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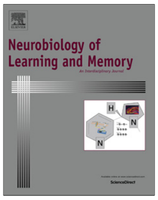

Review

Learning from the spinal cord: How the study of spinal cord plasticity informs our view of learning

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ABSTRACT

The paper reviews research examining whether and how training can induce a lasting change in spinal cord function. A framework for the study of learning, and some essential issues in experimental design, are discussed. A core element involves delayed assessment under common conditions. Research has shown that brain systems can induce a lasting (memory-like) alteration in spinal function. Neurons within the lower (lumbosacral) spinal cord can also adapt when isolated from the brain by means of a thoracic transection. Using traditional learning paradigms, evidence suggests that spinal neurons support habituation and sensitization as well as Pavlovian and instrumental conditioning. At a neurobiological level, spinal systems support phenomena (e.g., long-term potentiation), and involve mechanisms (e.g., NMDA mediated plasticity, protein synthesis) implicated in brain-dependent learning and memory. Spinal learning also induces modulatory effects that alter the capacity for learning. Uncontrollable/unpredictable stimulation disables the capacity for instrumental learning and this effect has been linked to the cytokine tumor necrosis factor (TNF). Predictable/controllable stimulation enables learning and counters the adverse effects of uncontrollable stimulation through a process that depends upon brain-derived neurotrophic factor (BDNF). Finally, uncontrollable, but not controllable, nociceptive stimulation impairs recovery after a contusion injury. A process-oriented approach (neurofunctionalism) is outlined that encourages a broader view of learning phenomena.

1. Introduction

For nearly 25 years, we have explored the plastic potential of the lower (lumbosacral) spinal cord asking: Can it learn; what are the mechanisms that regulate spinal plasticity; and how do these systems affect recovery after injury (for reviews, see Ferguson, Huie, Crown, Baumbauer et al., 2012; Grau et al., 2006, 2012)? In the course of conducting these studies, we have been forced to grapple with the definition of learning and the methods used to demonstrate it (reviewed in Allen, Grau, & Meagher, 2009; Grau & Joynes, 2001, 2005a, 2005b; Grau et al., 2006). The work has implications for our description of spinal function, recovery after spinal injury and, we suggest here, how we characterize brain-dependent learning.

In the sections that follow, I outline a framework for learning and then explore whether spinal mechanisms meet these criteria. As we will see, our findings forced us to re-examine how we characterize learning about stimulus–stimulus (S–S) and response-outcome (R–O) relations, in both cases encouraging a view that assumes environmental puzzles can be solved in multiple ways. Such a view fits well with a comparative approach (Papini, 2002), but instead of asking how the mechanisms that underlie learning vary across species, I ask how they vary across different levels of the nervous system (Jackson, 1931). I will push a process-oriented approach (neurofunctionalism) that focuses on detailing the functional properties of the underlying mechanism(s) (Grau & Joynes, 2005a, 2005b) and will suggest that this framework provides a useful vehicle for linking neurobiological observations with behavior.

My first aim is to convince the reader that spinal neurons can learn. Beyond this, I hope to encourage a broader view of what constitutes learning and will argue that doing so will enhance the relevance of the field to neurobiologists and those attempting clinical application.

2. Defining learning

Elucidating whether spinal mechanisms can learn requires a workable definition of this process. While this issue rose to the fore in our studies of instrumental learning (Grau, Barstow, & Joynes, 1998), the framework we derived can be applied more broadly. It builds upon a straight-forward classification scheme, outlined by Rescorla (1988) and implicitly adopted by others (e.g., Domjan, 2010). It asks whether an experience at *time 1* has a lasting effect (at *time 2*). Here, we use the term *experience* in the simplest sense, to indicate that the organism encountered an event(s) and/or a behavioral relation. From this perspective, whether the 'experience' gives rise to a conscious percept is irrelevant.

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We first sought some common criteria for learning (Grau et al., 1998). While we recognized non-neuronal cells can influence neural function (Perea, Navarrete, & Araque, 2009; Vichaya, Baumbauer, Carcoba, Grau, & Meagher, 2009), we limited our definition of learning to behavioral changes linked to neural plasticity (Table 1, Criterion 1). Neural function may be altered as a result of development, injury, or experience. We limited learning to the last of these possibilities (Criterion 2). Finally, we required that the consequence of learning (the memory) extend beyond the contingencies used to induce it—that the experience has a lasting effect on performance (Criterion 3).

Building on these common criteria, we can distinguish the three most widely-studied forms of learning with an additional criterion (4). We state these in terms of observable events involving exposure to a single stimulus (S), the relation between two stimuli, and the relation between an organism generated response (R) and a S. In each case, the experience can generate either an alteration in an observable response or have a more subtle effect that requires additional manipulations to infer (e.g., as in latent inhibition and sensory preconditioning).

For each category of learning, researchers have developed some routine methodologies. Single stimulus learning is typically studied by examining the effect of stimulus preexposure, with the result being a decrement (habituation) or increment (sensitization) in its behavioral and/or psychological effect. S–S learning is generally explored using the procedures of Pavlov (Pavlovian conditioning), wherein the presentation of the unconditioned stimulus (US) is made conditional upon another cue (the conditioned stimulus [CS]; Staddon, 2005). Instituting a temporal relation can affect the magnitude of the response elicited by the paired CS (the CS+) relative to an unpaired cue (the CS−). Similarly, learning about R–S relations is usually studied using a biologically significant S (e.g., food or an aversive shock). In instrumental conditioning, a contingency is established between the performance of a particular R and the presentation of the S, which is often referred to as the outcome (O). When a R–O relation exists, the O is controllable.

As Rescorla (1988) notes, when described in this abstract way (Criterion 4), these three types of time-1 experience encompass the majority of behavioral studies on basic learning processes:

> "They involve teaching the organism about the existence of a stimulus, about the relation of that stimulus to other stimuli in its environment, and about the relation of that stimulus to the animal's own behavior. One might argue that if we can understand how organisms learn these three things about a stimulus, we will have close to a complete characterization of how they learn about events in their environment."

Rescorla (1988) also reminds us that a demonstration of learning requires that we address two basic issues. First, we must employ an experimental control that equates subjects on every factor except the target dimension (Criterion 4). For example, if the aim is to demonstrate that subjects have encoded a relationship between two stimuli (S1 and S2), compare conditions that equate exposure to the stimuli and vary the temporal relation. In this case, one group might be exposed to these events in a paired manner while another receives these stimuli explicitly unpaired. If these training conditions (time-1) yield differential performance at time-2, the S1–S2 relation must matter.

The second basic issue concerns our inference of learning; to demonstrate that experimental treatments at time-1 matter, we must test groups under common conditions at time-2. To illustrate the importance of this factor, let's consider how stimulus intensity affects the development of habituation. If stimulus intensity is manipulated across groups, those exposed to weaker levels of stimulation will likely exhibit a greater decline in response magnitude during training (time-1; Thompson & Spencer, 1966). From this, it might be concluded that the magnitude of habituation declines as stimulus intensity is increased. But notice that we are comparing performance across groups that differ in two ways: their prior experience on earlier trials and the intensity of the eliciting stimulus. To evaluate how the time-1 experience affects habituation, subjects must be tested at time-2 under common conditions. In this case, subjects could be tested with *both* weak and strong stimuli. When this is done (Davis & Wagner, 1968), it is generally found that intense stimulation yields greater habituation. When tested in the appropriate manner, we reach the opposite conclusion. A further advantage of this approach is that the time-2 test, by necessity, must occur after the time-1 experience, providing some evidence that the time-1 experience has a lasting effect (Criterion 3).

For all of the behavioral phenomena we will discuss, researchers have confirmed that spinal neurons play a pivotal role (Criterion 1; e.g., see Crown, Ferguson, Joynes, & Grau, 2002; Durkovic, 2001; Groves & Thompson, 1970; Joynes, Ferguson, Crown, Patton, & Grau, 2003; Patterson, 1976). Likewise, controls have been included to demonstrate that the behavioral change observed at time-2 is related to the subject's experience at time-1 (Criterion 2). And in seeking evidence that training affects performance when subjects are tested under common conditions, we gain some indication that the experience had a lasting effect (Criterion 3). We acknowledge that the term *lasting* will remain ill-defined. At a minimum, we will look for evidence that a behavioral effect lasts hours, and will be most comfortable when it endures for a day or more.

3. Structural organization of the spinal cord

Before we examine whether spinal neurons can learn, we need a basic understanding of how this system is organized. Key components are illustrated in Fig. 1. Anatomists have grouped the segments of the spinal cord into four sections: cervical, thoracic, lumbar, and sacral (Fig. 1A). Within each section, segments are numbered along the rostral-caudal axis. A cross-section of the spinal cord (Fig. 1B) reveals an outer ring of axons (the white matter) that relay signals between the brain and spinal cord. Commu-

Table 1

Common criteria
1.The behavioral modification depends on a form of neural plasticity
2.The modification depends on the organism's experiential history
3.(a) The modification outlasts (extends beyond) the environmental contingencies used to induce it; (b) The experience has a lasting effect on performance
Single stimulus learning
4.Exposure to a stimulus alters the response elicited by the target event
Stimulus–stimulus learning
4.Imposing a temporal relationship between two stimuli alters the response elicited by one, or both, stimuli
Response-stimulus learning
4.Imposing a temporal relationship between a response and a stimulus alters the response