CLASSICAL PERSPECTIVES

David Marr's theory of cerebellar learning: 40 years later

Piergiorgio Strata[1,2]

[1] *Department of Neuroscience and National Institute of Neuroscience-Italy, University of Turin, Corso Raffaello 30, 10125 Turin, Italy*

[2] *EBRI-Santa Lucia Foundation (IRCCS), via del Fosso di Fiorano 64, 00143 Rome, Italy*

Email: piergiorgio.strata@unito.it

Until the sixties, the prevalent view on the function of the cerebellum was that of a structure involved in the control of posture and movements. This concept emerged in the early studies by Flourens (1824) who wrote that 'all movements persist following ablation of the cerebellum: all that is missing is that they are not regular and coordinated'. He thus introduced the concept of movement *coordination*, a property which had not previously been considered by physiologists. Towards the end of the century Luciani (1891) described the three basic symptoms of cerebellar lesion: asthenia, atonia and astasia while Holmes (1917) provided a detailed picture of human pathology. A complete collection of data on this early phase of cerebellar physiology and pathology can be found in the classical book by Dow & Moruzzi (1958).

A new era in cerebellar physiology started in the 1960s in the laboratories of John Eccles, Janos Szentágothai and Masao Ito with the description of the cerebellar wiring. By means of electro-physiological analysis and morphological studies Eccles and Szentágothai provided for the first time a complete picture of the functional architecture of the cerebellar cortex, identifying the excitatory and the inhibitory nature of each cell type. In the same period Ito showed the inhibitory nature of the Purkinje cells, a finding dismantling the dogma that inhibitory neurons are short local cells switching an excitatory signal into an inhibitory one. This entire new story has been described in the book by Eccles *et al.* (1967).

David Marr did his doctorate in theoretical neuroscience under the supervision of Giles Brindley who was the first to view this structure as representing a Hebbian type of synaptic plasticity (Brindley, 1964). The results of Marr's dissertation were published in the form of three journal papers between 1969 and 1971. By theoretical speculation and by correlating architectural wiring and function, he provided an original insight into the function of three major brain structures, cerebellum, neocortex and archicortex. The three papers aim at providing a unitary theory of mammalian brain and complement each other in as far as all structures work as a statistical pattern of recognition and association. They are still relevant at present.

In the first paper, published in *The Journal of Physiology*, Marr (1969) proposed that the cerebellar cortex has the task of learning motor skills for movement and posture. The basic assumption was that synaptic connections are modified by experience, a general issue that at that time had poor experimental evidence. Inspired by the work of Eccles, Ito and Szentágothai, for the first time he suggested a role for the two main excitatory inputs to the cerebellar cortex: the mossy fibres and the climbing fibres. The signals carried by the mossy fibre input project to the extraordinarily high number of granule cells (10^{11} in human) whose axons, the parallel fibres, contact the Purkinje cell dendrites. In this huge network contextual information is finely represented. The parallel fibre to Purkinje cell synapses could be reinforced through a long-lasting increase of the synaptic efficacy (long-term potentiation) when a simultaneous activation of the climbing fibres occurs. By this mechanism each Purkinje cell can learn to respond to a large number of different patterns of activity in the mossy fibres. Thus, the climbing fibres act as an error-detecting device during the learning of a motor task. This view maintains that motor memory resides at least in part in the cerebellar cortex at the level of the synapses between the parallel fibres and the Purkinje cells. Albus (1971) proposed a long-term depression at this level. Marr's theoretical paper represented a milestone in the history of cerebellum (Glickstein *et al.* 2009).

Marr's theory was formulated in a sufficiently concrete form to be experimentally tested. Ito and collaborators tested this theory experimentally by using as a model the adaptation of the vestibulo-ocular reflex to a change in the visual stimulation pattern. Later, he and his associates demonstrated for the first time a long-term depression of the parallel fibre to Purkinje cell synapses following a conjunctive stimulation of parallel fibres and climbing fibres by recording synaptic fields (Ito & Kano, 1982), Purkinje cell firing and EPSPs in slices (see Ito, 2001).

Since then, there has been a flurry of papers testing different mechanisms of learning and memory processes in the cerebellum by using several other approaches at molecular, cellular and behavioural level. The central and debated issue that follows up Marr's paper is the role of climbing fibres in motor learning. By some the cerebellum is still regarded as a control machine rather than an associative learning device (Rokni *et al.* 2008) and long-term depression in the parallel fibres to Purkinje cells synapses is denied a role in learning (Welsh *et al.* 2005). However, several other established views are now emerging in favour of learning (see Hansel *et al.* 2001; Ohtsuki *et al.* 2009). In cats, cutaneous receptive fields are enlarged when only parallel fibres are stimulated, or reduced when the climbing fibres are also stimulated (Jörntell & Ekerot, 2002). It has also been shown that in monkey, during behavioural learning, climbing fibres have a causal role in the induction of cerebellar plasticity during a simple motor learning task by depressing simple-spike responses (Medina & Lisberger, 2008). In addition, other experiments showed that climbing fibres are not simply an all-or-none device for the induction of long-term potentiation (Marr, 1969) or long-term depression (Albus, 1971) in the parallel fibre to Purkinje cell synapses. Instead, the number of action potentials in each climbing fibre burst is variable and it encodes olivary oscillations that may influence both timing and learning aspects of cerebellar functions (Mathy *et al.* 2009), thus integrating the two major theories on climbing fibres. Interestingly, signals carried by only climbing fibres or by parallel fibres are sufficient for motor learning with an additive effect when both signals are present (Ke *et al.* 2009). Thus, motor learning may not be exclusively linked to climbing fibre activity (Ohtsuki *et al.* 2009). Finally,

climbing fibre to Purkinje cell synapses are endowed with a high degree of structural and functional plasticity (Strata & Rossi, 1998; Hansel & Linden, 2000; Ohtsuki *et al.* 2009).

Thus, after 40 years since Marr's paper, motor learning and cerebellum is still a central and debated issue in studying cerebellar function as shown by the large community of scientists involved (see Strata *et al.* 2009). The concept of a single memory locus does not apply to any memory system in the brain and also Marr's model remains a plausible component of a much larger learning system that includes sites of plasticity elsewhere in the cerebellum and outside the cerebellum as well. These concepts are now being extended to non-motor function of cerebellum (Strick *et al.* 2009). The available data represent several little stones that need to be implemented and assembled to form a full mosaic for a better comprehensive view by associating molecular, cellular and behavioural experiments.

Marr's paper is one of the best examples of a theory that directly relates the function of a neural system to its neuronal structure. Its importance is not limited to the cerebellar physiology. Indeed, the same concept also had a great impact on other brain models and had an influence on other areas. Therefore, Marr should be credited for having contributed substantially to the creation of the new discipline of Computational Neuroscience.

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