and shoulder girdle muscles.

LGMD is genetically heterogeneous with a dominant form (LGMD-1A) mapping to 5q and four recessive forms (LGMD-2A, 2B, 2C, 2D) mapping to 15q, 2p, 13q, and 17q, respectively; the latter two co-map with the γ- and α-sarcoglycan genes. Lim *et al.* (*2*) have now demonstrated that LGMD in the old order Amish of southern Indiana is linked to markers on 4q, indicating the existence of another locus (LGMD-2E), and have shown that this locus is the β-sarcoglycan gene at 4q12. The homozygous missense mutation in the affected members results in loss of all three sarcoglycans from the muscle membrane. This result was surprising because the Amish of northern Indiana, despite a common European origin (the Canton of Bern, Switzerland), exhibit LGMD-2A caused by mutations in the gene at 15q15 that encodes the muscle-specific proteolytic enzyme calpain-3 (*12*).

Further evidence for β-sarcoglycan involvement comes from Bönnemann *et al.* (3), who analyzed cDNA from 62 unrelated dystrophin-positive patients with muscular dystrophy and found one individual with mutations in the β-sarcoglycan gene. This was a 3-year-old female with moderate muscle weakness and dystrophic changes similar to a DMD or SCARMD phenotype. One allele carried a stop codon mutation and the other an 8-bp duplication that resulted in a stop codon. Her muscle biopsy was positive for dystrophin immunostaining but negative for the three sarcoglycans, similar to the biopsies from the Amish, indicating that the sarcoglycan complex may act as a functional unit distinct from the dystroglycan complex. This complex is also deficient in the cardiomyopathic hamster, although a specific mutation has not yet been reported.

The dystrophin complex is clearly required for the maintenance of normal muscle. The sarcoglycan complex is certainly as important as dystrophin, and loss-of-function mutations in the dystrophin gene or any of the three sarcoglycan genes results in a severe phenotype. Mutations that cause partial loss of function (missense or non–frame-shifting deletions) in dystrophin produce a milder BMD phenotype and in the sarcoglycans appear to cause a mild LGMD. To complete the picture, loss-of-function mutations in the merosin gene have recently been described in severe congenital muscular dystrophy (CMD) (*13*), and merosin is deficient in the dystrophic dy/dy mouse (*14*, *15*). To date, no genetic lesions have been described for α- or β-dystroglycan that bridge between dystrophin and merosin.

The function of the complex remains a mystery. Is it merely structural, protecting the integrity of the membrane? Or do the proteins of the complex have other, nonstructural roles? Could they form the stretch-activated calcium channel that is defective in DMD muscle? Many questions remain without answers, but at least we now know the questions.

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Cracking the Neuronal Code

David Ferster and Nelson Spruston

To control behavior, the central nervous system employs approximately one trillion (10^{12}) neurons, all connected in networks of unfathomable complexity. The challenge for neuroscientists is to learn how these networks do their job. For decades, most neurophysiologists have assumed that a neuron's information content is contained solely in its firing rate, the number of action potentials it sends down its axon in any given period. An alternative view—that temporal firing patterns contain information—although considered somewhat heretical, is gaining attention as a result of new theoretical and experimental approaches.

Consider the firing pattern of the neuron in the figure. Three groups of 10 action potentials occurring in a 100-ms period travel down the axon, each group occurring in a different temporal pattern (three insets). According to the rate code hypothesis, the timing of each change in firing rate would indicate when an event occurred, and the strength of the increase might report how strong the stimulus was (*1*). In each case, however, the "what" of the stimulus would be the same; any single neuron could code for the presence of only a single stimulus property. By averaging the firing rates of a number of neurons responding to the same stimulus property, the nervous system could determine the strength of that stimulus at any point in time. By considering the activity of many such populations responding to different stimulus properties, the exact nature of a complex stimulus could be deciphered, as originally postulated in the line-labeling models of neuronal coding in peripheral nerves (*2*, *3*).

In contrast to the rate code model, the temporal code hypothesis holds that the firing pattern of an individual neuron could report different "whats," even while the average firing rate remained unchanged. A single neuron like the one in the figure could report the presence of three different stimuli with the three different temporal firing patterns shown in the insets. Such a temporal code could, in principle, resolve some of the apparent ambiguity of the information provided by neurons of the visual cortex. The response of each cortical neuron is dependent on many different features of a stimulus—for example, its orientation, its length, or its contrast. A rate code requires that the brain determine the exact nature of the stimulus by comparing the output of many different neurons; in a temporal code, one neuron could unambiguously code changes in a single feature of the stimulus by emitting one of a large repertoire of temporal output patterns (*4*).

Despite the appeal of packing a large amount of complex information into the spike train of a single neuron, the temporal code hypothesis has yet to be universally accepted. In many parts of the brain, neurons fire in highly irregular temporal patterns. But do such patterns encode different events, or are they merely random noise superimposed on a basic firing rate?

One approach to this question is to consider the mechanisms whereby irregular firing might arise. The long-standing "integrate and fire" models of neuronal function produce highly regular firing patterns (*5*). Two alternative models (*6*–*8*) have suggested different mechanisms for generating the highly irregular spike intervals observed in the visual cortex. One model is well suited to precise temporal coding; the other is a random process that precludes such coding.

The first model is based on the concept that rapidly rising depolarizations are required to trigger action potentials that accurately reflect the timing of synaptic in-

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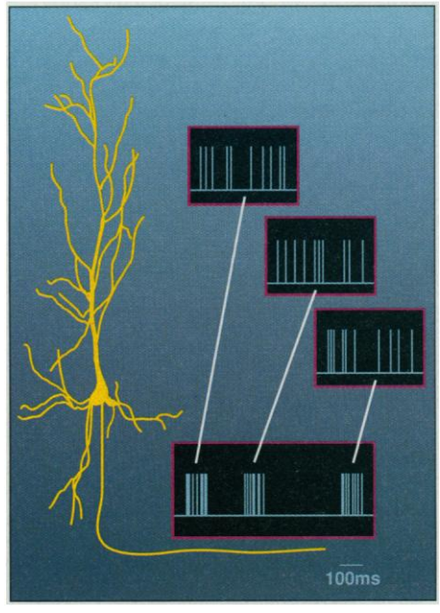
puts (9). Softky and Koch suggest that such events are generated when a sufficient number of synaptic inputs are activated simultaneously (5, 7). In this model, then, single events generated several milliseconds apart must be prevented from summating to produce slow depolarizations to threshold, so synaptic potentials must decay more quickly than dictated by the passive electrical properties of the neuron. To allow coincidence detection, Softky and Koch incorporated dendritic K^+ conductances tuned to accelerate the decay of synaptic potentials (10). In addition, Na^+ conductances in the dendrites of the model amplify synaptic potentials, thus reducing the number of coincident synaptic inputs required to fire a spike. There is little evidence, however, that dendritic conductances shape synaptic inputs in the service of coincidence detection.

Contrasting this coincidence model is the "random walk" model (6, 11). In this model, a stimulus evokes a barrage of temporally uncorrelated excitatory and inhibitory synaptic events that step the membrane potential up and down in random temporal patterns. A slight preponderance of excitation increases the frequency with which the membrane potential reaches threshold. Because this model lacks specialized dendritic conductances, synaptic inputs can summate over longer periods, thereby degrading the ability of the cell to generate meaningful temporal patterns. The precise timing of synaptic inputs is therefore not reported in the resulting spike train, and only the rate of firing contains information.

Considerable experimental evidence suggests that rate codes can explain many types of neuronal integration. Countless descriptions of receptive fields in sensory physiology, from the early classical studies to modern quantitative measurements, report the correlation between sensory stimuli and neuronal firing rates averaged over many trials. Similarly, motor output often correlates with firing rates. As such studies increase in complexity, however, a simple rate code may be rendered inadequate as a predictor of behavior.

Evidence for temporal codes is more limited, but is growing: (i) In frontal cortex, temporal patterns that are spread across two or three neurons recur with precisely defined interspike intervals and may be associated with specific behavioral events (12, 13). (ii) Although the average firing rates of groups of neurons in the auditory cortex encode only the onset and offset of long-lasting auditory stimuli, the degree of synchronization among groups of neurons (a temporal code) indicates the duration of the stimulus (14). In the visual system, synchronization among neurons responding to different image features may indicate that those features belong to the same object (15). A group of synchronously firing neurons would likely fire their postsynaptic targets more readily than a group of unsynchronized neurons. (iii) The synchronous firing of adjacent retinal ganglion cells defines a region closely approximating the overlap between their receptive fields (16). Thus, the retina may use a temporal code to build a more precise representation of a visual image than could be encoded by the firing rates of individual ganglion cells. (iv) In hippocampal place cells, the phase of action



The language of the brain. In each case, the average firing rate of the action potentials is the same (100 Hz), but the temporal pattern differs, as shown in the three insets. Do these three patterns represent the same event in the neural code, or does the brain use information in the temporal patterns of action potentials to distinguish among different events?

potentials relative to the hippocampal theta rhythm corresponds to whether the animal is entering or leaving the cell's place field (17). Here the timing reference for a spike in one cell is not another spike in the same cell or in other cells, but the phase of an oscillating field potential. Such oscillations may be generated by networks of interneurons and provide an important "context" for the firing of principal neurons (18). Hopfield (19) recently proposed a model for generating precisely such phase relations and suggested that neuronal networks could process phase-coded information more effectively than the raw rate-coded information provided by sensory afferents. Note, however, that none of these temporal codes precludes a rate code being superimposed on it simultaneously. Hippocampal place cells, for example, clearly signal by their rates whether the animal is within the place field, independently of whether the animal is entering or leaving that field (20).

All of these results show the existence of unique temporal spike patterns in the brain. Proving that these patterns constitute a temporal code, however, is a daunting task. Shadlen and Newsome, for example, recorded spike trains from direction-selective neurons in area MT of the monkey visual cortex while the monkey repeatedly viewed the same pattern of moving random dots (8). The temporal pattern of action potentials evoked by each presentation of the stimulus was complex, but similar from trial to trial. There is no evidence, however, that this is a temporal code reporting "what" sort of event has occurred, as opposed to "when" and "how strong" the variations in the direction signal were buried within the noisy stimulus. A rapid increase in spike rate associated with a change in the movement signal occurring at the same point during each trial will, after all, reliably trigger a spike within a very small time window. A series of such events recorded within a single cell during presentation of a complex stimulus could mimic temporal codes, as could rapid changes in rate that occurred simultaneously in several neurons. Clear proof for a temporal code would require that distinct stimuli could reliably produce different temporal spike patterns. Shadlen *et al.* have searched for such unique patterns and failed to find them, but many investigators continue to look for meaning in the temporal pattern of action potential firing. Whether or not they find it will profoundly influence our view of neuronal codes.

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