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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 from lesion studies in humans and from experimental lesion in rats on perceptual and cognitive processing are reviewed with special emphasis on cerebellar sequencing properties. Evidence converges in highlighting 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 discussed.

Introduction

Many groups are generating anatomical, experimental, functional neuroimaging, and clinical data that stress the importance of corticocerebellar interactions in many nonmotor domains, such as cognition, emotion, and affective processing (Timmann and Daum 2007; Schmahmann 1997). This evidence has increased our understanding of cerebellar functions but has raised questions with regard to what the

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cerebellum actually does (Bower and Parsons 2003; Ito 2006). Thus, the aim of many groups has been to identify the underlying processes that explain the cerebellum's function in many domains. Specifically, regarding the cerebellum and cognition, the complex variety of cognitive functions involved implicates 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 – incidentally through experience or intentionally through explicit effort. To recognize that stimuli are presented in a certain order, the information on 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 cerebellar functional domains, which has been demonstrated for the sensory (Bower 1997), motor (Thach et al. 1992), and behavioral (Leggio et al. 2008) domains.

Here the chapter reviews 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 has long been demonstrated (Gao et al. 1996), as has its role in predicting somatosensory events (Bower 1997). 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 (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, preceded by a small cerebellar response. If this standard protocol is modified, interrupting the regularity of the flow of stimuli by omitting somatosensory peripheral stimuli at random, 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 compared with 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 longstanding 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 an 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 hemisphere contralateral to the spared hemocerebellum) or in its absence (the hemisphere contralateral to the damaged hemocerebellum). s-MMN responses to stimuli that were applied in an unexpected area (from the first to fifth finger) were recorded easily in the cortical hemisphere with the cerebellar input but were absent in the cortical hemisphere that was not reached by the cerebellar input (Fig. 76.1). A similar MMN approach has been also 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).

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.

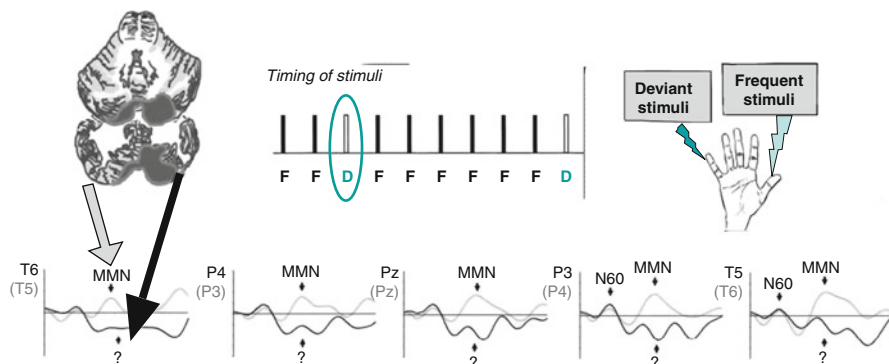


Fig. 76.1 s-MMN response in focal Cb patients. Event-related potentials in patients with focal cerebellar damage (lesion described in *upper right corner*) during the “oddball” protocol difference traces. Traces obtained after stimulation of the unaffected hand (*gray arrow*) are superimposed over those 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)

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 are compared with those 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 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).

Nevertheless, in the cited study, differences emerged 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 hemocerebellum performed poorly on script sequences that were based on pictorial material, and patients with lesions in the right hemocerebellum failed to generate script sequences that required verbal elaboration (Fig. 76.2). These differences in content are consistent with the current understanding of functional lateralization in the cortex and of crossed cerebello-cortical 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 cerebello-cortical loops.

Acquisition of Procedures

Spatial functions must be examined to analyze cerebellar function in 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. Furthermore, to correctly solve spatial tasks, behavioral sequences must be acquired and put into action.

One of the most common tests that are 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. Thus, to solve this test, 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 hemocerebellectomy (HCb) (see also Molinari et al. ► Chap. 70, “Hemocerebellectomy”, this volume), cerebellar

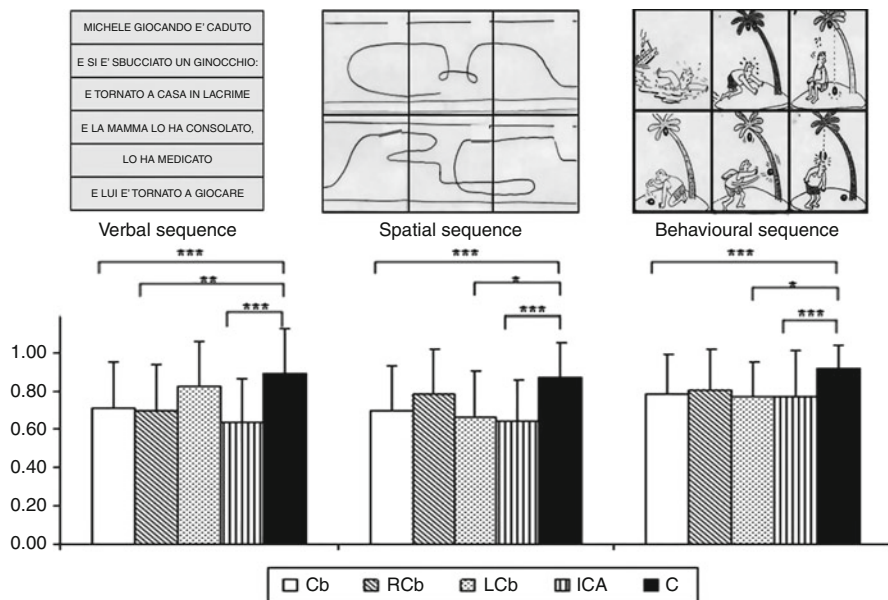


Fig. 76.2 Sorting card test results are altered in cerebellar patients independently of sequencing factor. Set of cards representative of three factors. Verbal factor: Michel fell while playing and he bruised his knee; he went back home crying and his mother comforted him. She medicated him and he went 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)

damage impaired the acquisition of the procedures that were required by the MWM (Petrosini et al. 1998). Although hemocerebellectomized (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 performed 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.

This experimental setting and the possibility of preventing further learning using a cerebellar lesion allow one to examine the individual steps that constitute the repertoire of procedures that is 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) to them. 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. 76.3). Overall, experimental data from studies on lesions support the model of a nonmotor origin of cerebellar impairments in visuospatial learning (Molinari et al. 1997; Gomez-Beldarrain et al. 1998).

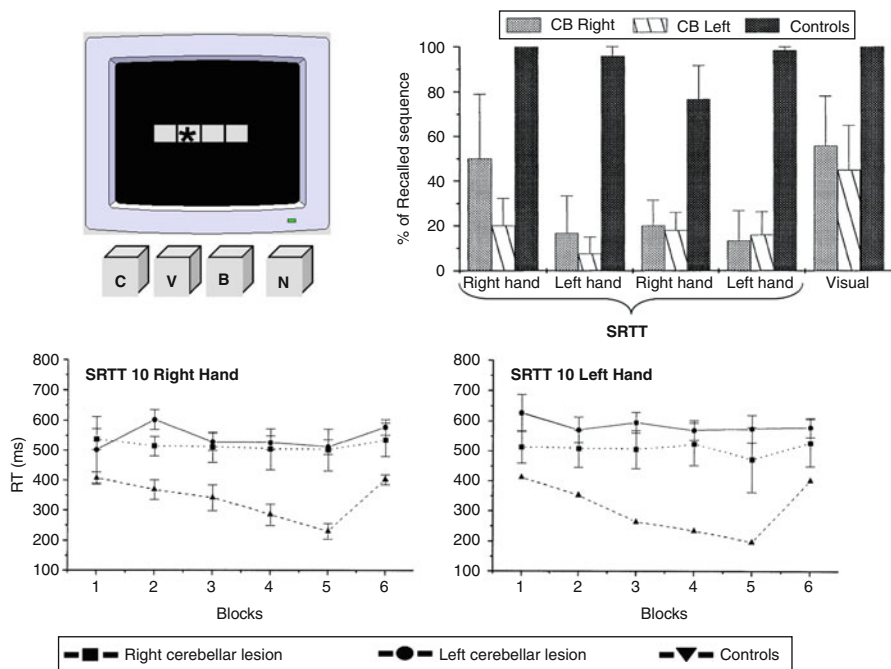


Fig. 76.3 Serial reaction time task (SRTT). The SRTT was administered with the subject facing a video screen on which an asterisk appeared in one of four squares. The subject was instructed to press the key corresponding to the asterisk that appeared (*upper left*). Recognition of the presented sequences as the percentage of recall during the SRTT 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 SRTT with sequences of 10 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)

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.

Shin and Ivry (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. Yet, 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).

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 phonemically 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, highly dependent on cerebellar functioning (Marvel and Desmond 2010; Chiricozzi et al. 2008), and recognize the last word sound–next word sound phonemic correspondence. 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).

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 hemispheric cerebellum, 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 reductions 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 effects the sequential and hierarchical combination of stored forms and abstract representations into complex structures, thus building a rule-governed structure.

The cerebellum has been proposed to mediate 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; Marien 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 affect 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 that is necessary to create the allograph by translating allo-graphic 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 hand-writing-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 intervenes 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; Marien 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. The findings on somatosensory analysis, script recognition, acquisition of procedures, visuospatial learning, speech, and writing ability after cerebellar damage suggest that temporal and spatial information must be compared with regard to sequence detection to understand cerebellar deficits across modalities. The hypothesis that sequence detection is the cerebellum's chief contribution to brain function requires confirmation; nevertheless, it links the multifarious impairments that are reported in patients with cerebellar damage.

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