Krubitzer and Kaas, 1990; Nascimento-Silva et al., 2003). Since V2 is more binocularly sensitive than V1 (Peterhans, 1997; Roe and Ts'o, 1997), such variation may mean that there are subtle species differences in close-range stereopsis.

Similarly, differences between catarrhines and platyrrhines exist in V1. In catarrhines, including humans and the squirrel-monkey-sized talapoin (*Miopithecus*), and in some platyrrhines (i.e., spider monkeys and capuchins), ocular dominance columns are readily apparent with CO staining in V1 after monocular inactivation or enucleation. Until recently, however, ocular dominance columns were questionable in other platyrrhines, i.e., squirrel monkeys (Hess and Edwards, 1987; Florence and Kaas, 1992; Horton and Hocking, 1996). There is also unexplained variation in clarity of ocular dominance columns among individual squirrel monkeys (Horton and Hocking, 1996; J. Horton, pers. comm.).

All primates examined thus far have CO blobs in V1 (Fig. 2), even nocturnal prosimians (Livingstone and Hubel, 1982; Condo and Casagrande, 1990; Krubitzer and Kaas, 1990; Lachica et al., 1993; Preuss et al., 1993; Horton and Hocking, 1996; Preuss and Kaas, 1996; Preuss, in press). Indeed, blobs are not confined to primates; they have also been found in other mammals with frontally directed eyes, e.g., ferrets (*Mustela putorius*) and domestic cats (Creshe et al., 1992; Murphy et al., 1995; Horton and Hocking, 1996). Blobs in V1 receive input from LGN P and M layers only indirectly. Direct input to V1 blobs comes only from LGN K layers (Livingstone and Hubel, 1982; Hendry and

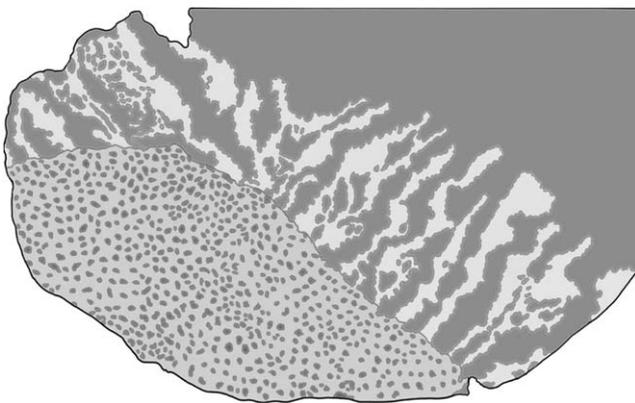


Fig. 2. Cytochrome oxidase blobs in visual area V1 and stripes in visual area V2. Blobs are universal in primates, but stripes vary, being more obvious in anthropoids than in prosimians and more variable in contrast or width among platyrrhines than among catarrhines. Redrawn from Horton (1984).

Yoshioka, 1994). Cells in CO blobs of diurnal primates are most responsive to color, a known P attribute (Livingstone and Hubel, 1982), but Allman and Zucker (1990) pointed out that they must also serve another purpose because nocturnal primates do not have color vision. Despite the ubiquity of V1 blobs in primates, platyrrhines still show some variability. Capuchins are similar to Old World anthropoids in having blobs that lie in register with ocular dominance columns; squirrel monkeys have blobs that do not (Horton and Hedley-Whyte, 1984; Hess and Edwards, 1987; Florence and Kaas, 1992; Horton and Hocking, 1996).

Platyrrhines also exhibit greater variation in lamination patterns of the LGN and in color vision (Clark, 1941; Jacobs et al., 1996; Jacobs and Deegan, 1999, 2001; Hendry and Reid, 2000). The greater variability of platyrrhine visual systems relative to catarrhines has eluded explanation. Given the absence of any other hypothesis to account for this difference, I note that the variability in platyrrhine visual systems is consistent with the overall theme of the hypothesis proposed here. In other words, I suggest that visual-system variability in platyrrhines is at least partly a consequence of their interrupted evolutionary co-existence with venomous snakes and the possible radiation of modern platyrrhine genera in the absence of venomous snakes.

The P pathway and the role of frugivory in anthropoid brain expansion

Frugivorous primates have more expansive P pathways and larger brains than folivores within higher taxa (e.g., within platyrrhines, *Ateles* vs. *Alouatta*, and within hominoids, *Pan* vs. *Gorilla*; Barton, 1998, 1999, 2000). Thus, it has been hypothesized that frugivory favored larger brains to remember the location of fruits, the distribution of which is spatially and temporally more variable than leaves (Clutton-Brock and Harvey, 1980; Milton, 1988). Alternatively, since the P pathway is strongly associated with color vision, frugivory has been hypothesized to have favored visual specialization via trichromatic color vision, which enables primates to detect red and orange fruits against a background of green foliage or to detect fruit quality and ripeness more easily (Polyak, 1957; Mollon, 1989; Barton, 1998, 1999; Sumner and Mollon, 2000; Regan et al., 2001; Smith et al., 2003).

Each LGN P layer is separated by a K layer (in addition to K layers between the M layers (Hendry and Reid, 2000). As described in the previous section, the P pathway is most highly developed in catarrhines, as indicated by their highly interdigitated LGN P layers. Platyrrhines, in contrast, are more variable in the degree of interdigitation of P layers. In addition, catarrhines are all invariably trichromatic, whereas in platyrrhines (except howler monkeys), all males and some females are dichromatic (De Valois and Jacobs, 1968; Jacobs, 1995). Since primates vary in the number of P layers, and since K layers separate P layers, primates also vary in the number of layers devoted to the K pathway in direct relation to the number of P layers present. In addition, K cells are found

interspersed within the P and M layers (Hendry and Yoshioka, 1994; Hendry and Reid, 2000). It is possible, therefore, that the P and K layers expanded together and that selection on the K pathway also indirectly, and ultimately, favored expansion of the P pathway.

The mechanism underlying the co-evolution of the K and P pathways is proposed by the following: The hypothesis that constricting snakes favored larger brain size via greater visual specialization in primates identifies a diet of ripe fruit or nectar as a requirement for, and as a cause of, visual specialization and brain enlargement, but not as the ultimate cause. Recall that high CO activity reflects high levels of neuronal metabolic activity and that brains are highly metabolically active tissues. Heightened CO activity is, however, potentially costly in that it can lead to excitotoxicity and neuronal death (Lucas and Newhouse, 1957; Olney, 1969, 1990; Choi, 1988; Meldrum and Garthwaite, 1990) without protection against overexposure to glutamate, the main excitatory neurotransmitter in the central nervous system (Orrego and Villanueva, 1993). Glutamate is an amino-acid derivative of glucose (Feldman et al., 1997: 392), and it has widespread effects on the brain. Of particular relevance here is its ability to enhance fear-related learning in the amygdala (Walker and Davis, 2002) and to enhance learning in color discrimination tasks (Popke et al., 2001).

Overexposure to glutamate can be minimized by eating glucose, a sugar found in flowers and ripe fruit (Henneberry, 1989; Romano et al., 1993; Guyot et al., 2000). If frugivores indeed have larger brains and higher basal metabolic rates than folivores or insectivores of the same body size (Clutton-Brock and Harvey, 1980; Armstrong, 1983; Barton et al., 1995; Martin, 1996), the difference could be a result of the neuroprotectant property of glucose, obtained from a diet of fruits and flowers.

Brain expansion is evident in the earliest primates (Radinsky, 1975, 1977; Jerison, 1990). As suggested above, some of the earliest primates may have had a generalized diet that included fruits, flowers, and nectar (Sussman, 1991), as well as arthropods (Cartmill, 1972, 1974). Such a diet in the ancestor of the first primates could have initiated a positive feedback system in which mothers' consumption of sugars both permitted greater CO activity in visual systems early in fetal development (because glutamate is a derivative of glucose) and was required (because glucose is a neuroprotectant).

With the appearance of venomous snakes, selection for greater orbital convergence would have continued for its advantages in increasing stereopsis in near space. The fear module, the K pathway (the predominant visual input into the fear module's pre-attentional predator detection system), and associated cortical visual areas would have also continued to expand. However, expansion of the brain would have increased the need for glucose to protect against increased CO activity and excitotoxicity. Expansion of the K pathway (and the brain) could therefore continue only if the P pathway could also expand. With its emphasis on object recognition, the P pathway would have initially helped those with a diet of fruits, flowers, and nectar to locate foods (and perceive snakes and other

salient objects near them). Later, with its emphasis on color, the P pathway would have helped such primates locate foods with the highest levels of sugars (Sumner and Mollon, 1996), thereby more effectively protecting the expanding brain against excitotoxicity.

The importance of sugar to frugivorous primates today is illustrated by the finding that wild spider monkeys (*Ateles geoffroyi*) eat fruits with higher sugar levels while avoiding fruits on the same tree with lower sugar levels (Riba-Hernandez et al., 2003). Fruits that are red or orange when ripe typically provide more sugars than other individuals of the same species that are still green and unripe (Sanchez et al., 2000; Iglesias et al., 2001). Fruit and flower consumers with good color vision could thus use color to identify fruits and flowers with high sugar levels.

In an experimental study that replicated natural conditions, trichromatic saddleback (*Saguinus fuscicollis*) and red-bellied (*S. labiatus*) tamarins learned to find ripe, red fruits faster than dichromatic tamarins, and they also found and ate more ripe fruits (Smith et al., 2003). In a field study designed to investigate a different question, naïve wild vervet monkeys (*Cercopithecus aethiops*) were provided with novel foods, i.e., raisins and carrots. They were only attracted to the raisins if a slice of carrot was placed next to the raisins. Once the carrot was used as “bait” they quickly learned to eat the high-sugar raisins, but they never ate the carrot (Isbell, unpublished data). Chinese safflower (*Carthamus tinctorius*) flowers that are dark red with streaks of yellow are most strongly neuroprotectant (Romano et al., 1993). Although the range of tested colors was unspecified, colors of safflower flowers can range from white to purple, with yellow-orange being the most common (Smith, 1996).

There are also parallels in birds, another group of animals that has excellent color vision. Among frugivorous birds, silvereyes (*Zosterops lateralis*) apparently also use color as a cue for sugar content when they choose fruits. The importance of sugar is revealed by their preference for sugar over color when sugar and color were experimentally dissociated (Giles and Lill, 1999; Stanley et al., 2002).

Of course, trichromatic color vision is only useful to diurnal mammals. With few exceptions among diurnal mammals, only primates include fruits and flowers as a major part of their diet. Tree shrews (Tupaiainae), once thought to be primates partly on the basis of characteristics of their visual systems (Clark, 1959), appear to be among the few diurnal mammals that begin to approach primates in their degree of frugivory (Emmons, 2000). Such a diet would have been most beneficial to catarrhines, the primates that were under the most unrelenting pressure to be able to detect venomous snakes ahead of any forelimb step, reach, or grasp. This could help to explain why invariable trichromacy evolved only in catarrhines.

The necessity of having glucose readily available to protect against excitotoxicity suggests that a diet of young leaves, which are not high in sugars, could not have served as a preadaptation for greater visual specialization and larger brains, though it might have served as a selection pressure favoring trichromacy in some primates (Lucas et al., 1998; Dominy

and Lucas, 2001). Howler monkeys, the only invariably trichromatic platyrrhine (Jacobs et al., 1996; Kainz et al., 1998; Regan et al., 1998), are more folivorous than frugivorous (Crockett and Eisenberg, 1987) and more folivorous than many platyrrhines without invariable trichromacy. The evolution of trichromacy in a predominantly folivorous primate is consistent with a recent argument that color vision is more important in discriminating young red leaves from mature green leaves than fruits from foliage (Dominy and Lucas, 2001). It appears, however, that trichromacy evolved in howler monkeys and catarrhines independently (Hunt et al., 1998; Kainz et al., 1998), in which case the selective pressure favoring the evolution of trichromacy may be specific to them. In addition to red, other colors, including yellow and brown, also stand out from green foliage to trichromats [see Greene (1997:39) and Sumner and Mollon (2003) for examples]. Sumner and Mollon (2000) suggested, therefore, that trichromatic color vision is valuable not just for finding red leaves or red fruits, but for distinguishing any rare and important object from green foliage. In the case of howler monkeys, one could reasonably argue that trichromacy uniquely evolved to distinguish live, healthy leaves from dead and dying leaves. The debate about the importance of particular classes of foods in color vision is far from resolved.

One thing is more obvious: trichromacy per se did not drive brain expansion. Howlers have very small brains for their body size (Harvey et al., 1987) and are among the most inactive of primates (Crockett and Eisenberg, 1987), both of which suggest a dearth of metabolic activity. Their sluggishness has, in fact, been directly attributed to their diet, which is lower in ripe fruits compared to more classically frugivorous catarrhines (Milton, 1980; Terborgh, 1983; Crockett and Eisenberg, 1987). Other small-brained primates that have (variable) trichromacy are red ruffed lemurs (*Varecia variegata rubra*) and Coquerel's sifaka (*Propithecus verreauxi coquereli*) (Tan and Li, 1999; Jacobs et al., 2002). All of these may be cases of independent evolution of trichromacy (SurrIDGE et al., 2003).

It is important to emphasize that independently evolved trichromacy in howlers and other primates does not invalidate the hypothesis presented here that snakes were the ultimate selection pressure favoring visual specialization in primates *because visual systems include a great deal more than color vision*. What is suggested is that the evolution of the catarrhine form of invariable trichromacy was fueled by the need to protect brains from increasingly greater metabolic demands resulting from selection to evolve the neural capability for detecting venomous snakes pre-attentively, and therefore, quickly and reliably. Ironically, trichromacy appears to be less effective than dichromacy in breaking camouflage (Anonymous, 1940; Morgan et al., 1992; Buchanan-Smith et al., 2005). The possibility exists that greater orbital convergence in catarrhines (Barton, 2004), with the advantage it provides in breaking camouflage and in improved stereopsis, may have evolved, in part, to diminish the drawbacks in detecting snakes that developed when trichromacy evolved.

Why visual specialization and brain expansion did not also occur in other mammals, or how anthropoids became diurnal

Any hypothesis for characteristics described as unique to primates is incomplete unless it can explain why those characteristics did not also evolve in other mammals. The absence of a similar expansion in brain size and neural areas devoted to vision in non-primate mammals that are also prey of snakes is puzzling until one recognizes that they lack the dietary pre-adaptation that made visual specialization the inevitable anti-predator solution for primates. Expansion of the visual system appears to come at a cost to olfaction (Barton et al., 1995; Gilad et al., 2004). For small early mammals that did not include large amounts of fruits or nectar in their diets, the cost was likely prohibitive because plants could not benefit from evolving strongly attractant odoriferous seeds and leaves, which are damaged by consumers. The evolutionary path toward visual specialization would have been available only to those small mammals, here called proto-primates, whose diet included nectar or fruit (though not to the exclusion of arthropods) because plants would have benefited from evolving more strongly odoriferous fruits and flowers, just as they evolved more colorful fruit, to keep attracting seed and pollen dispersers. Frugivorous and nectivorous proto-primates could therefore afford to expand their visual systems and reduce their olfactory systems, with the eventual result being today's primates.

With the appearance of venomous snakes, the early expansion of the visual system would have continued and become even more important, while olfaction would have become even less important. These changes would have been accompanied by gradual changes in circadian rhythms. Evidence that olfaction is involved in activity periods is shown by experimental removal of olfactory bulbs in rodents and mouse lemurs (*Microcebus murinus*). Olfactory bulbectomy immediately results in a change in circadian rhythm of body temperature and in increased locomotor activity during photopic conditions (periods of greater light) (Perret et al., 2003). Similarly, gradual decline in olfactory ability over evolutionary time may have resulted in greater activity under photopic conditions that would have generated a positive feedback loop between visual gain and olfactory loss leading to more photopic activity, which drove further visual gain and olfactory loss and so on. The end result would have been largely frugivorous, highly visual, olfactorily diminished, diurnal primates, i.e., anthropoids similar to those known today.

Among anthropoids, natural selection via snakes was most persistent for those that remained in the Old World. The expansion of the visual system and reduction in the olfactory system in primates appears to have culminated in catarrhines when they gained invariable trichromacy and lost a number of olfactory receptor genes that were not lost by platyrrhines (Yokoyama and Yokoyama, 1989; Gilad et al., 2004).

This scenario suggests that the ancestral condition of olfactorily guided locating, reaching for, and grasping food would have been supplanted by visually guided locating, reaching,

and grasping as olfaction became less important. Importantly, it suggests that this adaptive shift might have occurred rather late in primate evolution, perhaps only in anthropoids. Although diurnal frugivorous prosimians have smaller olfactory systems than nocturnal frugivorous prosimians, all prosimians still have well developed olfactory systems (Barton et al., 1995), and they still use olfaction (and hearing) in food acquisition (Charles-Dominique, 1977; Sussman, 1991; Crompton, 1995). To test this idea, experiments of the kind that were described above for rodents would need to be conducted on diurnal and nocturnal prosimians. Unfortunately, given the precarious conservation status of most prosimians, such studies may be difficult and even unethical.

For small mammals that are not seed or pollen dispersers, widespread alternatives to visual specialization as a means for detecting snakes have been retention of olfaction (Dell'Omo and Alleva, 1994; Randall et al., 1995) and evolved physiological resistance to snake venoms (see Daltry et al., 1996; reviewed in Pérez and Sánchez, 1999). Populations of ground squirrels living sympatrically with rattlesnakes (*Crotalus viridis*) exhibit venom resistance in proportion to rattlesnake density. Where rattlesnakes are non-existent, ground squirrels have no evolved venom resistance at all (Poran et al., 1987). Even mammals that are not recognized as having venom resistance may fare better the greater their evolutionary exposure to venomous snakes. An examination of snakebites in domestic cats and dogs in Australia revealed that cats were more than twice as likely to survive untreated snakebites as dogs, suggesting that cats have a greater tolerance than dogs for snake venoms (Mirtschin et al., 1998). Felids evolved in Eurasia by about 20 Ma (Martin, 1989) and so have co-existed with venomous snakes since their origin. Canids, on the other hand, evolved in North America in the Oligocene (Martin, 1989), whereas venomous snakes apparently arrived in North America from Asia later, in the early Miocene (Gloyd and Conant, 1990).

With its emphasis on movement detection, non-primate mammals may often require activation of their Y pathway to reliably detect snakes visually. This is descriptively suggested by the following passage in Grant (2001: 70):

The other day they [the dogs] streamed past a huge puff-adder which was lying like a log on a patch of bare ground. Its head and neck were doubled back along its body, ready to strike. Wasp, Sambu's daughter, passed within two feet of it. I called her away, but sensing from my voice that I had seen something exciting and dangerous, Wasp turned back to investigate. To my horror she passed within striking distance of the snake again without seeing it. It never moved!

Perhaps a poor ability to detect venomous snakes visually in peripersonal space explains why dogs are bitten by snakes most often on their heads (Hackett et al., 2002). California ground squirrels often miss detecting immobile rattlesnakes amid a heterogeneous landscape of small stones, short grasses, and other vegetation, but they easily detect moving snakes (Coss and Owings, 1985). Returning to primates, the

possibility of venom resistance is worth investigating in tarsiers, a nocturnal faunivore that, unusually for primates, eats venomous snakes (Niemitz, 1984).

Non-mammalian models for primate visual systems

The studies described above suggest that the combination of dietary preadaptations and selective pressures was so unique to primates that no other mammals may be appropriate as models for reconstructing primate visual evolution. Birds, on the other hand, may well be informative. First, they have an advantage over mammals in being so distantly related to primates that similarities are more likely to be analogous than homologous. Second, like many primates, many birds are diurnal and have excellent vision. Third, both birds and primates have large eyes relative to body weight (Brooke et al., 1999; Ross, 2000; Kirk and Kay, 2004). Fourth, like primates, many birds are frugivorous, nectivorous, or insectivorous. Finally, many birds are eaten by snakes, and conversely, snakes are eaten by many birds (Greene, 1997; Weatherhead and Blouin-Demers, 2004; Webb and Whiting, 2005), so there has likely been ample opportunity for snakes to have acted as selective pressures on birds. This is not to say that snakes were the driving force behind all the visual adaptations of both birds and primates; birds may have had the same dietary preadaptations and activity patterns, but they did not have the same pattern of co-existence with snakes that primates had. It is merely to point out that there may be parallels worth exploring further.

Raptors are a case in point. Although anthropoids are unique among mammals in the degree of their visual acuity, diurnal raptors surpass anthropoids (Ross, 2000; Kirk and Kay, 2004), and they have been used to support the visual predation hypothesis (Ross, 2000). Indeed, the importance to raptors (and other birds that require precision to eat, e.g., hummingbirds) of close-range stereopsis is highlighted by the existence of not one but two foveae in each eye (Walls, 1942; Güntürkün, 2000; Edelstam, 2001). Raptors have a temporal fovea for close-range binocular viewing and stereopsis and a central fovea for long-distance, lateral viewing; most other birds have only a central fovea or an area centralis (Walls, 1942; Güntürkün, 2000; Tucker, 2000). Raptors also have fairly convergent orbits (Edelstam, 2001). [Recall, however, that diurnal visual hunters should not need convergent orbits according to the nocturnal visual predation hypothesis (Cartmill, 1992).]

Cartmill (1992: 107–108) stated that “adaptive explanations must be general enough to predict similar adaptations in other cases and they must be rejected if those predictions are not borne out.” In fact, raptors are an excellent taxon for testing the hypothesis that visual specializations evolved in primates to detect snakes. Raptors are diurnal visual predators, but within the raptors, there are some that have specialized as snake predators (Brown, 1976; Ferguson-Lees and Christie, 2001). If snakes have indeed been a major force in the evolution of visual specialization in primates, then one would predict that snake-eating raptors would converge with primates

in having greater orbital convergence and larger eyes than raptors that are not snake specialists and thus do not have as persistent a need to detect snakes.

As predicted, although raptors in general have larger eyes for their body weight than other birds (Brooke et al., 1999), eagles and falcons that specialize in eating snakes have even larger eyes than other raptors (Edelstam, 2001; Ferguson-Lees and Christie, 2001). Snake specialists also often have larger heads than other raptors (Edelstam, 2001; Ferguson-Lees and Christie, 2001), presumably because larger heads can house larger eyes. Thus, African snake eagles (*Circaetus* spp.) differ from other African eagles in having large eyes and large, owl-like heads and necks (Brown, 1976; Zimmerman et al., 1999; Ferguson-Lees and Christie, 2001: 445–455), and the South American laughing falcon (*Herpetotheres cachinnans*) is described as having “obviously large eyes and head (owl-sized but not especially owl-like)” (Ferguson-Lees and Christie, 2001: 812). The larger eyes of snake eagles and laughing falcons indicate greater visual acuity, since visual acuity in both diurnal birds and diurnal mammals increases dramatically with increasing eye size (Kiltie, 2000; Ross, 2000; Kirk and Kay, 2004).

Birds that require precision while feeding, whether they are raptors or other birds, e.g., ground hornbills (*Bucorvus leadbeateri*), rock doves (*Columba livia*), and common starlings (*Sturnus vulgaris*), tend to have similar binocular fields (Martin and Katzir, 1999; Martin and Coetsee, 2004). Eagles that are snake-eating specialists are said, however, to have greater binocular vision than other diurnal raptors (Edelstam, 2001; but see Martin and Katzir, 1999). Edelstam (2001) stated that their greater binocularity is necessary because of the great precision that is required when handling dangerous prey (for a review of struggles between raptors and snakes, see Perry et al., 2001). The existence of larger eyes and greater binocularity in two distantly related taxa of snake-eating raptors on two different continents appears to satisfy Cartmill’s (1992) demand. They provide clear-cut, independent cases of visual system evolution and adaptation to snakes in non-primates.

Tarsiers are often used as support for the nocturnal visual predation hypothesis because they are nocturnal, insectivorous, and have the largest orbits of any mammal of their body size (Cartmill, 1992; Ross, 2000). The tarsier is also exceptional among nocturnal primates in possessing a retinal fovea (Fleagle, 1999). The exceptionally large eyes in raptors that specialize in eating snakes suggest that attributing the tarsier’s unusual visual adaptations entirely to nocturnal insectivory may be premature. In addition to preying upon insects, tarsiers prey upon snakes, including venomous snakes (Niemitz, 1984). Animals that eat venomous snakes must have the visual acuity to quickly distinguish the heads of snakes from the rest of their bodies and the stereopsis to judge the distance to the snakes’ heads when they attack.

A genetic correlate to visual expansion?

Anthropoids have larger brains relative to body size than prosimians (Barton, 1999), and basal metabolic rates are

correlated with brain size, particularly at birth (Armstrong, 1983; Martin, 1996). The neocortex is also a metabolically demanding tissue (Aiello et al., 2001). As mentioned in the context of V2 stripes, metabolic activity is reflected in CO activity in cells. Cytochrome oxidase is an enzyme complex in the electron transport chain of the mitochondria, and it is critical for aerobic energy metabolism (Capaldi, 1990; Kadenbach et al., 2000).

Rapid evolutionary changes in genes for CO have been found in 1) primates relative to other mammals; 2) anthropoids relative to prosimians; and 3) catarrhines relative to platyrrhines (Table 2). These changes are suggested to have been driven by expansion of the neocortex (Wu et al., 2000; Grossman et al., 2001; Goldberg et al., 2003), about half of which is devoted to vision (Barton, 1998). It is often inferred that decelerated rates of evolution after acceleration indicate stabilizing selection following directional selection (Goodman, 1982; Grossman et al., 2001; Wildman et al., 2002; but see Li and Grauer, 1997). If this interpretation is correct, then catarrhines have been subjected to the most persistent directional selection of all the primates. The higher-level taxonomic differences in evolutionary change in the genes for CO are consistent with the pattern of differential evolutionary co-existence with venomous snakes.

Figure 3 provides a cladogram that summarizes the changes described in the text that have occurred in the visual systems of the major clades of primates relative to activity pattern, diet, and snakes.

Frequently asked questions

Why is this hypothesis stronger than the nocturnal visual predation hypothesis?

The nocturnal visual predation hypothesis was developed to explain the evolution of the suite of primate characteristics that includes orbital convergence, enhanced vision, grasping hands and feet, nails, and large brains (Cartmill, 1972, 1992). It states that all of these characteristics evolved as a result of visually guided manual capture of arthropods in a nocturnal primate ancestor. This hypothesis is perhaps the longest

standing and most influential of all hypotheses thus far proposed. Recently, however, research has begun to expose weaknesses in the hypothesis.

Bloch and Boyer (2002) have questioned whether all the primate traits evolved together. Based on their work with *Carpolestes*, a fossil mammal that may be related to primates, they suggested instead a pattern of mosaic evolution, in which grasping extremities and nails evolved before visual changes. Indeed, there are numerous examples of arboreal non-primate mammals with grasping hands or feet and nails but without the visual specializations that are unique to primates (Walker et al., 1975; Whishaw, 2003; Percequillo et al., 2004).

The visual links to reaching and grasping are also being challenged by neurological evidence. As described above, Barton (2004) showed that the degree of orbital convergence is not correlated with the number of neurons in the LGN M layers, which are a part of the dorsal visual processing stream involved with reaching and grasping. Orbital convergence is, however, positively correlated with the size of the primary visual area, the neocortex, and the number of neurons in the LGN P layers. Recall that the P pathway is part of the ventral visual processing stream, and is associated with visual acuity, object perception, and fine-grained stereopsis in peripersonal space. Barton's results suggest that, for primates, the act of reaching for and grasping prey could not have favored orbital convergence. Research on humans supports this conclusion in that successful reaching and grasping does not require binocular input as long as other environmental cues are available, as occurs under normal viewing conditions (Watt and Bradshaw, 2000). Orbital convergence appears instead to have evolved for the benefits of seeing clearly that which is in the lower visual field within peripersonal space (Cartmill, 1992; Barton, 2004). This now rather generalized view of the function of orbital convergence opens up the possibility of multiple potential benefits of being able to see clearly in front of oneself, with different benefits perhaps being more likely than others, depending on the specific requirements of particular taxa.

As the nocturnal visual predation hypothesis convincingly argues, one benefit is for predators to be able to see and judge the distance to their prey. This is clearly useful for owls and carnivores, and even diurnal raptors, but, as mentioned above, the data do not support a visual connection between orbital convergence and reaching and grasping in primates. I have already mentioned the benefit of seeing clearly in front for birds that require precise movements of the bill to obtain other foods, e.g., nectar or fruits. Another benefit might be in seeing walkways and hazards. For example, uneven terrain, e.g., unseen holes in the ground, has the potential to cause injury to legs, leaving injured animals more vulnerable to predators. Yet another benefit might be in seeing parasites while grooming. Although grooming has been investigated in primates mainly in the context of sociality, the potential for involvement of the P pathway in grooming is suggested by the positive correlation between the number of P cells in the LGN and group size, which is itself positively correlated with the number of grooming dyads within groups (Barton, 1996, 2000; Kudo and Dunbar, 2001; see also below). Grooming is

Table 2
COX genes and their patterns of nonsynonymous rates of change in primates

Gene	Source
Acceleration in the anthropoid lineage before the platyrrhine/catarrhine divergence	
COX1	Andrews and Easteal, 2000; Wu et al., 2000
COX2	Adkins and Honeycutt, 1994; Adkins et al., 1996
COX4	Lomax et al., 1992; Wu et al., 1997; Wildman et al., 2002
COX7AH	Schmidt et al., 1999
COX8L	Goldberg et al., 2003
Deceleration in platyrrhines relative to catarrhines	
COX2	Adkins et al., 1996; Ascunce et al., 2002
COX4	Wu et al., 1997
COX7AH	Schmidt et al., 1999
COX8L	Goldberg et al., 2003

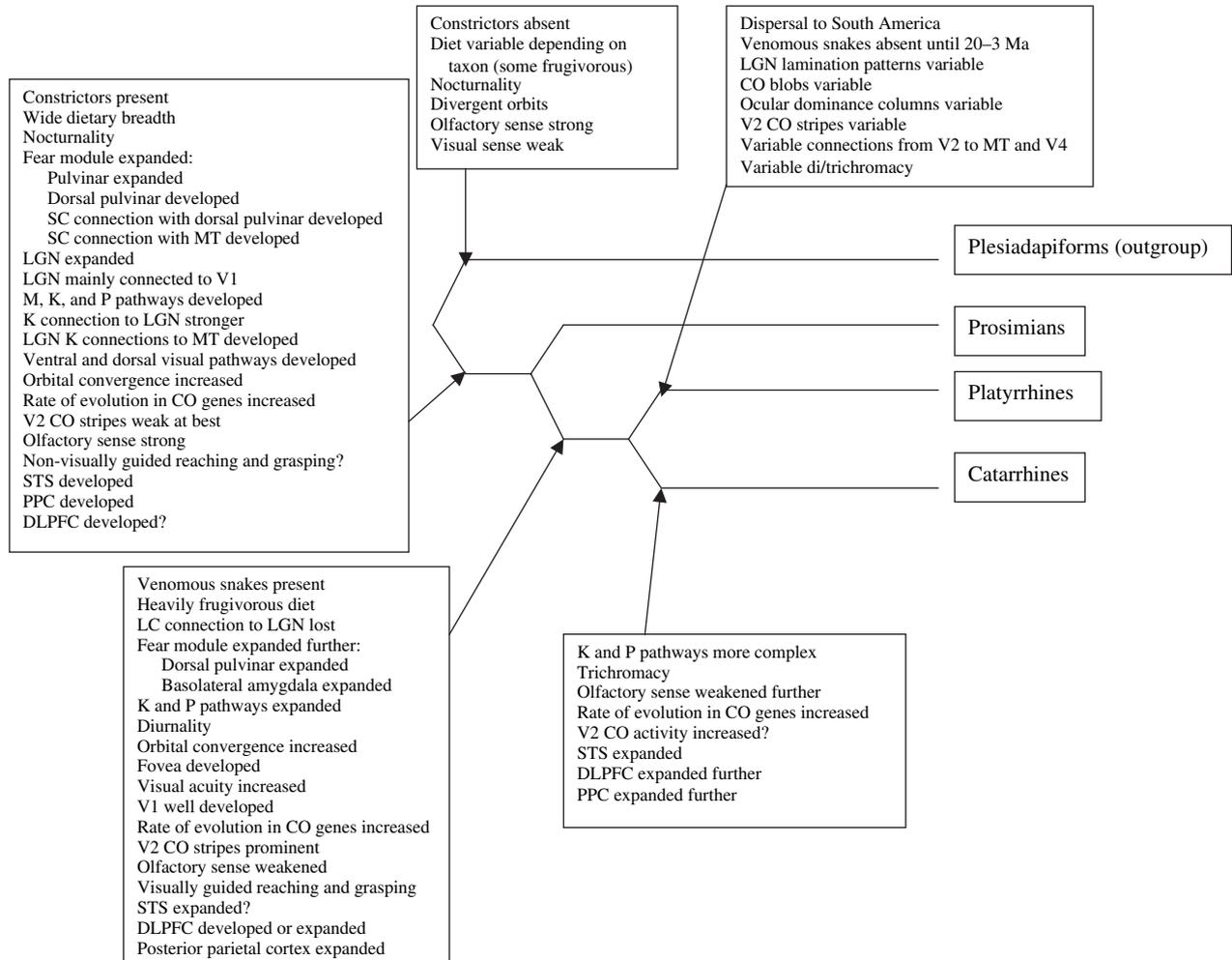


Fig. 3. Hypothetical cladogram showing behavioral, neurological, and morphological changes in the visual systems of primates discussed in the text. It is hypothesized here that the initial changes leading to primates occurred as a result of evolutionary exposure to constrictors, and that later changes leading to anthropoids occurred as a result of evolutionary exposure to venomous snakes. Differences in the visual systems of platyrrhines and catarrhines are less documented than those between prosimians and anthropoids. Existing evidence indicates greater variability in platyrrhine visual systems, hypothesized here to be a result of interrupted co-existence with venomous snakes upon dispersal to South America.

common among many primates, and although visual involvement in grooming cannot be explored further here, we may benefit from giving it greater attention in the future. Finally, as I have hypothesized here, another benefit is in avoiding certain predators. Most predators are obviously best detected visually from far distances, but when predators are small and cryptic, as snakes often are, it may be impossible, and yet also unnecessary, to detect them from far away. The danger from most snakes becomes real only when they are in peripersonal space.

The evidence against orbital convergence for reaching and grasping in primates and the numerous potential benefits of orbital convergence in enabling animals to see clearly what is in front of themselves suggest that it is time to reassess the evolution of orbital convergence in primates. Orbital convergence may have evolved in owls and cats for the benefit of judging the distance to their prey, but that does not automatically mean that orbital convergence evolved in primates for the same reason. Although numerous cases of convergence in

unrelated taxa clearly do exist, attributing similar outcomes to similar causes in unrelated lineages can also be risky. For example, greater intelligence evolved in both octopuses and primates but most likely not under the same selective pressure. Similarly, no one would argue that the same selective pressure favored increased body size in both prey and predators. The need for caution has been already suggested above by tarsiers, with their large eyes and their diet of insects *and* snakes.

Perhaps the real question is not why primates evolved orbital convergence, but why more mammals did not. As discussed above, this can be answered by the fact that there is a clear trade-off between vision and olfaction. Heavy dependence on olfaction simply eliminates the option of enhancing orbital convergence. Thus, as expected, there are both nocturnal and diurnal mammals with divergent orbits and both predators and plant foragers with divergent orbits (Ravosa and Savakova, 2004).

In addition to being challenged by morphological evidence for mosaic evolution, neurological evidence against an

association between orbital convergence and reaching and grasping, and more than one good adaptive reason for seeing clearly in front of oneself, the nocturnal visual predation hypothesis is limited in addressing only the origin of primates. While it was broad in the sense that it sought to explain the entire suite of primate characteristics, it did not seek to address differences in vision among primates. It also did not address mechanisms for the evolution of visual specialization. Alternative hypotheses that are more comprehensive in their explanation of a trait are, by definition, stronger, all else being equal.

In contrast to the nocturnal visual predation hypothesis, the hypothesis presented here is consistent with new findings from fossils and neuroscience. It accepts mosaic evolution of the various primate characteristics, and it does not require a neurological connection between orbital convergence and reaching and grasping. Furthermore, its coverage of primate visual systems is comprehensive. It is supported by molecular, paleobiogeographical, immunological (see below), and behavioral evidence by parallels in unrelated avian taxa, whose own visual systems have clearly been affected by snakes, and by extensive neuroscientific evidence. Neuroscientific support is crucial because visual systems are largely neurological.

This hypothesis goes further than all other existing hypotheses on primate origins by emphasizing mechanism in the evolution of visual specialization. *How* a characteristic came to be is an important and yet often overlooked component of *why* it came to be. This hypothesis posits not only *that* snakes affected the visual systems of primates, it also explores *how* they could have done so. In exploring this mechanism, the hypothesis also addresses other puzzles that are important to primate visual specialization, e.g., how plants could have favored a concomitant reduction in olfaction, how anthropoid primates could have become diurnal, and how visual and brain expansion could have occurred as a result of a frugivorous diet. These are some of the strengths of the hypothesis.

To some, it may seem inconceivable that visual changes in the earliest primates, visual changes in anthropoids, visual differences between catarrhines and platyrrhines, and variation within the visual systems of platyrrhines could all be ascribed to only one factor, that is, variation in evolutionary exposure to constricting and venomous snakes. Others, however, will recognize that it simply employs the same perspective as previous hypotheses that attribute variation in a host of other primate characteristics to variation in predator pressure (reviewed in Cheney and Wrangham, 1987). To provide several examples, in baboons, large male body size, large canines in males, and large groups have been attributed to predation pressure from large felids (Leutenegger and Kelly, 1977; Dunbar, 1988); monogamous groups of langurs and gibbons have been attributed to the absence of felids (Dunbar, 1988); and multi-male social groups of colobus monkeys in Africa and howlers in the Neotropics have been attributed to the presence of monkey-eating eagles, whereas single-male social groups of langurs in southern and southeastern Asia have been attributed to the absence of monkey-eating eagles (van Schaik and Hörstermann, 1994). Indeed, some have attributed variation in group size, social structure, and sociality among all primates

entirely to variation in predation pressure (Alexander, 1974; van Schaik, 1983; Terborgh and Janson, 1986). Critics of the inclusiveness of this hypothesis are challenged to explain why it would be easier, or more likely, for primates to evolve large bodies or large, complex groups in response to predators than to modify the mammalian visual system in response to the same threat.

What about sociality?

Dunbar (1992) proposed that the demands of sociality (i.e., the need to recognize and remember a large number of individuals or to maintain social relationships) favored large brain size in primates. Since the first primates were likely to have been small and nocturnal, and since most small, nocturnal extant mammals (including primates) are solitary foragers with or without shared home ranges (Isbell, 2004), the social complexity hypothesis probably cannot address the initial cause of brain expansion and visual specialization in primates.

As an explanation for variation within primates, however, the hypothesis is supported by the positive correlation between living in larger groups and having larger brains (Dunbar, 1992; Barton, 2000; Barton and Aggleton, 2000). Indeed, the number of P neurons in the LGN is not only correlated with the degree of orbital convergence, the size of V1, and the neocortex, but also with group size (Barton, 2000, 2004). A couple of issues need to be resolved, however, before this hypothesis can be advanced further.

First, it must explain why sheep (*Ovis aries*), which are not known for having large brains, are still able to visually recognize and remember as many individuals as there are in a typical baboon group, even after a year of separation (Kendrick and Baldwin, 1987; Kendrick et al., 2001). In both primates and sheep, the temporal cortex is a major site of facial recognition and memory (Gross et al., 1972; Damasio et al., 1982; Perrett et al., 1992; Kanwisher et al., 1997; Kendrick et al., 2001).

Second, it will be difficult to determine whether enhanced visual communication was the ultimate cause of brain expansion or a secondary benefit of a P pathway that expanded for other reasons. In this context, it needs to account for the co-evolution of the P and K pathways.

Finally, potential confounding factors still need to be sorted out. These include home range size, frugivory, and activity period, each of which can be positively correlated with group size and brain size depending on the statistical methods used (Clutton-Brock and Harvey, 1977, 1980; Sawaguchi, 1988, 1992; Barton, 1999, 2000; Deaner et al., 2000). While the social complexity hypothesis remains attractive, it will be difficult to test until these problems are resolved (Deaner et al., 2000).

Are venomous snakes really a risk to primates?

In primates, levels of the stress hormone cortisol become elevated in response to snakes but not more neutral objects, e.g., fish (Wiener and Levine, 1992; Levine et al., 1993). Indeed, snakes are so predictable in eliciting fear responses

from primates that they are often used as the stimulus in studies of the amygdala (e.g., Kalin et al., 2001; Amaral, 2002). But just how significant are venomous snakes in the lives of wild primates? This question is difficult to answer. There is only a handful of published cases of envenomation of non-human primates (Chism et al., 1984; Corr ea and Coutinho, 1997; Barrett et al., 2004). In a 13-year study of rhesus macaques, post-mortem investigation of nine monkeys found dead in their sleeping trees in the morning revealed the cause of death to be snakebite. An additional 35 monkeys are suspected to have died from snakebite (I. Malik, pers. comm. to D. Hart). Other cases are anecdotal. Two female chacma baboons (*Papio hamadryas ursinus*) were killed by a cobra (*Naja nivea*) in a cave (Barrett et al., 2004), an infant patas monkey was killed when it played too close to a puff adder (Chism et al., 1984; J. Chism, pers. comm.), a buffy tufted-ear marmoset (*Callithrix aurita*) was killed when it approached too closely to a jararaca (*Bothrops jararaca*) (Corr ea and Coutinho, 1997), and a galago (*Galago senegalensis*) was pursued and killed by a black mamba (*Dendroaspis polylepis*) (D.L. Cheney, pers. comm.). The rarity of documented cases of envenomation is not actually surprising, however, given the difficulty of determining the cause of mortality of any kind in wild primates and the speed with which venomous snakes strike. Predation by constrictors has been documented more often (e.g., Chapman, 1986; Cheney and Wrangham, 1987; Heymann, 1987; Shine et al., 1998; Burney, 2002; Gursky, 2002; Tello et al., 2002), but since constriction takes longer than envenomating strikes, predation by constriction is easier to witness. The paucity of observations of interactions of primates with venomous snakes cannot be taken as evidence that deaths from venomous snakes are few and the risk is low. The logic that has been applied to infanticide, another rarely seen cause of death, also applies to venomous snakebites: births are also seldom observed in primates but we know they occur (Silk and Stanford, 1999).

Defensive behavior, e.g., alarm calling or physical attack, is perhaps the best indication of the risk that venomous snakes pose to primates. Vervets, for example, emit an acoustically distinct vocalization when they detect snakes (Seyfarth et al., 1980), and a white-faced capuchin (*Cebus capucinus*) was observed to beat a terciopelo, or fer-de-lance (*Bothrops asper*), with a stick in Costa Rica (Boinski, 1988). It is unclear, however, whether the monkeys made a distinction between venomous snakes and constrictors because both kinds of snakes occur sympatrically at those sites (Isbell, pers. obs.; S. Boinski, pers. comm.). Evidence of such a distinction is clearer among patas monkeys on the Laikipia Plateau of central Kenya. Over seven years, 32 of 107 alarm calls (30%) that were given by patas monkeys to animals other than domestic dogs and other primates were directed at puff adders and other unidentified but non-constricting snakes (Isbell, unpub. data). The monkeys could not have confused puff adders with pythons (*Python sebae*), the only African genus of constrictors, because pythons do not occur at that location. Bonnet macaques (*M. radiata*) in southern India distinguish between pythons (*P. molurus*), to which they respond with alarm calls,

and cobras (*Naja naja*), to which they respond with startle and flight (Ramakrishnan et al., 2005).

Although it is impossible to quantify the rate of mortality from snakebites in non-human primates, the rate of mortality from venomous snakes in humans is estimated at more than 150,000 deaths per year, mostly in the tropics (White, 2000). Humans are at greatest risk just before dusk and in the few hours after dark, when their vision becomes poorer and they are still walking about outside (Jacobs, 1993; Spawls et al., 2002). Surely, if we grant that predators such as leopards (*Panthera pardus*) have been strong selective pressures on primates (Alexander, 1974; van Schaik, 1983; Terborgh and Janson, 1986; Cheney and Wrangham, 1987; Dunbar, 1988; Isbell, 1994, 2004; Isbell and Van Vuren, 1996), we must accord venomous snakes at least the same consideration; they are just as deadly, whether they bite in defense or bite to consume, and they occur at higher densities (e.g., Macartney et al., 1988).

Venomous snakes were likely to have been more consumptive of primates in the distant past when many of the earliest suggested anthropoid primates, e.g., *Eosimias* and *Bahinia*, were, at less than 600 g, the size of modern-day prey of venomous snakes (Greene, 1997; Kingdon, 1997; Beard, 2002; Egi et al., 2004; Gebo, 2004; Kay et al., 2004). Larger primates, e.g., *Pondaungia* and *Amphipithecus* (Egi et al., 2004), would likely have been inadvertent victims, exacerbated possibly by selection on snakes to avoid their own predators through more effective camouflage (Greene, 1997). Ancient contact between venomous snakes and catarrhines is suggested by an endogenous retrovirus in the Asian Russell's viper (*Vipera russellii*), which is more closely related to catarrhine type D retroviruses (Mason-Pfizer monkey virus and langur endogenous virus) than a platyrrhine type D retrovirus (squirrel monkey retrovirus) (Andersen et al., 1979). Endogenous viruses are often evolutionarily very old (Johnson and Coffin, 1999; van der Kuyl et al., 2000). Given our knowledge that transfer of nonhuman primate retroviruses to humans typically involves physical contact (Weiss and Wrangham, 1999; Wolfe et al., 2004), it is conceivable that the retrovirus was transferred to the Russell's viper upon contact with a catarrhine primate millions of years ago.

Do catarrhines detect snakes faster, from a greater distance, or more reliably than platyrrhines?

Since evolutionary exposure to venomous snakes was interrupted for platyrrhines at the time of their arrival in South America, it might be predicted that catarrhines would have an advantage in detecting snakes. This remains to be investigated. It is tempting to take the differences in LGN lamination, rates of gene evolution for CO genes, and potentially different levels of CO activity in the brain (at least in the more binocularly responsive V2) as hints that they do. Compared to macaques, squirrel monkeys have fewer cells in V2 stripes that integrate both color and orientation or both color and disparity (Hubel and Livingstone, 1987). The more frequent blending of CO stripes without intervening pale stripes in macaques also implies that there may be greater mixing of color and disparity (Roe and

Ts'o, 1997) or greater metabolic activity for enhanced pre-attentive alertness in catarrhines than in platyrrhines (Levitt et al., 1995). In addition, though snakes are not suggested here to have directly favored trichromacy, it is possible that trichromacy may currently be useful for detecting earth-colored snakes. Colors of terrains such as earths and dead vegetation tend to be yellows, oranges, reds, or browns (Hendley and Hecht, 1949; Nagle and Osorio, 1993; Sumner and Mollon, 2000). Terrestrial viperids, in particular, are similarly colored (Greene, 1997). Many venomous snakes are cryptically colored not to avoid detection by their prey, many of which are nocturnal mammals and not trichromatic, but to avoid their predators, many of which are birds that, like catarrhines, have excellent color vision (Greene, 1997). While dichromatic platyrrhines may be better able to break through the snakes' camouflage (Anonymous, 1940; Morgan et al., 1992), trichromatic platyrrhines and catarrhines may be better able to distinguish among the various earth colors (Lythgoe and Partridge, 1989). This could give them an edge over dichromats in detecting at least the earth-colored snakes. Perhaps catarrhines also have an edge over platyrrhines in detecting snakes under real-life conditions where snakes are often coiled up and partially obscured by leaves, soil, sticks, and grass. Under these conditions, the pattern consistency of snakes is disrupted, making them difficult even for humans to detect (Coss, 2003).

Greater difficulty in detecting snakes amid leaf litter or grass might also help to explain the puzzle of why there are no habitually terrestrial platyrrhines, whereas many catarrhines are terrestrial or semi-terrestrial. (Since Madagascar has no viperids, elapids, or deadly colubrids, prosimians would be expected to come down to the ground, and indeed, terrestrial travel is common in some species.) Platyrrhines appear to be more hesitant than catarrhines in coming close to the ground and they spend more time scanning the ground. Increasing vigilance closer to the ground, a behavior normally attributed to the risk posed by mammalian carnivores, not snakes, has been documented in at least four platyrrhine but no catarrhine genera thus far (van Schaik and van Noordwijk, 1989; Müller et al., 1997; Di Fiore, 2002; Miller, 2002; Prescott and Buchanan-Smith, 2002), despite the fact that mammalian carnivores are clearly dangerous to catarrhines (Busse, 1980; Hoppe-Dominik, 1984; Isbell, 1990; Boesch, 1991; Tsukahara, 1993; Isbell and Enstam, 2002). Indeed, Hankerson and Caine (2004) recently showed that compared to controls, the presence of a model snake in the evening caused captive Geoffroy's marmosets (*Callithrix geoffroyi*) to delay going to the ground to forage for insects the next morning. They also became more vigilant, as measured by time spent inspecting the area where the snake had been observed and the number of times the area was inspected. To summarize the differences, platyrrhines often appear to behave as if they know something dangerous could be on the ground but they must concentrate to see it, whereas catarrhines often appear to behave as if they know they will see the dangerous object if it is there.

If platyrrhines detect snakes less reliably than catarrhines, they might also, like other mammals, rely more on movement to detect snakes. Support for this comes from a study of snake-

naïve cotton-top tamarins (*Saguinus oedipus*). The tamarins used movement as a cue for potential danger and displayed fear as much to a moving rat as to a snake, and more to a moving snake than to a still snake (Hayes and Snowdon, 1990). More research needs to be conducted to directly address the question of whether catarrhines can more effectively detect snakes than platyrrhines.

The variable pattern of evolutionary co-existence of primates and venomous snakes might also help to explain the absence of particular niches among primates outside of Madagascar. For example, with one exception (Fernandez-Duque, 2003) cathe-meral primates are found only in Madagascar (Fleagle, 1999). If venomous snakes have acted as a selective pressure favoring specialized visual systems, diminished olfaction, and diurnality, it stands to reason that those primates with more generalized visual systems, i.e., useful under both nocturnal and daylight conditions, would have been selected against.

Testing the hypothesis

The evidence presented here suggests that evolutionary exposure to snakes contributed significantly to the evolution of neural structures in mammals for detecting and avoiding snakes, and that variation in evolutionary exposure to venomous snakes resulted in variation in the extent of visual specialization among primates on the geographic scale of large landmasses. Using Cartmill's (1992: 108) approach of providing an adaptive explanation that is "general enough to predict similar adaptations in other cases," I have offered one test of the hypothesis: like primates, raptors in several continents that specialize in eating snakes have larger eyes and apparently greater binocularity than their closest relatives. Available evidence from multiple fields, including neuroscience and behavior, also consistently supports the hypothesis.

In proposing this hypothesis, I have provided other essential predictions that, if rejected, would fail to support the core hypothesis. I have also suggested an evolutionary scenario of increasing visual specialization with a number of more minor hypotheses and predictions that would not cause the core hypothesis to be rejected if one or another is refuted. Predictions from both the core hypothesis and the scenario are listed in Table 3.

The hypothesis is testable by examining the predictions of the core hypothesis. For example, one might examine whether primates can visually detect snakes more quickly or more reliably than other mammals. If so, then one might also examine whether there is a gradation in the ability of primates from the landmasses of Madagascar, the New World, and Africa/Asia to detect snakes under natural conditions, e.g., partially hidden and with color-matched backgrounds. Absence of such a gradation would be inconsistent with biogeographic evidence of a gradation in evolutionary co-existence of venomous snakes and primates. One might also examine whether Malagasy prosimians and anthropoids react differently to snakes. A recent study suggests, in fact, that they do. Whereas Old World monkeys uniformly react fearfully to snakes, wild brown mouse lemurs (*Microcebus rufus*) are more variable and often

Table 3

Predictions of the core hypothesis and corollary predictions

Core hypothesis

Some of the unique characteristics of primates, i.e., visual specialization and expanded brains, evolved in the context of visual detection of snakes. Differential evolutionary exposure to venomous snakes led to differences in visual specialization among primates.

Core predictions¹

1. Primates detect immobile snakes faster, or more reliably, or from a greater distance than other mammals.
2. Venomous snakes (viperids and elapids) have never existed on Madagascar.
3. Prosimians have less specialized visual systems than anthropoids.
4. Venomous snakes arrived in South America after platyrrhines.
5. Platyrrhines radiated in the absence of venomous snakes.
6. Platyrrhines have more variable visual systems than catarrhines (not an artifact of sampling bias).
7. Venomous snakes evolved in Africa or Asia before catarrhines radiated.
8. Catarrhines have the most specialized visual systems of the primates.
9. Catarrhines detect snakes faster, or more reliably, or from a greater distance than platyrrhines and prosimians.

Status²

- Novel prediction
 Prediction supported
 Prediction supported
 Novel prediction
 Novel prediction
 Prediction supported
 Prediction supported
 Prediction supported
 Novel prediction

Corollary hypotheses and predictions³*A. The K pathway*

10. The primate K pathway has been modified by natural selection.
11. The primate pulvinar has been modified by natural selection.
12. The K pathway, via the SC-pulvinar visual system, helps to pre-consciously detect stimuli related to fear and anxiety.
13. The K pathway is most developed in catarrhines, less so in platyrrhines, and least in diurnal prosimians, i.e., the K pathway is involved with “vision for detection.”

- Needs investigation
 Needs investigation
 Needs investigation
 Novel prediction

B. The P pathway

14. The P pathway is least developed in prosimians, more developed in platyrrhines, and most developed in catarrhines.
15. The diet of the earliest primates included fruits, flowers, and nectar.
16. Fruiting trees and primate color vision co-evolved.
17. Trichromacy in howler monkeys evolved to distinguish dead from live leaves.
18. Invariable trichromacy evolved to assist in finding fruits/flowers with high sugar content to protect brains from increasingly greater metabolic demands of visual systems under pressure to detect snakes quickly.
19. The P pathway expanded to protect the brain from increasingly greater metabolic activity under selection to detect venomous snakes quickly.
20. The neuroprotectant property of glucose enabled the expansion of brain size in frugivores.
21. The P and K pathways co-evolved.

- Prediction supported
 Prediction supported
 Needs investigation
 Novel hypothesis
 Novel hypothesis
 Novel hypothesis
 Novel hypothesis
 Novel hypothesis

C. Evolution of COX genes

22. COX gene evolution in primates is related to expansion of the neocortex.
23. COX gene evolution in primates is related to expansion of the visual system.
24. COX gene evolution, cytochrome oxidase activity, and evolutionary time of exposure to venomous snakes covary in primates.

- Needs investigation
 Novel hypothesis
 Novel hypothesis

D. Cell response properties

25. Cells in V2 are more responsive than cells in V1 to attributes of snakes.
26. Cells in the fear module and associated cortical visual areas are highly responsive to features of snakes.
27. High metabolic activity in V2 stripes increases the basal level of pre-attentional alertness needed to detect snakes and other dangerous stimuli quickly.

- Prediction supported
 Novel prediction
 Novel prediction

E. Differences in visual systems, as reflected in behavior

28. Non-primates rely more than primates on movement to detect snakes.
29. Tarsiers (and perhaps other nocturnal African and Asian primates) have some venom resistance but diurnal primates do not.
30. Catarrhines can detect partially occluded snakes faster, or more reliably, or from a greater distance than platyrrhines.
31. Prosimians (and perhaps platyrrhines) rely more than catarrhines on movement to detect snakes.
32. Trichromats detect earth-colored snakes faster or more reliably than dichromats.
33. Platyrrhines lack habitual terrestriality as a result of poorer ability to detect snakes.
34. Visual guidance of reaching and grasping evolved only after the prosimian/anthropoid divergence.
35. Cathemeral primates outside Madagascar were selected against because their visual systems were insufficiently specialized to detect venomous snakes in a timely manner.

- Novel prediction
 Novel prediction
 Novel prediction
 Novel prediction
 Novel prediction
 Novel hypothesis
 Novel hypothesis
 Novel hypothesis

F. Retroviruses

36. Retroviruses can be used to understand paleotropic relationships, which may be datable.

- Needs investigation

¹ Core predictions are those that should be essential to confirm in order for the hypothesis to be supported.

² Under the category “Status,” predictions that are supported are those with direct or indirect evidence. Predictions or hypotheses that are novel are suggested here for the first time and require investigation. Some predictions or hypotheses that are not novel and have been suggested by others need investigation before they can be considered supported with evidence.

³ Corollary hypotheses and predictions are those that are not essential to the core hypothesis if they are refuted but would support the core hypothesis if they are confirmed.

do not even recognize snakes as dangerous (Deppe, 2005). Investigation of neural differences might also provide insights. One might, for example, quantify baseline activity of CO or cerebral blood flow in primates from different landmasses and then compare the extent of short-term change in CO activity or cerebral blood flow in visual areas or the fear module after exposure to venomous snakes and more neutral objects, such as tree branches and flowers. No change could be used as evidence against the hypothesis. In light of the known responsiveness of neurons in STS and IT to faces and other complex and salient images, it might also be interesting to examine whether single cells in these areas respond as vigorously to snakes.

Conclusion

The foregoing attempts to explain the origin of primates, the origin of anthropoids, and the origin of differences between catarrhines and platyrrhines. In support of the hypothesis that the need to avoid snakes was ultimately responsible for the unique visual systems of primates, and to at least some extent, for variation in the visual systems within primates, I have

provided extensive neurological and other evidence for these differences. A full understanding of the evolution of primates will only be achieved when both proximate and ultimate levels of inquiry are incorporated. This is particularly true for visual systems and other adaptations that are strongly neurological. Similarly, I have included a scenario of the proximate mechanisms that would have operated to help produce the visual systems of primates. For those who are less interested in proximate mechanisms and are primarily interested in the bottom line, Figure 4 condenses the hypothesis to its main steps and conclusions.

I have taken advantage of recent findings in fields ranging from molecular genetics and neuroscience to paleontology and plate tectonics to propose a new hypothesis born out of behavior and ecology. In closing, it is well worth drawing attention to the detailed observations made nearly 100 years ago by scientists who had far less at their disposal:

We wish first to record the extremely interesting fact that Lemurs differ markedly from true Primates, inasmuch as they exhibit no fear of snakes whatever. It was most curious to notice how, when we approached adjoining cages, the one with

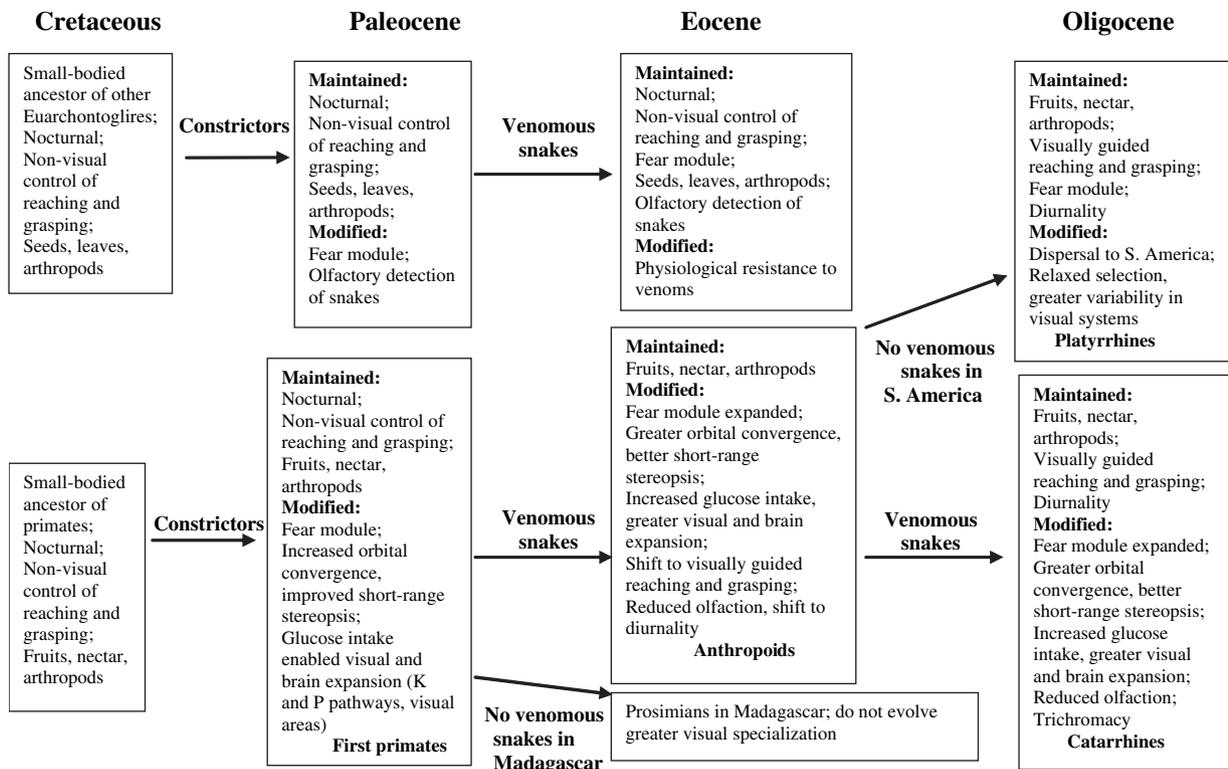


Fig. 4. Hypothesized steps involved in the acquisition of primate characteristics contrasted with non-primates. A small-bodied, nocturnal mammal with a diet that was limited to seeds, leaves, and grasses evolved olfactory sensitivity to constricting snakes, and its descendents later added physiological resistance to venomous snakes to their repertoire. In contrast, a small-bodied, nocturnal mammal with a diet that included (but was not necessarily restricted to) fruits or nectar evolved visual specialization and larger brains to detect snakes. A high-glucose diet in the presence of constricting snakes would have enabled initial expansion of the visual systems and brains of the first primates. Malagasy prosimians would have retained these traits because selection did not intensify in Madagascar. The appearance of venomous snakes in the rest of the Old World would have selected for greater expansion of visual systems and brains. Expanded visual systems were accompanied by diminution of olfaction, causing an adaptive shift to diurnality and visually guided locating, reaching, and grasping of more odoriferous fruits and flowers in anthropoids. When platyrrhines dispersed to South America, where venomous snakes had not yet arrived, they were no longer constrained by venomous snakes. Their radiation in the absence of venomous snakes resulted in variable visual systems. In catarrhines, continued selection for greater visual specialization coupled with high energetic requirements of maintaining larger and more active brains eventually culminated in even larger brains and even greater expansion and specialization of their visual systems, including invariable trichromatic color vision.

lemurs the other with monkeys, carrying with us writhing snakes, how the monkeys at once fled back shrieking, whilst the lemurs crowded to the front of the cage, displaying the greatest interest and not the smallest perturbation when a snake was brought so close to them that its tongue almost touched their faces. We got the impression that had the lemurs been given the opportunity, they would at once have seized and tried to devour the snake. The South American monkeys showed fear in irregular and sometimes slightly marked form. Spider-monkeys (*Ateles*) were quite as excited and alarmed as any Old World monkey. Some of the larger Cebidae did not retreat, but uncovered their canines and looked as if they were ready to show fight. Some small specimens retreated but showed no special alarm, others were nearly indifferent. The Old World monkeys of all the genera in the Society's Collection recognised the snakes instantly and bolted panic-stricken, chattering loudly and retreating to their boxes or as high up as possible in the larger cages. Our large Baboons, including the huge Mandrill, were even more panic-stricken, jumping back in the greatest excitement, climbing as far out of reach as possible and barking. Of the Anthropoids, the Gibbons were least timid; one small agile Gibbon (*Hapale agilis*) [*sic*] showed no fear and very little curiosity; a larger one of the same species and a Hoolock receded but without showing panic. It is possible that the very markedly arboreal habits of the Gibbons have brought them so much less in contact with snakes that their fear of snakes is partly obliterated. The Chimpanzees, except one baby which was indifferent, recognized the snakes at once and fled backwards, uttering a low note sounding like "huh, huh." They soon got more excited and began to scream, getting high up on the branches or on the wire-work of their cages, but all keeping their eyes fixed on the snakes.

P. Chalmers Mitchell and R.I. Pocock (1907: 793–794).

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