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# Cerebellum and Detection of Sequences, from Perception to Cognition

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**Abstract** The idea that cerebellar processing is required in a variety of cognitive functions is well accepted in the neuroscience community. Nevertheless, the definition of its role in the different cognitive domains remains rather elusive. Current data on perceptual and cognitive processing are reviewed with special emphasis on cerebellar sequencing properties. Evidences, obtained by neurophysiological and neuropsychological lesion studies, converge in highlighting comparison of temporal and spatial information for sequence detection as the key stone of cerebellar functioning across modalities. The hypothesis that sequence detection might represent the main contribution of cerebellar physiology to brain functioning is presented and the possible clinical significance in cerebellar-related diseases discussed.

**Keywords** Cognition · Autism · Schizophrenia · Somatosensory cortex · Motor cortex · Ataxia

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## Introduction

Nowadays, cerebellar contribution to a wide range of cognitive, emotional, and sensory functions is well established [1–4]. More then 10 years ago, sequence detection and generation has been suggested as a possible key to address cerebellar function [5, 6]. Since then, sequencing properties of cerebellar processing have been extensively investigated in animal models [7–10] as well as in human lesion [11–18] or functional activation studies [19]. In spite of this wide interest and cooperative effort, the role of the cerebellum in sequencing remains elusive.

We will endorse the idea that sequencing is the basic model of cerebellar functioning not linked to any singular modality of state estimation. We will argue that the cerebellum intervenes whenever a feed-forward control is needed by identifying patterns that allow a response to be anticipated. This general mechanism would act on simple responses like eye blinking as well as on complex social behavior.

## Sequence Processing for Cerebro-Cerebellar Cross Talk in the Motor–Sensory Domain

It is generally accepted that cerebellar input has a facilitatory effect on the contralateral cerebral cortex and indeed chronic cerebellar damage reduces the excitability of the contralateral motor cortex [20]. On the other hand, experimental and clinical data are not so straightforward, suggesting that cerebellar stimulation may have different effects on the cerebral cortex [21, 22] [23]. At present, nature and functional significance of the cerebellar influence over the cerebral cortex is the object of a large debate [4, 24].

Whatever is the effect of the cerebellar input on the cerebral cortex, it is widely accepted that it conveys information for sensory motor integration [25]. This issue was elegantly addressed in rats by transcranial magnetic stimulation [26, 27]. In rats, as in man, sustained somatosensory stimulation enhances excitability of the contralateral motor cortex [28, 29]. This effect is lost if the cerebellar input is blocked [26, 27]. Thus, the cerebellum is a link in the cross talk between somatosensory and motor cortices. How does it work? Somatosensory influences on motor cortex are mediated by cerbello-M1 circuits or the cerebellar output directly affects the somatosensory cortex.

The parietal cortex projects to the cerebellum via the pontine nuclei in a topographically organized manner [30] and it receives the cerebellar return loop through the thalamus [31, 32]. Cerebellar influences on the parietal somatosensory cortex have been demonstrated in patients with unilateral cerebellar lesions by somatosensory-evoked potentials [33]. Early components of somatosensory-evoked potentials were unaffected by cerebellar damage; conversely, N24 and P24 later components were profoundly reduced in the absence of the cerebellar input. This observation indicates that the cerebellar input influences directly, and not through the motor cortex, the excitability of the interneurons of the parietal cortex [33].

What is the message sent by the cerebellum to the parietal interneurons? Some hints may be derived from a MEG study that compared expected and unexpected sensory stimuli [34]. By inserting a random omission in a regular train of somatosensory stimuli, it was evidenced that cerebellar activity is markedly enhanced after unpredictable omissions, as if cerebellar activity codes change in expectancy [35]. The role of cerebellar processing in predicting sensory events has been reviewed by Nixon [24] and it has been recently addressed in a somatosensory mismatch negativity (S-MMN) study in patients with unilateral cerebellar lesions [15]. S-MMN is thought to be generated by an automatic change-detection cortical process activated by differences between current and prior inputs. When the S-MMN protocol is applied to subjects with unilateral cerebellar lesions, S-MMN response is absent or abnormal in the cortical hemisphere lacking the cerebellar input (Fig. 1). The cited study demonstrates that cerebellum, at least in regard to somatosensory information, must be considered an essential part of the MMN circuit. What could the cerebellum be doing? Considering involvement in prediction of sensory events [24] and the long-standing idea that the cerebellum acts as a comparator [4], it is conceivable that, within the cerebellum, actual input and preceding stimuli are compared and discordances are tested. If the incoming stimulus corresponds to the predicted one, cerebellar output is minimal; if a discrepancy–error signal is detected then activity in the cerebellum increases and a large area of the cerebral cortex is alerted by enhancing its excitability. Is this mode of operation limited to the somatosensory system or is it active also in other sensory domains? No studies addressing the visual domain are at present available, while preliminary data seem to indicate

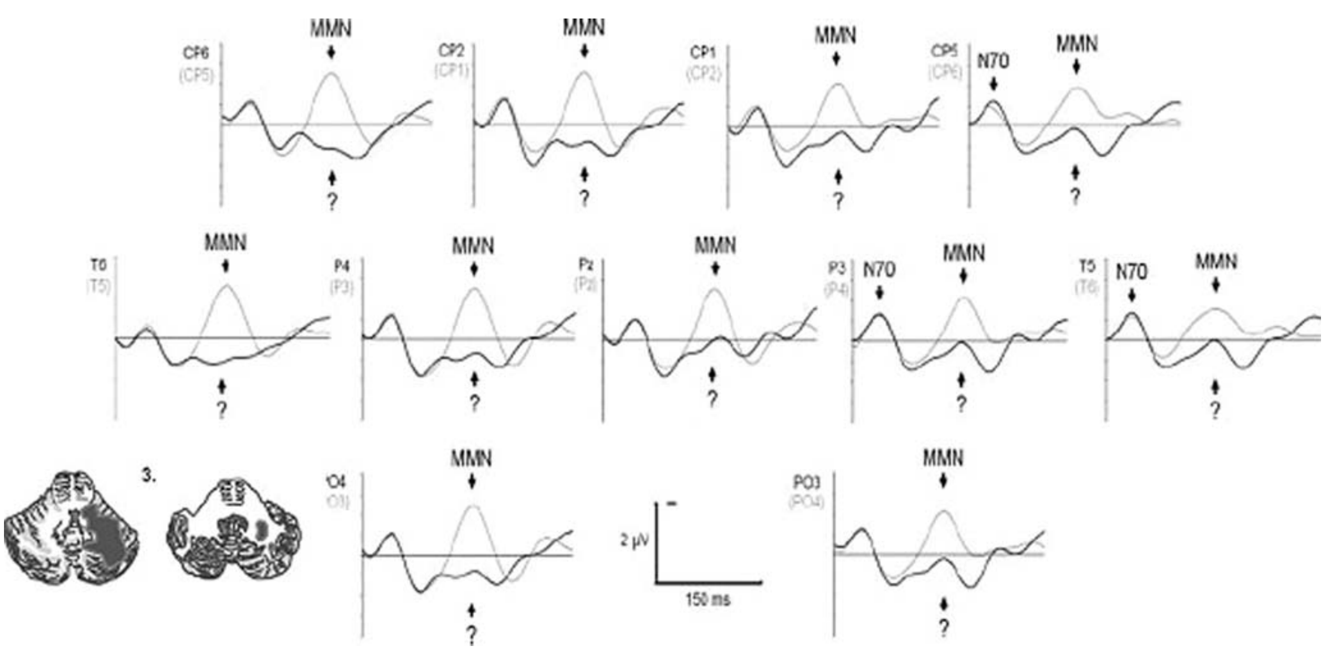


**Fig. 1.** ERPs obtained from subjects with left cerebellar lesion during the "oddball" protocol difference traces. Lesion extension is depicted in the *lower left corner*. Traces obtained after stimulation of the unaffected right hand (*gray*) are superimposed over those obtained after stimulation of the affected left hand (*black*). Corresponding leads are also superimposed (T5–T6, P3–P4, etc.). Negativity is upward. The S-MMN response is clearly lacking after affected hand stimulation. (modified from [15])

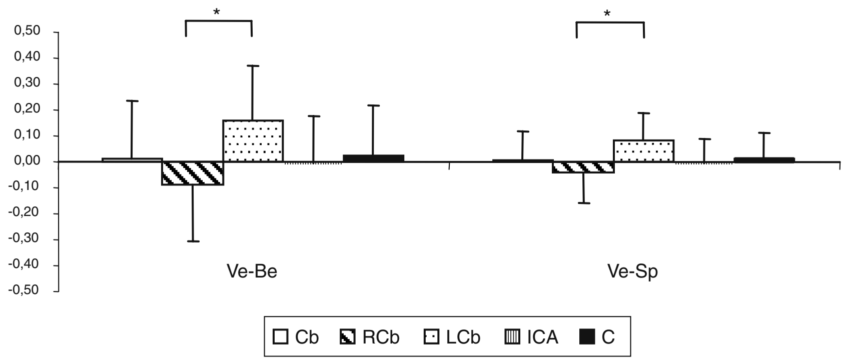


**Fig. 2.** Histograms of the verbal vs behavior (*Ve–Be*) and verbal vs spatial (*Ve–Sp*) mean indexes in subjects with cerebellar right (*RCb*) or left (*LCb*) damage (Cb and control groups). Ve–Be in the card sorting test. Note how the indexes present opposite direction according to the side of the cerebellar lesion. See text for further details $*P<0.05$ (from [38])

that cerebellar lesion does not affect MMN in the auditory domain [15].[1] On the other hand, the importance of the cerebellar processing for speech perception [36] suggests a possible involvement also in auditory processing. It would be important to develop dedicated studies to fully answer this issue.

## Cognitive Sequences

As reviewed in the previous sections, in the somatosensory domain, the cerebellum compares sequences of incoming stimuli to detect similarities and differences in order to predict what is coming next or to alert if a prediction is not fulfilled. If this is the basic operational model of the cerebellum, then its fingerprints should be recognizable in all domains of cerebellar functions. A number of studies have addressed this topic in the sensory motor domains [24, 37]. Much less is known on cerebellar sequence processing in nonmotor domain. The role of the cerebellum in sequencing across verbal, spatial, and behavioral cognitive domains has been recently addressed in a lesion study [38].

The widely diffuse Picture Arrangement subtest (PAs) of the Wechsler Adult Intelligence Scale Revised (WAIS-r) is considered to investigate mainly sequential thinking [39]. In this test, subjects have to reconstruct the correct sequence in a set of cards depicting brief stories or in which object position indicates a chronological order. To correctly execute the test, it is necessary to identify relations between events–objects, to decide priority, and to chronologically order the cards. In this test, subjects with cerebellar lesions generally score within the normal range [38, 40]. However, when data are compared to matched controls, significant differences are present. The presence of subclinical defects that are evident only when more sensible measures than cut off values are considered is a common event in studying cognitive functions in subjects with cerebellar lesions. Performances within normal ranges, with impairments observed when more specific tests or ad hoc reference data are used, have been reported in visuospatial [13], verbal fluency [41], and short-term memory functions [42].

In the PAs, various aspects of the material to be sequenced have to be taken into account at the same time and it cannot be sorted out if the cerebellum influences sequences per se or if it is related to the properties of the material processed. To solve this aspect, we developed sets of cartoon-like drawings–texts to specifically differentiate among verbal, spatial, and behavioral sequencing [38]. In this new test, subjects with cerebellar damage presented scores lower than control scores, independent of the material processed. If performances were grouped either according to lesion type, focal vs degenerative, or according to lesion side, then the importance of the material processed became evident. Degenerative pathologies uniformly impair performances throughout modalities. In the cases of focal damage, mirror-like profiles are present. In the cases of left cerebellar damage, subjects score lower with behavioral than with verbal material. On the contrary, in the cases of right cerebellar damage, subjects present worse performances with verbal than with behavioral material (Fig. 2). Thus, cerebellar damage impairs sequencing of cards independently of whether spatial, verbal, or behavioral strategies are needed. Nevertheless, comparison between right and left lesions indicates that each cerebellar hemisphere is prevalent in processing sequences for different domains. Cortico-cerebellar loops are known to be organized in paralleled grossly independent circuits in

[1] While the present article was in press, an article addressing the MMN in the auditory domain appeared (Detecting violations of sensory expectancies following cerebellar degeneration: A mismatch negativity study by Torgeir Moberget, Christina M. Karns, Leon Y. Deouell, Magnus Lindgren, Robert T. Knightb, Richard B. Ivry. Neuropsychologia 46(2008) 2569–2579) reporting auditory MMN impairment in patients with cerebellar atrophies, particularly evident in the time domain.

which motor, visuomotor, and cognitive functions are processed [43]. In this framework, the anatomo-functional specializations observed in verbal–behavioral and in verbal–spatial contrasts of sequence processing [38] suggest that the same mode of operation exists in the different channels while the final functional output is determined by the use that the cortex makes of the cerebellar sequencing function.

## Clinical Relevance of Cerebellar Cognitive Sequencing

The cerebellar importance in identifying predictable sequences in the behavioral domain may be of relevance for the understanding of pathophysiological mechanisms in different clinical conditions in which a cerebellar involvement has been hypothesized such as schizophrenia [44] and autism [45]. Behavioral or script sequencing can be defined as the process that allows for the correct recognition of spatial and temporal relations among behaviorally relevant actions [46]. Script sequencing has been considered to be sustained by frontal lobe and basal ganglia circuits and it requires the ability to plan ahead [47]. The demonstration that script sequencing is impaired after cerebellar damage indicates that the cerebellum also has to be included in the script network and opens up interesting perspectives. Card-sequencing impairment can be interpreted as a prediction deficit. The role of the cerebellum in predicting events is well established in other domains such as sensory processing [24], eye movements [48], motor control [49], and time perception [50]. We can consider sorting cards of behavioral content as a laboratory model to test the ability to understand the world and the people around us. Impairment in detecting action chains has been recently reported in autism [51] and in particular impairment in the PAs of the WAIS-r has been shown to correlate with negative symptoms and social functioning in schizophrenia [52]. Taken together, the data reviewed here indicate that the forward model of cerebellar computing has to be applied also to the cognitive–behavioral domain and its impairment has to be considered in addressing the cerebellar role in behavioral-related disorders such as autism and schizophrenia.

As stated before, sequencing requires comparing previous and ongoing stimuli and to accomplish this task requires the maintenance of data in a working memory buffer. In line with the importance of the cerebellum in both verbal [42] and spatial [53] working memory functions, it is tempting to hypothesize a specific importance of cerebellar processing in maintaining short-term memory buffers. Cerebellar influence on working memory is multifaceted [42, 54] and sequencing is not a unitary function. In this context, it would be interesting to address in comparison cerebellar sequencing and working memory functions in a devoted study.

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