

Spinal Neurons Exhibit a Surprising Capacity to Learn and a Hidden Vulnerability When Freed from the Brain's Control

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The Forgotten Gray

If asked to describe the function of the spinal cord, many focus on its role in relaying neural impulses between the brain and periphery, a function subserved by the outer band of axons that form the white matter. Similarly, discussions of the restoration of function after injury often center on how to bridge the injured white matter, avoiding the seemingly more difficult issue of restoring the appropriate pattern of neural innervation. This characterization of spinal cord function ignores the inner region of neurons, the central gray, an area responsible for the local processing of afferent and efferent impulses. The central gray is typically seen as having fixed architecture that serves to direct neural traffic and organize some primitive responses (spinal reflexes). Only recently has its capacity to orchestrate some complex behaviors (eg, stepping) and to learn been recognized [1].

Demonstrating that a System Can Learn

The claim that the spinal cord can learn brings to the fore a basic question: what is learning? We have addressed this question by outlining a list of criteria [2]. Although we apply these criteria to a particular situation (spinal

learning), they are applicable to any paradigm where learning is thought to operate.

We have identified three basic criteria for learning, which stipulate that the change in performance must: 1) depend on experience; 2) be neuronally mediated; and 3) have a lasting effect. The first condition precludes behavioral changes that are due to the genes alone (eg, development). Elaborating on criterion 1, we require that the experience falls within the normal operational bounds of the system, a caveat that rules out changes attributable to injury. The second criterion precludes non-neural modifications (eg, muscle fatigue, receptor adaptation). Criterion 3 clarifies the link to memory—the causal experience must have an effect that extends beyond the training episode and is evident when subjects are tested under common conditions [3].

From this foundation, a fourth criterion can be used to specify the conditions required to demonstrate a particular type of learning. For example, Pavlovian conditioning depends upon the relationship between two stimulus events whereas instrumental learning depends on the relationship between a response and an outcome (eg, reinforcer).

Instrumental Learning within the Spinal Cord

Research has shown that spinal neurons can support both Pavlovian and instrumental conditioning [2,4]. Here, we focus on instrumental learning because we believe that it has greater implications for the recovery of function after injury.

Studies examining spinal processing often focus on the lumbosacral enlargement, a region that integrates and organizes signals to and from the hind legs. To detail what this system can do on its own, researchers isolate it from the brain by transecting the spinal cord in the thoracic region, leading to paraplegia. Rats that have undergone this operation require special care but show surprisingly few signs of distress. Further, because the transection blocks

sensory signals to the brain, they “feel” no pain when stimuli are applied to the lower body.

We introduce an instrumental response-outcome (R-O) relationship by administering shock to one hindleg whenever that leg is extended. In our laboratory, shock is generally applied to the tibialis muscle using a procedure similar to that used in humans for functional electrical stimulation (FES), a procedure used to artificially drive muscles to perform a specific function (eg, pedaling a bike) and/or maintain muscle tone [5]. Shock to the tibialis muscle causes a flexion response that lifts the leg and terminates the shock. Naturally, an intact animal given shock whenever its leg is extended quickly learns to maintain the leg in a flexed position, thereby minimizing shock exposure. What is surprising is that this behavioral change emerges (albeit, more slowly) after communication with the brain has been eliminated [6].

The fact that transected rats exhibit an increase in flexion duration (our index of learning) implies that the environmental relationship affects performance (criterion 1). Does this change in performance depend on neurons within the spinal cord (criterion 2)? Evidence suggests that it does, because cutting the neural connection to the spinal cord (the sciatic nerve), or inactivating spinal neurons using the Na⁺ channel blocker lidocaine prevents learning [7]. Further studies have isolated the region where learning occurs [8].

Although encouraging, we still lacked evidence that the instrumental (R-O) relationship was critical (criterion 4). The problem was that shock alone (independent of its relationship to the subject’s behavior) might sensitize the motor output, causing a prolonged flexion that could be erroneously attributed to the R-O contingency. We have addressed this issue in two ways. One is by including subjects that are experimentally coupled (yoked) to the rats receiving controllable shock (master group). Each yoked rat receives shock at the same time, and for the same duration, as their master partner. Because yoked rats receive shock independent of leg position, the stimulus is uncontrollable. Even though they receive the same amount of shock, yoked rats never exhibit an increase in flexion duration (ie, they do not learn) [6]. The second way we have assessed the importance of the R-O relation is by degrading the temporal contiguity between the target R (leg position) and the O (shock). Instrumental learning typically requires immediate feedback; when feedback (the O) is delayed, learning deteriorates. Because disrupting temporal contiguity (by delaying shock onset) in our spinal learning paradigm eliminated learning [6], we concluded that spinal neurons are sensitive to instrumental (R-O) relations.

We addressed criterion 3 by later testing master, yoked, and untreated (unshocked) rats under common conditions with response-contingent (controllable) shock [6]. Master rats quickly reacquired the instrumental response, exhibiting a savings effect that enabled learning relative to the previously unshocked controls. Amazingly, yoked rats, which had previously received uncontrollable shock,

exhibited a learning deficit. These subjects responded to shock in a mechanical fashion, exhibiting a high rate of responding but no increase in flexion duration. It appears that prior exposure to a stimulus that activates pain (nociceptive) fibers in an uncontrollable fashion engages a mechanism that disables subsequent learning, producing a learning deficit that is reminiscent of learned helplessness [9]. Further study revealed that just 6 minutes of intermittent shock applied to the leg or tail in an uncontrollable manner undermines learning for up to 48 hours, that the maintenance of the deficit depends on protein synthesis, and that its expression is mediated by a kappa opioid [10–12].

Naturalistic Stimuli Impact Spinal Function

We hypothesized that other types of uncontrollable stimulation could adversely affect spinal cord plasticity. This could arise in the natural environment from injury and inflammation, events that are known to produce an increase in mechanical reactivity (allodynia) indicative of neuropathic pain [13,14]. At a physiologic level, inflammation induces a lasting increase in neural excitability within the spinal cord (central sensitization) that is mediated by cellular mechanisms linked to memory [15]. For example, like long-term potentiation within the hippocampus, the induction of central sensitization depends on the release of an excitatory amino acid (glutamate) and the N-methyl-D-aspartate (NMDA) receptor.

We examined whether inflammation affects instrumental learning in spinalized rats by microinjecting a small amount of an irritant (formalin or capsaicin) into one hind paw. We found that manipulations that induced central sensitization inhibited instrumental learning. We also showed that uncontrollable shock induced a behavioral manifestation of central sensitization (allodynia) and that drug manipulations (eg, pretreatment with an NMDA antagonist) that block the induction of central sensitization prevented the shock-induced learning deficit [16]. On the basis of these observations, we suggested that uncontrollable shock may disrupt selective response modifications (instrumental learning) because it causes excessive glutamate release that diffusely saturates NMDA-mediated plasticity [17]. This over-excitation could also undermine spinal cord function by engaging destructive cellular processes that lead to cell loss [18].

Brain Systems Normally Protect Spinal Neurons

The results described above were obtained in spinally transected rats. In intact animals, brain systems regulate spinal cord function through descending tracts. Under normal conditions, these fibers may exert a dampening effect [19] that prevents over-excitation within the spinal cord and thereby helps preserve spinal cord function [20]. Supporting this, we showed that uncontrollable stimulation does not

impair spinal function in intact animals. This brain-dependent protective effect is due to serotonergic fibers that descend through the dorsolateral funiculus [21].

We reasoned that manipulations that disrupt brain function, such as surgical anesthesia, might disrupt the brain-dependent protection of spinal cord circuits. Supporting this, we showed that uncontrollable stimulation disrupts spinal cord function in intact anesthetized subjects [22]. This is clinically important, because uncontrolled nociceptive input could inadvertently impact spinal cord function during the course of surgery.

Uncontrollable Stimulation Undermines Recovery

The brain-dependent protection of spinal cord circuitry could also be disrupted by a contusion injury, a bruising of the spinal cord tissue due to a sudden blow, or deformation. In addition, the cellular cascades initiated by such an injury could increase vulnerability to other physiologic stressors. This is an important consideration because contusion injuries are often accompanied by peripheral tissue damage (eg, in war and car injuries). Tissue damage, and the associated inflammation, would drive pain fibers and, potentially, induce destructive cellular processes (excessive glutamate release) that further undermine function.

To examine whether uncontrollable nociceptive stimulation affects recovery after a contusion injury, we used the MASCIS impactor (W.M. Keck Center for Collaborative Neuroscience, Piscataway, NJ) to contuse the thoracic spinal cord in anesthetized rats [23]. A moderate injury was induced that caused a nearly complete paralysis that waned after a few days. Over the next 2 weeks, subjects typically recover partial hind-limb function and some capacity for weight-supported stepping. We applied uncontrollable stimulation within 2 days of injury. Just 6 minutes of uncontrollable stimulation dramatically impaired recovery, and this effect was evident 6 weeks later. Importantly, shock exposure only undermined recovery if the stimulus was uncontrollable; exposure to an equivalent amount of controllable shock had no adverse effect. Uncontrollable stimulation also delayed the recovery of bladder function, led to increased mortality, disrupted the recovery of sensory function, and led to greater loss of white and gray matter at the site of injury.

We have begun to examine how the adverse effect of uncontrollable stimulation can be prevented. Early observations suggest that intrathecal lidocaine has a protective effect [24]. Cooling spinal cord tissue may also enhance recovery by reducing neuronal excitability [25]. Surprisingly, systemic opiate treatment does not have a beneficial effect and, at a high dose, increases mortality in subjects after uncontrollable stimulation [26].

Summary and Implications

We have shown that, when freed from the brain's tutelage, the spinal cord shows a surprising capacity to learn. Similarly, others have shown how the spinal circuitry that underlies stepping can be modified through experience [27]. These behavioral observations are complimented by a host of physiologic data demonstrating that spinal neurons support NMDA-mediated plasticity and correlates of learning, such as long-term potentiation [28]. Today, the question is not whether spinal neurons can learn but, rather, when and how.

Removing the brain's input also unveils a vulnerability, a maladaptive effect that appears to arise when there is a source of uncontrollable afferent input. It was suggested that this leads to an over-excitation that saturates plasticity, inhibits adaptive response modifications, and undermines recovery after injury.

Restoring function after an injury to the white matter will require both bridging the gap and encouraging the appropriate pattern of neural innervation. The difficulty of the latter task depends on the central gray's capacity to adapt. If we assume that the system is hardwired by nature, with little capacity to organize behavior or to adapt, restoration of function will require that we duplicate the original pattern of neural innervation, a major technological barrier. If, instead, we see the spinal cord as a more sophisticated neural system, capable of organizing some complex behaviors (eg, stepping), and with some capacity to self-organize as a function of experience, the goal of restoring function is more tractable. From this perspective, there is reason to expect that even a limited neural bridge could help trigger surviving circuits and that the appropriate pattern of innervation might be shaped through training.

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