

subject to neuromodulation¹⁰, and that the intrinsic properties of neurons will govern how they respond to synaptic drive. This early work provided a library of possible mechanisms¹¹ that could, in principle, account for some of the state-dependence in pain processing. Nonetheless, nothing is more satisfying than learning exactly how the cellular and synaptic mechanisms in a particular circuit contribute to its function. The finding that most or all deep dorsal horn

neurons are subject to neuromodulation is an important step forward in understanding early stages of pain processing.

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A switch for oscillatory bursting

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A recent article in *Nature* suggests that inhibitory feedback can switch the firing of sensory neurons between two signaling modes that may be used to process distinct sensory stimuli.

Weakly electric fish have long been a favorite preparation for studying the neural computations underlying specific behaviors¹. A new paper in *Nature* from Doiron *et al.*² now demonstrates a behaviorally relevant role for inhibitory feedback in electric fish. Whether this feedback is active or not determines whether sensory neurons fire in an oscillating or a tonic mode, which may correspond to two different modes of transmission for sensory information.

Fish such as *Apteronotus leptorhynchus* (Fig. 1) discharge their electric organ rhythmically and continuously at high frequencies, about 1000 times per second. This results in an electric field that surrounds the fish and fluctuates rapidly in a sinusoidal pattern. Through the so-called P-receptors, a class of electroreceptors that are distributed over the whole skin surface, the fish can detect alterations in the amplitude of these fluctuations, thereby obtaining information about objects in its vicinity (Fig. 2).

Two patterns of amplitude modulation convey different signals with different behavioral relevance. Small objects, such as the invertebrates on which these fish prey, cause local modulations of the field, affecting only those receptors on the patch of skin closest to the object. A

different pattern is produced by signals from other fish of the same species, whose own electrical fields are used to convey courtship or aggression-related signals. These signals produce a global amplitude modulation, which affects receptors across the whole surface of the responding fish.

Doiron *et al.*² set out to determine how the electroreception system responds to these two classes of stimuli. To mimic prey signals, they used a small dipole electrode close to the skin, and to mimic the signals from conspecifics, they used two large electrodes situated on either side of the fish. They recorded from the pyramidal cells of the electrosensory lateral line lobe (ELL), the hindbrain nucleus that receives input from the electrosensory receptors. These cells receive sensory information from the P-receptor afferents, which fire in response to changes in the amplitude of the fluctuating electrical field. In addition to this direct sensory input, these

cells also receive input from local circuitry within the ELL, as well as feedback from higher brain areas, through three distinct pathways³. Because they provide the sole output from the ELL related to electric field amplitude, these pyramidal cells are key elements in the electrosensory pathway, and understanding their responses is central to understanding how the fish processes electrosensory information.

The authors report that the pyramidal cells show two distinct firing modes in response to the two types of stimuli (see also ref. 4). Local stimuli produce a pattern of firing with a classical, almost textbook appearance. The interspike interval (ISI) distribution reveals a refractory period followed by a peak at about 10 ms and a tail that decays exponentially. This distribution is the signature of a tonic pattern of firing, in which cells fire in an irregular and nearly random manner. In contrast, the global stimulus produces a different ISI distribution, in which the first peak is much sharper and is followed by a second smaller peak before the tail. Moreover, a two-dimensional plot of successive ISIs reveals a distinct pattern in response to the global stimuli, in which short (~10 ms) intervals tend to be followed either by another of the same duration or by much longer (20–40 ms) intervals. This is characteristic of neurons firing rapid bursts of 2–3 spikes at a frequency of ~100 Hz, followed by longer intervals amid isolat-

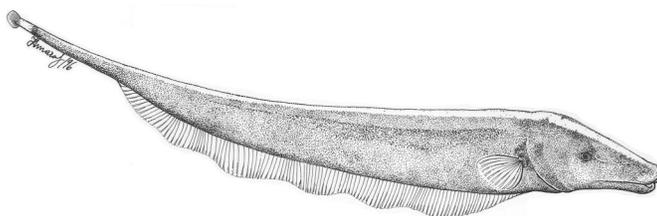


Fig. 1. Drawing of *Apteronotus leptorhynchus* (brown ghost knifefish), a weakly electric fish from South America that reaches about 30 cm in size.

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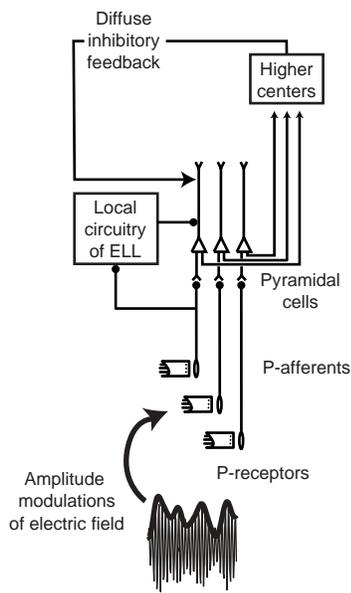


Fig. 2. Schematic of the neural pathways that process amplitude modulations of the electric field (bottom). P-receptors are distributed over the skin surface and are contacted by afferent fibers (P-afferents) that convey information to pyramidal cells and interneurons in the ELL, a structure in the hindbrain of the fish.

ed tonic spikes—in other words, a pattern of oscillatory firing (see also ref. 5).

How can the same cells show two different firing patterns depending on the nature of their sensory inputs? One possibility is that the two different behaviors can be explained entirely in terms of intrinsic conductances within the pyramidal cells themselves^{6–8}. Alternatively, the oscillatory behavior might somehow be generated by local circuitry within the ELL. A third possibility, which had been suggested by previous work⁹, is that oscillations may depend on feedback from higher brain regions. Doiron *et al.*² now provide both theoretical and experimental evidence that this third explanation is the correct one. The authors construct a simple and elegant network model based on the observation that pyramidal cells receive a delayed and spatially diffuse inhibitory feedback from a higher-order structure called the nucleus praeminentialis dorsalis. In most of their simulations, pyramidal cells are represented as leaky integrate-and-fire neurons, but the authors also confirmed the main result using more realistic model neurons with two compartments and intrinsic bursting properties. The pyramidal neurons transmit their spikes to a population of neurons corresponding to a subset of cells in the n. praeminentialis dorsalis, and this population in turn sends a delayed inhibitory signal back to all of the pyramidal cells. Doiron *et al.* con-

firm that this simple model can indeed generate the two types of firing observed in response to the two different stimuli. Delayed negative feedback is known to be capable of producing oscillatory behavior, and the key point about the authors' model is that this feedback is stronger in response to the global stimulation, when a large number of pyramidal cells activate the inhibitory cell population synchronously¹⁰.

The authors then sought to test their model experimentally. In a technically challenging experiment, they used local injection of a reversible sodium channel antagonist to block transmission along the fiber tract that conveys the inhibitory feedback to the ELL. Gratifyingly, blocking this pathway prevented the oscillatory response to the global stimulus, and the oscillations reappeared after the drug had worn off. This result, combined with the theoretical simulations, provides strong evidence that feedback from higher brain structures is responsible for toggling the firing state of the pyramidal cells from tonic to bursting behavior in response to global stimulation of the electrosensory system.

The authors raise the interesting possibility that the two firing modes correspond to two different signal-processing modes. Indeed, they provide some preliminary evidence that this may be the case; in the supplementary information accompanying the paper, they use a stimulus estimation technique that can detect coding changes through changes in the instantaneous firing rate¹¹, and they find that the tonic mode is better suited to encoding details of amplitude modulations in the electrical field.

These findings may also have a broader significance beyond the electrosensory system of weakly electric fish. Similar mechanisms have been proposed to operate in the mammalian thalamocortical system, where the thalamic relay neurons can switch between tonic firing and bursting in response to feedback from the cortex^{12,13}. Weakly electric fish, however, is a particularly attractive system for pursuing this question, given that its circuitry is relatively well character-

ized and that mimicking behaviorally relevant stimuli is relatively straightforward.

A number of interesting questions remain to be addressed. It is still not clear exactly what attributes of the local stimulus are encoded in the tonic mode (especially as the performance of pyramidal cells in coding amplitude modulations usually lags behind that of the P-receptors). We might learn more from making recordings during behaviorally relevant episodes such as prey capture, although such experiments will not be easy, or from using a combination of simulation and behavioral techniques¹⁴. Yet regardless of what exactly is being encoded in the two modes, it should now be possible to characterize the temporal and spatial scales over which the switching mechanism operates. The answers are likely to provide important general insights into the role of feedback during sensory processing.

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