electrons are born, which may be viewed as an effective damping of Ψ_f^{Ni} in nickel. An essential question, though, is what distance an electron can propagate within the sample and still be detected as an electron populating Ψ_f^{Ni}. Finally, the high potential energy of the photoelectron, more than 20 eV above the Fermi level, makes it a highly excited state with an extremely short lifetime (t = 200 as). The distance d over which this electron can propagate with a velocity v without losing energy due to interaction with the solid is referred to as the inelastic mean free path. However, it is not obvious which v is the appropriate one. Tao *et al*. discuss that consideration of the group velocity of the electron inside Ni results in too-small values for d. To obtain this quantity in agreement with values from the literature, propagation of the electron inside nickel as a free electron has to be assumed, which is supported by earlier work on magnesium (*11*) and excited state theory. Essentially, the photoelectron leaves the crystal before it can experience the surrounding solid.

The experimental scheme and findings of Tao *et al*. might have widespread implications for future analysis of the electronic structure of solid materials. The extremely short inelastic mean free path of just a few angström makes photoemission a surface-sensitive method prone to complications if one aims at the electronic structure of three-dimensional bulk materials. Current efforts use x-ray photon energies in photoemission (*16*). However, the use of low photon energy in the UV spectral range promises bulk sensitivity in some limits as well, while providing ample opportunity for time-resolved experiments that address correlations in complex materials (*17*). Tao *et al*. have shown that attosecond spectroscopy of solids has the potential to analyze the fundamental processes limiting bulk sensitivity in photoemission and to develop this prominent spectroscopy further beyond current limitations. ■

REFERENCES

1. Z. Tao *et al.*, *Science* **353**, 62 (2016).
2. P. B. Corkum, *Phys. Rev. Lett.* **71**, 1994 (1993).
3. M. Hentschel *et al.*, *Nature* **414**, 509 (2001).
4. F. Krausz, M. Ivanov, *Rev. Mod. Phys.* **81**, 163 (2009).
5. A. L. Cavalieri *et al.*, *Nature* **449**, 1029 (2007).
6. C. Lemell *et al.*, *Phys. Rev. A* **79**, 062901 (2009).
7. A. K. Kazansky, P. M. Echenique, *Phys. Rev. Lett.* **102**, 177401 (2009).
8. E. E. Krasovskii, *Phys. Rev. B* **84**, 195106 (2011).
9. Q. Liao, U. Thumm, *Phys. Rev. Lett.* **112**, 023602 (2014).
10. S. R. Leone *et al.*, *Nat. Photon.* **8**, 162 (2014).
11. S. Neppl *et al.*, *Phys. Rev. Lett.* **109**, 087401 (2012).
12. S. Neppl *et al.*, *Nature* **517**, 342 (2015).
13. M. Lucchini *et al.*, *Phys. Rev. Lett.* **115**, 137401 (2015).
14. K. Klünder *et al.*, *Phys. Rev. Lett.* **106**, 143002 (2011).
15. R. Locher *et al.*, *Optica* **2**, 405 (2015).
16. C. S. Fadley, *J. Electron Spectrosc. Relat. Phenom.* **190**, 165 (2013).
17. L. Rettig *et al.*, *Nat. Commun.* **7**, 10459 (2016).

10.1126/science.aag1090

ANTHROPOLOGY

The evolutionary path of least resistance

Evolution favored teeth with thicker enamel over sharply crested teeth in hominins confronted with tough diets

By **P. S. Ungar**[1] *and* **L. J. Hlusko**[2]

Paleontologists typically reconstruct past behavior by assuming that function follows form. But there can be more than one function for a given form, and different forms can serve the same function. Deconstructing these relationships can be complicated. Here, we use an example from human evolution—markedly different tooth morphologies in early hominins—to show that insights about the underlying genetic architecture of form can help us to better infer function and deepen our understanding of evolution.

In the eastern and South African fossil record of human evolution during the Plio-Pleistocene (about 2.7 to 1.2 million years ago), there is a group of species with remarkably specialized craniodental anatomy. Exemplified by *Australopithecus/Paranthropus boisei* from eastern Africa and *A./P. robustus* from South Africa, these hominins evince large, flat, thickly enameled teeth (see the figure), heavily buttressed jaw and face, and attachment sites indicating massive chewing muscles (*1*). These characteristics are often interpreted as adaptive for crushing hard foods; the first fossil found was nicknamed the "nutcracker" man. But recent studies call into question a simple form-function relationship between masticatory morphology and diet (*2*), fueling a long-standing debate over their evolutionary relationships (*3*).

"Because the same anatomical solution may emerge from different adaptive challenges, genetic architecture provides a key piece of the puzzle when inferring function from form in the fossil record."

The carbon isotope values for *A./P. robustus* indicate that this species had a mixed diet of leaves, fruits, grasses, and sedges; a range of microscopic use-wear pitting on its teeth is consistent with only occasional consumption of hard objects. In contrast, *A./P. boisei* has carbon isotope values indicating a diet dominated by grasses or sedges. A pattern of dental microwear scratches on its teeth, along with an extreme gross tooth wear gradient, is consistent with grinding or milling softer, tougher, and perhaps more abrasive foods. So despite their similar masticatory morphology, chemical and wear traces of the foods eaten suggest that these two species differed markedly in their diets (*3*). Neither was a specialized "nutcracker," notwithstanding a craniodental toolkit that at first glance suggests otherwise.

One argument against the idea that *A./P. boisei* ate tough foods is the observation that no living leaf-eating primate has flat teeth. Gorillas, for example, have comparatively long shearing crests rather than blunt cusps, presumably because blades are more efficient for fracturing tough leaves (see the figure) (*4*).

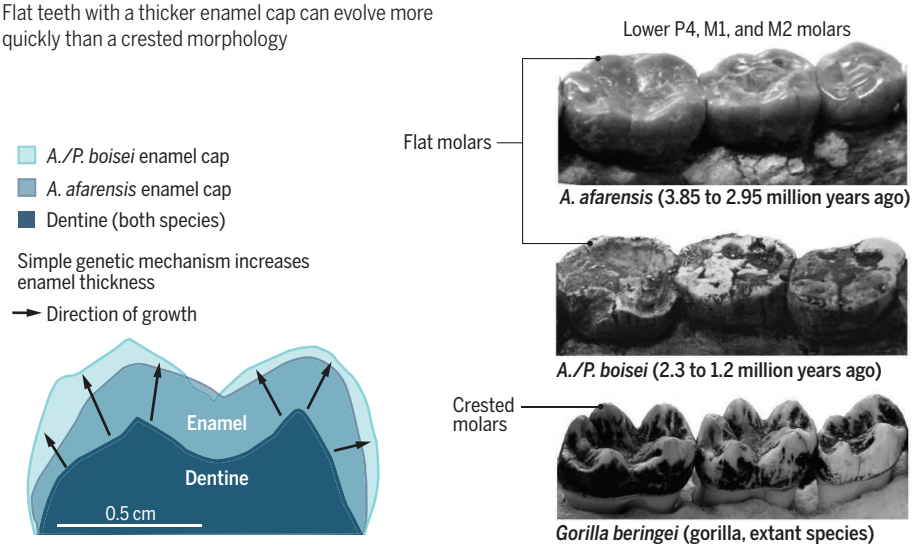
We propose that although a flat-toothed grinding platform may be suboptimal for fracturing tough foods relative to a bladed (crested) morphology, it is a better solution than the smaller, less thickly enameled molars of *A./P. boisei*'s predecessor, *Australopithecus afarensis* (see the figure) (*5*). The latter lived between about 3.85 and 2.95 million years ago, whereas *A./P. boisei* lived between about 2.3 and 1.2 million years ago. The flat teeth of *A./P. boisei* would have been particularly advantageous when combined with masticatory structures capable of generating and transmitting repetitive loads associated with heavy grinding of tough vegetation. The key piece of evidence that unlocks this evolutionary puzzle lies in the genetic architecture of tooth shape.

Knowledge of genetic architecture of tooth shape comes mainly from developmental genetics research on mice, animals that last shared a common ancestor with humans about 70 million years ago. Despite

[1]*Department of Anthropology, University of Arkansas, Fayetteville, AR, USA.* [2]*Human Evolution Research Center, University of California, Berkeley, CA, USA. Email: pungar@uark.edu*

Morphology and development of hominin molars

Flat teeth with a thicker enamel cap can evolve more quickly than a crested morphology



this evolutionary distance, there are numerous reasons to assume that the main mechanisms are similar (*6*). From a subset of the 300 genes involved in mouse molar development, Salazar-Ciudad and colleagues (*7*) have developed an in silico model of tooth development that shows how reaction-diffusion processes can modify cusp patterning. This model works well for the teeth of seals (which are essentially two-dimensional). However, it does not extend to more complex structures such as the rectangular teeth of most primates, nor does it explain why cusps with different heights form. Tooth cusp patterning is genetically complex. Consequently, the selection that leads to changes in cusp patterning has to persist over long periods of time. The paleontological record confirms this, showing that although shearing cusps have evolved repeatedly, they did so on time scales of many millions of years.

Had the *A./P. boisei* lineage persisted for longer than ~2 million years, perhaps their descendants might have eventually wound up with spiky, crested cusps more like those of gorillas. But the evolution of humans' closest relatives occurred over a much shorter interval, one in which selection would have acted first and foremost on phenotypes that were already variable within and between populations, and whose genetic architecture facilitated a rapid response.

At least four independent lines of evidence indicate that enamel thickness is such a phenotype in primates (see the figure). First, quantitative genetic analyses demonstrate that enamel is highly variable and heritable, without causing other phenotypic changes (*8*). Second, thicker enamel correlates with more abrasive diets across extant primates, which suggests that both fracture risk and abrasiveness can select for it (*9*). Third, enamel thickness is highly variable among closely related species (*10*). Fourth, there is evidence of selection in noncoding regions of two genes involved in enamel formation across the great apes (*11*).

Although sharp shearing crests may be better for fracturing tough plant parts, evolution tends to follow the path of least resistance. That path is defined by the structure of the underlying genetic covariance (*12*). Over the shorter time frames of hominin evolution, highly variable, highly heritable molar enamel thickness, with its simple genetic architecture, was probably the phenotypic response that came first when these creatures were confronted with a mechanically challenging diet. Because the same anatomical solution may emerge from different adaptive challenges, genetic architecture provides a key piece of the puzzle when inferring function from form in the fossil record. ■

REFERENCES AND NOTES

1. A. L. Smith *et al.*, *Anat. Rec.* **298**, 145 (2015).
2. For example, the present authors disagree about which genus these two species belong to; P.S.U. classifies them within the distinct genus *Paranthropus* and L.J.H. includes them in *Australopithecus*. Hence, here we use slashes to acknowledge both nomenclatures. L.J.H. also prefers Hominidae to Homininae, but for ease of discussion, we use hominin herein.
3. P. S. Ungar, M. Sponheimer, *Science* **334**, 190 (2011).
4. P. W. Lucas, *Dental Functional Morphology: How Teeth Work* (Cambridge Univ. Press, 2004).
5. A. Walker *et al.*, *Nature* **322**, 517 (1986).
6. L. J. Hlusko, R. D. Sage, M. C. Mahaney, *J. Exp. Zool.* **316B**, 21 (2011).
7. I. Salazar-Ciudad, *Curr. Opin. Genet. Dev.* **22**, 585 (2012).
8. L. J. Hlusko *et al.*, *Am. J. Phys. Anthropol.* **124**, 223 (2004).
9. J. D. Pampush *et al.*, *J. Hum. Evol.* **64**, 216 (2013).
10. A. Kato *et al.*, *Am. J. Phys. Anthropol.* **155**, 447 (2014).
11. J. E. Horvath *et al.*, *J. Hum. Evol.* **73**, 75 (2014).
12. D. Schluter, *Evolution* **50**, 1766 (1996).

10.1126/science.aaf8398

NEUROREGENERATION

Promoting CNS repair

What influences glial and neuronal response to neurodegeneration?

By **Evan G. Cameron** *and* **Jeffrey L. Goldberg**

A developmental loss of intrinsic reparative capacity and the inhibitory environment in injury and disease contribute to regenerative failure in the central nervous system (CNS). The same factors are thought to hinder endogenous and exogenous regenerative therapies, including cell-based replacement (*1*, *2*). In neurodegenerative disorders, the contributions of microglia, astrocytes, and peripheral immune cells may be both harmful and beneficial. For example, resident microglia and peripheral cells of the innate immune system promote inflammation and cell death (apoptosis) in response to CNS injury, but immune cell activation also has been associated with neuroprotection and repair (*3*). This duality suggests that stimulating protective functions while minimizing proapoptotic and inhibitory signals could prove critical in treating neurodegenerative disease. On page 43 of this issue, Neves *et al.* (*4*) show that a neurotrophic signaling pathway in microglia and innate immune cells that is activated in disease or injury can be leveraged to promote neuroprotection and tissue repair.

Neves *et al.* identify a conserved injury response pathway in innate immune cells that is mediated by mesencephalic astrocyte-derived neurotrophic factor (MANF), a macrophage-dependent, prosurvival signaling molecule. In a mouse model of progressive retinal degeneration, the authors found that macrophage-derived MANF exerts neuroprotective effects on damaged photoreceptors, and enhances transplanted photoreceptor integration that restored visual function.

Macrophages clear debris and produce pro- and anti-inflammatory cytokines in response to injury or in degenerative disease. The course of macrophage activation is influenced by the extrinsic environment, which drives their acquisition of either an M1 (inflammatory/proapoptotic) or M2 (anti-inflammatory/tissue-protective) phenotype, both of which

Department of Ophthalmology, Stanford University, Stanford, CA 94303, USA. Email: ecamer1@stanford.edu