# Cerebellar Sequencing for Cognitive Processing

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Marco Molinari and Maria Leggio

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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 the cerebellar role in the different cognitive domains remains obscure. Current data on perceptual and cognitive processing from lesion studies in humans and from experimental lesion studies in rats are reviewed with special emphasis on cerebellar sequencing properties. Evidence converges in highlighting sequence detection as the keystone of cerebellar functioning across modalities. The hypothesis that sequence detection might represent the main contribution of cerebellar physiology to brain functioning is presented and discussed.

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## Introduction

Many groups are generating anatomical, experimental, functional neuroimaging and clinical data that stress the importance of corticocerebellar interactions in many non-motor domains such as cognition, emotion, and affective processing (Timmann and Daum 2007; Schmahmann 1997). This evidence has broadened our understanding of cerebellar functions but has raised questions regarding how the cerebellum explicitly contributes to non-motor operations (Bower and Parsons 2003; Ito 2006). Thus, many investigators have attempted to identify the underlying processes that explain the cerebellum's function across domains. Specifically regarding the cerebellum and cognition, the complexity and variety of cognitive functions implicate the influence of the cerebellum on the cerebral cortex as the key to understanding basic cerebellar processing (Molinari et al. 2002). Early in cerebellar research, sequence processing was proposed as the basic functional mechanism of the motor (Braitenberg et al. 1997) and cognitive (Molinari and Petrosini 1997) domains. Acquiring and acting on a sequence of events is a fundamental ability that leads to knowledge of sequence structure – both incidentally through experience and intentionally through explicit effort. To recognize that stimuli are presented in a certain order, the information concerning a single stimulus must be kept active in a working memory system and compared with subsequent stimuli. With regard to the prediction of sensory events (Nixon 2003; Bastian 2006) and the capacity to process comparators (Ito 2008), it is conceivable that sequencing requires cerebellar processing. If detecting and generating sequences are basic cerebellar operations, they should be active in all domains of cerebellar function. This prediction has been demonstrated for the sensory (Bower 1997), motor (Thach et al. 1992), and behavioral (Leggio et al. 2008) domains.

This chapter reviews the sequencing hypothesis of cerebellar function and interprets the deficits observed after cerebellar damage in this light.

## Somatosensory Processing

The importance of the cerebellum in sensory processing (Gao et al. 1996) and its role in predicting somatosensory events (Bower 1997) have long been demonstrated. Despite the efforts in this area of research, the cerebellar contribution to sensory prediction has not been defined (Bo et al. 2008).

In a magneto-encephalographic (MEG) study, Tesche and Karhu (2000) analyzed the neural signals that were generated in the somatosensory cortex and cerebellum by expected or unexpected sensory stimuli. This approach allowed the investigators to monitor the temporal sequence of cerebrocerebellar interactions in the processing of incoming somatosensory information.

Classically, somatosensory evoked potential (SEP) protocols are based on continuous peripheral stimulations at a fixed frequency. Under such conditions, each stimulus is associated with sustained activity in the parietal cortex and preceded by a small cerebellar response. If this standard protocol is modified by omitting somatosensory peripheral stimuli at random, thereby interrupting the regularity of the flow of stimuli, the cortical and cerebellar responses change (Tesche and Karhu 2000).

As a result of this omission, no activity is recorded in the cerebral cortex, as expected, but a notable response develops in the cerebellum. Cerebellar activity is much greater when the peripheral stimulus is omitted than when it is present. Thus, the cerebellum detects the absence of a somatosensory stimulus rather than its presence. Absence signals can be understood only as an indication that something that is expected has not appeared (Ivry 2000).

Since in the SEP protocol, stimuli are presented according to a fixed time frame, and considering the long-standing model of cerebellar involvement in timing (Ivry et al. 2002), it was suggested that cerebellar activity in the absence of an expected somatosensory stimulus signaled not the absence of a sensation but rather a deviation from the expected timing. Nevertheless, timing is not the only parameter that allows prediction. By definition, sequences are based on relationships in time and space. If the fundamental mode of cerebellar function is sequencing – not timing – then its importance should also be evident in processing sequence relationships outside of the time domain.

The importance of cerebellar processing in making predictions outside of the time domain was addressed in a somatosensory mismatch negativity (s-MMN) study in subjects with unilateral cerebellar lesions (Restuccia et al. 2007). According to Naatanen and Michie's MMN model (Naatanen and Michie 1979), s-MMN is generated by an automatic cortical change detection process that is activated by differences between current and previous inputs (Takegata et al. 2001). This process can be achieved only if a memory representation of the standard input is available for comparison with the current input.

Usually, this cerebral response is evoked in the auditory domain, presenting a deviant stimulus within a regular sequence of identical stimuli (Alain et al. 1998). The MMN response in the somatosensory domain has seldom been analyzed

(Akatsuka et al. 2005). Restuccia et al. (2007) developed a novel MMN paradigm specifically to use changes in stimulus location – within a time-locked sequence of stimuli – as key characteristics of the deviant stimulus.

To this end, a protocol in which electrical stimulation of the left fifth finger was interspersed among frequent electrical stimulation of the left thumb was adopted. After obtaining reliable and consistent s-MMN responses in healthy subjects, the same paradigm was used to assess s-MMN in subjects with unilateral cerebellar lesions (Restuccia et al. 2007). This approach is powerful, because it allows s-MMN capabilities to be tested in the same patient in the presence of cerebellar processing (the cerebral hemisphere contralateral to the spared hemicerebellum) or in its absence (the cerebral hemisphere contralateral to the damaged hemicerebellum). s-MMN responses to stimuli that were applied in an unexpected area (from the first to fifth finger) were easily recorded in the cerebral hemisphere with the cerebellar input but were absent in the cerebral hemisphere contralateral to the damaged cerebellar hemisphere (Fig. 1). A similar MMN approach has also been used to evaluate cerebellar prediction in the auditory time domain (Moberget et al. 2008).

MMN studies in cerebellar patients support the model in which cerebellar processing is required to detect the novelty of incoming auditory and somatic sensory stimuli in the domains of time (Moberget et al. 2008) and space (Restuccia et al. 2007).

The hypothesis that pattern detection and prediction represent a specific cerebellar role in perception is appealing, and compelling data from various sources indicate sequence detection as the cerebellar operational mode in perception (Baumann et al. 2015; Leggio and Molinari 2015).

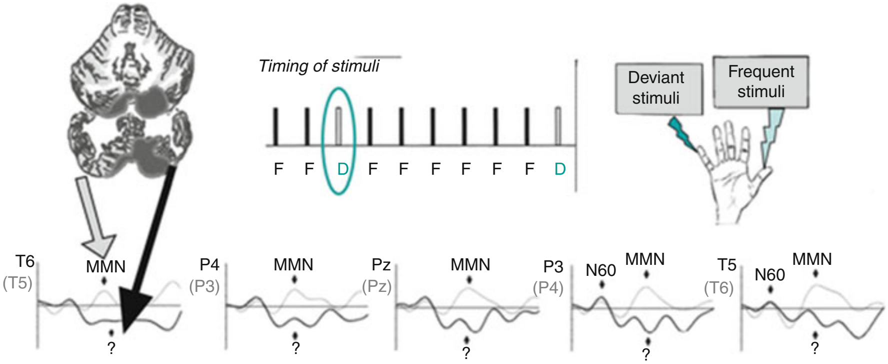

**Fig. 1** s-MMN response in focal Cb patients. Event-related potentials in patients with focal cerebellar damage (lesion described in upper right corner) during the “oddball” protocol difference traces. Traces obtained after stimulation of the unaffected hand (gray arrow) are superimposed over those obtained after stimulation of the affected hand (black arrow). The s-MMN response is clearly absent when the cerebellar input is damaged. (Data from Restuccia et al. 2007)

## Cognition

With regard to analyzing cognitive deficits in patients with cerebellar lesions, if the basic operational mode is linked to sequencing events, an impairment in sequencing within each affected domain should be evident.

## Scripts

According to theories on cognition, scripts constitute a class of organized structures that are stored as knowledge networks for the representation of events, stories, and action sequences. Scripts usually follow a temporally organized sequence of actions within boundaries that define the beginning and end (Crozier et al. 1999). Script sequencing is considered to be sustained by the frontal lobe and basal ganglia circuits, and it requires the ability to plan (Tinaz et al. 2006). In this circuit, the cerebellum is not present; nevertheless, according to the proposed importance of the cerebellum in sequencing, it is highly conceivable to regard the cerebellum as an important station of the script processing neural network.

One of the most frequently used tasks to evaluate script processing is the picture arrangement subtest (PA) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). This subtest primarily examines sequential thinking; to successfully execute the PA, a subject must identify relationships between events and objects, assign priority, and order cards chronologically (Orsini and Laicardi 2000). To do so, subjects must extract several elements from a complex array of sensory information to understand spatial, temporal, and semantic relationships to predict the next card and reconstruct a logical sequence.

Generally, this test adequately evaluates sequence processing. Overall, in subjects with cerebellar pathology, WAIS-R and PA scores fall within the normal range (White et al. 2000). Conversely, when cerebellar patients' performance on the PA is compared with that of ad hoc matched controls, they appear to master small string fragments only (Leggio et al. 2008).

As discussed, the PA test requires one to process different aspects of the stimuli to sequence the cards correctly. To determine whether the importance of cerebellar processing in sequencing is independent of or related to the content that is analyzed, a new version of the PA test, based on various sets of cartoons with material-controlled content, has been recently developed (Leggio et al. 2008). This test analyzes sequencing in three domains: verbal, pictorial, and spatial abstract. Verbal scripts are related to the processing of the lexical components of language, pictorial scripts require the use of spatial and temporal information, and abstract scripts can rely exclusively on spatial information. Thus, this tool makes it possible to examine sequencing performance based on the material that is used.

Returning to the cerebellum and sequencing, it would be expected that subjects with cerebellar pathologies perform poorly, independently of the information that is relevant to correctly sorting the cards in order. Consistent with this hypothesis, subjects with cerebellar lesions are impaired in sorting cards in all three domains, regardless of the sequencing category tested (Leggio et al. 2008).

Differences emerged, however, with regard to etiology and lesion topography. While cerebellar degenerative disorders uniformly affected performance in all modalities, focal lesions evoked disparate profiles, depending on the side that was affected. In fact, patients with lesions of the left hemicerebellum performed poorly on script sequences that were based on pictorial material, and patients with lesions in the right hemicerebellum failed to generate script sequences that required verbal elaboration (Fig. 2). These differences in content are consistent with the current understanding of functional lateralization in the cortex and of crossed cerebellocortical connections.

These data suggest that cerebellar sequencing is not linked to the elaboration of specific content but that different content can be processed in disparate cerebellocortical loops.

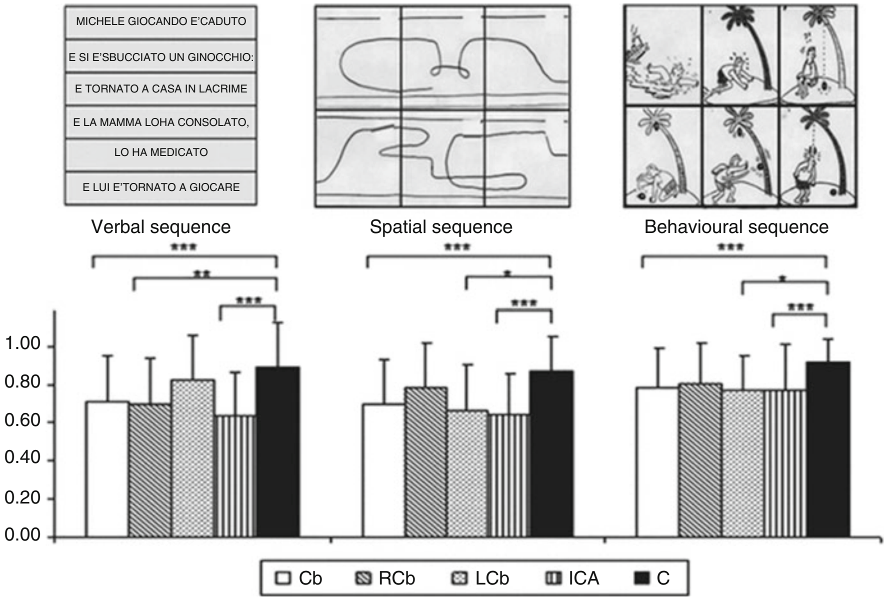

**Fig. 2** Sorting card test results are altered in cerebellar patients independent of sequencing factor. Set of cards representative of three factors. Verbal factor: Michel fell while playing and he bruised his knee; he went back home crying and his mother comforted him. She medicated him and he went back to play. Spatial factor. Behavioral factor. Histograms of mean ratio of repetition RR scores in patient and control groups. *Cb* patients affected by cerebellar pathologies, considered as a whole group, *RCb* patients affected by focal cerebellar lesions on the right side, *LCb* patients affected by focal cerebellar lesions on the left side, *ICA* patients affected by idiopathic cerebellar ataxia, *C* control subjects. *$p$ <0.05; **$p$ <0.005; ***$p$ <0.001. (Data from Leggio et al. 2008)

## Acquisition of Procedures

The cerebellum also appears to contribute to spatial cognition. Spatial ability requires the close integration of environmental (sensory) information and acts of exploration (motor), thus mimicking the sensorimotor role that is typically attributed to cerebellar circuits. To correctly solve spatial tasks, behavioral sequences must be acquired and put into action.

One of the most common tests used to examine spatial abilities in animals is the Morris water maze (MWM) (Morris 1984), in which rats are trained to search for and find a hidden or visible escape platform in a tank that is filled with opaque water. Rats must develop spatial competence and acquire a specific sequence of procedures to (1) search for the escape platform by swimming across the pool and uniformly scanning the surface, (2) avoid visiting sectors of the pool that have already been explored, and (3) develop the skills to reach the platform using the most direct route. These explorative strategies are learned as a sequence from the least to most efficient.

In studies using a rat model of hemicerebellectomy (HCb) (see also ▶ Chap. 78, "Hemicerebellectomy" by Molinari et al.'s, this volume), cerebellar damage impaired the acquisition of the procedures that were required by the MWM (Petrosini et al. 1998). Although hemicerebellectomized (HCbed) rats could escape from the pool, they could do so only with very long latencies, because they failed to develop efficient exploration strategies. Conversely, when spatial MWM procedures were acquired before cerebellar damage, the execution of spatial tasks was not impaired, and the animals explored the entire pool, reaching the platform with the correct trajectories (Leggio et al. 1999; Petrosini et al. 1998).

These findings demonstrate that cerebellar circuitries mediate the acquisition of spatial procedural components without affecting spatial data processing. According to the theory on cerebellar function in sequencing (Braitenberg et al. 1997; Molinari et al. 2008), the above-described deficit in the acquisition of spatial procedures is attributed to difficulties in detecting and generating the appropriate behavioral sequences (e.g., recognition of the spatial environment, putting explorative strategies into action, building a spatial map template) (Graziano et al. 2002).

Rats can learn spatial procedures not only through execution but also through observation, for which cerebellar processing is also required (Leggio et al. 2000a). In the observation-learning paradigm, rats repeatedly observe conspecifics, exploring the pool and applying various strategies to solve the MWM. When the entire repertoire of explorative strategies (circling, extended searching, or direct finding) is observed by unlesioned animals, they can solve the task easily after developing cerebellar lesions. Conversely, when the HCb is performed before observational training, no learning occurs. Thus, HCb impedes further learning freezing acquired competencies. Through this approach, Petrosini et al. (2003) demonstrated that the acquisition of spatial exploratory skills has an organizational structure that can be dissected into its simpler units of behavior (Petrosini et al. 2003), and these units assume the value of autonomous behavioral steps that can be assembled or not. Thus, behavioral units can be singularly acquired by exploiting the potential offered by the combination of the block of learning elicited by the cerebellar lesion with the observation of each single behavioral unit (circling, extended searching, or direct finding) put into action in exploring a water maze (Petrosini et al. 2003).

On this basis, the experimental setting by Leggio et al. (2000a) and the temporal dependence of preventing acquisition by inducing a cerebellar lesion allow one to examine the individual steps that constitute the repertoire of procedures needed to solve the MWM. If rats are allowed to observe just one of the procedures that are put into action during the MWM before cerebellar damage is induced, they will acquire only the step that is observed without developing the competence to complete the entire procedural sequence (Graziano et al. 2002). These experimental findings underscore the importance of sequencing in solving the MWM and characterizing cerebellar impairments as they relate to sequence processing.

## Visuospatial Processing

Procedural learning refers to the process by which repeated exposure to a task results in improved performance. This increase in performance can be achieved through explicit and/or implicit learning mechanisms. The serial reaction time task (SRTT; Nissen and Bullemer 1987) is used widely to study procedural learning. SRTT is based on the generation of a motor response to stimuli, usually visual, that are organized in fixed or random sequences and recording the reaction times (RTs). The degree of procedural learning is reflected by the progressive reduction in RT when stimuli are organized in a fixed predictable order. This test is the benchmark method of analyzing sequence detection and acquisition. Subjects can improve their motor response only if they recognize, implicitly or explicitly, the sequential presentation of different spatial positions.

Several groups (Molinari et al. 1997; Pascual-Leone et al. 1993; Maschke et al. 2002) have studied the relationships between the cerebellum and sequence learning in subjects with cerebellar damage using the visuospatial SRTT, all of whom confirmed that such patients fail to improve their performance on presentation of a repetitive fixed sequence, as evidenced by the lack of difference between RTs to random and sequenced stimuli.

Following cerebellar damage, sequence recognition is also impaired. The dominance of sequence recognition over motor control of the cerebellar deficit is clearly indicated by the poor performance on tests in which sequence recognition and no motor responses are required (Molinari et al. 1997). Conversely, if sequence information is provided explicitly before the SRTT, then sequence predictability decreases the RT (Fig. 3). Overall, experimental data from studies on the effects of lesions support the model of a non-motor origin of cerebellar impairments in visuospatial learning (Molinari et al. 1997; Gomez-Beldarrain et al. 1998). Yet, existing difficulties in acquiring sequences implicate sequence detection as the pivotal mechanism that is induced by cerebellar damage, at least in the space domain.

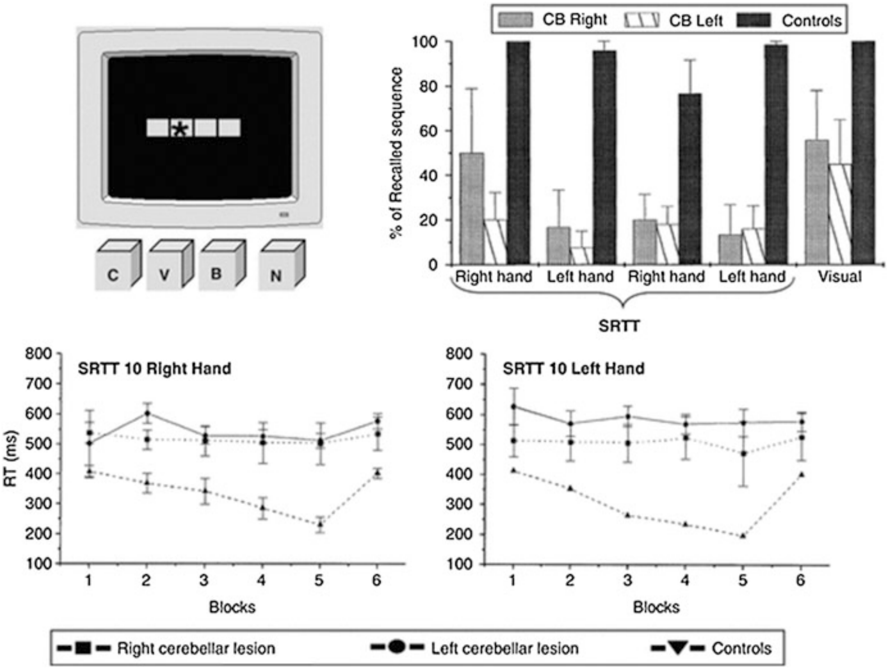

**Fig. 3** Serial reaction time task (SRTT). The SRTT was administered with the subject facing a video screen on which an asterisk appeared in one of four squares. The subject was instructed to press the key corresponding to the asterisk that appeared (upper left). Recognition of the presented sequences as the percentage of recall during the SRRT or only after visual presentation in subjects with focal cerebellar right or left damage. Note the extensive impairment in all conditions (upper right). Reaction times in milliseconds during right and left hand SRRT with sequences of ten items in subjects with right or left focal cerebellar damage. Underline indicates random blocks. Note the lack of a reduction in RT in the various blocks in cerebellar patients under all conditions. (Data from Molinari et al. 1997)

Shin and Ivry (2003) examined patients with cerebellar damage using a version of the SRTT in which two sequences – based on spatial or temporal parameters – were presented simultaneously. Responses were based on the spatial sequence, and the temporal sequence was incidental to the task.

Spatial and temporal sequences were presented using different spatial and temporal intervals. Specifically, the spatial location of visual stimuli was the basis of the principal sequence that required key pressing responses. The second sequence was based on the intervals between stimuli. The two sequences were correlated, and their relations modified in the different trials.

In this paradigm, normal subjects learned both spatial and temporal (incidental) sequence components. The two dimensions, space and time, were integrated into a single sequence. In fact, modulation of the phase shift between the two modalities clearly affected the RT. Subjects with cerebellar damage were unable to acquire the response-relevant, space-based, or time-based incidental sequence (Shin and Ivry 2003).

Notably, in the same study, Parkinson patients were examined, generating different patterns. These patients acquired spatial and temporal sequences but were unable to integrate them into a single complex, multimodal sequence like the controls. Thus, the impaired procedural learning in Parkinson patients is unrelated to learning sequences but is linked to higher-level processing, such as sequence integration. The existence of cerebellar procedural learning deficits indicates that the cerebellum governs the formation of sequential associations in the spatial and temporal domains.

The association of cerebellar damage and impaired sequence recognition has not been noted in all studies. For example, no impairments were reported in patients with mixed degenerative and focal cerebellar pathologies who acquired and discriminated simple sequences of sensory stimuli (Frings et al. 2004). Similarly, cerebellar patients did not develop any impairments in the acquisition of simple auditory and visual sequences (Frings et al. 2006).

The conflicting findings on sequence recognition in SRTT studies have been attributed to differences in motor requirements and sequence complexities of the various paradigms that have been used.

Although this issue remains unresolved, visuomotor associative learning data in cerebellar subjects (Richter et al. 2004; Timmann et al. 2004) suggest that sequence complexity is more relevant than motor components in explaining sequence recognition deficits. Additional data on the relative independence of motor versus cognitive cerebellar sequence impairments have come from a recent SRTT study, in which skill acquisition was tested under various conditions of executive demands, indicating that motor executive and cognitive executive functions are altered after the development of a cerebellar lesion, although the two functions might be subserved by parallel, segregated cerebellocortical circuits (Dirnberger et al. 2010).

More recently, studies on the navigational abilities in patients affected by cerebellar pathology have further supported the idea that the cerebellar role in spatial sequence processing is not linked to cerebellar motor control (Tedesco et al. 2017). The patients performed two navigational tasks requiring memorization of a sequence of spatial locations that were presented with different modalities. In one task, the sequence was demonstrated by an examiner walking on a carpet, and in the other, it was shown by a computer that lit up tiles in a sequence. Whereas the desired motor performance was the same in both tasks – i.e., walking on tiles on the carpet and reproducing the sequence that they had just seen – the subjects were impaired only when they had to reproduce the spatial sequence shown by the lit tiles. This indicates a key role of cerebellar processing unique to decoding a sequence of simple visuospatial stimuli, compared to when this information is embedded in motor behavioral acts.

The authors advanced the hypothesis that in the presence of cerebellar damage, there is a specific deficit in detecting and ordering single independent stimuli into a sequence when the maintenance of stimulus-response associations is more demanding. Indeed, whereas watching the examiner who performs the sequence on the carpet allows the patient to simulate the action mentally, such simulation cannot be triggered when the path is defined by a succession of tiles that light up consecutively (Tedesco et al. 2017).

## Language

In the language domain, there is evidence of cerebellar function in elaborating sequence strategies. Verbal fluency is the capacity to generate lists of words according to a given rule (a letter or a semantic category). Cerebellar patients can be impaired in their ability to generate lists of words according to the phonemic but not semantic rule. This modality-specific cerebellar influence is supported by evidence of selective impairments in clustering words phonologically (Leggio et al. 2000b; Stoodley and Schmahmann 2009). These data demonstrate that in cerebellar patients, impaired verbal fluency is specific for phoneme-related retrieval strategies.

Why does a cerebellar lesion differentially affect the phonemic and semantic retrieval of words? Letter fluency relies on the implementation of a less automatic and unusual modality of word searching in the lexicon at the phonological level, without reference to meaning. In contrast, when any category fluency task is performed, a semantic system that contains knowledge of the physical and functional properties of objects is activated, stimulating an initial and usually highly prototypical exemplar that triggers the automatic linkage with closely related semantic neighbors (Martin et al. 1994; Rosser and Hodges 1994). In summary, differences between semantic and phonological fluency tasks can be traced to strategies of retrieving cues.

The acquisition of a novel strategy of word retrieval (i.e., phonological word retrieval) requires several steps to be sequenced correctly. In fact, to obtain a phonemic cluster, a subject must couple the last word sequentially to the new words to keep the prototypical sound active within the working memory system which is highly dependent on cerebellar functioning (Marvel and Desmond 2010; Chiricozzi et al. 2008) and recognize the phonemic correspondence between the last word sound and the next word sound. When the retrieval and matching strategies are well learned (semantic cue retrieval), sequential processing is achieved without significant cerebellar involvement; when the strategies are novel (phonemic cue retrieval), however, the activities of the various functional modules are not synchronized, and significant cerebellar contribution is required to smooth and accelerate the sequence progressively (Leggio et al. 2000b; Mariën et al. 2014).

### Sequencing for Language Processing

Neuroimaging and clinical studies have demonstrated cerebellar involvement in several aspects of language. The ability to generate spoken words internally according to a specific rule involves the right posterolateral hemicerebellum, as demonstrated in noun-to-verb generation tasks (Fiez et al. 1992; Petersen et al. 1988) and antonym generation tasks (Gebhart et al. 2002).

Constrained spoken word association has been hypothesized to be based on the activation of specific cognitive modules. Initially, a large set of modules are active. On repetition of the trial, the activation pattern is trimmed to the essential ones. The cerebellum is very active initially, possibly because much cortical functional data are processed; as selection proceeds, less data are analyzed, and cerebellar activation decreases (Leggio et al. 2011). This hypothesis is supported by evidence of reduction in cerebellar activation when the ability to generate words is improved through practice (Raichle et al. 1994). The link between better performance and decreased cerebellar activation is likely attributed to the selection of correctly timed and sequenced modules. This selection is possible due to the ability to process cerebellar sequences (Leggio et al. 2011).

According to the declarative-procedural model, the mental lexicon and mental grammar correlate with disparate systems in the brain (Ullman 2004). Specifically, the memorized word-specific knowledge that forms the mental lexicon depends on the substrates of declarative memory. Conversely, the rule-governed combination of lexical items into complex representations – mental grammar – depends on the neural system that underlies procedural memory. This latter system affects the sequential and hierarchical combination of stored forms and abstract representations into complex structures, thus building a rule-governed structure.

It has been proposed that the cerebellum mediates the search for lexical items from declarative memory and the detection through error-based learning of the rules that underlie the regularities of complex structures (Ullman 2004). This hypothesis is supported by evidence of agrammatism after the development of focal cerebellar lesions (Silveri et al. 1994; Fabbro et al. 2000; Mariën et al. 2000; Schmahmann and Sherman 1998). Because the complex morphosyntactic operations that allow one to construct syntactically correct sentences require the use of sequential procedures within a defined temporal interval, cerebellar damage can impair the sequential and automatic computation of grammatical operations. Ultimately, the morphosyntactic processes that build up sentence representation are uncoupled, mental operations slow down, and the morphemes from working memory decay, resulting in sentence disintegration (Silveri et al. 1994).

## Sequencing for Writing

The writing process has two components: linguistic and motor. The former generates an orthography of words, and the latter converts abstract graphic information into motor instructions to execute script movements (Ellis 1988).

The motor component entails a peripheral process of writing that codifies the sequence of strokes necessary to create the allograph by translating allographic units (i.e., the representation of letter shapes) into writing movements. Impairments in the selection or execution of graphic motor patterns produce executive disorders – termed peripheral dysgraphias – that do not involve the spelling of words.

For example, spatial dysgraphia (Ardila and Rosselli 1993) is characterized by an acquired writing deficit that is marked by deletions and duplications of letters and strokes. Pathophysiologically, it is considered a consequence of a defect in the handwriting-specific mechanism that computes afferent visual and proprioceptive or attentional information to monitor one's position in letter and stroke sequences (Cubelli et al. 2000). The proper function of this sensorial feedback mechanism guarantees continuous updating of the graphic motor pattern with regard to which strokes or letters have already been produced in the writing process (Silveri et al. 1997).

Consistent with the hypothesis that the cerebellum is engaged in monitoring incoming sensory patterns, patients with focal or diffuse damage of the cerebellum can manifest omissions and repetitions of strokes and letters when they are asked to take dictation or copy words. Further, writing performance clearly deteriorates when patients are asked to write with their eyes closed – that is, when they cannot take advantage of visual feedback (Silveri et al. 1997, 1999; Mariën et al. 2007). Collectively, the data on subjects with cerebellar lesion-induced dysgraphia identify defects in sequencing the processing of incoming visual/kinesthetic inputs according to the functional module that is affected.

## Conclusion and Future Directions

In the neuroscience community, there is a consensus that cerebellar processing is required in a variety of motor, sensory, and cognitive functions (Schmahmann 2010). Nevertheless, its function in various domains remains undefined. The data on perceptual and cognitive processing in human lesions and in animal models reviewed here, as well as recent clinical findings (Tedesco et al. 2011), implicate sequence processing as the fundamental operational mode of the cerebellum.

According to this sequence detection theory, it is conceivable that the cerebellum is able to detect and simulate repetitive patterns of temporally or spatially structured events, regardless of whether they constitute sensory consequences of one's action in motor planning, expected sensory stimuli in perceptual prediction, or inferences of higher-order processes (e.g., cognitive elaboration or social cognition) (Fig. 4). The simulation allows internal models to be created (Ito 2008) that can be used to make predictions about future events involving any component, such as the body, other persons, and the environment (Baumann et al. 2015; Leggio and Molinari 2015).

This theoretical model has relevance to understanding the pathophysiological mechanisms in many clinical conditions, such as schizophrenia and autism, in which impairments in patterns of information processing and disruptions in error signal prediction have been implicated. This is a crucial issue that deserves further investigation and might have great clinical relevance.

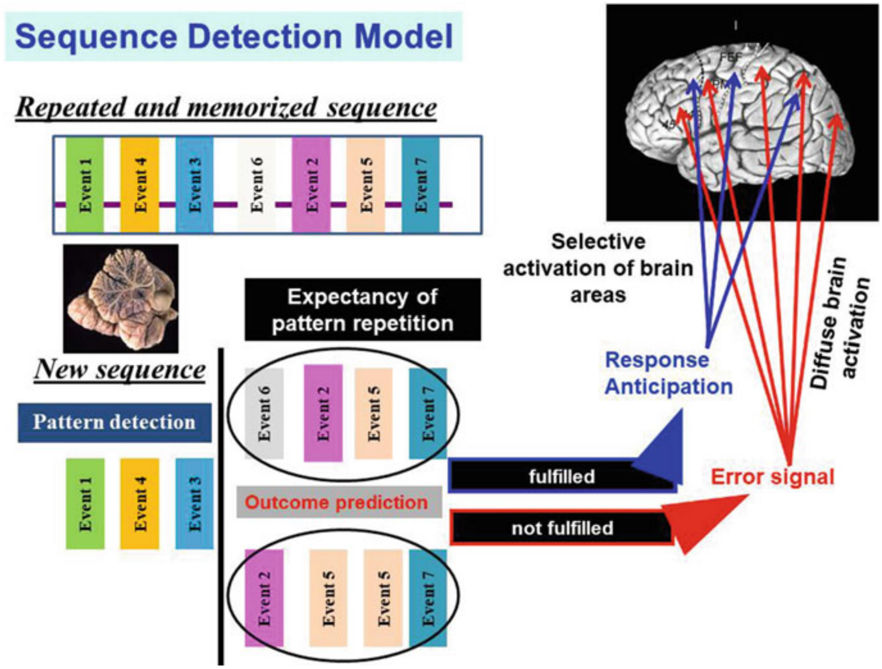

**Fig. 4** The sequence detection theory. According to the "sequence detection theory," the cerebellum detects and memorizes a pattern, creating an internal model. Thus, it expects specific incoming stimuli that are clearly defined by the underlying internal model. The correctness of the predictions is evaluated by comparing the incoming bottom-up information with top-down expectations. If the prediction holds, a signal is sent to alert select cortical areas, allowing the predicted stimulus to be perceived more efficiently. Conversely, presentation of an event that violates expectations effects more widespread brain activation that accelerates the processing of salient sensory information by the changing events and attunes the behavioral response to the new event

## Cross-References

- ▶ Autism Spectrum Disorders and Ataxia
- ▶ Cerebellum and Cognition
- ▶ Cerebellum and Schizophrenia: The Cerebellum Volume Reduction Theory of Schizophrenia
- ▶ State Estimation and the Cerebellum

## References

Akatsuka K, Wasaka T, Nakata H et al (2005) Mismatch responses related to temporal discrimination of somatosensory stimulation. Clin Neurophysiol 116:1930–1937

Alain C, Woods DL, Knight RT (1998) A distributed cortical network for auditory sensory memory in humans. Brain Res 812:23–37

Ardila A, Rosselli M (1993) Spatial agraphia. Brain Cogn 22:137–147

Bastian AJ (2006) Learning to predict the future: the cerebellum adapts feedforward movement control. Curr Opin Neurobiol 16:645–649

Baumann O, Borra RJ, Bower JM et al (2015) Consensus paper: the role of the cerebellum in perceptual processes. Cerebellum 14:197–220

Bo J, Block HJ, Clark JE, Bastian AJ (2008) A cerebellar deficit in sensorimotor prediction explains movement timing variability. J Neurophysiol 100:2825–2832

Bower JM (1997) Control of sensory data acquisition. Int Rev Neurobiol 41:489–513

Bower JM, Parsons LM (2003) Rethinking the "lesser brain". Sci Am 289:50–57

Braitenberg V, Heck D, Sultan F (1997) The detection and generation of sequences as a key to cerebellar function: experiments and theory. Behav Brain Sci 20:229–277

Chiricozzi FR, Clausi S, Molinari M, Leggio MG (2008) Phonological short-term store impairment after cerebellar lesion: a single case study. Neuropsychologia 46:1940–1953

Crozier S, Sirigu A, Lehericy S et al (1999) Distinct prefrontal activations in processing sequence at the sentence and script level: an fMRI study. Neuropsychologia 37:1469–1476

Cubelli R, Guiducci A, Consolmagno P (2000) Afferent dysgraphia after right cerebral stroke: an autonomous syndrome? Brain Cogn 44:629–644

Dirnberger G, Novak J, Nasel C, Zehnter M (2010) Separating coordinative and executive dysfunction in cerebellar patients during motor skill acquisition. Neuropsychologia 48:1200–1208

Ellis AW (1988) Normal writing processes and peripheral acquired dysgraphias. Lang Cognit Process 3:99–127

Fabbro F, Moretti R, Bava A (2000) Language impairments in patients with cerebellar lesions. J Neurolinguistics 13:173–188

Fiez JA, Petersen SE, Cheney MK, Raichle ME (1992) Impaired non-motor learning and error detection associated with cerebellar damage. A single case study. Brain 115(1):155–178

Frings M, Boenisch R, Gerwig M et al (2004) Learning of sensory sequences in cerebellar patients. Learn Mem 11:347–355

Frings M, Maschke M, Gerwig M et al (2006) Acquisition of simple auditory and visual sequences in cerebellar patients. Cerebellum 5:206–211

Gao JH, Parsons LM, Bower JM et al (1996) Cerebellum implicated in sensory acquisition and discrimination rather than motor control. Science 272:482–483

Gebhart AL, Petersen SE, Thach WT (2002) Role of the posterolateral cerebellum in language. Ann N Y Acad Sci 978:318–333

Gomez-Beldarrain M, Garcia-Monco JC, Rubio B, Pascual-Leone A (1998) Effect of focal cerebellar lesions on procedural learning in the serial reaction time task. Exp Brain Res 120:25–30

Graziano A, Leggio MG, Mandolesi L et al (2002) Learning power of single behavioral units in acquisition of a complex spatial behavior: an observational learning study in cerebellar-lesioned rats. Behav Neurosci 116:116–125

Ito M (2006) Cerebellar circuitry as a neuronal machine. Prog Neurobiol 78:272–303

Ito M (2008) Control of mental activities by internal models in the cerebellum. Nat Rev Neurosci 9:304–313

Ivry R (2000) Exploring the role of the cerebellum in sensory anticipation and timing: commentary on Tesche and Karhu (comment). Hum Brain Mapp 9:115–118

Ivry RB, Spencer RM, Zelaznik HN, Diedrichsen J (2002) The cerebellum and event timing. Ann N Y Acad Sci 978:302–317

Leggio M, Molinari M (2015) Cerebellar sequencing: a trick for predicting the future. Cerebellum 14:35–38

Leggio MG, Neri P, Graziano A et al (1999) Cerebellar contribution to spatial event processing: characterization of procedural learning. Exp Brain Res 127:1–11

Leggio MG, Molinari M, Neri P et al (2000a) Representation of actions in rats: the role of cerebellum in learning spatial performances by observation. Proc Natl Acad Sci USA 97: 2320–2325

Leggio MG, Silveri MC, Petrosini L, Molinari M (2000b) Phonological grouping is specifically affected in cerebellar patients: a verbal fluency study. J Neurol Neurosurg Psychiatry 69: 102–106

Leggio MG, Tedesco AM, Chiricozzi FR et al (2008) Cognitive sequencing impairment in patients with focal or atrophic cerebellar damage. Brain 131:1332–1343

Leggio MG, Chiricozzi FR, Clausi S et al (2011) The neuropsychological profile of cerebellar damage: the sequencing hypothesis. Cortex 47:137–144

Mariën P, Engelborghs S, Pickut BA, De Deyn PP (2000) Aphasia following cerebellar damage: fact or fallacy? J Neurolinguistics 13:145–171

Mariën P, Verhoeven J, Brouns R et al (2007) Apraxic agraphia following a right cerebellar hemorrhage. Neurology 69:926–929

Mariën P, Ackermann H, Adamaszek M et al (2014) Consensus paper: language and the cerebellum: an ongoing enigma. Cerebellum 13:386–410

Martin A, Wiggs CL, Lalonde F, Mack C (1994) Word retrieval to letter and semantic cues: a double dissociation in normal subjects using interference tasks. Neuropsychologia 32:1487–1494

Marvel C, Desmond J (2010) Functional topography of the cerebellum in verbal working memory. Neuropsychol Rev 20:271

Maschke M, Drepper J, Burgerhoff K et al (2002) Differences in trace and delay visuomotor associative learning in cerebellar patients. Exp Brain Res 147:538–548

Moberget T, Karns CM, Deouell LY et al (2008) Detecting violations of sensory expectancies following cerebellar degeneration: a mismatch negativity study. Neuropsychologia 46: 2569–2579

Molinari M, Petrosini L (1997) Is sequence in/sequence out a cerebellar mode of operation in cognition too? Behav Brain Sci 20:259–260

Molinari M, Leggio MG, Solida A et al (1997) Cerebellum and procedural learning: evidence from focal cerebellar lesions. Brain 120:1753–1762

Molinari M, Filippini V, Leggio MG (2002) Neuronal plasticity of interrelated cerebellar and cortical networks. Neuroscience 111:863–870

Molinari M, Chiricozzi F, Clausi S et al (2008) Cerebellum and detection of sequences, from perception to cognition. Cerebellum 7:611–615

Morris R (1984) Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods 11:47–60

Naatanen R, Michie PT (1979) Early selective-attention effects on the evoked potential: a critical review and reinterpretation. Biol Psychol 8:81–136

Nissen MJ, Bullemer P (1987) Attentional requirements of learning: evidence from performance measures. Cogn Psychol 19:1–32

Nixon PD (2003) The role of the cerebellum in preparing responses to predictable sensory events. Cerebellum 2:114–122

Orsini A, Laicardi C (2000) Factor structure of the Italian version of the WAIS-R compared with the American standardization. Percept Mot Skills 90:1091–1100

Pascual-Leone A, Grafman J, Clark K et al (1993) Procedural learning in Parkinson's disease and cerebellar degeneration. Ann Neurol 34:594–602

Petersen SE, Fox PT, Posner MI et al (1988) Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 331:585–589

Petrosini L, Leggio MG, Molinari M (1998) The cerebellum in the spatial problem solving: a co-star or a guest star? Prog Neurobiol 56:191–210

Petrosini L, Graziano A, Mandolesi L, Neri P, Molinari M, Leggio MG (2003) Watch how to do it! New advances in learning by observation. Brain Res Brain Res Rev 42(3):252–264

Raichle ME, Fiez JA, Videen TO et al (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex 4:8–26

Restuccia D, Della Marca G, Valeriani M et al (2007) Cerebellar damage impairs detection of somatosensory input changes. A somatosensory mismatch-negativity study. Brain 130:276–287

Richter S, Matthies K, Ohde T et al (2004) Stimulus-response versus stimulus-stimulus-response learning in cerebellar patients. Exp Brain Res 158:438–449

Rosser A, Hodges JR (1994) Initial letter and semantic category fluency in Alzheimer's disease, Huntington's disease, and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 57:1389–1394

Schmahmann JD (1997) Rediscovery of an early concept. Int Rev Neurobiol 41:3–27

Schmahmann J (2010) The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol Rev 20:236

Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome (see comments). Brain 121(Pt 4):561–579

Shin JC, Ivry RB (2003) Spatial and temporal sequence learning in patients with Parkinson's disease or cerebellar lesions. J Cogn Neurosci 15:1232–1243

Silveri MC, Leggio MG, Molinari M (1994) The cerebellum contributes to linguistic production: a case of agrammatic speech following a right cerebellar lesion (see comments). Neurology 44:2047–2050

Silveri MC, Misciagna S, Leggio MG, Molinari M (1997) Spatial dysgraphia and cerebellar lesion: a case report. Neurology 48:1529–1532

Silveri MC, Misciagna S, Leggio MG, Molinari M (1999) Cerebellar spatial dysgraphia: further evidence (letter). J Neurol 246:312–313

Stoodley CJ, Schmahmann JD (2009) Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44:489–501

Takegata R, Paavilainen P, Naatanen R, Winkler I (2001) Preattentive processing of spectral, temporal, and structural characteristics of acoustic regularities: a mismatch negativity study. Psychophysiology 38:92–98

Tedesco AM, Chiricozzi FR, Clausi S et al (2011) The cerebellar cognitive profile. Brain. https://doi.org/10.1093/brain/awr266.2011

Tedesco AM, Bianchini F, Piccardi L et al (2017) Does the cerebellum contribute to human navigation by processing sequential information? Neuropsychology 31:564–574

Tesche CD, Karhu JJ (2000) Anticipatory cerebellar responses during somatosensory omission in man (see comments). Hum Brain Mapp 9:119–142

Thach WT, Goodkin HP, Keating JG (1992) The cerebellum and the adaptive coordination of movement. Annu Rev Neurosci 15:403–442

Timmann D, Daum I (2007) Cerebellar contributions to cognitive functions: a progress report after two decades of research. Cerebellum 6:159–162

Timmann D, Drepper J, Calabrese S et al (2004) Use of sequence information in associative learning in control subjects and cerebellar patients. Cerebellum 3:75–82

Tinaz S, Schendan HE, Schon K, Stern CE (2006) Evidence for the importance of basal ganglia output nuclei in semantic event sequencing: an fMRI study. Brain Res 1067:239–249

Ullman MT (2004) Contributions of memory circuits to language: the declarative/procedural model. Cognition 92:231–270

White M, Lalonde R, Botez M (2000) Neuropsychologic and neuropsychiatric characteristics of patients with Friedreich's ataxia. Acta Neurol Scand 102:222–226