face metalloproteases not only modulate the strength of axon guidance signals but also are intimately involved in defining their outcome. To assess the impact of metalloprotease activity on the establishment of neural circuits, it will be important to examine genetically engineered mice in which ephrin-A2 is replaced by one of the mutated versions that are resistant to cleavage by Kuzbanian (*4*).

Eph receptors and ephrins are expressed by many embryonic cells including neural crest and endothelial cells, and new activities mediated by their bidirectional signaling pathways continue to be discovered (*1–3*). Because both ephrin-A and ephrin-B ligands can be shed from the cell surface (*4, 15, 16*), the phenomenon described by Hattori *et al.* is likely to represent a general strategy for the production of ephrin/Eph repulsive signals in many cell types.

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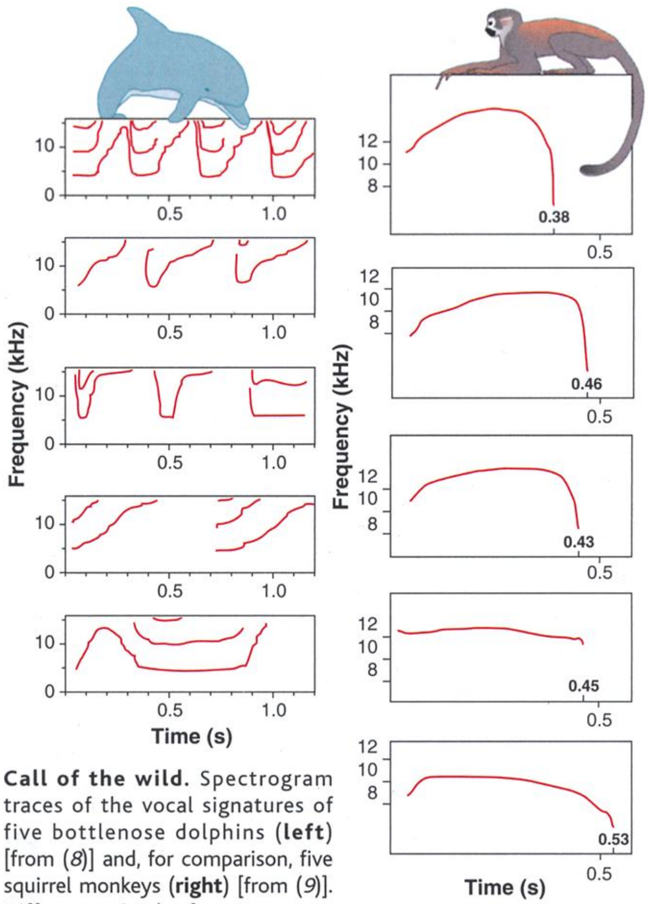
PERSPECTIVES: ANIMAL BEHAVIOR

Dolphins Whistle a Signature Tune

Peter L. Tyack

Imagine you are at home whistling a few bars of your favorite song. Wouldn't you be amazed if your pet dog or cat were able to reprise the melody? Whereas birds are skilled at imitation and parrots are famous for imitating human sounds, no terrestrial mammals—apart from us, the puzzling exception—are known to imitate the sounds that they hear (*1*). It has been difficult to study the evolutionary origin of vocal learning in humans because there are so few other mammals that have the ability to imitate sounds. The best evidence for vocal learning comes from marine mammals in whom sound imitation is highly developed. Captive dolphins are fantastic imitators of human sounds. Within seconds of hearing a tonal pattern for the first time, a captive dolphin can reproduce it accurately (*2*). Now, on page 1355 of this issue, Janik (*3*) reports his discovery that wild bottlenose dolphins imitate the learned whistles of other members of their group. This finding is consistent with the hypothesis that a dolphin will imitate the whistle of another dolphin (called whistle matching) to address that individual. The discovery that dolphins learn to imitate whistles, apparently as a form of addressing others in their group, is important for anyone interested in comparative studies of the evolution of vocal learning and labeling in mammals.

Bottlenose dolphins are highly social mammals and are usually seen in groups. These groups are fluid, with individuals joining and leaving on a minute-by-minute basis. Long-term studies in the wild have repeatedly shown that individual dolphins share strong social bonds with each other in these fluid groups. Pairs of adult males or a mother and her young calf may be sighted together continuously for 5 to 10 years or more. Animals with strong individual-specific social relationships usually have a communication system that includes "signature" signals for recognition (see the figure). Rather than producing specific vocal signatures, many animals encode signature information through individually distinctive anatomical features. For example, primates have distinctive facial features and have evolved perceptual mechanisms specialized for recognizing faces. Primates that can see one another in detail recognize individuals subtly in the absence of any vocal signal. I can locate a friend at the airport and recognize his face among hundreds of strange faces even though he is not making any specific vocal signal and may not even be aware that I am there. This form of visual communication is not useful for marine mammals because visibility underwater is often limited to one body length. Acoustic signals travel much better in the ocean than do visual signals, so it is not surprising that marine mammals have evolved vocal signals for maintaining contact and for broadcasting individual identity.



Call of the wild. Spectrogram traces of the vocal signatures of five bottlenose dolphins (**left**) [from (*8*)] and, for comparison, five squirrel monkeys (**right**) [from (*9*)]. Differences in the frequency pattern of the five dolphin signature whistles are far greater than differences in the signature peeps of the five squirrel monkeys.

If a friend calls you on the telephone, you can usually recognize the caller's identity by voice alone. Some animals re-

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ly upon similar voice cues to encode individual identity within their vocalizations. Whereas the recipient must learn to recognize the voice of each individual, the speaker does not need to learn to produce voice cues. Speaker-specific cues stem from natural differences in the air-filled vocal tracts of each person. Diving mammals are unable to rely upon such vocal cues for individual recognition because, as they dive, the volume of gases in the vocal tract is halved with each additional atmosphere of pressure—this change in the vocal tract renders voice cues unreliable.

Diving mammals that rely upon individual-specific social relationships must learn to produce individually distinctive vocal signature signals. The best-known example is the signature whistle of the bottlenose dolphin (see the figure). Whether in captivity or in the wild, these animals produce signature whistles with an individually distinctive frequency pattern. Bottlenose dolphin calves develop a stereotyped signature whistle during their first year of life. Development of a signature whistle is strongly influenced by learning—most dolphins develop signature whistles that are different from those of their parents, but similar to other sounds present in their environment at birth (*2*).

An isolated captive or wild dolphin is most likely to produce its own signature whistle, but occasionally may also imitate the signature whistle of an associate (*4*). In his study, Janik (*3*) analyzed whistles from wild dolphins and considered them matching if the same whistle was emitted by two separate dolphins within 3 seconds of each other. In this circumstance, it is likely that one of the dolphins was producing its signature whistle and the other was imitating it. Janik proposes that one dolphin may be imitating the signature whistle of another in order to address that individual. Captive dolphins have been shown to associate a newly learned whistle with an arbitrary human object (termed vocal labeling) (*5*). Janik now provides important evidence that vocal labeling is used by wild dolphins for social communication.

Anthropologists who analyze the increase in the ratio of brain to body mass in our hominid ancestors often call their field "the study of the evolution of intelligence." Research that relates cognition to neural circuitry in marine mammals is still in its infancy, but some species are known to invest heavily in brain tissue. Bottlenose dolphins, for example, have a brain to body mass ratio that is higher than that of most mammals and is close to that of humans. Theories of the evolution of intelligence that emphasize the suite of adaptations for tool use (including bipedal gait, opposable thumbs, and increased ability to manipulate objects) would not have predicted the large brain to body mass ratio in dolphins. Few mammals are less adapted for tool use than dolphins, porpoises, and whales (collectively called cetaceans)—selection for a hydrodynamic shape has reduced their appendages to fins, and they are poorly adapted for manipulating objects, compared with, say, a raccoon. Other theories explaining the evolution of large brains in primates emphasize the social aspects of intelligence (*6*). Dolphins provide a good fit for these models—both dolphins and higher primates learn the signals to establish both cooperative and competitive relationships within their social groups.

There is a healthy pressure in the biological sciences to study simple systems. Yet these do not capture all of the important features of life. The genetics of viruses do not tell us all we need to know about multicellular organisms. Similarly, studying social insects is unlikely to unfold to us the whole story about the evolution of social behavior in dolphins and humans. There is a growing appreciation among those who study communication and complex social behavior of the fascinating similarities in the ways that birds and mammals use vocal imitation to interact with specific individuals (*1, 7*). As Janik points out, these similarities may provide an important comparative perspective on how capabilities for imitation evolved in our hominid ancestors.

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PERSPECTIVES: IMMUNOLOGY

Therapeutic Manipulation of Gut Flora

Fergus Shanahan

Inflammatory bowel disease—a collective term embracing both ulcerative colitis and Crohn's disease—is a significant health-care problem affecting between 0.1% and 0.2% of the population in developed countries. These important and disabling conditions are characterized by diarrhea, pain, and other intestinal symptoms, and by lifelong relapses. Ulcerative colitis is confined to the mucosal layer of the large bowel, whereas Crohn's disease can affect any portion of the intestinal tract. The pathogenesis of inflammatory bowel disease is complex but appears to involve interactions among three essential ingredients: host genetic susceptibility, intestinal bacteria, and the gut mucosal immune response.

Despite impressive advances in drug therapy, most treatment strategies have two major limitations: first, they suppress or otherwise alter the host immune response, thereby neglecting the contribution of enteric bacterial microflora to disease pathogenesis; and second, current immunomodulatory drugs lack organ specificity, affecting both mucosal and systemic host responses and resulting in unpleasant side effects. On page 1352 of this issue, Steidler and colleagues (*1*) address both of these concerns in their report of a therapeutic approach for local drug delivery in two mouse models of colitis. They show that dietary administration of the murine enteric bacterium *Lactococcus lactis*—genetically engineered to produce the anti-inflammatory cytokine interleukin-10 (IL-10) within the gut—is therapeutically effective in the mouse models. Their work demonstrates that convergence of the traditional research avenues of immunology and microbiology into a hybrid discipline yields new therapeutic strategies for combating complex diseases.

The immune response in the intestinal mucosa is conditioned by the indigenous bacterial microflora with which it exchanges regulatory signals (*2*). In susceptible individuals, inflammatory bowel disease arises when the immune system misperceives danger within the normal gut microflora and interprets the harmless enteric bacteria as pathogenic in-

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