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THE CEREBELLUM AND EYE-BLINK CONDITIONING: LEARNING VERSUS NETWORK PERFORMANCE HYPOTHESES

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Abstract—Classical conditioning of the eye-blink reflex in the rabbit is a form of motor learning that is uniquely dependent on the cerebellum. The cerebellar learning hypothesis proposes that plasticity subserving eye-blink conditioning occurs in the cerebellum. The major evidence for this hypothesis originated from studies based on a telecommunications network metaphor of eye-blink circuits. These experiments inactivated parts of cerebellum-related networks during the acquisition and expression of classically conditioned eye blinks in order to determine sites at which the plasticity occurred. However, recent evidence revealed that these manipulations could be explained by a network performance hypothesis which attributes learning deficits to a non-specific tonic dysfunction of eye-blink networks. Since eye-blink conditioning is mediated by a spontaneously active, recurrent neuronal network with strong tonic interactions, differentiating between the cerebellar learning hypothesis and the network performance hypothesis represents a major experimental challenge. A possible solution to this problem is offered by several promising new approaches that minimize the effects of experimental interventions on spontaneous neuronal activity. Results from these studies indicate that plastic changes underlying eye-blink conditioning are distributed across several cerebellar and extra-cerebellar regions. Specific input interactions that induce these plastic changes as well as their cellular mechanisms remain unresolved.

Key words: eyeblink conditioning, interposed nucleus, associative learning, classical conditioning, memory.

Contents

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Abbreviations: BC, brachium conjunctivum; CR, conditioned response; CS, conditioned stimulus; IN, interposed nuclei; IO, inferior olive; UR, unconditioned response; US, unconditioned stimulus.

The classically conditioned eye-blink or nictitating membrane reflex is a unique type of associative learning in which the cerebellum plays a major role (Thompson, 1986, for review). In the delay conditioning paradigm, the conditioned stimulus (CS), a stimulus that normally does not evoke the reflex, is paired over successive trials and at a specific interval with an ensuing unconditioned stimulus (US), which is capable of eliciting the unconditioned response (UR) before the conditioning is initiated. In each trial the CS and US co-terminate (Fig. 1). As conditioning continues, a new eye-blink response, the conditioned response (CR), gradually develops in the interstimulus interval, and the peak of this response becomes progressively time-locked to the onset of the US. In addition, once acquired, the CR can be evoked by applying the CS alone.

In the early eighties of the last century, a very exciting observation was reported implicating the cerebellum in this type of learned behavior. Lesioning a specific region of the cerebellar nuclei disrupted the performance of the classically conditioned eye-blink reflex in the rabbit (Clark et al., 1984; Yeo et al., 1985). Subsequently, several reports were published demonstrating that the modulation of neurons in the critical regions of the cerebellar cortex and nuclei is associated with the CS, US and CR (Berthier and Moore, 1986; Berthier and Moore, 1990). In addition, substantial cerebellar involvement in this type of learning has been shown in other species (e.g. Skelton, 1988; Chen et al., 1996; Voneida et al., 1990), including humans (Lye et al., 1988; Solomon et al., 1989). Since these seminal observations, temporary and permanent lesion experiments have implicated the cerebellum in multiple processes underlying the classical conditioning of this reflex system, including acquisition, retention and consolidation (Bracha and Bloedel, 1996; Christian and Thompson, 2003; De Zeeuw and Yeo, 2005, for review). Finally, this dependence was found to extend to other types of conditioned reflexes. Manipulations of the cerebellar circuitry or permanent lesions in cerebellar patients disrupted instrumentally conditioned eyelid closure (Bracha et al., 2001) and classically conditioned withdrawal reflexes in the extremities of cats (Kolb et al., 1997; Bracha et al., 1999) as well as humans (Timmann et al., 2000). Because of the extensive data from several laboratories dealing with the classically conditioned eye-blink reflex in the rabbit, our review will focus on data acquired from this species.

It is generally agreed that eye-blink conditioning in the delay paradigm is controlled by a combination of brainstem eye-blink reflex circuits and the intermediate cerebellar network, which is superimposed over the UR system (Fig. 2). It has been proposed that the ipsilateral cerebellar

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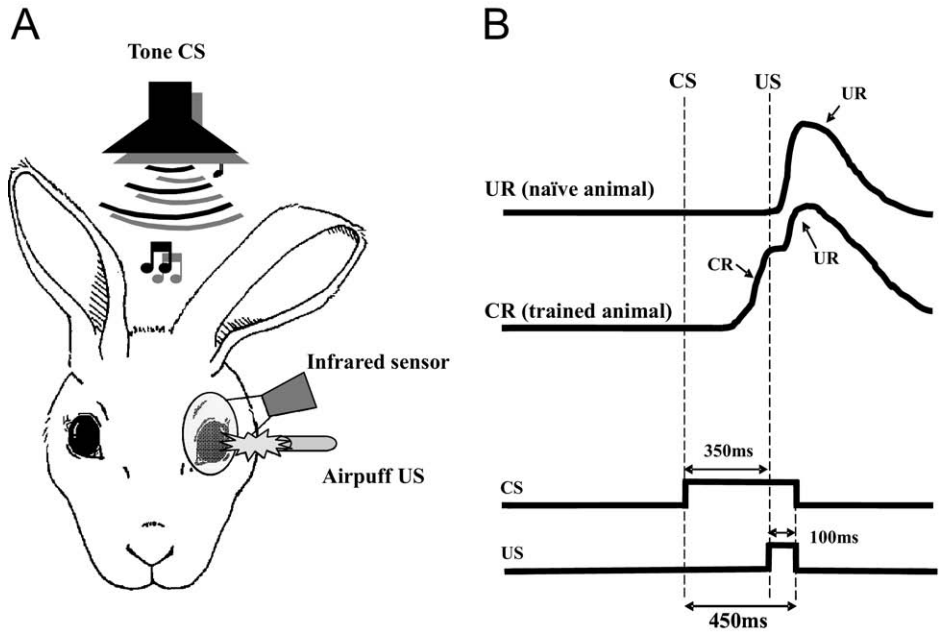

Fig. 1. Schematic of the eye-blink conditioning paradigm. (A) Rabbits are presented with a paired tone CS and air-puff US. Evoked eye blinks are recorded with an infrared sensor. (B) Idealized eye-blink records in naive and trained animals and the pulse diagram denoting the timing of stimuli. In the delay classical conditioning paradigm, the onset of the CS precedes the onset of the US and the stimuli co-terminate. Naive animals do not respond to the CS, but the US evokes reliably the hard-wired trigeminal unconditioned blink (UR, top; eye-blink trace). Over time, rabbits associate the CS with the US, and they learn to blink in anticipation of the upcoming aversive US. These associatively learned responses are called CRs (the second trace from the top.).

interposed nuclei (IN) and the cerebellar cortex are essential and perhaps sufficient sites of plastic changes for generating the cerebellar CR motor command. This theoretical position, the cerebellar learning hypothesis, has been extensively reviewed (Thompson, 1986; Christian and Thompson, 2003; Ohyama et al., 2002; Attwell et al., 2002b; Bracha and Bloedel, 1996), and therefore, it will only be briefly outlined here. The primary tenet of this hypothesis is derived from original concepts posited by Albus (1971) and Marr (1969), who deduced testable predictions based on the cerebellum's unique anatomical structure and synaptic organization. It is assumed that information about the CS and US arrives to the cerebellum via two distinct routes. The CS is conveyed through mossy fibers originating in pontine nuclei, whereas the US is coded in the discharge of climbing fibers originating in the inferior olive (IO). Information from the mossy and climbing fibers eventually converges on cortical Purkinje cells and cerebellar nuclear neurons. It is presumed that the heterosynaptic interaction at the points of convergence triggers local cellular plastic processes resulting in the changed responsiveness of Purkinje and/or nuclear cells. These plastic changes cause the network to respond to the CS mossy fiber signal by issuing a cerebellar nuclear "motor command" that triggers the CR.

Despite almost three decades of research examining the cerebellum's contribution to the acquisition, retention, and expression of the classically conditioned eye-blink reflex, a consensus regarding how this structure plays its important role in this behavior has not been reached. For example, in spite of numerous optimistic claims, specific contributions of the cerebellar cortex, cerebellar nuclei and extra-cerebellar substrates to plasticity that underlies learning are not known. This fundamental issue remains unresolved, mostly because of the lack of tools needed to interfere with learning without affecting both the local and global properties intrinsic to underlying circuits.

In this review we will first examine the conceptual underpinnings of experiments that tested the cerebellar learning hypothesis using local inactivation or manipulations of neurotransmitter signaling. We will outline the telecommunications network metaphor of eye-blink circuits, and we will show that some of the findings from studies that were designed based on this metaphor seem to disprove the cerebellar learning hypothesis or at the very least challenge some of its basic tenets. Then we will demonstrate that traditional cerebellar manipulations affect the spontaneous activity of neurons at the site of intervention and downstream from it, and that tonic interactions associated with this change can radically alter the functional state of the entire network. The tonic interactions in cerebellar systems have been largely overlooked in most discussions of the cerebellar learning hypothesis. We will argue that some of the pivotal observations that were declared to support this hypothesis can be ascribed to the effects that experimental manipulations had on the tonic activity of cerebellar circuitry and/or to methodological aspects of the experiments on which this view is based. We will present promising new data further supporting these arguments, and lastly, we will discuss approaches that