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Neural Basis of Rhythmic Behavior in Animals

Fred Delcomyn

General principles are important in biological science because they help unify observations made in widely different groups of organisms. The field of neurobiology has a number of such principles but few, if any, that apply broadly across the animal kingdom also address levels of organization beyond that of the single cell. This may be due partly to the greater apparent complexity of events at the multicellular level. For example, while it seems reasonable to believe that an action potential has a single physiological basis in all animals, it may not seem quite so obvious that the neural basis of a behavior like locomotion might be similar in animals as different as a cockroach and a cat. Yet there is no intrinsic reason why general principles of integration underlying simple behaviors should not exist.

Evidence presented over the last two decades overwhelmingly supports one such general principle: that the central nervous system does not require feedback from sense organs in order to generate properly sequenced, rhythmic movement during repetitive behaviors such as locomotion. Recognition of this principle will mean the resolution of a controversy nearly three-quarters of a century old, a resolution brought about in part by the recognition that the competing hypotheses underlying the controversy are not mutually exclusive.

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The Concept of Central Control

Rhythmic behaviors are those in which all or part of an animal's body moves in a cyclic, repetitive way; examples are walking, swimming, scratching, and breathing. Historically, there have been two main hypotheses about the neural mechanisms underlying such simple behaviors. These hypotheses were intended to explain the observation that contractions of the muscles that produce the behavior always occur in a rhythmic and predictable pattern, such as the alternation of extensor and flexor muscles in a limb during walking or the serial activation of body wall muscles during undulatory swimming.

The first hypothesis, peripheral control, holds that these rhythmic patterns are achieved through the use of sensory feedback from the moving parts of the body. One phase of the cycle of movement is thought to provide the sensory cues necessary for the proper timing of the next phase, so that loss of the normal sensory feedback disrupts the behavior.

The second hypothesis, central con-

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Summary. Timing of the repetitive movements that constitute any rhythmic behavior is regulated by intrinsic properties of the central nervous system rather than by sensory feedback from moving parts of the body. Evidence of this permits resolution of the long-standing controversy over the neural basis of rhythmic behavior and aids in the identification of this mechanism as a general principle of neural organization applicable to all animals with central nervous systems.

trol, holds that the central nervous system is intrinsically capable of providing the proper timing of muscle activation without requiring sensory feedback. That is, a single pacemaker neuron or a network of neurons, often referred to as a neural "oscillator" or central pattern generator (*1*), is thought to be able to produce a repetitive, rhythmic output. This output, in turn, directly or indirectly drives the muscles used in the rhythmic behavior in the proper sequence and with the proper temporal relationships. The emphasis here is thus on a system that is automatic and independent of necessary sensory feedback, although such feedback may modulate the intrinsic pattern.

The history of the controversy between central and peripheral control of rhythmic behavior has not been reviewed adequately. Briefly, it can be said that while both concepts had advocates quite early (*2*), the hypothesis of central control was overwhelmed by evidence presented in the 1930's and 1940's indicating that sensory feedback played an important role. During this period, the work of Sir James Gray and his collaborators (*3–5*) was especially persuasive. While Gray's work was not without flaws, it was unusually careful and thorough for its time and carried the day until important theoretical papers by von Holst (*6*) and Bullock (*7*) and new work with both invertebrate and vertebrate animals changed the prevailing view (*8*).

The principle of central pattern generation is now well established for a number of familiar behaviors. For example, Grillner (*9*) and Delcomyn (*10*), in their reviews of locomotion in vertebrates and invertebrates, respectively, and Stein (*11*) in his general review of locomotion, concluded that central control mechanisms were used in all animals studied. Similar conclusions were drawn in reviews of respiration in vertebrates by Wyman (*12*) and in invertebrates by Kammer (*13*). It has also been suggested that other behaviors such as chewing are generated centrally (*14*). And yet, because the evidence encompasses an unusual diversity of behaviors and animal groups, many neuroscientists outside the field of motor control are not yet aware of how widely the principle can be applied.

Table 1 lists every rhythmic behavior for which good evidence in support of the hypothesis that rhythmic behaviors are generated centrally has been obtained and the animal in which it was studied. Represented are 13 different activities ranging from walking to breathing, and nearly 50 species of animals distributed among 11 classes and 4 phyla. Before the generality of the concept of central generation of rhythmic behavior can be accepted, however, two questions must be dealt with successfully: the question of how strong the evidence is that is embodied in the work in Table 1, and the question of how to resolve the apparent conflict between the results that seem to support the hypothesis of peripheral control and the results that support the concept of central control.

The Case for Central Control

The evidence summarized in Table 1 is derived from isolation, deafferentation, and paralysis experiments (*15, 16*). The strongest evidence comes from studies in which all or part of the nervous system is isolated (that is, physically removed from the animal), and the motor pattern under study is recorded from the severed stumps of the appropriate nerve bundles. The objective of such experiments is to show that complete isolation of the nervous system from all possible sources of sensory feedback does not abolish the normal pattern of rhythmic bursts in motoneurons. The procedure has been carried out successfully in nearly half of the experiments in Table 1.

The results of isolation experiments must be interpreted with caution even though they do provide the most clear-cut evidence. The two main possible sources of error are (i) lack of proper identification of the behavior associated with the recorded motor output and (ii) the presence of unrecognized timing cues generated by injury discharge or electrical stimulation of sensory neurons.

It is essential that investigators demonstrate that a motor pattern recorded from an isolated (or deafferented) nervous system represents the pattern that, in an intact animal, would have produced the behavior under study. This requirement is usually met by comparing selected motor output from minimally dissected animals with that from isolated nervous systems (*17, 18*).

Undetected timing cues could also produce misleading results. For example, inputs from several injured or electrically stimulated sensory neurons firing at slightly different frequencies might interact to produce a repetitive timing cue as the neurons drift in and out of phase with one another (*19*). In many preparations, however, rhythmic output is generated by the isolated nervous system long after either injury discharge (*20*) or the stimulus required to elicit activity (*21*) has stopped. In other cases, random stimuli can be used to avoid creating beat frequencies.

The isolation experiments in Table 1 were designed to avoid these sources of error, and thus provide strong evidence in support of the idea of central pattern generation. Further, rhythmic activity was demonstrated in isolated nervous systems from four phyla and in association with all but one of the major types of behavior. The strongest evidence is not concentrated in only a few closely related animals or similar behaviors.

In nearly 40 percent of the studies, deafferentation, the second most powerful technique, was used. In this procedure, all or some of the sensory nerves that carry information into the nervous system are severed, and the effect of the operation on the ability of the nervous system to produce patterned motor output is studied. The objective here is the same as that in isolation experiments: to show that loss of presumably critical sensory feedback does not affect the production of rhythmic activity in motor neurons and, therefore, in muscles.

Deafferentation has a number of disadvantages, but it must be used in cases in which the nervous system will not survive the total disruption of its normal blood or tracheal oxygen supply, or in cases in which a stimulus more natural than an electrical shock is required to initiate rhythmic activity. The strength of the evidence provided by deafferentation experiments depends largely on the degree of deafferentation. In cases in which some part of the nervous system is isolated in situ, which I have included in the deafferentation category, the persistence of rhythmic output is nearly as convincing as it is in experiments in which the nervous system is completely sepa-

rated from surrounding tissues, although it is conceivable that small, undetected neural connections may still be providing timing cues. Such total deafferentation experiments have been conducted on both vertebrates (*22*) and invertebrates (*23*).

In other experiments, the part of the body that moves during the rhythmic behavior is completely deafferented, but other parts are not disturbed. For example, in Pearson and Iles' (*24*) study of cockroach walking, all legs and the thorax were deafferented, but the head and abdomen were not. Pearson and Iles argued that the rhythmic activity they recorded from severed leg nerves was produced by a central oscillator since no sensory input still available to the animal after deafferentation was excited in synchrony with the output and, therefore,

Table 1. Rhythmic activities for which evidence in support of the hypothesis of central control has been obtained.*

Behavior or activity	Animal (species)	Procedure (*15*)	Reference
Breathing or ventilation	Cat (*Felis domestica*?)†	Deafferentation	(*22*)
	Duck [*Anas platyrhynchos* (var.)]	Paralysis (curare)	(*57*)
	Goldfish (*Carassius auratus*)	Deafferentation	(*58*)
	Goldfish (*Carassius auratus*)	Paralysis (succinylcholine)	(*59*)
	Catfish (*Parasilurus asotus*)	Deafferentation	(*58*)
	Cockroach (*Blaberus craniifer*)	Isolation	(*60*)
	Cockroach (*Periplaneta americana*)	Isolation	(*61*)
	Cockroach (*Byrsotria fumigata*)	Isolation	(*62*)
	Locust (*Schistocerca gregaria*)	Deafferentation	(*63*)
	Dragonfly nymph (*Aeshna juncea*)	Isolation	(*64*)
	Lobster (*Homarus* sp.)	Deafferentation	(*65*)
	Hermit crab (*Pagurus pollicarus*)	Isolation	(*65*)
	Horseshoe crab (*Limulus polyphemus*)	Isolation	(*66*)
Feeding or chewing	Cat (*Felis domestica*?)	Paralysis (gallamine triethiodide)	(*67*)
	Rabbit (*Oryctolagus cunicula*?)	Deafferentation and paralysis (gallamine triethiodide)	(*68*)
	Barnacle (*Balanus cariosus*)	Isolation	(*20*)
	Barnacle (*Balanus hameri*)	Isolation	(*69*)
	Snail (*Helisoma trivolvis*)	Isolation	(*18*)
	Snail (*Lymnaea stagnalis*)	Isolation	(*70*)
	Marine gastropod (*Pleurobranchaea californica*)	Isolation	(*71*)
Locomotion			
Creeping	Sea hare (*Aplysia* sp.)	Isolation	(*72*)
Flying	Locust (*Schistocerca gregaria*)	Deafferentation	(*73*)
	Dragonfly (*Hemianax papuenisis*)	Deafferentation	(*74*)
Swimming	Toad (*Bufo bufo*)	Deafferentation	(*75*)
	Toad embryo (*Xenopus* sp.)	Paralysis (curare)	(*76*)
	Tench (*Tinca vulgaris*)	Deafferentation	(*25*)
	Loach (*Cobitis fossilis*)	Deafferentation	(*25*)
	Eel (*Anguilla vulgaris*)	Deafferentation	(*25*)
	Dogfish shark (*Squalus acanthias*)	Deafferentation and paralysis (curare)	(*47*)
	Salp (Tunicate) (*Thalia democratica*)	Isolation	(*77*)
	Salp (Tunicate) (*Salpa fusiformis*)	Isolation	(*77*)
	Nudibranch mollusk (*Tritonia diomedia*)	Isolation	(*21*)
	Leech (*Hirudo medicinalis*)	Isolation	(*41*)
Walking or hopping	Cat (*Felis domestica*?)	Deafferentation and paralysis (curare)	(*44*)
	Rabbit (*Oryctolagus cunicula*?)	Paralysis (gallamine triethiodide)	(*78*)
	Toad (*Bufo marinus*)	Deafferentation	(*43*)
	Cockroach (*Periplaneta americana*)	Deafferentation	(*24*)
	Milkweed bug (*Oncopeltus* sp.)	Deafferentation	(*79*)
Scratching	Cat (*Felis domestica*?)	Paralysis (gallamine triethiodide)	(*80*)
Sound production	Chicken (*Gallus domesticus*?)	Paralysis (curare)	(*81*)
	Frog (*Rana pipiens pipiens*)	Isolation	(*17*)
	Cricket (*Gryllus campestris*)	Deafferentation	(*82*)
Miscellaneous			
Eclosion	Moth (*Hyalophora cecropia*)	Isolation	(*83*)
Intestinal movements			
Gastric mill	Lobster (*Panulirus interruptus*)	Deafferentation	(*84*)
	Lobster (*Panulirus argus*)	Isolation	(*85*)
	Crab (*Cancer pagurus*)	Isolation	(*86*)
Hindgut	Lobster (*Homarus gammarus*)	Deafferentation	(*87*)
Heartbeat‡	Lobster (*Homarus americanus*)	Isolation	(*88*)
	Lobster (*Panulirus interruptus*)	Isolation	(*89*)
	Horseshoe crab (*Limulus polyphemus*)	Isolation	(*90*)
	Leech (*Hirudo medicinalis*)	Isolation	(*91*)
Shell opening	Mussel (*Anodonta cygnea*)	Isolation	(*23*)
Swimmeret beating	Crayfish (*Procambarus clarkii*)	Deafferentation	(*92*)

*Confirmatory work has not been included unless a different experimental procedure was used. The references list the original work first and then more recent work or reviews of work in the particular system. †Species names of common domestic animals, followed by a question mark, were not given by the authors: the probable species name is listed. ‡Most studies of the activity of heart ganglia do not attempt to show that sensory feedback from the beating heart is not necessary for rhythmic output and, therefore, have not been included.

none could have provided timing cues. Although this argument is not unassailable, it is nevertheless a strong one.

In some experiments, even the moving body parts were only partly deafferented. Such experiments were usually conducted because the animal would not tolerate more extensive surgery. With one exception (*25*), experiments of this sort have not been included in Table 1, because it could be argued that intact sensory nerves near the deafferented part could provide timing cues. Thus, experiments in which one or two limbs of a monkey (*26*), mouse (*27*), bird (*28*), or newt (*29*), or a few segments of a polychaete worm (*30*) were deafferented, do not provide sufficiently strong evidence in favor of central pattern generators to be used to establish the generality of the principle.

The exception is a series of experiments carried out by von Holst (*25*) on fish. In his experiments, so much of the body (one-third or more) was deafferented, without disruption of proper coordination of head and tail (during swimming), that it becomes difficult to deny the central control of this behavior.

Deafferentation experiments are technically easy to carry out on vertebrates due to the almost complete physical separation of sensory afferents from motor axons at their place of entry into the spinal cord. Nevertheless, extensive or complete spinal deafferentation is rarely a successful procedure because eliminating all or most sensory input in a vertebrate depresses the central nervous system so much that in most cases the animal can be induced to perform any rhythmic behavior only with great difficulty, if at all (*31*). In addition, sense organs in the head are still intact and able to provide input that might provide timing cues.

To circumvent these problems, some investigators use a paralytic agent to eliminate all possible movement during the time in which the animal is generating patterned motor output. The objective of such experiments is to show that patterned output can be produced in motor neurons in the absence of patterned sensory feedback. If the animal is totally paralyzed, no muscular contraction can take place, and the consequent lack of movement means that no sensory feedback that is time-locked to the motor activity can be occurring either. The main advantage of this procedure is that only the sensory input associated with movement is absent. Other sensory signals are unaffected, so the debilitating effects of surgical deafferentation are not manifest.

Experiments with pharmacological agents only provide good evidence if side effects of the drugs do not produce spurious results. The main drugs used as paralytic agents have been curare (*d*-tubocurarine chloride) and Flaxedil (gallamine triethiodide). Curare can cross the blood-brain barrier but only in dosages considerably higher than those normally used for paralysis (*32*) and, therefore, effects of this drug on the brain should be negligible. The effects of the paralytic agent on elements of the neuromuscular effector system other than the power-producing muscles are also important. One such element is the muscle spindle since the small muscle fibers that are part of each spindle have their own innervation. Normally, excitation of the spindle muscle excites the spindle sense receptors, which can reflexly excite the motoneurons innervating the power muscle in which the spindle is situated. Fortunately, studies have shown that normal doses of both curare and Flaxedil paralyze the spindle muscle as well as the power muscle (*33*), so that during paralysis, activation of the spindle motoneurons by the central nervous system cannot reflexly influence activity in the motoneurons that innervate the power muscle, even though spindle stretch receptors are still functional. In general, then, these paralysis experiments also provide strong evidence in support of the hypothesis of central control.

The Case Against Central Control

The main argument used against the hypothesis of central control was that reflexes are competent in individual cases to produce the rhythmic movements under study, and that elimination of these reflexes by deafferentation or isolation of the nervous system abolishes the rhythmic behavior or rhythmic motor output. Gray and his various collaborators supported this argument for both invertebrate and vertebrate animals. In two early papers (*3*, *34*), for example, they showed that leeches and earthworms exhibited a number of responses during swimming, crawling, or "walking" that seemed to form a chain of reflexes in which each movement provided the trigger for the next throughout the entire cycle of the behavior. In addition, in their hands, an isolated nerve cord yielded no sign of any rhythmic motor output.

Gray and Lissmann (*4*, *35*) reported similar results with toads and frogs. They showed first that a toad whose spinal cord had been severed just behind the head could be made to step by reflex action simply by being held against a slowly rotating drum; the stimulus to step was stretch of a leg. This and other results led them to propose that a chain of reflexes could account for walking. Later experiments in which toads were totally deafferented along the spinal cord seemed to reveal a complete lack of coordinated walking after the surgery, and Gray and Lissmann argued that sensory feedback was essential for proper expression of this rhythmic behavior. A study of the dogfish shark (*36*), which also showed the absence of rhythmic motor activity after elimination of sensory feedback, has also been used to support the argument that a rhythmic behavior is peripherally controlled.

Another argument against the concept of central pattern generation that has been used more recently is that, if altering sensory feedback in an animal results in an alteration or disruption of normal rhythmic movements, then the proper sensory feedback is required to produce the normal rhythm. This is the argument used to interpret the well-known observation that insects immediately change gait when their middle pairs of legs are removed (*37*).

Mellon (*38*) used this line of reasoning to explain his findings in the scallop. A scallop swims by rapidly opening and closing its shell. Shell closing is powered by contraction of the strong adductor muscle, and opening is effected by the springlike action of the elastic shell hinge as the adductor relaxes. Mellon investigated the neural basis of this rhythmic behavior by recording from the motor nerves to the main adductor muscle under various circumstances. His most significant finding was that, if he bound the shell closed, he could abolish the normal rhythm of alternating contraction and relaxation. The bivalved scallop ceased to fire its adductor muscle. Mellon concluded that the nervous system of the scallop required feedback from receptors in the adductor muscle itself in order to signal that the muscle should start to contract. In other words, this was apparently a classical case of coordination or pattern generation by sensory (peripheral) control.

Several other investigators have also demonstrated the capability of particular sensory input to disrupt or arrest the normal cycle of motor output in a variety of animals (*39*, *40*) but, for reasons discussed below, none has used his evidence to support the hypothesis of peripheral control.

Resolution

On the basis of the evidence embodied in Table 1, there is no doubt that many specific rhythmic behaviors are generated by central mechanisms. Yet, studies such as those summarized above provide arguments against this explanation in certain instances. Thus, it would seem difficult to justify a claim that central control mechanisms are universal. Analysis of all the evidence will show that even strong peripheral modulation of a rhythmic activity does not preclude a central mechanism, and that both hypotheses have elements of truth in them.

First, the evidence that absence of feedback will result in cessation of some rhythmic behaviors, especially the evidence provided by older work is not very good in view of detailed modern studies. Although Gray *et al.* (*3*, *34*), for example, reported that they were unable to record rhythmic neural activity in leeches and other annelids after complete isolation of the nerve cord, Kristan and Calabrese (*41*) were successful in recording such activity from isolated nerve cords of leeches. This success, however, came only after repeated attempts at such recording (*42*). In other instances as well, modern techniques have yielded different results. For example, reported that they were unable to record rhythmic neural activity in subsequent behavior seem to be affected by the amount of incidental damage the surgery does (*43*) as well as the way the animal is held or manipulated after the surgery (*44*). Thus, with sufficient care, animals will behave well after surgery that was previously thought to be totally debilitating (*43*).

Changing standards have also affected the view of what constitutes a complete and well-documented report, especially with regard to behavioral changes. Gray and Lissmann (*4*, *35*) reported that toads with totally deafferented spinal cords showed no signs of coordinated ambulation. Yet a more recent study by Harcombe and Wyman (*43*) clearly showed that even totally deafferented toads would take steps and use their legs in the normal sequence at least part of the time. It therefore seems possible that a quantitative study of filmed sequences of stepping by Gray and Lissmann would have produced quite a different conclusion than did their unaided observations of the toads.

In sum, repetition of the most carefully executed experiments performed by Gray and his co-workers on leeches and toads, in which neural or behavioral rhythmic output is eliminated by the removal of sensory feedback, has failed to substantiate the original conclusions. This fact, together with the mass of evidence showing that peripheral cues are not necessary for timing, throws serious doubt on the validity of other older work from which support for peripheral control has been drawn.

Second, there is a question of whether the hypothesis of peripheral control actually is supported by experiments that result in a change in behavior or motor output after alteration of normal sensory input. This hypothesis states that peripheral sensory feedback is required for the generation of a normal motor pattern. The hypothesis of central control, on the other hand, merely requires that the nervous system be able to generate properly timed rhythmic output in the absence of such feedback. It does not address the question of the role this feedback normally plays. But this is the crux of the matter.

There is no question that sensory feedback during the performance of a behavioral act plays an important part in stabilizing the behavior (*45*). But such stabilization can be done entirely at the level of individual motoneurons, without in any way interfering with or impinging on the central neural network responsible for producing the basic rhythmic excitation of those motor neurons.

Further, many experiments have now shown that, for some behaviors in some animals, sensory feedback can drive or shut off a rhythmic behavior, and it can do so without being necessary for normal expression of the behavior. Swimming in dogfish sharks provides a good example. It has long been known that a dogfish shark whose nerve cord has been severed just behind the head (spinalized) and which has been deafferented along more than half the length of its body, will swim for many hours without any special stimulus (*46*). In addition, recent work by Grillner *et al.* (*47*) has shown that the motor outputs to parts of the body separated by the region of deafferentation are well coordinated even when the animal is rendered motionless by injection of curare. (Curare paralyzes the muscles without abolishing activity in either motor neurons or sensory nerves. The animal's immobility, however, prevents any rhythmic timing signals from being produced in the sensory neurons.) The central origin of this swimming rhythm seems established beyond reasonable doubt (*48*).

Yet, the timing of the swimming rhythm can also be driven or changed through appropriate sensory input. For example, if the tail of a spinalized dogfish paralyzed by curare is grasped and moved back and forth at a frequency different from that of the spontaneous swimming rhythm, then recordings from motoneurons innervating the swimming musculature will show coordinated bursts at the new, imposed frequency, not at the natural one (*49*). In other words, sense organs in the body must be sending signals to the central nervous system indicating that the body is bending, and the central nervous system must be responding by ordering the contraction of appropriate swimming muscles—apparently a clear case of peripheral control. In addition, the "automatic" swimming of spinal preparations can be completely suppressed by giving the animal a strong stimulus such as grasping the body tightly or bending it to one side and holding it there. Similar forced driving of a locomotor rhythm has been demonstrated in cats (*50*) and, over a more limited range, in locusts (*51*).

The apparent conflict between results that show that swimming can proceed in the absence of sensory feedback and those that show that phasic sensory input can nevertheless drive that same behavior may be resolved by considering events at the level of individual neurons. One current idea of how central patterns are generated is that motor neurons are driven by a network of interneurons capable of generating an alternating or cyclic pattern of output when excited by a continuous input. A network with such a property is referred to as a neural pattern generator, or oscillator, and evidence (*52*) suggests that each appendage or part of the body with its own cycle of movement is controlled by its own oscillator. It is thought that in the spinal cord of the dogfish shark, a series of such oscillators is coupled to each other to ensure proper coordination (*47*).

The sensory driving result must still be explained. If some sensory input is fed back onto components of each oscillator rather than just onto follower neurons, such feedback could reset the rhythm, in a fashion similar to the way in which current injection into cells that are thought to be part of an oscillator will reset the rhythm of motor output driven by it (*53*). Interjection of brief sensory stimuli in a spinalized dogfish during swimming will reset the rhythm (*46*). A repetitive sensory input provided to one or more oscillators and timed to advance or retard the oscillator's output just a bit, could drive oscillators to the frequency of the sensory input. Not even all oscillators would need to be stimulated since the driven ones could bring the ones to

which they were coupled into line. Similarly, a strong continuous stimulus delivered to the oscillators could effectively freeze them so that they would stop producing any rhythmic output at all.

This kind of interaction between sensory signals and central oscillators has been proposed to account for the strong effects of certain kinds of stimuli on rhythmic behavior in some animals. For example, the rhythmic alternation of extensor and flexor muscle bursts in one leg of a cat or a cockroach can be arrested by preventing extension of the leg during part of the cycle of leg movements (*54*). In the cockroach, specific receptors have been described at a leg joint that will inhibit the production of bursts of flexor motoneurons when they are stimulated (*39*). Mellon's report (*38*) of inhibition of swimming in scallops can be interpreted in a similar way and, therefore, does not seem to require that this behavior be timed only by phasic feedback from sense organs, as he suggested.

It is clear from this analysis that the only way to show conclusively that sensory feedback is necessary for the timing of rhythmic muscle activity is to demonstrate not only that altering the timing of sensory input will alter the rhythm of the output but also that, in the same preparation, elimination of sensory input will result in total loss of rhythmic output. This should be combined with experimental identification of the specific sensory input used for the timing. No such demonstration has yet been made. In addition, reinvestigation of the results that provided the strongest and most direct support for the peripheral control hypothesis (the early toad deafferentation and leech isolation work), has shown them to be in error. And finally, sensory driving of rhythmic output has been shown to be possible in animals that clearly are capable of generating such output centrally. In sum, no unequivocal experimental data support the idea that peripheral feedback is necessary for the generation of properly timed rhythmic motor output. In sharp contrast, the evidence from isolation, deafferentation, and paralysis experiments provides overwhelming support for the idea that all nervous systems are capable of generating properly timed rhythmic output in the absence of peripheral feedback.

In stressing the presence of central mechanisms for the production of all properly timed motor output, however, it is easy to overlook the enormous influence of sensory feedback in certain cases. While the formal stance of proponents of the concept of peripheral control was that sensory feedback was necessary for proper motor output, in practice they often merely wanted to show that such feedback was capable of producing proper output. In some specific instances, such as that of the dogfish shark discussed above, it can. Thus, as is so often the case in long-standing controversies, the position today encompasses at least some aspects of the original views of both sides.

Conclusion

The current concept of the central generation of rhythmic behavior is quite different from that first proposed more than half a century ago. Such change is inevitable as understanding of the nervous system grows. Much of the impetus to the original controversy was provided by argument over the question of whether nervous systems could generate "spontaneous" activity or whether all meaningful output had to be driven by specific sensory stimulation (*55*), an issue that is now dead.

Finally resolving the controversy allows concentration on new problems. In the field of control of rhythmic activity, the new problems seem to fall into three areas: (i) the nature of an oscillator, (ii) the interaction of oscillators, and (iii) the way in which sensory input interacts with oscillators and their output to shape the final motor output. The nature of oscillators, that is, what connections and what electrical properties of neurons are necessary to produce the characteristics observed in actual oscillators in animals, is being widely studied (*52*). How oscillators interact to effect coordination between different parts of an animal has been considered only theoretically, but this question is clearly of fundamental importance for an understanding of the neural basis for rhythmic behavior (*11*). Finally, how the final motor output is shaped under the influence of sensory feedback is a question receiving considerable attention in both vertebrates and invertebrates (*56*). While more is probably known about this latter aspect of motor control than any other, many questions remain. For example, one such question is how the oscillators in spinal cords of dogfish can be reset by a wide range of driving inputs while those controlling flight in locusts can be influenced only over a relatively narrow range (*51*).

Nonetheless, resolution of the central versus peripheral control controversy should have far-reaching benefits. It will be enormously valuable for neurobiologists to know that generalizations about neural organization above the cellular level can be supported. It has been an article of faith among many neuroscientists that studies on any one particular organism will be useful for the understanding of other organisms as well, even though few general principles of multicellular organization have been identified. Widespread recognition of the generalization discussed here should stimulate a search for other such generalizations and remind researchers that even work that may seem irrelevant to mammalian nervous systems can contribute not only to neuroscience but also to medicine.

Finally, in view of the diversity of the cellular organization of even the few oscillators partly described today (*52*), it seems possible that oscillators may have evolved many times in the animal kingdom. This suggests a significant evolutionary pressure, and natural questions arise about what the peculiar biological advantage is of building a control system for rhythmic behavior on neural oscillators, and whether it is even possible to devise a workable system of control based only on peripheral timing cues. Recognition that systems of oscillators are universal will lead to a better understanding of motor control. This may even influence such practical areas as the design of human prostheses, where neurobiologists could direct engineers away from unproductive mechanisms of control. Whether or not any direct medical benefit is realized, there seems little doubt that the study of the neural basis of rhythmic behavior will bring neuroscientists much closer to the ultimate goal of understanding how nervous systems function.

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