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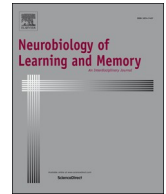
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Graded error signals in eyeblink conditioning

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ABSTRACT

Minimizing errors is an important aspect of learning. However, it is not enough merely to record if an error occurred. For efficient learning, information about the magnitude of errors is critical. Did my tennis swing completely miss the target or did I hit the ball, but not quite in the sweet spot? How can neurons – which have traditionally been thought of as binary units – signal the magnitude of an error? Here I review evidence that eyeblink conditioning – a basic form of motor learning – depends on graded signals from the inferior olive which guides plasticity in the cerebellum and ultimately tunes behavior. Specifically, evidence suggests that: (1) Error signals are conveyed to the cerebellum via the inferior olive; (2) Signals from the inferior olive are graded; (3) The strength of the olivary signal affects learning; (4) Cerebellar feedback influences the strength of the olivary signal. I end the review by exploring how graded error signals might explain some behavioral learning phenomena.

1. Learning... at the right pace

To deal with constantly changing environments organisms have evolved the ability to learn; if a behavior or a sensory event is followed by pain, then avoid that behavior or stimulus. This might seem like a sensible strategy, but if it is treated as an imperative, then organisms would soon be unable to do anything because, just like a Raindance is sometimes followed by rain, all stimuli and behaviors are sometimes followed by pain. Organisms thus face a challenge to determine how much evidence they need before they infer an association. Setting the bar too low will result in responses to random coincidences, i.e., superstitious behavior (Skinner, 1948); setting the bar too high delays the acquisition of potentially life-saving associations.

One way to minimize this problem is to grade errors and rewards. Something that is followed by a life-threatening event should be avoided at all costs. However, the cause of moderately painful events can be investigated further. Perhaps the co-occurrence was merely a coincidence? Maybe a slight behavioral alteration will result in a reward instead of pain.

A behavior is rarely executed perfectly on the first trial. Rather, like songbirds trying to mimic their parents (Doupe & Kuhl, 1999), organisms gradually tune their behavior through endless repetitions – continually learning from their errors. Importantly, the degree to which a behavior needs to be corrected is typically proportional to the size of the error produced. This review focuses on how error signals are

graded at the neural level and the role that graded error signals play in a specific type of motor learning: eyeblink conditioning.

2. Eyeblink conditioning

2.1. Eyeblink conditioning depends on the cerebellum

A subject who is presented with a tone followed by a corneal air-puff will, after some repetitions, begin to blink in response to the tone. In more formal terms: repeatedly pairing a neutral conditional stimulus (CS), with a blink-eliciting unconditional stimulus (US), will lead to the subject producing a conditional blink response (CR) to the tone CS (Hilgard & Campbell, 1936; Kehoe, 1983b; Moore, 2002). Eyeblink conditioning is dependent on the cerebellum. We know this based on evidence from lesioning studies (McCormick & Thompson, 1984; Yeo, Hardiman, & Glickstein, 1984, 1985a, 1985b), pharmacological studies (Hardiman, Ramnani, & Yeo, 1996), neurophysiological studies (Halverson, Khilkevich, & Mauk, 2015; Hesslow, 1994a; Jirenhed, Bengtsson, & Hesslow, 2007 Chap. 45; Ten Brinke et al., 2015), optogenetic studies (Heiney, Kim, Augustine, & Medina, 2014), and patient studies (Gerwig et al., 2005; Gerwig, Kolb, & Timmann, 2007; Wu et al., 2018).

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2.2. Neural mechanisms

That the cerebellum is crucial for eyeblink conditioning is widely accepted. However, the precise mechanism(s) involved is still up for debate. Most researchers agree that changes in the simple spike firing in Purkinje cells play a crucial role (Halverson et al., 2015; Halverson, Khilkevich, & Mauk, 2018; Jirenhed & Hesslow, 2011, 2016; Jirenhed et al., 2007; Johansson, Jirenhed, Rasmussen, Zucca, & Hesslow, 2014; Svensson, Jirenhed, Bengtsson, & Hesslow, 2010; Ten Brinke et al., 2015; Wetmore et al., 2014). However, the exact mechanisms triggering this change in simple spike activity is a topic of active research. Blocking mGluR7 receptors abruptly abolished learned Purkinje cell pause responses, suggesting that these receptors are involved in the generation of the response (Johansson, Carlsson, Rasmussen, Yeo, & Hesslow, 2015). But the evidence points to several other mechanisms that need to be considered. These include activation of molecular layer interneurons that inhibit Purkinje cells (Boele et al., 2018; Ten Brinke et al., 2015) and long-term depression of parallel fiber to Purkinje cells synapses (Boele et al., 2018; Freeman & Steinmetz, 2011).

In addition, evidence suggests that processes elsewhere in the cerebellum also contribute to learning. These include CS elicited activation of the inferior olive (Ohmae & Medina, 2015; Ten Brinke, Boele, & De Zeeuw, 2019), mossy-fiber collaterals to the cerebellar nuclei (Boele, Koekkoek, De Zeeuw, & Ruigrok, 2013), and projections from the cerebellar nuclei to the cerebellar cortex (Gao et al., 2016). A key aim in the near future should be to establish if these mechanisms are contradictory and/or complementary. (Gao, van Beugen, & De Zeeuw, 2012; Hesslow, Jirenhed, Rasmussen, & Johansson, 2013).

2.3. CS and US pathways

The CS and US are transmitted to the cerebellum via two afferent pathways: the mossy fibers and the climbing fibers. Depending on the modality and intensity, almost any stimulus can activate either or both of these afferent pathways. However, past research has shown that the CS is transmitted predominantly by the mossy fiber afferents from the pontine nuclei (Freeman & Rabinak, 2004; Hesslow, Svensson, & Ivarsson, 1999; Steinmetz, Rosen, Chapman, Lavond, & Thompson, 1986), whereas the US is transmitted predominantly by the climbing fibers originating in the inferior olive (Mauk, Steinmetz, & Thompson, 1986).

3. The inferior olive

3.1. Climbing fibers and complex spikes

Climbing fibers are axons from the inferior olive (Desclin, 1974; Eccles, Llinas, & Sasaki, 1966) – a collection of nuclei located in the medulla oblongata. After entering the cerebellum via the inferior cerebellar peduncle, some climbing fiber collaterals project to the cerebellar nuclei (De Zeeuw, van Alphen, Hawkins, & Ruigrok, 1997; Shinoda, Sugihara, Wu, & Sugiuchi, 2000; Sugihara, Wu, & Shinoda, 1999). But the primary target of the climbing fibers are Purkinje cells in the cerebellar cortex (Apps & Garwicz, 2005).

An extracellular recording from a Purkinje cell will reveal two types of responses. Simple spikes are generated by parallel fiber excitation and by an intrinsic mechanism in the Purkinje cells (Cerminara & Rawson, 2004; Johansson, Jirenhed, Rasmussen, Zucca, & Hesslow, 2018). When an action potential in the climbing fiber depolarizes its target Purkinje cell via its powerful synaptic connection (Palay & Chan-Palay, 1974), a complex spike will appear in the extracellular record (Eccles et al., 1966; Rasmussen, Jirenhed, Wetmore, & Hesslow, 2014) (see Fig. 1).

3.2. The inferior olive regulates firing in Purkinje cells

The inferior olive plays a dual role in cerebellar function with respect to Purkinje cells: it regulates background firing and it sends information about errors that induce learning. The olive controls the intrinsic firing rate in Purkinje cells (Cerminara & Rawson, 2004; Colin, Manil, & Desclin, 1980; De Zeeuw et al., 2011; Demer, Echelman, & Robinson, 1985; McKay et al., 2007; Rawson & Tilokskulchai, 1981; Zucca, Rasmussen, & Bengtsson, 2016). Silencing the inferior olive will lead to a substantial increase in Purkinje cell activity (Montarolo, Palestini, & Strata, 1982). But if climbing fibers are silenced for a long time using a genetic approach, simple spike firing eventually returns to normal (White & Sillitoe, 2017). The opposite is also true. Increasing olivary activity will lead to a decrease in Purkinje cell simple spike activity (Andersson & Hesslow, 1987a, 1987b; Rawson & Tilokskulchai, 1981). This silencing of Purkinje cells is gradual: the higher the climbing fiber activity, the lower the firing rate in Purkinje cells. At around 4 Hz Purkinje cells become silent (Zucca et al., 2016).

Error transmission (see below) involves changes in climbing fiber activity which could, at least in theory, change the background activity. However, computational models show that if US related plasticity is balanced, then background activity will remain stable (Kenyon, Medina, & Mauk, 1998a, 1998b).

3.3. The inferior olive convey error messages

A large body of evidence demonstrates that the inferior olive plays a key role in cerebellar motor learning (Bengtsson & Hesslow, 2013; Gilbert & Thach, 1977; Ito, 2001). During VOR adaptation, a retinal slip – when the subject fails to maintain focus on a fixed point in the environment – typically elicits a complex spike (Ito, 2013; Kimpo, Rinaldi, Kim, Payne, & Raymond, 2014; Nguyen-Vu et al., 2013; Simpson & Alley, 1974). On a smooth pursuit task in which a monkey tracks a visual target using a joystick, errors activate the inferior olive (Junker et al., 2018; Medina & Lisberger, 2008).

Similarly, during eyeblink conditioning, the US activates the inferior olive and elicits a complex spike in Purkinje cells controlling that control the eyelid (Jirenhed et al., 2007; Rasmussen et al., 2014; Rasmussen, Jirenhed, & Hesslow, 2008). Simple spike activity in cerebellar Purkinje cells also appears to play a role in signalling errors (Popa, Streng, Hewitt, & Ebner, 2016; Streng, Popa, & Ebner, 2018), and can do so even in the absence of modulation of climbing fiber activity (Ke, Guo, & Raymond, 2009). Nevertheless, the evidence suggests that the inferior olive provides the cerebellum with information about errors on a wide range of different tasks. Given its role in conveying instructive signals to the cerebellum, it is no surprise that inactivating the inferior olive or manipulating the climbing fiber signal impedes learning as well as the expression of conditioned responses (Welsh & Harvey, 1998; Yeo, Hardiman, & Glickstein, 1986; Zucca et al., 2016).

But how does the inferior olive convey the magnitude of an error? Information from neurons is often encoded in the firing rate; this is also true in the cerebellum (De Zeeuw et al., 2011). However, even if we discount the fact that rate coding is a wasteful way to transmit information (Gallistel, 2017), it is unlikely that the inferior olive would use rate coding because its firing rate is only around one hertz (Armstrong, Cogdell, & Harvey, 1973; Eccles, Ito, & Szentagothai, 1967; Lang, Sugihara, Welsh, & Llinás, 1999; Rasmussen et al., 2014). At such a low frequency it is unlikely that a Purkinje cell, which only receives input from one climbing fiber (Palay & Chan-Palay, 1974), can extract information about error magnitude based on frequency. If Purkinje cells share information about climbing fiber input with other Purkinje cells then the frequency of climbing fiber input to that group could conceivably play a role. However, there is another alternative which has gained traction in recent years: error magnitude is conveyed within a single climbing fiber burst.

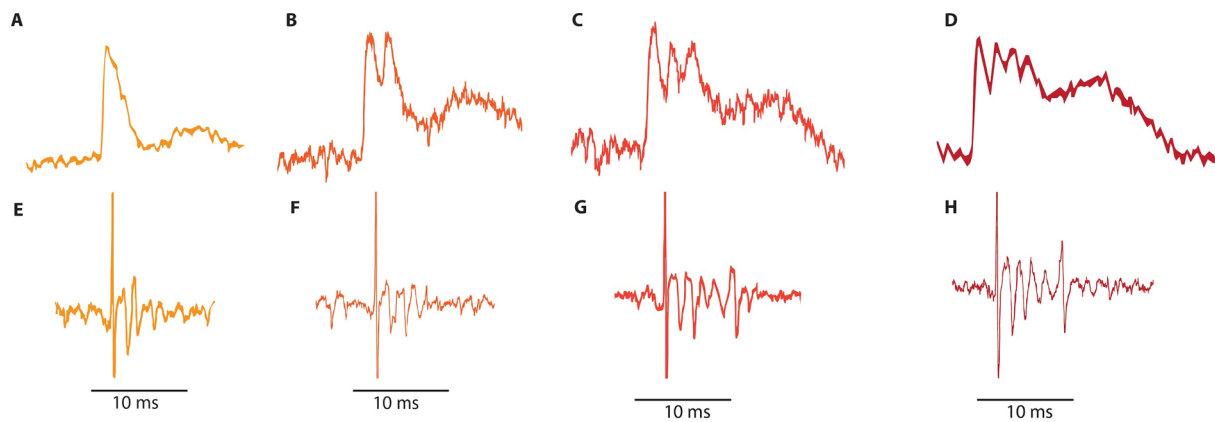


Fig. 1. The inferior olive fires graded signals. (A–D). Spontaneous climbing fiber responses recorded from a single Purkinje cell dendrite in the cerebellar cortex of a decerebrated ferret, using a sharp glass electrode. The data shows that even within a single cell climbing fiber input can elicit variable responses. (E–H) Spontaneous complex spikes from extracellular records from a single Purkinje cell. Complex spikes – like dendritic responses – vary even in a single cell.

4. Olivary signals are graded

4.1. The olive fires in bursts

Olivary neurons, like most cells in the brain, work according to the all-or-none principle (Adrian, 1914). However, more than 50 years ago, it was observed that the olive fires in high-frequency bursts containing a variable number of spikes (Eccles et al., 1966). This finding has been replicated many times since, and it is now clear that excitation of the inferior olive elicits a burst containing 1–6 spikes (Armstrong & Harvey, 1968; Armstrong & Rawson, 1979; Crill, 1970; Maruta, Hensbroek, & Simpson, 2007; Mathy et al., 2009; Yang & Lisberger, 2014). In other words, olivary activity is graded. The variable strength of olivary signals is also evident from calcium imaging of Purkinje cell dendrites. Compared to a spontaneous olivary signal, input derived from sensory stimulation elicits a stronger calcium spike in the Purkinje cell dendrites (Najafi, Giovannucci, Wang, & Medina, 2014a, 2014b). Similarly, activating neighbouring GABAergic interneurons prior to climbing fiber activation, results in a smaller calcium signal (Rowan et al., 2018). These studies suggest that the strength of the olivary signal depends on the event that triggered the olive. The implications of this insight have been partially explored before (Gilbert, 1974; Najafi & Medina, 2013; Rasmussen & Hesslow, 2014). However, I would argue that we have only just scratched the surface of the implications of this potentially paradigm-shifting discovery.

4.2. The shape of complex spikes

Does the number of spikes in a climbing fiber burst influence the shape of the resulting complex spike? As mentioned, a climbing fiber signal typically contain 1–6 spikes (see Fig. 1A–D). Coincidentally, extracellularly recorded complex spikes typically contains 1–6 secondary spikes (Eccles et al., 1966; Thach, 1967; Warnaar et al., 2015; Yang & Lisberger, 2014) (see Fig. 1E–H). It is tempting to assume that the number of spikes in the climbing fiber signal determines the number spikelets in the complex spike. But this cannot be true because even a single climbing fiber pulse can generate a complex spike with multiple secondary spikes (1986b; Campbell & Hesslow, 1986a; Ekerot, Gustavsson, Oscarsson, & Schouenborg, 1987; Thach, 1967).

So what determines the shape of a complex spike? The spikelets are generated in the axons of the Purkinje cells (Davie, Clark, & Häusser, 2008). Hence the shape of a complex spike depends primarily on the placement of the electrode relative to the cell. But if the electrode is stationary relative to the cell, other factors do influence the shape of the complex spike.

Factors influencing the shape of complex spikes include the

preceding input to the Purkinje cell (Campbell & Hesslow, 1986b); the simple spike firing rate before the complex spike (Burroughs et al., 2017; Gilbert, 1976; Servais et al., 2004); the shape of the preceding complex spike (Maruta et al., 2007); the level of synchrony in the inferior olive (Lang et al., 2014); and how long time has passed since the preceding complex spike (Warnaar et al., 2015). Moreover, stimulating inhibitory interneurons adjacent to Purkinje cells affect dendritic calcium levels and the number of dendritic spikes (Callaway, Lasser-Ross, & Ross, 1995; Ross & Werman, 1987), which in turn has a small but measurable effect on the shape of complex spikes (Rowan et al., 2018).

In addition to these factors, the shape of a complex spike and the time between the complex spike and the next simple spike is also affected by the number of spikes contained in the climbing fiber burst that elicited the complex spike (Mathy et al., 2009; Rasmussen et al., 2013). This means that even though the content of the climbing fiber signal does not determine the number of secondary spikes following the initial complex spike, it does play a role. This opens up for the possibility of probabilistic inferences about the content of the climbing fiber signal based on the shape of the complex spike.

5. Cerebellar feedback influences the strength of the olivary signal

5.1. The nucleo-olivary pathway

The final processing of all cerebellar output occurs in the cerebellar nuclei, which in turn project to motor nuclei (Freeman & Steinmetz, 2011; Pacheco-Calderón, Carretero-Guillén, Delgado-García, & Gruart, 2012), to the thalamus (Gao et al., 2018), back to the cerebellar cortex (Ankri et al., 2015; Gao et al., 2016; Houck & Person, 2014, 2015), and to the inferior olive via the nucleo-olivary pathway (Dietrichs & Walberg, 1981; Graybiel, Nauta, Lasek, & Nauta, 1973) (see Fig. 2).

The nucleo-olivary pathway is inhibitory (Andersson, Garwicz, & Hesslow, 1988; Bengtsson & Hesslow, 2006; De Zeeuw, Holstege, Calkoen, Ruigrok, & Voogd, 1988; Hesslow, 1986; Najac & Raman, 2015; Nelson, Mugnaini, & Strata, 1989). This means that when the cerebellum sends output to motor nuclei in the brainstem, or the thalamus, it is accompanied by inhibition of the inferior olive (Hesslow & Ivarsson, 1996). Consequently, motor output from the cerebellum – such as a conditional response – inhibits the inferior olive, resulting in a negative feedback loop (Andersson et al., 1988; Bengtsson & Hesslow, 2006, 2013; Bengtsson, Svensson, & Hesslow, 2004; Hesslow, 1994b; Kenyon et al., 1998a, 1998b; Mauk & Donegan, 1997; Rasmussen & Hesslow, 2014).

One unusual feature of the nucleo-olivary pathway is that signals arrive with an unusually long delay. Following electrical stimulation of the nucleo-olivary pathway, the maximum inhibition of the olive occurs

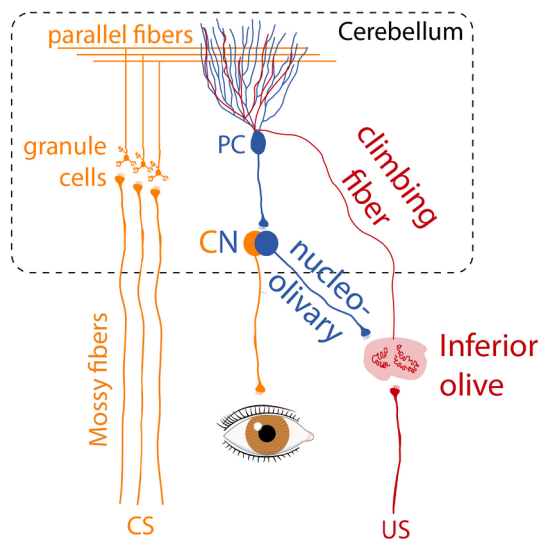


Fig. 2. A simplified model of the cerebellar network. The conditional stimulus (CS) reach the cerebellum via mossy fibers that synapse on granule cells. The axons of granule cells become parallel fibers that synapse on Purkinje cells. The inferior olive conveys the unconditional stimulus (US). The climbing fibers make many synapses on a single Purkinje cell. Purkinje cells (PC) are inhibitory. Pauses in their spontaneous firing cause disinhibition of the cerebellar nuclei. Disinhibition of the cerebellar nuclei leads to (1) motor activation, and (2) increased inhibition of the inferior olive and hence increased suppression of the US signal.

30–60 ms later (Bazzigaluppi, Ruigrok, Saisan, De Zeeuw, & de Jeu, 2012; Best & Regehr, 2009; Hesslow, 1986; Najac & Raman, 2015; Svensson, Bengtsson, & Hesslow, 2006). This delay means that the maximum inhibition of the olive coincides with the arrival of the instructive signal (Lepora, Porrill, Yeo, & Dean, 2010), which supports the view that the nucleo-olivary pathway is part of a negative feedback system.

5.2. Closing the loop: The cortico-nuclear-olivary-cortical connection

A Purkinje cell projects to the cerebellar nuclei, the cerebellar nuclei projects to the olive, and the olive projects back to the Purkinje cell (Apps & Garwicz, 2005; Dietrichs & Walberg, 1986) (see Fig. 2). Consequently, it should be possible to manipulate the olivary input to a specific Purkinje cell by manipulating the firing rate of that same Purkinje cell. Accordingly, high-frequency stimulation of the climbing fibers, which silences Purkinje cell activity (Rawson & Tilokskulchai, 1981; Zucca et al., 2016), inhibits the olivary input to the Purkinje cells (Andersson et al., 1988). That a Purkinje cell can influence its own activity has also been observed at the single cell level using optogenetics. Optogenetic stimulation of Purkinje cells results in more suppression of the cerebellar nuclei thus reducing nucleo-olivary inhibition of the inferior olive, which, in turn, increases complex spike activity (Chaumont et al., 2013).

Likewise, learning induced changes in Purkinje cell activity also appears to influence activity within this loop. During eyeblink conditioning, Purkinje cells acquire a pause response (Halverson et al., 2015; Jirenhed et al., 2007; Ten Brinke et al., 2015). The evidence indicates that these learned pause responses suppress the olive in the same way that optogenetically induced pause responses do (Hesslow & Ivarsson, 1996; Hesslow, 1994b; Sears & Steinmetz, 1991). As the CS-induced Purkinje cell pause response widens, there is a corresponding increase in the suppression of complex spike activity during the last part of the CS (Fig. 3B–D). Moreover, the delay between the pause response and the suppression of complex spike activity is consistent with the long delay in the nucleo-olivary pathway (2014; Rasmussen et al., 2008). As

a result, the probability that a US presented after a CS elicits a complex spike is smaller after conditioning (Nicholson & Freeman, 2003; Sears & Steinmetz, 1991). This effect is gradual: the stronger the Purkinje cell pause response, the lower the probability that the US induces a complex spike (Rasmussen, Zucca, Johansson, Jirenhed, & Hesslow, 2015) (Fig. 3A). Put another way: inhibition of climbing fibers is a signal for extinction (Medina, Nores, & Mauk, 2002), but see also (Zbarska, Bloedel, & Bracha, 2008).

5.3. Learning correlates with the strength of the olivary signal

Above I have showed that the inferior olive provides the cerebellum with instructive error signals in several different learning paradigms. But it is not the entire story. In VOR adaptation, some types of errors elicit a complex spike whereas other mistakes do not (Kimpo et al., 2014). The probability that an error elicits a complex spike depends in part on what type of error it is (Junker et al., 2018). This suggests that error may at least sometimes be transmitted in other ways.

In 1974 Gilbert proposed that the number of spikes in the olivary signal could potentially guide learning (Gilbert, 1974). This claim has since gained traction in the scientific literature, especially in the last decade. Compared to a single spike, a climbing fiber burst enhances short and long term plasticity in vitro (Mathy et al., 2009). In vivo recordings during visually guided saccades (Herzfeld, Kojima, Soetedjo, & Shadmehr, 2018), and on a smooth pursuit task (Yang & Lisberger, 2014) shows that the size of an error correlates with the duration of the resulting complex spike and that the duration of the complex spike correlates with the amount of plasticity induced (Yang & Lisberger, 2014). During conditioning, the probability that a peripheral US elicits a complex spike in the Purkinje cell decreases if the US is preceded by a learned Purkinje cell pause response: the longer the pause, the stronger the inhibition (Rasmussen et al., 2015). Spontaneous complex spike activity during the CS is also suppressed (Rasmussen et al., 2014).

Auxiliary evidence that graded error signals exist can be found in computational learning models which shows that learning depends on (Herreros & Verschure, 2013; Rasmussen & Hesslow, 2014), or is more efficient (Bouvier et al., 2018), if error signals are graded. Taken together, these studies suggest that the content of the climbing fiber signal affects learning. However, while it is clear that a learned response can affect the probability of olivary activation, we still don't know if a learned response can affect the strength of an olivary response. For example, can a conditioned blink response reduce the number of spikes in the olivary burst elicited by the US?

5.4. Changing the direction of learning experimentally

Correlation does not equal causation. To demonstrate causality, it is desirable to experimentally manipulate the strength of the olivary signal and observe how it affects learning. When a single climbing fiber pulse did result in a learned pause response in Purkinje cells, Jirenhed et al. (2007) switched to a burst-like stimuli to induce learning. This, burst-like stimuli induced learning consistently.

Following up on this, we subsequently examined plasticity in the cerebellar cortex in response to a variable number of climbing fiber stimulation pulses. First, we placed a simulation electrode directly into the climbing fibers pathway. Then we applied a conditioning paradigm in which we paired forelimb stimulation as a CS, and a climbing fiber burst as the US. As expected, this reliably induces a Purkinje cell pause response (Jirenhed & Hesslow, 2016; Jirenhed et al., 2007). When the CS elicited a clear pause response, we switched from a burst-like stimulus to a single stimulation pulse. Although a single pulse was strong enough to elicit a complex spike, the switch to a single pulse resulted in extinction of the pause response (Rasmussen et al., 2013). When we switched back to a burst-like stimulus, the pause reappeared (see Fig. 4). This experiment shows that the strength of the olivary signal determines the direction of learning. Moreover, in line with predictions

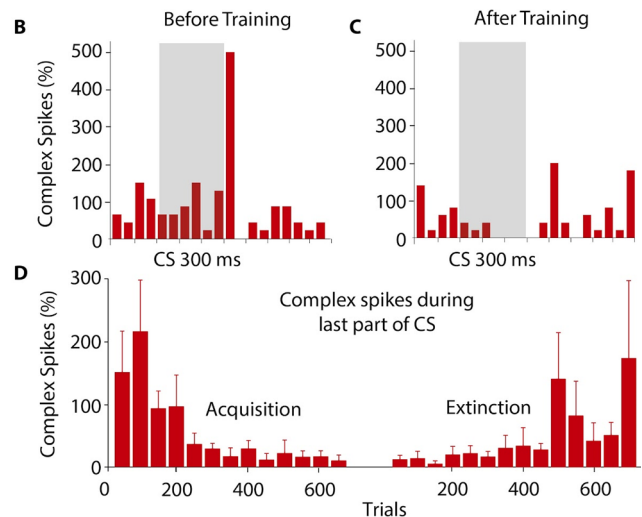
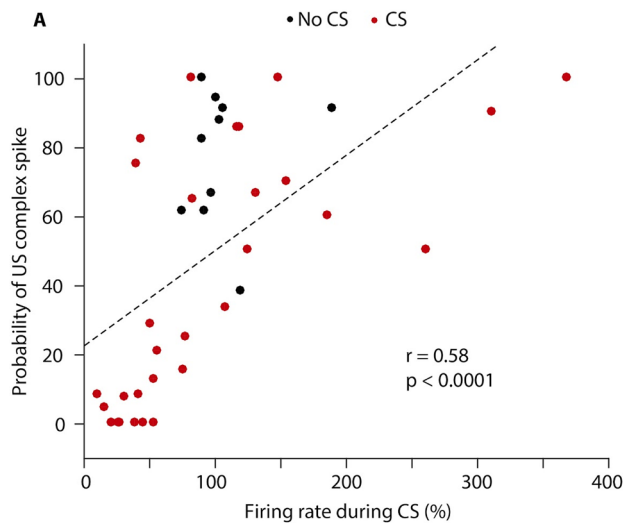


Fig. 3. Learning affects the excitability of the inferior olive. (A) Shows data from Rasmussen et al. (2015) which shows that there is a positive correlation between the learned simple spike pause responses that have been linked to the expression of behavioral CRs (Jirenhed & Hesslow, 2016). (B–C) Illustrates changes in complex spike activity before and after eyeblink conditioning adapted from (Rasmussen et al., 2014). Before training (B) complex spike activity is relatively unaffected by the CS. In contrast, following training (C) there is a strong suppression of complex spike activity in the end of the CS period. D Shows that the complex spike activity in the end of the CS (last 100 ms) changes gradually during the acquisition phase of eyeblink conditioning. Extinction results in a gradual restoration of complex spike activity during the CS.

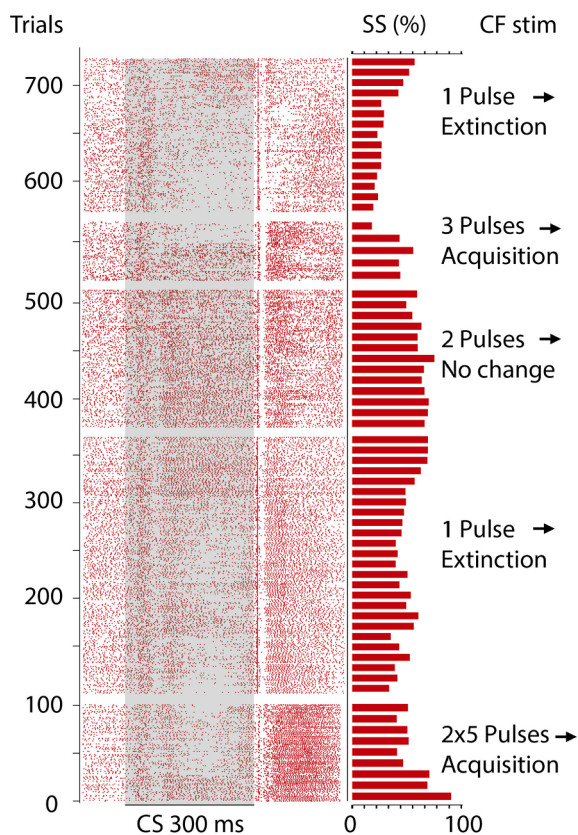


Fig. 4. The direction of learning is determined by the gradation of the olivary signal. Raster plot illustrating simple spike activity of a single Purkinje cell recorded extracellularly for several hours during training. The cell was initially trained using burst stimulation of the climbing fibers as the US until a pause response developed. The pause response was extinguished when we switched from using a burst to using a single stimulus and then reacquired when switching to a burst containing three (but not two) climbing fiber pulses. Adapted from Rasmussen et al. (2013).

from theoretical models (Kenyon et al., 1998a, 1998b), the results suggest that there is an equilibrium level at which the climbing fiber signal does not induce plasticity in any direction.

6. Translating the Rescorla-Wagner model into neural code

6.1. The Rescorla-Wagner model

Imagine that you are about to hit a tennis ball that is flying towards you. Your brain anticipates the trajectory of the ball and initiates a motor program detailing the series of muscle contractions that will allow you to strike the ball. The cerebellum receives an efference copy (Miall & Wolpert, 1996) and computes how the execution of the motor program, as well as the impact of the ball, will activate various sensory systems. If these sensory predictions match the actual sensory outcomes, then no changes are necessary; the motor program did what it was supposed to do. If on the other hand, you expected to hit the ball and watch it fly in a perfect arc over the net – only to miss the shot entirely – then you likely did something wrong in which case you should try to learn from the mistake.

In other words, prediction errors cause learning and learning aims to minimize prediction errors. Or as Rescorla and Wagner put it: learning depends on the level of surprise (Rescorla, Wagner, Black, & Prokasy, 1972). Though some findings are hard to reconcile with it (Miller, Barnet, & Grahame, 1995; Schmajuk, 2010), the Rescorla-Wagner model has successfully predicted a large number of learning phenomena that seem counterintuitive, at least on a superficial level (Miller et al., 1995; Rescorla, 1970) (see Table 1).

6.2. Neural mechanisms

Despite its predictive success in psychology and behavioral sciences, the neural mechanisms underlying the Rescorla-Wagner model remain somewhat elusive. For eyeblink conditioning, the evidence reviewed here and elsewhere point to a plausible neural implementation of the Rescorla-Wagner model. (Kenyon, Medina, & Mauk, 1998a; Mauk & Donegan, 1997; Raymond & Medina, 2018). Following previous papers (Najafi & Medina, 2013; Rasmussen & Hesslow, 2014), I will argue that error magnitude is encoded in the number of spikes in the climbing

Table 1

Summary of learning phenomena. Simplified recipes for the induction of the learning phenomenon discussed above.

	Stage 1	Stage 2	Outcome
Conditioning	CS + US		CS → CR
Extinction	CS + US	CS	CS → No CR
Blocking	CS _A + US	CS _A & CS _B + US	CS _A → CR; CS _B → No CR
Overshadowing	CS _A & CS _B + US		CS _A → CR; CS _B → No CR*
Overexpectation	CS _A + US; CS _B + US	CS _A & CS _B + US	CS _A → CR↓ ; CS _B → CR↓

* Whether conditioning occurs to CS_A or CS_B depends on which stimuli are used and how salient they are.

fiber burst.

Paired stimulation of the mossy fibers and climbing fibers induces plasticity in the cerebellar cortex (Jirenhed et al., 2007). If larger errors results in more spikes within a burst and more plasticity (Rasmussen & Hesslow, 2014), then we have a more adaptive system. As learning progresses, errors become smaller, and the plasticity resulting from a single trial will also become smaller. Some evidence indicates that olivary activity can reach an equilibrium where input from the olive to Purkinje cells does not induce plasticity (Kenyon et al., 1998a; Rasmussen et al., 2013).

In more cognitivist terms we can say that the cerebellar output plays a dual role: it drives behavior and sends sensory predictions via the nucleo-olivary pathway to the inferior olive. The sensory prediction is subtracted from the input to the olive. If the sensory input equals the sensory prediction then no further learning will take place (Dean & Porrill, 2014; Kenyon et al., 1998a; Lepora et al., 2010; Mauk & Donegan, 1997; Rasmussen & Hesslow, 2014). Thus, rather than merely signaling errors, olivary activity reflects the appropriateness of the cerebellar cortex response to a particular stimulus (Popa et al., 2016). Within this framework, it is possible to explain a number of phenomena that were predicted by the Rescorla-Wagner model and which have since been demonstrated in several experimental paradigms.

7. Blocking, overshadowing, and overexpectation

7.1. Kamin blocking

To demonstrate Kamin blocking, you begin by pairing CS_A and the US. When CS_A consistently elicits a CR, you proceed to present CS_A and CS_B as a compound stimulus, still followed by the US. Despite pairing CS_B and the US, no learning will occur in response to CS_B (Gallistel, 1993; Kamin, 1969; Mackintosh, 1971). It is as if learning to CS_B has been 'blocked' by the existing association between CS_A and the US. One way to think about it is that CS_B does not provide any information not already provided by CS_A; therefore CS_B will be ignored. In Rescorla-Wagner terms, the existing association between CS_A and the US is already strong and therefore it is unsurprising when the US appears after CS_A even though it is presented together with CS_B as a compound. Blocking has been observed in a number of different setups including, fear conditioning (McNally, Pigg, & Weidemann, 2004), autoshaping in pigeons (Khallad & Moore, 1996), eyeblink conditioning in rabbits (Kehoe, Schreurs, & Amodè, 1981; Kim, Krupa, & Thompson, 1998; Merchant & Moore, 1973) and in humans (Martin & Levey, 1991).

At the neural level, CS_A, after being paired with the US, induces a pause response in the Purkinje cells. This pause response disinhibits the cerebellar nuclei which in turn increases inhibition of the inferior olive. The result is that CS_A inhibits the inferior olive, thus suppressing the US signal. So even though the US is presented after CS_B the US signal does not reach the cerebellar cortex, at least not in full strength. As a result, no learning ensues.

7.2. Overshadowing

Overshadowing, a phenomenon first described by Ivan Pavlov (Pavlov, 1927), can be demonstrated by pairing a compound CS

(CS_A + CS_B) and the US. For example, Pavlov would train his dogs with a tone and visual stimuli as a compound stimulus, followed by the US. Later, when Pavlov tested the stimuli individually, it became clear that the dogs had formed an association to one of the two CSs (usually the auditory stimulus), but not to the other. It was as if the dogs ignored one of the two stimuli, i.e., it was overshadowed. Overshadowing has been demonstrated not only for conditioning of the salivary response (Pavlov, 1927), but also in fear conditioning (Mackintosh, 1971), and eyeblink conditioning (Kehoe, 1982).

At the neural level overshadowing may occur because as soon as a weak association to one stimulus has started to emerge, it will inhibit the olive and weaken the US, making it more difficult to form an association to the other CS. Overshadowing is not as straightforward to explain as blocking because one must assume that the inhibition of the inferior olive begins early during conditioning. It is also not clear how the cerebellum selects which stimuli to form an association to. Studies have shown that the more salient of a CS pair usually overshadows the less salient stimulus (Kehoe, 1983a). Perhaps the more salient stimulus elicits a more distinctive mossy fiber input, which speeds up the association.

7.3. Overexpectation

Overexpectation is closely related to Kamin blocking. First, you pair CS_A and the US until CS_A consistently elicits a CR. Next, you pair CS_B and the US until CS_B also elicits a CR. Crucially, CS_A and CS_B should never be presented as a compound during training because that might lead to overshadowing or blocking (see above). When both CSs elicit CRs, you proceed to pair CS_A and CS_B as a compound, still followed by the US.

Initially, the compound CS will lead to a stronger CR, a phenomenon known as summation. But, gradually the response to both CSs as well as the compound stimulus weakens. This phenomenon is known as overexpectation because it is as if the simultaneous presentation of two stimuli that are both associated with the US result in an overexpectation, which triggers a stronger response. Overexpectation has been demonstrated in instrumental conditioning (Lattal & Nakajima, 1998), fear conditioning (Kamin & Gaioni, 1974; McNally et al., 2004; Rescorla, 1970), conditioning of the nictitating membrane (Kehoe & White, 2004).

At the neural level, there is evidence that a CS that has been paired with the US inhibits the inferior olive (Nicholson & Freeman, 2003; Rasmussen et al., 2015; Sears & Steinmetz, 1991). When two CSs are presented simultaneously, it results in a stronger pause response in the Purkinje cells as well as more inhibition of the inferior olive (Rasmussen et al., 2015). Ultimately, this ought to cause partial extinction of the CRs. For this model to be accurate a single CS cannot cause a 100% suppression of the US signal because then you would not get summation.

8. Experimental predictions

This review has shown that: (1) the inferior olive conveys error messages to the cerebellum; (2) the firing from the inferior olive is graded; (3) nucleo-olivary feedback influences olivary activity; and (4)

the strength of the olivary signal influences learning. Together, these findings point to a plausible neural implementation of the Rescorla-Wagner model as well as explanations for several learning phenomena at the neural level. As shown above, there is a substantial body of evidence supporting these claims. However, the Rescorla-Wagner model has also failed on a number of accounts (Miller et al., 1995). These problems should also be taken into account if we want to understand learning at the neural level. Below I provide a list of testable predictions that follow from the logic I have used above.

8.1. Predictions

8.1.1. Conditioning is faster with a more salient CS

A necessary assumption to explain overshadowing is that conditioning can occur at different rates depending on the saliency of the CS. Factors that make a stimulus more salient should thus result in faster conditioning. A louder tone should induce faster conditioning, and a clearly visible light should also induce faster conditioning than a dim, barely visible, light.

8.1.2. Stimulation of the nucleo-olivary pathway can alter olivary burst size

Stimulation of the nucleo-olivary pathway reduces the size of peripherally elicited olivary field potentials (Bengtsson & Hesslow, 2006; Svensson et al., 2006). Stimulating the nucleo-olivary pathway before the US also causes extinction of a previously acquired CR (Bengtsson, Jirenhed, Svensson, & Hesslow, 2007). However, no one has tested whether stimulation of the nucleo-olivary pathway can influence the number of spikes in the olivary bursts. This is necessary for a graded control of the US strength. Testing this would require intracellular recordings from Purkinje-cells and the ability to stimulate the nucleo-olivary pathway.

8.1.3. A Purkinje cell pause reduce the number of spikes in a climbing fiber burst

A related prediction is that learned pause responses in Purkinje cells can influence the number of spikes in the olivary discharge. Given that pause responses disinhibit the nuclei and, consequently, increases nucleo-olivary inhibition, a Purkinje cell pause response can be compared with stimulation of the nucleo-olivary pathway. So if nucleo-olivary stimulation can influence the strength of the olivary signal, then Purkinje cell pause responses should have the same effect.

8.1.4. Activation of the nucleo-olivary pathway influence the shape of complex spikes

As discussed above, there is some evidence that all else being equal, the shape of complex spikes is partially determined by the number of spikes in the climbing fibers. If the two prior predictions are correct then activation of the nucleo-olivary pathway, through direct stimulation or indirectly through the expression of a CR, should also influence the shape of complex spikes. Unlike the two prior predictions, testing this prediction only requires extracellular recordings from Purkinje cells and the ability to stimulate the nucleo-olivary pathway or activate it through conditioning.

8.1.5. There exists an equilibrium level of olivary excitability

In a previous study, we followed one Purkinje cell for more than 1000 paired forelimb and climbing fiber presentations (Rasmussen et al., 2013). When we applied burst-like stimuli of three or more spikes, the cell developed a pause response. When we applied a single stimulus to the climbing fibers, the pause gradually disappeared. When we applied two stimuli, the activity during the CS did not change (see Fig. 4). According to the Rescorla-Wagner model, there exists such an equilibrium for learning. We predict that such an equilibrium-level exists at the neural level as well. Depending on the number of spikes in the olivary signal you will get either acquisition, extinction, or no change in behavior.

9. Conclusion

I have reviewed evidence that the olive fires in bursts and that the number of spikes in a burst influences learning. I have also reviewed evidence suggesting that eyeblink conditioning increases nucleo-olivary inhibition, resulting in a negative feedback loop that regulates cerebellar learning. Combining these two lines of evidence points to a plausible neural implementation of the Rescorla-Wagner model along with learning phenomena derived from the model.

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