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Paleoneurology: A Sight for Four Eyes

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The 'third eye' of the pineal complex is a curious component of the vertebrate brain associated with light sensation and melatonin production. A fossil lizard with a 'fourth eye' now calls for a reinterpretation of pineal evolution.

> *"The part of the body in which the soul directly exercises its functions is not the heart at all, or the whole of the brain. It is rather…a certain very small gland [the pineal organ] situated in the middle of the brain's substance…"*
>
> René Descartes, *The Passions of the Soul*, 1649 [1]

It's perhaps understandable that our knowledge of the function and evolution of the pineal organ has been murky, because, as Descartes noted, it is indeed a very small structure buried deep within the brain of humans and other mammals. Although perhaps few people today subscribe to Descartes' view of the pineal organ as the 'seat of the soul', it retains an almost mystical quality in some quarters. Pop cultural references abound, suggesting ways (and selling products, of course) to 'activate the pineal' with cannabis or 'harmonic sound wave technology' to achieve enlightenment (psychedelic or spiritual). Fortunately, there is also a rich scientific literature on the neuroscience and clinical neuroendocrinology of the pineal gland, revealing that the organ may have less to do with the soul and enlightenment and more to do with responding to light/dark cycles and mediating circadian and seasonal rhythms via production of the hormone melatonin [2]. The mammalian pineal organ is complicated enough, but when other vertebrates are taken into account, we now speak of a 'pineal complex' involving multiple organs that emphasize the photosensory component. That is, they often are 'eyes' with structures comparable to the cornea, lens, retina, and visual pigments (opsins) that we typically associate with our normal, lateral eyes and which breach the skull to appear on the top of the head [3,4]. In fact, when considering the pineal complex of vertebrates we now need to distinguish between 'lateral eyes'

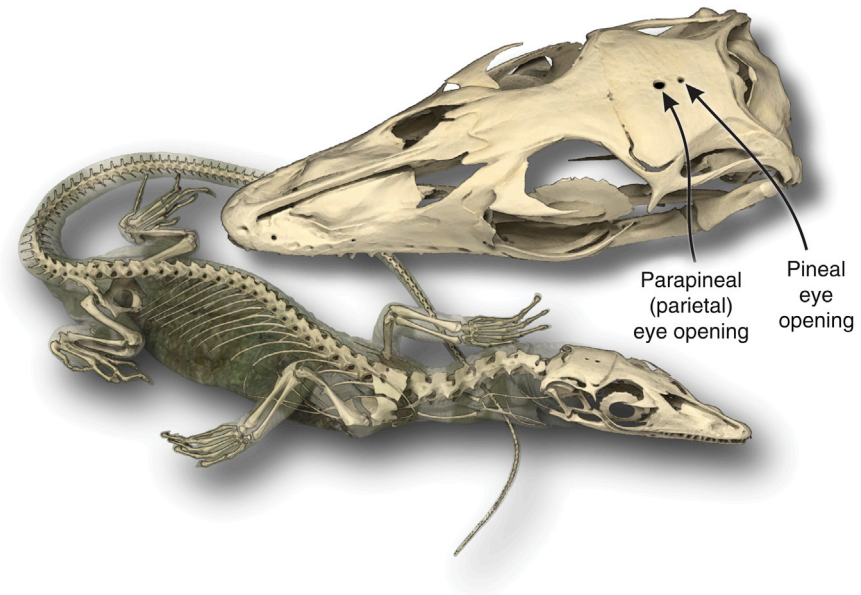

Figure 1. A four-eyed fossil lizard.
The 49 million-year-old fossils of the extinct monitor lizard *Saniwa ensidens* uniquely and atavistically display both pineal and parapineal (parietal) eyes on the top of their heads, along with normal lateral eyes. (Digital image based on microCT scan of extant *Varanus* monitor, modified to reflect the new findings of *S. ensidens* [5]; by R. C. Ridgely of WitmerLab at Ohio University.)

(the eyes with which you're reading these words) and 'median (midline) eyes' within or on top of the head. Indeed, the median eye formed by a component of the pineal complex is widely known as 'the third eye' [3]. A new paper by Krister Smith and colleagues in this issue of *Current Biology* [5] now presents evidence from a fossil lizard for the first identifiable case of a jawed vertebrate with not just a third, but a fourth eye (Figure 1), both of which are part of the pineal complex, thus shedding new light, as it were, on the evolution of the entire complex.

Light-sensitive organs (in a broad sense, visual organs) are widespread among invertebrates and vertebrates, and pineal evolution extends back to the very beginnings of vertebrates [6]. The pineal complex is comprised of a pineal organ and a parapineal organ, both of which derive from a portion of the forebrain called the diencephalon, specifically the epithalamus. Anatomically, the parapineal sits in front of the pineal on the midline, but debates have raged about whether they originally were paired organs (that is, left and right, like the lateral eyes) that subsequently diverged in function and position [7] or whether they truly were always separate midline structures [8]. Regardless, both pineal and parapineal organs were almost certainly photosensory at their evolutionary origins [6], and remain so to varying extents in the species that retain them today. Indeed, the evolutionary history of the pineal complex is complicated in that some extant groups (mammals and birds) have lost the parapineal organ and one extant group (crocodilians) has apparently lost both components almost entirely [6]. Thus, in most extant vertebrates, the pineal organ is the major component, and its function largely centers on photosensitive neuroendocrine production of melatonin.

An exception would seem to be lizards. Most lizards have a prominent and externally visible 'third eye' (with cornea, lens, etc.) in the midline of the tops of their heads. This eye traverses an opening in the center of their bony skull roof, commonly called the parietal foramen in which this eye sits (named for the parietal bones that flank the opening). It turns out that this well-formed third or, as it's commonly known, parietal eye of lizards is thought to derive from the parapineal organ, and the pineal organ sits behind it more deeply within the bony brain cavity, as in other vertebrates [9,10]. So, most extant vertebrate groups emphasize the pineal gland whereas lizards emphasize the parapineal gland. The kicker is that there is a huge diversity of extinct tetrapods (land vertebrates), such as the famous sail-backed *Dimetrodon*, that often show a single large midline parietal foramen in their skull roofs [9–11]. Is this 'third eye' opening for a parapineal (parietal) eye or a pineal eye? Both ideas have been proposed [10,12].

Enter *Saniwa ensidens*, the 49-million-year-old fossil lizard that sparked Smith and colleagues' [5] re-exploration — and indeed revision — of pineal-complex evolution in this issue of *Current Biology*. Fossils of this outwardly routine species, a close kin of extant monitor lizards (*Varanus*), have long been known and have been well studied recently [13,14]. Smith and colleagues [5], however, noticed a couple of specimens that showed something remarkable, which is not one midline opening in the skull roof as in other lizards, but two. These fragmentary fossil specimens had sat in the Yale Peabody Museum collection, barely noticed, for almost 150 years, but these authors had the insight to wonder whether they were facing a 'four-eyed' animal. Indeed, at the end of their exhaustive studies, Smith and colleagues [5] came to the conclusion that the larger normal-looking parietal foramen in the front must have been for the parapineal organ as in other lizards, and the smaller 'accessory' foramen behind must have been for the pineal organ. Moreover, the cup-like bone surface on the outer part of the accessory foramen is consistent with the presence in life of cornea- and lens-like structures. In other words, *Saniwa ensidens* had both parietal (parapineal) and pineal eyes!

This completely unexpected finding has a number of important implications. For example, there is no longer any debate that it is the parapineal component of the pineal complex that forms the parietal eye in lizards, and that the parapineal/parietal opening should no longer be termed the 'pineal foramen' in lizards as it still is sometimes. It also tips the scales toward the notion that the pineal complex probably is natively a midline system rather than a paired system that got evolutionarily tugged into its midline alignment. But, although it's good to clean up the nomenclature and nail down the original anatomy, the truly remarkable point is that *Saniwa* had a photoreceptive pineal eye that peered out of the top of its

head. Such a feature was thought to have been lost hundreds of millions of years ago back when the earliest vertebrates with jaws evolved, at which point the pineal gland sunk deeper into the brain cavity and lost its eyelike function. In 1893, Belgian paleontologist Louis Dollo formulated the Law of the Irreversibility of Evolution, which simply states: that which is lost shall not be regained [15]. Some laws are meant to be broken, and the re-evolution of a pineal eye in *Saniwa* is not the first atavism to be reported. Still, it's not a common occurrence, and it's so rare in this case that it raises new questions.

How could a pineal eye simply re-evolve? Few details of the developmental genetics of the pineal complex are known, but the similarities in the tissue types and visual pigments between the lateral eyes and pineal complex perhaps reflect commonalities in genetic regulation [6] such that slight modification of regulatory pathways could change their developmental fates. Minimally, *Saniwa* seems to demonstrate the latent capability of the system to generate a true pineal eye. But why *Saniwa*? What's special about this lizard? Nothing is special, as far as we can tell. Smith and colleagues [5] offer some suggestions, but it's fair to say that the functional benefit of having both parapineal and pineal eyes remains obscure. This finding also means that all of a sudden we're no longer sure which organ — pineal or parapineal eye — was peeking through the parietal foramen of a host of extinct ancient tetrapods. As is often the case in science, we progress by changing our search image, and the analysis of *Saniwa* requires that change for both paleontologists and developmental neuroscientists. While the pineal may not be the seat of the soul, it still has some mysteries to reveal.

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