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Review

Cerebellar learning mechanisms

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ABSTRACT

The mechanisms underlying cerebellar learning are reviewed with an emphasis on old arguments and new perspectives on eyeblink conditioning. Eyeblink conditioning has been used for decades a model system for elucidating cerebellar learning mechanisms. The standard model of the mechanisms underlying eyeblink conditioning is that there two synaptic plasticity processes within the cerebellum that are necessary for acquisition of the conditioned response: (1) long-term depression (LTD) at parallel fiber-Purkinje cell synapses and (2) long-term potentiation (LTP) at mossy fiber-interpositus nucleus synapses. Additional Purkinje cell plasticity mechanisms may also contribute to eyeblink conditioning including LTP, excitability, and entrainment of deep nucleus activity. Recent analyses of the sensory input pathways necessary for eyeblink conditioning indicate that the cerebellum regulates its inputs to facilitate learning and maintain plasticity. Cerebellar learning during eyeblink conditioning is therefore a dynamic interactive process which maximizes responding to significant stimuli and suppresses responding to irrelevant or redundant stimuli.

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1. Introduction

The cerebellum plays a role in learned adjustments to movement amplitude and timing. The most intensively investigated cerebellar learning paradigms include eyeblink conditioning (Freeman and Steinmetz, 2011; McCormick and Thompson, 1984a), conditioned limb flexion (Mojtahedian et al., 2007; Voneida, 2000), learned adjustments to load change (Gilbert and Thach, 1977), gaze-reach calibrations (Norris et al., 2011), gain and timing modification of the vestibulo-ocular reflex (Boyden et al., 2004; Raymond et al., 1996a), and learned smooth pursuit eye movements (Medina and Lisberger, 2008). The current review will focus primarily on old arguments and new perspectives on the mechanisms underlying cerebellum-dependent eyeblink conditioning.

2. Early theories of the neural mechanisms underlying cerebellar learning

The mechanisms underlying cerebellar learning were first addressed in computational models by Marr (1969) and Albus (1971). These models posit that modification in the efficacy of parallel fiber-Purkinje cell synapses is the primary mechanism underlying cerebellar learning. A key component of the Albus (1971) model is that cerebellar Purkinje cells undergo learning-related inhibition. Purkinje cell axonal projections are the sole output of the cerebellar cortex and are exclusively inhibitory. Thus, learning-related inhibition of Purkinje cells releases the cerebellar deep nuclei and vestibular nuclei from inhibition and drives learned. The current interpretation of this inhibitory mechanism is that parallel fiber-Purkinje cell synapses undergo long-term depression (LTD) during learning (Ito and Kano, 1982; Linden, 1994; Linden and Connor, 1991, 1995; Linden et al., 1991). One of the first studies to show an LTD-like mechanism *in vivo* found decreases in Purkinje cell simple spike activity during a task requiring monkeys to modify wrist movements to compensate for changes in load (Gilbert and Thach, 1977). This demonstration of an LTD-like reduction in Purkinje cell activity is consistent with the Albus model, but it does not prove that the LTD-like mechanism or the cerebellar cortical circuitry is necessary for learning.

3. Neural mechanisms of cerebellar learning in eyeblink conditioning

In the standard delay eyeblink conditioning procedure a conditioned stimulus (CS) that does not elicit eyelid closure before training, typically a tone or light, is followed by an unconditioned stimulus (US) that elicits an eyeblink reflex before training, such as a puff of air to the cornea or a brief shock in the periorbital area (Deaux and Gormezano, 1963; Gormezano et al., 1962; Schneiderman et al., 1962). Repeated paired presentations of the CS and US result in the development of an "eyeblink" conditioned response (CR) which includes eyelid closure, nictitating membrane movement, and eyeball retraction (Deaux and Gormezano, 1963; Gormezano et al., 1962; Schneiderman et al., 1962). This complex of adaptive responses occurs during the CS with maximum eyelid closure, nictitating membrane movement, and eyeball retraction occurring at the onset of the US (Fig. 1). The eyeblink conditioning CR is therefore determined by an association in which the CS predicts the presentation of the US and when it will occur.

3.1. *Essential role of the cerebellum in eyeblink conditioning*

Richard Thompson and his colleagues were the first to show that the cerebellum is necessary for eyeblink conditioning (McCormick et al., 1982). They found that lesions of the cerebellum ipsilateral to the conditioned eye block acquisition and abolish retention of eyeblink conditioning (Lincoln et al., 1982; McCormick et al., 1982; McCormick and Thompson, 1984a). Conditioning of the contralateral eye is completely intact following ipsilateral cerebellar lesions. Subsequent studies found that lesions localized to the dorsolateral anterior interpositus nucleus and medial dentate nucleus abolish eyeblink CRs (Clark et al., 1984; Lavond et al., 1985; Yeo et al., 1985). The lesion studies showed that the cerebellum is necessary for acquisition and retention of eyeblink conditioning, but did not prove that the memory underlying the CR is stored within the cerebellum.

The strongest evidence that the memory underlying eyeblink conditioning is stored within the cerebellum comes from a series of studies that used reversible inactivation methods. Inactivation of the intermediate cerebellum ipsilateral to the conditioned eye results in blockade of acquisition and the rate of learning following cessation of the inactivation is the same as in naïve animals, indicating that no savings was established during training with cerebellar inactivation (Fig. 2) (Clark et al., 1992; Freeman et al., 2005; Krupa et al., 1993; Nordholm et al., 1993). This is a critical point because inactivation could have suppressed expression of the CR but still allowed associative learning to occur upstream or downstream of the cerebellum. These effects alone are not sufficient to demonstrate that the

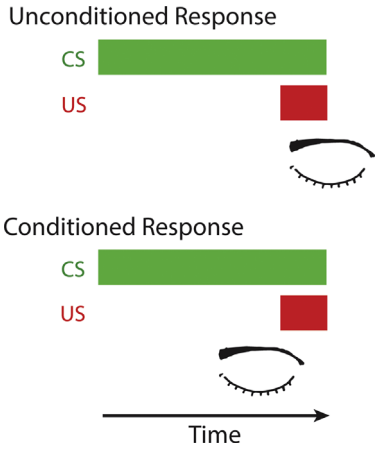

Fig. 1 – Diagram of eye-blink conditioning procedure and timing of the conditioned response. At the start of training an unconditioned response (eyelid closure) occurs after the onset of the unconditioned stimulus (US). With repeated presentations of the conditioned stimulus (CS) and the US a conditioned eyelid closure starts before the onset of the US.