

One cannot build theories of cerebellar function on shaky foundations: Induction properties of long-term depression have to be taken into account

BEHAVIORAL AND BRAIN SCIENCES
19:3: 440-441, 1996

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Abstract

The theories of cerebellar function presented in this BBS special issue cannot be reconciled with the established induction properties of cerebellar LTD. At the same time, the authors presenting their research on cerebellar LTD do not appear very interested in function. System physiologists and cell biologists need to collaborate more if we are to make progress in understanding cerebellar function.

Thach introduces his paper by describing the steps necessary to understand brain structure and function ([sect. 1, para. 1](#)). The only non-behavioral data he mentions is connectivity. This seems to align him with most of the neural networks field (Hertz *et al.* 1991), which does not consider cellular properties to be relevant to the functioning of neural circuits either. Probably **Thach** would agree that properties of specific neurons, including for example ion channel kinetics and types of synaptic receptors expressed, are relevant to brain function. But his paper is typical for cerebellar system physiologists, who often neglect single neuron physiology in their reasoning.

This is symptomatic of the almost complete separation between the fields of research on synaptic plasticity and of system analysis of cerebellar function, which is quite noticeable in this issue of BBS. Although the issue is called "Controversies in Neurosciences", most contributors neatly keep to their side of the fence. The cell biologists (**Crépel *et al.***, **Linden** and **Vincent**) describe their particular views on how long-term depression (LTD) is induced, often covering the possible metabolic pathways involved in great detail. But they do not address the issue of the functional significance of synaptic plasticity in the cerebellum. In fact, **Linden** ([abstract](#)) explicitly says this is not the purpose of his article, while **Crépel *et al.*** ([sect. 1, para. 4](#)) limit their discussion to conventional references to Marr (1969) and Albus (1971). **Kano** ([sect. 8, para. 3](#)) briefly describes a possible function of the potentiation of inhibitory inputs. But one cannot call the suggested role of LTD-enhancement very imaginative.

It cannot be said that cerebellar system physiologists lack imagination, as is

apparent from the widely different theories on cerebellar function presented by **Houk et al**, **Smith** and **Thach**. Their theories seem to have only three ideas in common: each claims to have extensive experimental support for their particular proposal, the cerebellum is involved in motor learning and LTD is the neuronal mechanism of this learning. How is it possible that starting with the same body of experimental knowledge, scientists can arrive at such divergent ends? The simplest explanation is that the problem of cerebellar function is underconstrained, or, in other words, that the available data allows for many different interpretations. This is certainly true in some aspects; for example the contribution of other brain regions to motor control has not been completely defined either. Unfortunately this is not the only cause; instead it seems that several system physiologists are not aware of experimental evidence reported in the last five years. In fact, **Smith** and **Thach** both implicitly assume that cerebellar LTD will provide the substrate for the kind of learning that has been proposed by Marr (1969) , Albus (1971) and Ito (1984). However, as reviewed recently (De Schutter 1995), several aspects of cerebellar LTD induction do not fit well with the Marr-Albus-Ito theories. I will refer here only to the most serious problem, referred to as the "temporal credit assignment problem" by **Houk et al.** (sect. 4.1, para. 7) and also described by **Linden** (sect. 3, last para.). It has been shown both in decerebrated animals and in slice that climbing fiber stimulation must precede parallel fiber stimulation to obtain LTD induction (Ekerot & Kano 1989; Schreurs & Alkon 1993; Karachot *et al.* 1994). This is impossible to reconcile with the proposed role of the climbing fiber as an error signal (Albus 1971). Karachot *et al.* (1994) have actually demonstrated that no LTD is induced in slice when inputs are timed like they are presumed to occur in the classical conditioning of the nictating membrane reflex (Thompson 1988; see also **Houk et al.**, sect. 3.6, first para. and **Thach**, sect. 3.4).

The contribution of **Simpson et al.** in this volume is refreshing. They conclude that the function of the climbing fiber input in the rabbit's vestibulocerebellum remains a mystery (sect. 6). I think this is a fair description of cerebellar function in general. Moreover, I'm afraid that the field will not make much progress unless we bring the cell and system physiologists closer together. I already mentioned the problems associated with fitting cerebellar LTD into a theory that assumes that the climbing fiber input is an error signal. But the opposite also happens too frequently. Many theories of cerebellar function not presented in this volume simply neglect LTD altogether (e.g. Bloedel 1992; Welsh *et al.* 1995). **Houk et al.** (sect. 4.1, para. 8) at least take the trouble to analyze the problems associated with attributing a function to cerebellar LTD. But their suggested solution, an additional, hereto experimentally unrecognized way to induce LTD, is unlikely to be true.

Considering the complexity of the network in which the cerebellum is embedded (Ito 1984) and our lack of knowledge about many properties of this network, including even the neural code (Ferster & Spruston 1995), it is too early to generate specific theories on how the cerebellum participates in motor control or cognition. This does not exclude theories on a more basic

level. For example, detailed modeling of single cells can provide new insights. **Houk et al.** (sect. 3.3, para. 4) have used this approach to analyze bistability of the Purkinje cell dendrite (Yuen *et al.* 1995), but the validity of their extremely simplified model is questionable. Detailed modeling of the Purkinje cell (De Schutter & Bower 1994a) has revealed important properties of this neuron's active dendrite. For example, parallel fiber inputs get amplified so that even inputs contacting the most distal parts of the dendrite have the same access to the soma as more proximally located inputs (De Schutter & Bower 1994b). The modeling work has also suggested a new hypothesis on the function of cerebellar LTD (De Schutter 1995). Because these hypotheses are defined at the neuronal level, they immediately suggest experiments which can falsify the theory. This is something that I found lacking in the papers by **Houk et al.**, **Smith** and **Thach**.

In conclusion, system physiologists need to take cellular properties more into account. To achieve this goal both sides will need to contribute. For example, at the system level the firing properties of the neurons need to be studied in more detail. This can lead to some surprising results, as shown by **Simpson et al.** in this volume. At the cell biology level too much emphasis has been placed on identifying receptors and metabolic pathways. This has spawned a literature full of details which are often specific to the experimental conditions used, e.g. cell culture (**Linden**) or the effect of trans-ACPD in slice (**Crépel et al.**, sect. 1.3). Unfortunately this does not tell us much about the induction requirements of LTD in the context of behavioral learning. For example, it seems that about 100 climbing fiber-parallel fiber pairings at the natural firing frequency of climbing fibers (1 to 4 Hz) are sufficient to induce LTD (Ekerot and Kano 1989; Ito 1989; Schreurs and Alkon 1993). But, while 100 pairings seems a reasonable number to learn something, it is unlikely that in real life such pairings would occur at 1 Hz. For example, if LTD is involved in motor learning one might expect one pairing during each failed motor execution; which, depending on the task, might take tens of seconds to several minutes. Nobody has ever reported if LTD could be induced in slice with a low frequency of pairing (0.01 to 0.10 Hz).