Chapter 9
A Role for the Cerebellum in Language and Related Cognitive and Affective Functions

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9.1 Introduction

At the beginning of the twentieth century, several authors defined the role of the cerebellum as a modulator of motor functions including diadochokinesia, tonus, coordination, and motor speech production (Babinski 1902; Luciani 1891; Holmes 1922). Although from time to time clinical case descriptions and experimental evidence from animal studies dating back to the early part of the nineteenth century suggested an association between cerebellar pathology and a variety of nonmotor cognitive and affective dysfunctions, a causal relationship remained unexplored and was dismissed for several decades. During the past three decades converging evidence from a wealth of neuroanatomical, neuroimaging, and clinical studies has unambiguously demonstrated that the cerebellum is also involved in cognitive, affective and linguistic processing. Neuroanatomical studies revealed that the cerebellum is closely linked in a reciprocal way to the autonomic, limbic, and associative regions of the supratentorial cortex[1] (for a review, see Schmahmann 2004). In addition, cortical areas send information to the cerebellum via the basilar pons (Schmahmann and Pandya 1997), and deep cerebellar nuclei send information back to the cortical association areas through dentatothalamic pathways (Middleton and Strick 1997) (Fig. 9.1).

[1] Refers to all of the cerebral cortex lying above and anterior to the tentorium cerebelli. It is that part of the dura that 'tents' the cerebellum on its superior surface separating it from the inferior occipital cortex.

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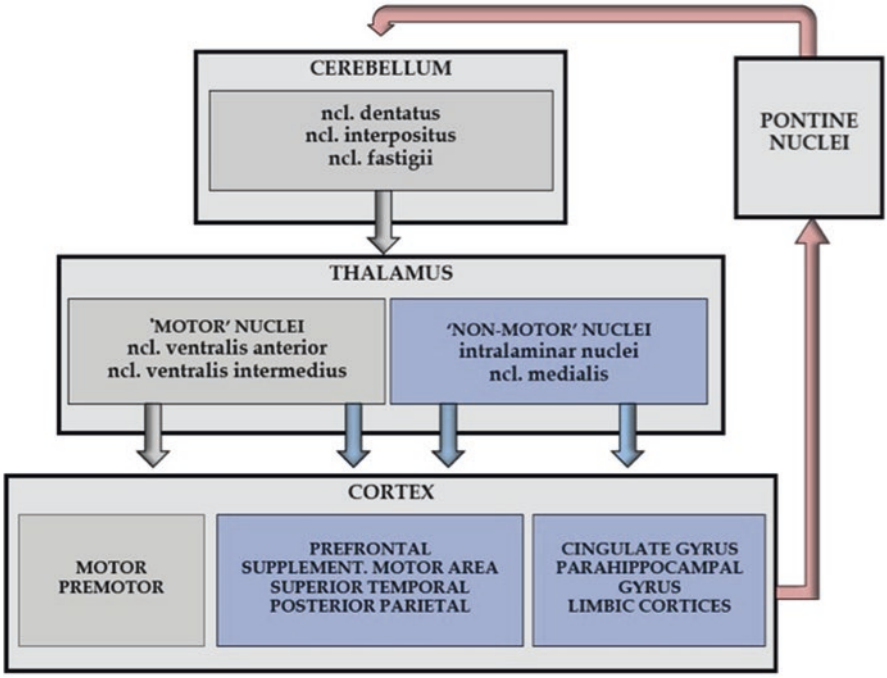

Fig. 9.1 Diagram depicting the cerebello-cerebral connectivity network underlying cognitive and affective processes. The feedback or efferent loop originates from the deep nuclei of the cerebellum that project to the motor (*grey*) and nonmotor (*blue*) nuclei of the thalamus. In turn, the motor nuclei of the thalamus (ncl. ventralis anterior and intermedius) project not only to motor and premotor cortices (*grey arrow*) but also to nonmotor areas among which are the prefrontal cortex, the supplementary motor area, the superior temporal and posterior parietal regions (*blue arrow*). The nonmotor nuclei of the thalamus project to the cingulate gyrus, the parahypocampal region, and the limbic cortices (*blue arrows*). The feedforward or afferent system of the cerebello-cerebral circuit is composed of corticopontine and pontocerebellar mossy fiber pathways (*red arrows*) (after Schmahmann and Pandya (1997) and from Mariën et al. (2013b)).

Studies with positron emission tomography (PET) in healthy subjects have provided evidence for cerebellar involvement in nonmotor language functions. Indeed, PET investigations of healthy subjects revealed a consistent and simultaneous activation of the supratentorial language areas (Broca's area) and the right cerebellar hemisphere during a semantic word association task (Petersen et al. 1988, 1989). In-depth neuropsychological investigations of an etiologically heterogeneous group of patients with focal and diffuse cerebellar lesions allowed clinicians to identify a variety of generally mild but clinically significant linguistic, cognitive, and affective deficits after cerebellar damage. This approach resulted in a large number of case reports describing cognitive and linguistic symptoms following isolated cerebellar lesions. Subsequently, many studies with a robust methodology including large cohorts of patients with cerebellar disorders and carefully matched healthy controls were performed to identify the multifaceted modulatory role of the cerebellum in a variety of nonmotor cognitive and affective functions.

In this chapter a concise overview of the modulating role of the cerebellum in language as well as in a variety of related cognitive and behavioral-affective processes is presented.

9.2 The Cerebellum and Language

9.2.1 Verbal Fluency and Lexical Retrieval

In the late 1980s, PET activation studies with healthy subjects provided the first evidence in support of the emerging view that the cerebellum might be implicated in linguistic processes (Leiner et al. 1986). In a PET experiment with healthy subjects, Petersen et al. (1988, 1989) showed that during the production of semantically related verbs in response to visually presented nouns, activation of dominant Broca's area and the contralateral cerebellar hemisphere occurred. For the first time a consistent pattern of activation was shown that was not due to motor verbal responses but to nonmotor linguistic processes subserving semantic word association processes. Notwithstanding variations on the original task design, subsequent studies in healthy subjects consistently reproduced activation of the right lateral cerebellum during word generation tasks (Raichle et al. 1994; Papathanassiou et al. 2000). Hubrich-Ungureanu et al. (2002) investigated the pattern of lateralized activations in a left and right-handed volunteer by means of functional magnetic resonance imaging (fMRI) during a silent verbal fluency task. In the right-handed subject with typical left hemisphere language dominance, regions of activation not only included the language dominant left fronto-parietal cortex but, as expected, also the contralateral right cerebellar hemisphere. In the left-handed subject with atypical right hemisphere language dominance a reversed pattern of language activation was found, reflected by crossed cerebral-cerebellar activations involving the right cerebral and the left cerebellar hemisphere. The study concluded that cerebellar involvement in language processing is contralateral to the activation of the cerebral cortex, even under conditions of different language dominance. As demonstrated in Fig. 9.2a, b, this crosswise functional cerebello-cerebral network subserving lexical retrieval processes was found in a right-handed patient with atypical cerebral language dominance. Atypical activations of Broca's homologue in the right hemisphere were accompanied by contralateral activations in the left cerebellar hemisphere during an fMRI noun to verb association task.

The role of the cerebellum in phonemic and semantic fluency tasks has recently also been investigated by means of Transcranial Magnetic Stimulation (TMS) using continuous theta burst stimulation (cTBS) (Arasanz et al. 2012). Twenty-seven healthy subjects were randomly assigned to one or two groups for application of cTBS to the posterior-lateral cerebellum, and the left or right cerebellar hemisphere. The subjects first participated in a phonological verbal fluency task (with letters F, A, S or P, R, W) followed by a semantic verbal fluency task consisting of the categories animals or groceries. Arasanz et al. (2012) hypothesized that the number of

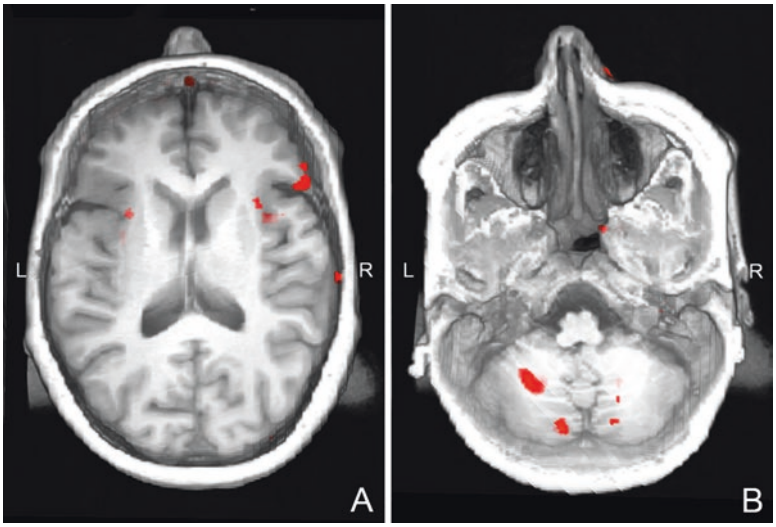

Fig. 9.2 fMRI images of the brain using a verb generation task disclosing predominantly activation in the right prefrontal and insular regions (**a**) associated with activation in the left cerebellar hemisphere (**b**)

category switches between the subcategories of words is a measure of mental flexibility, which is the highest during the first 15 s of the task. It was found that within the first 15 s of each trial, subjects with right cTBS had significantly lower switching scores after stimulation. In addition, the study also provided evidence in favor of the hypothesis that the cerebellum is crucially implicated in executive control via a dense network of cerebello-cerebral connections to the (pre)frontal cortex (Petersen et al. 1989; Raichle et al. 1994; Martin et al. 1995; Grabowski et al. 1996; Schlösser et al. 1998; Gourovitch et al. 2000; Papathanassiou et al. 2000; Hubrich-Ungureanu et al. 2002; Arasanz et al. 2012).

A number of clinical studies of patients with focal and diffuse cerebellar damage have confirmed the involvement of the cerebellum in word production processes. In an early study, Fiez et al. (1992) described a 41-year-old, right-handed lawyer who despite high-level conversational skills presented with semantic retrieval deficits after a vascular lesion of the right cerebellar hemisphere. Leggio et al. (1995, 2000) compared patients with focal and degenerative left and right cerebellar lesions with healthy control subjects using cluster analysis. They showed that right cerebellar damage particularly affects phonological fluency while sparing semantic fluency. However, a small number of subsequent studies disclosed no evidence of a lateralized impact as reduced verbal fluency was observed in patients with either left or right cerebellar lesions (Cook et al. 2004; Whelan and Murdoch 2005). These observations contrast with a recent study of Schweizer et al. (2010) who investigated 22 patients with chronic, unilateral cerebellar lesions (12 patients with left and ten patients with right cerebellar lesions). These authors demonstrated that the patient

group with right cerebellar damage produced significantly fewer words in a phonemic fluency task in comparison to both the patient group with left cerebellar damage and the group of healthy control subjects. Performance characteristics of the right cerebellar lesion group were highly similar to the performance characteristics of patients with left prefrontal lesions. On the basis of these overt resemblances, Schweizer et al. (2010) suggested that the findings reflect a lateralized network effect consisting of a supratentorial, left prefrontal, and infratentorial right cerebellar system for the modulation of attention/executive function tasks.

9.2.2 Syntax Impairment

A number of studies have demonstrated that grammatical and syntactic disorders may result from focal cerebellar damage. Disruption of grammatical processing was for the first time described by Silveri et al. (1994) who found an association between focal vascular damage of the right cerebellum and transient expressive agrammatism, characterized by the omission of free-standing grammatical morphemes, the omission of auxiliaries and clitics, and substitutions of bound grammatical morphemes. Single-photon emission computed tomography (SPECT) scan of the brain showed a relative hypoperfusion affecting the entire left cerebral hemisphere, more stable and consistent in the left posterior temporal region. This patient's selective speech production impairment was, however, interpreted as a non-linguistic, "peripheral" disorder and it was hypothesized that agrammatism may be the result of the patient's adaptation to a deficit outside the mental linguistic system. In agreement with the view that the cerebellum acts as a controller and regulator of the temporal aspects of motor as well as nonmotor processes (timing hypothesis) this deficit was considered to be the result of a general timing disorder. Since then, several other patients have been reported who presented with expressive and/or receptive agrammatism following cerebellar damage (Mariën et al. 1996; Gasparini et al. 1999; Zettin et al. 1997). Strelnikov et al. (2006) investigated the brain mechanisms underlying prosodic segmentation and pitch processing in syntactically correct perception of phrases using PET. Twelve right-handed healthy subjects listened to phrases in which different prosodic segmentation substantially changed the meaning of the phrase. Activation was seen in the right dorsolateral prefrontal cortex and medial posterior area of the right cerebellum. According to the authors, the right posterior prefrontal cortex represents the functional overlap of brain networks of emotion, prosody, and syntax perception, whereas the right cerebellar activation was related to the assessment of time intervals necessary for different sensorimotor and cognitive activities (Ivry and Richardson 2002; Salman 2002), as in the estimation of phonetic and semantic borders of syntagmata, or to the maintenance of the phrase structure in working memory during processing (Mariën et al. 2001).

9.2.3 Aphasia

The notion of cerebellar-induced aphasia (Hassid 1995; Fabbro et al. 2000, 2004) emerged as a result of a co-occurrence of a spectrum of linguistic impairments affecting the phonological, lexico-semantic, and syntactic domains to different degrees after acute cerebellar damage. Mariën et al. (1996, 2000) described a 73-year-old, right-handed patient who presented with a dynamic aphasia-like language disorder after an ischemic lesion in the vascular territory of the right superior cerebellar artery. The patient's language disorder was characterized by a marked dissociation between nearly normal imposed (e.g., naming, repetition) and severely disrupted spontaneous language consisting of a severe lack of spontaneous speech initiation, and effortful and fragmented attempts to formulate ideas. In addition, there were word-finding difficulties in conversational speech, marked expressive and receptive agrammatism, and reading and writing deficits. Mariën et al. (1996, 2000) labelled their patient's language disorder as *cerebellar-induced aphasia*. In this patient, follow-up SPECT studies revealed a significant hypoperfusion in the right cerebellum and in the anatomoclinically suspected prefrontal language region of the left hemisphere. At follow-up, changes in perfusional patterns paralleled the alterations in the neurolinguistic profile. Aphasia-like phenomena following right cerebellar damage were considered to result from a loss of excitatory impulses through the cerebello-ponto-thalamo-cortical pathways (Mariën et al. 1996). In agreement with these findings, Mariën and coworkers subsequently reported an additional number of right-handed patients who presented aphasic symptoms in association with cognitive and behavioral problems after right cerebellar damage (Mariën et al. 2007, 2009; Baillieux et al. 2010; De Smet et al. 2012).

Karacı et al. (2008) evaluated in 20 patients with ischemic lesions of the cerebellum and 20 control subjects the effects of focal cerebellar damage on language functions and the relation between these functions and lesion type, age, and education level. A variety of aphasic symptoms were identified at the level of speech production, comprehension, repetition, naming, reading, and writing. However, with respect to lateralization (left vs. right) and vascular territory (posterior inferior cerebellar artery (PICA) vs. superior cerebellar artery (SCA)), no significant effects were found. Recently, Blancart et al. (2011) described an 83-year-old right-handed man who suffered from aphasia after a left cerebellar infarction. Dysarthria, anomia, agrammatism, comprehension deficits, reading and writing difficulties characterized this patient's speech and language. Two months post-stroke, anomia, and agrammatism still persisted while reading and writing abilities had improved and comprehension had nearly normalized. In addition, cognitive and behavioral-affective abnormalities were reported, including disorientation, apathy, stiff and obsessive behavior, aggressiveness, and daytime hypersomnia. PET studies demonstrated hypometabolism in the left cerebellar hemisphere and the bilateral temporoparietal regions. Based on these findings, Blancart et al. (2011) suggested that the left cerebellar infarction was responsible for the language deficits in the acute phase and that the cerebellar lesion played a major precipitating role in the development of cognitive and behavioral problems two months post-onset. Although the authors

mention the concept of crossed aphasia following left cerebellar injuries, no information is provided with regard to supratentorial language dominance nor did they elaborate on the mechanism of ipsilateral cortical diaschisis[2], a phenomenon observed following focal cerebellar damage (De Smet and Mariën 2012).

9.2.4 Alexia and Dyslexia

Although reading impairment may follow cerebellar damage, only a handful of patients have been reported in the literature. Moretti et al. (2002a) investigated the impact of cerebellar lesions on reading skills in ten patients with cerebellar vermis/paravermis lesions compared to ten right-handed controls. The patient group demonstrated a lower degree of accuracy in reading words and sentences. They made errors both at letter and word level. The authors suggested that acquired dyslexia in patients with cerebellar damage may be related either to imperfect oculomotor control (nystagmus), or to disruption of the cerebellar-encephalic projections connecting the cerebellum to the supratentorial areas implicated in language as well as in attentional and alerting processes.

Mariën et al. (2009) reported a patient who after an ischemic stroke in the vascular territory of the right superior cerebellar artery (SCA) presented with the cerebellar cognitive-affective syndrome (CCAS) associated with visual dyslexia and surface dysgraphia. Acute phase data revealed a generalized cognitive decline and mild transcortical sensory aphasia. In the lesion phase of the stroke (i.e., 3 weeks to 4 months poststroke), neurobehavioral abnormalities mainly comprised executive dysfunctions, disrupted divided attention, deficient visual–spatial organization and a range of behavioral abnormalities. In-depth neurolinguistic investigations of reading and writing skills were consistent with a diagnosis of visual dyslexia and surface dysgraphia. Reading of words and performance on visual lexical decision tasks involving words and nonwords was severely disrupted and predominantly characterized by visual errors. In addition, writing irregular and ambiguous words resulted in regularization errors (phonologically plausible errors based on phoneme-grapheme correspondence rules). In the absence of any structural damage in the supratentorial brain regions, a quantified SPECT study showed a relative hypoperfusion in the right cerebellar hemisphere and the left medial frontal lobe (Fig. 9.3).

Mariën et al. (2009) hypothesized that the cognitive and linguistic deficits result from functional disruption of the cerebellar-encephalic pathways, connecting the cerebellum to the frontal supratentorial areas which subserve attentional and planning processes. Functional disruption of the anatomoclinically suspected brain regions was reflected on SPECT by the phenomenon of crossed cerebello–cerebral diaschisis.

[2] Diaschisis, a concept introduced at the beginning of the twentieth century by Constantin Von Monakow, stands for the distant functional impact of a brain lesion on an anatomically connected and structurally intact brain region. Depressed function of this intact region is considered to result from a decrease or loss of excitatory impulses from the anatomically connected, lesioned area.

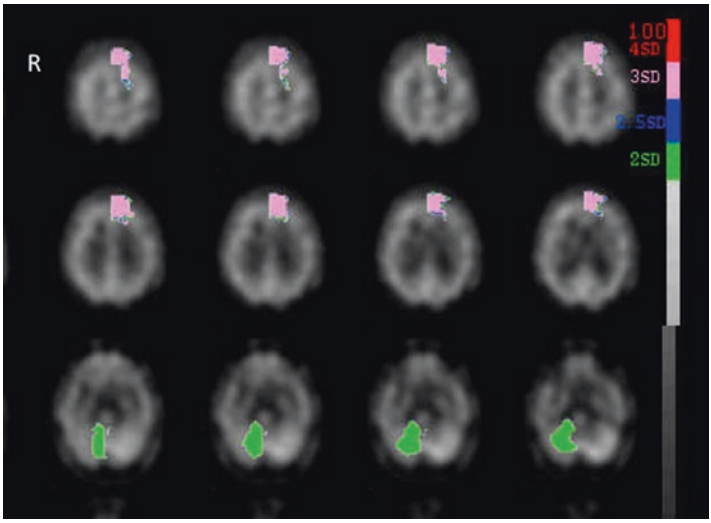

Fig. 9.3 Quantified ECD-SPECT scan 5 weeks after a right cerebellar stroke shows a hypoperfusion in the right cerebellar hemisphere and the left medial frontal area (crossed cerebello-cerebral diaschisis)

Possible involvement of the cerebellum in the pathogenesis of dyslexia has recently been postulated as well in a large number of studies (Nicolson et al. 2001; Finch et al. 2002; Rae et al. 2002; Eckert et al. 2003; Pernet et al. 2009). Structural MRI studies conducted in adults with dyslexia have demonstrated cerebellar anomalies (Brown et al. 2001; Rae et al. 2002). Fawcett and Nicolson (1999) studied 59 dyslexic children and 67 matched control subjects and showed subtle cerebellar-related abnormalities in the dyslexic group such as difficulties in motor skills, automatization, information processing, speed, and balance. On the basis of these "soft neurological signs," Nicolson et al. (1995, 1999, 2001) introduced the "cerebellar deficit hypothesis" to explain dyslexia. According to this hypothesis, the automatization of learned skills such as articulation, reading, spelling, and phonological abilities is disrupted as a result of a cerebellar dysfunction (Fawcett and Nicolson 1999; Nicolson et al. 1995). A cerebellar deficit in young children might induce a delay in the automatization process of articulation, causing deficits in phonological awareness. Therefore, cerebellar maturational impairments might result in a "phonological core deficit," which provides an explanatory framework for various aspects of developmental dyslexia (Nicolson et al. 1999). Evidence to support this hypothesis was provided by a PET study in six dyslexic adults versus an age-matched control group of six healthy subjects (Nicolson et al. 1999) who performed either an automatic prelearned sequence or a novel sequence of finger movements. In the group of the dyslexics, significantly lower brain activations were found in the right cerebellar cortex and the left cingulate gyrus when executing the prelearned sequence and in the right cerebellar cortex when learning the new sequence. Baillieux et al. (2009) investigated 15 dyslexic children and seven carefully matched

(age, gender, IQ) control subjects by means of functional neuroimaging (fMRI) using a noun-verb association paradigm. Comparison of activation patterns between dyslexic and control subjects revealed distinct and significant differences in activation patterns at both the cerebral and cerebellar level. Control subjects showed well-defined and focal activation patterns bilaterally distributed in the frontal and parietal lobes and the posterior regions of the cerebellar hemispheres. The dyslexic children, however, presented widespread and significantly more diffuse activations at the cerebral and cerebellar levels. Cerebral activations were observed in frontal, parietal, temporal, and occipital areas. Activations in the cerebellum were found predominantly in the cerebellar cortex, including Crus I, Crus II, hemispheric lobule VI, VII and vermal lobules I, II, III, IV, and VII (Fig. 9.4). Given the widespread activation in the cerebellum in the dyslexic group the authors suspected a defect of the intra-cerebellar distribution of activity, suggesting a disorder of the processing or transfer of information within the cerebellar cortex.

Nicolson and Fawcett (2011) published a review on the role of the cerebellum in various developmental disorders such as dyslexia, dysgraphia, and procedural learning and suggested that according to the cerebellar deficit hypothesis only the language-related cerebellar regions, including lobules VI and VIIB, are involved in dyslexia. Other regions in the cerebellum may be affected as well. According to their neural systems framework, dyslexia is associated with the language-based component (Broca's area and the right lateral cerebellum), whereas dysgraphia is

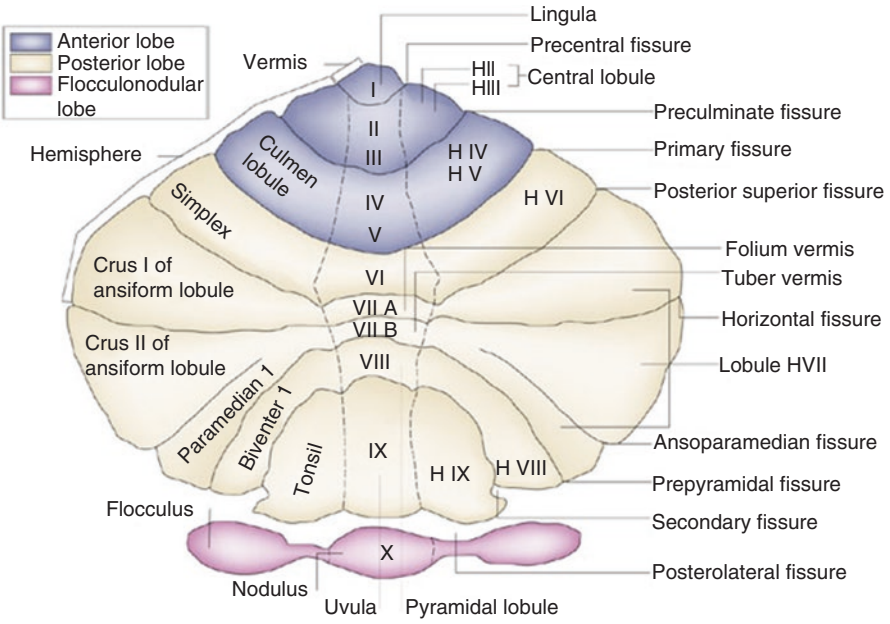

Fig. 9.4 Cerebellar cortical anatomy: view of the cerebellar cortex presenting the lobes and lobuli by name and number (after Manni and Petrosini 2004)

primarily related to the motor component (the motor cortex and the cerebellum). The neural systems framework is derived from Ullman's (2004) model of a procedural learning motor system for motor skills such as handwriting and a procedural learning system for language skills and habits. This model includes the frontal cortex, the parietal cortex, the superior temporal cortex, and some subcortical structures such as the basal ganglia and the cerebellum. Consequently, Nicolson and Fawcett (2011) suggested that developmental dyslexia arises from impaired performance of the "procedural learning system for language," which comprises the prefrontal cortex (around Broca's area), the parietal cortex, the basal ganglia and the cerebellum. It is possible that dyslexic children also have difficulties with the motor procedural learning system but these seem not necessary to induce dyslexia.

9.2.5 Agraphia

Agraphia is a generic term denoting various types of writing disorders that result from acquired neurological damage. On the basis of their semiological characteristics, agraphic phenomena can be classified as either of the central (linguistic) or the peripheral (non-linguistic) type. The central agraphias comprise lexical (or surface) agraphia, phonological agraphia, deep agraphia, semantic agraphia and agraphia due to impairment of the graphemic buffer and they involve disruption of the linguistic system: they are characterized by qualitatively similar spelling errors across all output modalities (e.g., in written as well as in oral spelling, typing, letter selection, and sequencing). The peripheral agraphias, on the other hand, consist of allographic agraphia, apraxic agraphia, motor execution agraphia (micrographia and megalographia), hemianoptic agraphia, and afferent or neglect dysgraphia). These forms of agraphia do not result from damage to the linguistic system itself but from neurological problems (motor or sensory deficits) which primarily compromise the ability to correctly execute the manual production of letters. As a result, the peripheral agraphias are characterized by a clear qualitative dissociation between inferior handwritten and superior non-handwritten forms of spelling (e.g., mental spelling, typing, letter selection). Impaired writing may relate to cerebellar impairments.

Silveri et al. (1997, 1999) described two patients with spatial dysgraphia, characterized by segmented and dysmetric writing movements. It was hypothesized that a discoordination between the planning of the graphic motor patterns generated by supratentorial structures and the peripheral, proprioceptive afferences during ongoing writing movements may have caused the spatial dysgraphia. The functional pathway responsible for the peripheral control of writing might include the left cerebellum and the contralateral supratentorial structures.

Mariën et al. (2007) described a 72-year-old right-handed civil engineer who presented with apraxic agraphia, mild aphasia, dysexecutive symptoms, and behavioral and affective changes after a hemorrhagic lesion affecting the right cerebellar hemisphere. At one-year follow-up, apraxic agraphia, executive dysfunctions, and behavioral changes persisted (Fig. 9.5).

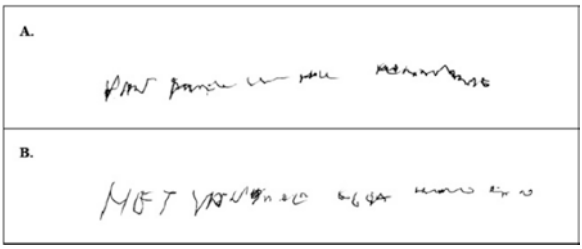

Fig. 9.5 Handwriting sample demonstrating the characteristic features of apraxic agraphia including poor and irregular letter formation, spatial distortions, stroke omissions resulting in incomplete letter forms, redundant insertions of anomalous strokes, and illegible scrawls: writing of lower (1**a**) and upper (1**b**) case words to dictation at 1 month

Quantified SPECT studies at 1 and 6 months post-stroke revealed perfusion deficits in the right cerebellar hemisphere as well as in the medial and lateral regions of the left prefrontal hemisphere. De Smet et al. (2012) reported three additional cases with apraxic agraphia following vascular damage to the cerebellum. The first patient presented with dysarthria, disrupted language dynamics, mild comprehension difficulties, reduced verbal fluency, and apraxic agraphia. Deficits in memory, attention, visuo-spatial planning, and executive functions were found as well. The patient's neurolinguistic deficits were consistent with a diagnosis of dynamic aphasia associated with anomia and apraxic agraphia. The second patient had ataxic dysarthria, apraxic agraphia, and mild attention problems. The third patient presented with disturbed frontal problem-solving, impaired mental flexibility, and apraxic agraphia. Although the patient occasionally had difficulties recalling the shapes of some graphemes, letter recognition was entirely normal. No difficulties were found matching lower- and upper-case letters and vice versa. Given the absence of sensorimotor disturbances affecting the writing limb acute vascular ischemic damage to the cerebellum could be held responsible in all three cases for the writing disturbance matching a diagnosis of apraxic agraphia.

Apraxic agraphia reflects damage to processing components involved in the programming of skilled movements for writing. Mechanisms responsible for this disruption include the destruction or disconnection of stored graphic motor engrams or damage to systems associated with translating the information on graphic motor engrams into graphic innervatory patterns to specific muscles (Rapcsak and Beeson 2000). Graphic motor engrams are stored in the parietal lobe, whereas the frontal premotor areas (dorsolateral premotor cortex and the supplementary motor area) are involved in translating these programs into graphic innervatory patterns (Rapcsak and Beeson 2000). Consequently, parietal damage results in the destruction of stored spatiotemporal representations for writing movements and frontal premotor lesions interfere with the execution of appropriate motor commands to specific muscle systems. However, De Smet et al.'s (2012) survey clearly revealed that no cases have been reported in whom apraxic agraphia resulted from isolated vascular lesions restricted to the prefrontal lobe. In addition, analysis of the study corpus consisting of 25 vascular cases reported since the first description by Heilman et al. (1973)

showed that apraxic agraphia may also occur after various lesion locations (for a review see De Smet et al. 2012). Given structural neuroimaging evidence of unaffected prefrontal and parietal areas, Mariën et al. (2007) and De Smet et al. (2012) hypothesized that their patients' writing deficits result from damage to the cerebellar–encephalic projections, connecting the cerebellum to the prefrontal supratentorial areas which subserve attentional and planning processes (Moretti et al. 2002b). Clinical observations of patients with prefrontal lobe dysfunctions also suggest that complex aspects of writing such as planning and maintaining attention may be disturbed (Ardila and Surloff 2006). This view of a functional disruption of the prefrontal brain regions is supported by SPECT findings which revealed the phenomenon of cerebello–cerebral diaschisis, reflecting the functional impact of the cerebellar lesion on a distant supratentorial region crucially involved in the execution of written language, due to a lack of excitatory impulses (Baron et al. 1981; Marien et al. 2001). A similar pattern of decreased perfusion in the anatomoclinically suspected prefrontal and cerebellar brain regions crucially involved in the planning and execution of skilled motor actions was recently identified in a 15-year-old left-handed patient with apraxic dysgraphia (Mariën et al. 2013a). It was hypothesized that in the absence of structural brain damage, disrupted development of handwriting skills in this patient might reflect incomplete maturation of the cerebello-cerebral network involved in planned skilled actions (Mariën et al. 2013a).

A few functional neuroimaging studies with fMRI have shown involvement of the right cerebellar hemisphere in writing beyond the pure motor control level (Katanoda et al. 2001; Longcamp et al. 2003). Beeson et al. (2003) conducted an fMRI study on the neural substrates of writing and main cerebral activation was seen in the superior part of the left parietal lobe and left inferior and middle frontal gyri. Their study confirmed the role of the superior parietal and frontal premotor areas in translating orthographic information into appropriate hand movements.

9.2.6 Metalinguistic Skills

In a number of studies Murdoch and coworkers investigated higher-level language skills and metalinguistic abilities in patients with cerebellar lesions (Cook et al. 2004; Whelan and Murdoch 2005; Murdoch and Whelan 2007). Murdoch and Whelan (2007), for instance, described ten patients with left primary cerebellar strokes who experienced difficulties with definitions and multiple definitions tests, with figurative and ambiguous language tests, with word association tasks, with antonym/synonym generation, and with the interpretation of semantic absurdities. These observations support the hypothesis that left cerebellar damage may disrupt high-level language skills. In addition, Murdoch and coworkers argued that tasks involving the manipulation of novel situations and lexico-semantic operations, as well as the development of language and monitoring strategies require frontal lobe support in their manipulation (Copland et al. 2000). Although frontal lobe involvement may explain the presence of language deficits after left cerebellar damage, the authors alternatively suggested that left cerebellar lesions may induce language

deficits typically associated with right cerebral damage (Kempler et al. 1999) via the phenomenon of crossed cerebello-cerebral diaschisis. Although no functional neuroimaging studies were conducted in this study, Murdoch and Whelan (2007) concluded that the cerebellum is involved in the process of refining and modulating language functions presumably via excitatory impulses reaching the prefrontal cortex from the cerebellum via the basal ganglia and the thalamus.

9.2.7 Summary

In addition to its long-established crucial role in coordinating motor speech production, clinical and experimental studies with patients suffering from etiologically different cerebellar disorders have identified involvement of the cerebellum in a variety of nonmotor language functions as well. A wealth of studies has demonstrated that the cerebellum is crucially implicated in various aspects of linguistic processing, including motor speech planning, language dynamics and verbal fluency, phonological and semantic word retrieval, expressive and receptive syntax processing, various aspects of reading and writing and even aphasia-like phenomena resembling dynamic and transcortical motor aphasia.

9.3 Cerebellar-Induced Syndromes

9.3.1 The Cerebellar Cognitive Affective Syndrome (CCAS)/ Schmahmann's Syndrome

Although from time to time, descriptions of clinical cases and experimental evidence from animal studies dating back to the early part of the nineteenth century already suggested an association between cerebellar disorders and nonmotor cognitive and affective dysfunctions, a causal relationship remained unexplored for several decades. In the mid-1900s investigators started to examine a possible causal relationship between the cerebellum and cognition and emotion exemplified by the work of Snider, Dow, Heath, Cooper, and others (see Schmahmann 2010 for a review). This line of research laid a robust foundation for the rediscovery of the concept by Leiner and colleagues (e.g., 1989) who hypothesized that more recently evolved parts of the cerebellum contribute to learning, cognition and language, and by Schmahmann and colleagues (see Schmahmann 2010 for a review) who introduced the influential dysmetria of thought hypothesis; the latter provides an historical, clinical, neuroanatomical, and theoretical framework within which a cerebellar role in higher cognitive and affective processes could be considered. In this theory, the cerebellum is considered to act as a modulator of behavior function, maintaining it around a homeostatic baseline appropriate to the context. In the way the cerebellum regulates motor function (rate, force, rhythm, and accuracy of movements), it regulates the speed, capacity, consistency, and appropriateness of affective and cognitive processes.

In the late 1990s, Schmahmann and Sherman (1998) introduced in a much cited paper the concept of cerebellar cognitive affective syndrome (Schmahmann's Syndrome; Manto and Mariën, 2015) to identify a range of cognitive and affective disturbances in patients with isolated cerebellar lesions. Based upon bedside screening and formal neuropsychological testing of 20 patients, Schmahmann and Sherman (1998) identified a range of cognitive, linguistic, and affective symptoms following cerebellar damage. The core features of this syndrome consist of (1) executive dysfunctions such as disturbances in planning, set-shifting, abstract reasoning, and working memory, (2) visuo-spatial deficits, such as impaired visuo-spatial organization and memory, (3) mild language symptoms including agrammatism and anomia, and (4) behavioral-affective disturbances, consisting of blunting of affect or disinhibited and inappropriate behavior. Anatomoclinical analysis revealed that lesions of the posterior lobe of the cerebellum (PICA territory) resulted in cognitive symptoms, while the vermis was consistently damaged in patients with behavioral-affective disturbances (Schmahmann and Sherman 1998). In contrast to subjects with SCA lesions, Exner et al. (2004) found a consistent pattern of memory impairment, executive disturbances and emotional withdrawal in patients with infarcts in the PICA territory. However, Neau et al. (2000) did not find any differences between the cognitive consequences of infarctions in the PICA or the SCA territory. Furthermore, patients with SCA lesions have been reported with clinically significant cognitive or linguistic disturbances (Mariën et al. 2001, 2009). Baillieux et al. (2010) investigated 18 adult patients with isolated cerebellar damage of whom 15 (83%) presented with cognitive impairments and/or behavioral-affective disturbances. Analysis of the neuropsychological profiles revealed a clear tendency of functional lateralization within the cerebellum: left cerebellar damage was related to typical non-dominant, right-hemisphere dysfunctions, such as attention deficits and visuo-spatial disturbances, while right cerebellar damage was associated with typical dominant, left-hemisphere deficits, such as disrupted language skills. There were no significant differences between SCA and PICA lesions. In addition, functional neuroimaging studies by means of quantified ECD SPECT demonstrated an association between supratentorial hypoperfusion and the observed neuropsychological deficits: Seven out of eight patients with frontal hypoperfusion presented with associated neuropsychological deficits, including executive dysfunction and/or behavioral disturbances.

Tedesco et al. (2011) investigated the expression of CCAS with respect to vascular lesion topography and the involvement of the deep cerebellar nuclei. Contrary to Baillieux et al. (2010), these authors did not find a lateralization effect but an effect of lesion distribution according to the vascular territory involved. Patients with PICA lesions performed significantly worse than patients with SCA lesions on tasks assessing verbal memory, language, visuo-spatial abilities. In addition, patients with lesions of the deep cerebellar nuclei had statistically significant lower scores for visuo-spatial memory, executive functions, attention, visuo-spatial, and sequencing skills. Although many studies have demonstrated a large spectrum of cognitive deficits following focal cerebellar damage, Alexander et al. (2012) only found minimal impairments in the chronic phase. Patients with right cerebellar lesions performed significantly worse on verbal fluency tasks and response control on the Stroop task

in comparison to patients with left cerebellar damage and controls. It was suggested that clinically significant impairments in patients with focal cerebellar lesions are usually transient or mild. Their findings provide support for the hypothesis that lateralized cerebellar lesions may cause impairments in a parallel manner to contralateral prefrontal lesions.

Although clinical case descriptions dating back to the early part of the nineteenth century from time to time suggested an association between congenital cerebellar pathology and a variety of nonmotor cognitive as well as affective dysfunctions, a possible correlation was dismissed for decades. Steinlin et al. (2003) were among the first who reported in a study group of 11 adult patients with pure non-progressive congenital ataxia (with and without cerebellar hypoplasia) a consistent association between a number of cognitive and affective disturbances consistent with Schmahmann's Syndrome and congenital pathology of the cerebellum. Chheda et al. (2002) found a significant correlation between severity of motor, cognitive and affective deficits, and the extent of agenesis in their group of patients consisting of six children and two adults. CCAS in this group was characterized by executive dysfunction, visuo-spatial impairment, behavioral abnormalities, marked prosodic difficulties, and expressive language disturbances affecting two cases. CCAS was also found in a number of genetic conditions primarily affecting the cerebellum both structurally and functionally such as Gillespie syndrome (Mariën et al. 2008) and Joubert syndrome (Tavano et al. 2007). Tavano and Borgatti (2010) confirmed the presence of CCAS in a group of children and adults with different types of congenital malformative lesions of the cerebellum but observed a wide variability of cognitive and affective dysfunctions indicating different subtypes of CCAS.

From an anatomical point of view there is still no consensus regarding the anatomical parts of the cerebellum that subserve cognitive modulation. However, the symptoms observed in Schmahmann's Syndrome are consistent with predictions derived from anatomical and neuroimaging studies, which show extensive neural circuits connecting the prefrontal, temporal, posterior parietal, and limbic cortices with the cerebellum (Desmond 2001). According to Schmahmann (2004), these anatomical circuits constitute the structural basis for functional subunits, reflecting a topographic organization of motor, cognitive, and affective processing in the cerebellum, in which the anterior cerebellar lobe is mainly involved in motor functions, the posterior parts of the cerebellum in higher cognitive modulation, and the posterior vermis in affective processing (Stoodley and Schmahmann 2010; Stoodley et al. 2012). However, several studies and case reports demonstrate that there may be substantial variability regarding the functional anatomy of the cerebellum (Neau et al. 2000).

9.3.2 The Posterior Fossa Syndrome (PFS)

The posterior fossa syndrome (PFS), which may develop following acute cerebellar damage, is characterized by a broad range of linguistic, cognitive, and behavioral-affective disturbances (Pollack 1997). PFS may be considered as an aetiologically

heterogeneous condition affecting both children and adults, but it most often occurs in paediatric patients after cerebellar tumor surgery. Although PFS has been documented in more than 350 cases, it is quite rare in adults (approximately 25 cases). In addition, PFS associated with vascular aetiologies is only reported in a very limited number of three adult cases (for a review see Mariën et al. 2013b). De Smet and Mariën (2012) described an adult patient with PFS following surgical evacuation of an intracerebellar hematoma. After 45 days of akinetic mutism, the patient's cognitive and behavioral profile closely resembled CCAS, characterized by visuo-spatial and attentional deficits, impaired frontal planning and problem solving, memory problems, reduced verbal fluency, decreased language dynamics and frontal-like behavioral problems such as apathy, behavioral and verbal inhibition, loss of facial expressions, and a withdrawn attitude. The authors suggested that in this patient, post-mutism cognitive and affective symptoms were related to the perfusional deficits in the anatomoclinically suspected prefrontal and right temporal cortical areas which subserve executive processing, behavioral–affective processes and spatial cognition.

Mariën et al. (2013c) reported longitudinal neuropsychological follow-up findings and pre- and postoperative SPECT in an adult patient with cognitive, behavioral, and affective symptoms before and after resection of an ependymoma in the posterior fossa This is the first patient in whom the phenomenon of pathological laughing and crying (PLC) was observed in the context of PFS, and the case provides evidence for the recently acknowledged role of the cerebellum in the contextual regulation of emotions and affect. During the phase of akinetic mutism, aggravation and marked extension of the perfusional deficits in the prefrontal brain regions were found. Mariën et al. (2013c) hypothesize that the phenomenon of cerebello-cerebral diaschisis in this patient suggests that PFS results from decreased transmission of excitatory impulses from the deep nuclei of the cerebellum through the dentatothalamic connections to the cortical areas crucially involved in cognition and behavioral and affective regulation (Mariën et al. 2001, 2003, 2009; Catsman-Berrevoets and Aarsen 2010; Miller et al. 2010).

As evidenced by a close parallels between SPECT and clinical findings, CCAS as well as PFS seem to reflect functional disruption of the cerebello-cerebral network involved in cognitive, behavioral, and affective functions. These findings may indicate that both syndromes share overt semiological features and a common pathophysiological substrate. Consequently, CCAS and PFS may both be regarded as cerebellar-induced clinical conditions showing different aspects of a spectrum that range in degree of severity and symptom duration.

9.4 Mechanisms of Cerebellar Involvement in Cognitive and Linguistic Processing

Several hypotheses have been advanced to explain the role of the cerebellum in various cognitive and linguistic processes such as non-motor associative learning, working memory, visuo-spatial abilities, verbal fluency, syntax, reading, and writing. The phenomenon of cerebello-cerebral diaschisis has often been suggested as a

possible functional explanation of the cognitive, linguistic, and affective deficits in patients with cerebellar lesions (Mariën et al. 1996). Cerebello-cerebral diaschisis reflects the metabolic impact of a cerebellar lesion on a distant, but anatomically and functionally connected intact supratentorial region. Cortical regions crucially involved in cognitive and affective processing might become functionally suppressed because cerebellar damage induces a decrease or a loss of transmission of excitatory impulses from the deep nuclei of the cerebellum via the cerebello-pontothalamo-cerebral pathways to the supratentorial brain regions (Mariën et al. 2001). Numerous studies have convincingly demonstrated the crosswise functional impact of focal cerebellar damage on distant supratentorial regions that subserve cognitive processes and they contributed to the view of a functionally lateralized and topographic organization of the "cognitive cerebellum" (Botez-Marquard et al. 1994; Gottwald et al. 2004). However, the few reports of language deficits after left cerebellar lesions suggest that the correlation between the type of language disorders and cerebellar lateralization of linguistic functions may not be absolute (Cook et al. 2004; Fabbro et al. 2004; Murdoch 2010).

Another explanation for the involvement of the cerebellum in spatial function, language, verbal memory, and sequence processing is the sequencing hypothesis (Molinari et al. 2008). Evidence in support of this hypothesis is provided by animal models (Leggio et al. 1999), clinical (Silveri et al. 1994; Molinari et al. 2004), and functional neuroimaging studies (Doyon et al. 2003). This theory emphasizes the importance of the cerebellum in detecting patterns of incoming stimuli (temporal and spatial information) or in central circuit activities (Molinari et al. 2008). In order to accomplish the task of comparing previous and ongoing stimuli, data must be maintained in a working memory buffer. Cerebellar sequence processing should be considered within the network of cerebello-cortical connections. Consequently, damage to the cerebellum, depending on the cerebello-cerebral loop involved, may provoke different functional impairments such as defective processing of sensory stimuli (Leggio et al. 2011). Leggio et al. (2008) investigated the sequencing hypothesis across verbal, spatial, and behavioral domains in patients with focal or atrophic cerebellar damage. The authors administered a set of tests involving cartoon-like drawings to differentiate between verbal, spatial, and behavioral sequencing and found that patients with cerebellar damage had lower scores than control subjects irrespective of the material processed. When comparing right versus left cerebellar damage, patients with right cerebellar lesions obtained lower scores on tests requiring verbal processing, whereas patients with left cerebellar damage had lower scores on tests requiring the processing of non-verbal behavioral stimuli.

Another theory postulates that the cerebellum significantly contributes to the prediction of feedback or outcomes associated with sensory input or actions (Bellebaum and Daum 2011). The cerebellum provides internal models which need to be continuously modified and updated, based on the results of the comparison of their output with the output of the "controlled object" (real or imagined situations) (Ito 2008). Thus, if the predictions of the internal model do not accurately match reality an error signal is generated. Consequently, errors in predictions may result in deficits in error processing and error correction. Timmann et al. (2002) and Richter et al. (2004) demonstrated that patients with cerebellar damage may be impaired in

associative learning tasks which might be due to an inability to update the internal model based on error feedback (Bellebaum and Daum 2011). According to this mechanism, the cerebellum does not only play an important role in the generation of predictions based on sensory stimuli but also in the generation of temporally accurate predictions. Evidence in support of this hypothesis was presented by clinical data of patients with cerebellar lesions who were impaired in the judgment of the duration of an auditory stimulus and the velocity of a moving visual stimulus (Ivry and Keele 1989; Ivry and Diener 1991). Patients with cerebellar lesions may also experience severe distortions during duration-discrimination tasks, suggesting a critical role of the cerebellum in the representation of temporal information (Hetherington et al. 2000; Spencer et al. 2007). This mechanism is also suggested to be involved in verbal working memory. According to Desmond et al. (1997), predictive control of the articulatory control process is necessary in order to update the phonological store dynamically. Consequently, prediction and updating are essential concepts in cerebellar processing of verbal working memory. Marvel and Desmond (2010) investigated cerebellar activity during the encoding, maintenance, and retrieval phases using a verbal working memory task and tried to find out whether cerebro-cerebellar activity is associated with the prediction of successful performance on a trial-by-trial basis. The authors found that the supplementary motor area and the dorsal cerebellar dentate are involved in encoding, and that the pre-supplementary area and the ventral dentate circuit are involved in retrieval. In addition, activity during the maintenance phase in the prefrontal lobe and the ventral dentate predicted subsequent accuracy of response to the probe during the retrieval phase. As a result, the study data consistently showed that the cerebro-cerebellar pathway is involved in accuracy prediction of successful performance.

9.5 Conclusion

The involvement of the cerebellum in cognitive, linguistic, and affective modulation has been overlooked for a very long time, due to its prominent role in motor functioning (Beaton and Mariën 2010). Although substantial progress has been made in understanding the functional role of the cerebellum in language and cognition, the precise role of the cerebellum in neurocognitive processing is not clear yet. Several pathophysiological and cognitive neuropsychological mechanisms have been suggested to explain various cognitive and linguistic deficits in patients with cerebellar lesions, including the phenomenon of cerebello-cerebral diaschisis, the sequencing hypothesis, and the role of the cerebellum in generating predictions. However, all hypotheses need further investigation to allow more consistent and firmer conclusions to be drawn about the exact nature of cerebellar computation. In addition, the question of a lateralized cerebellar involvement in cognitive modulation remains to be clarified. Although it has been demonstrated that specific cerebellar subsystems are involved in motor, cognitive, and affective processing, a better understanding of the functional topography of the cerebellum may clarify the contradictory findings with respect to neurobehavioral structure-function correlations.

Another area of interest in this relatively new research area relates to the prognosis of cognitive deficits following cerebellar damage. At present little is known about the long-term cognitive outcome. Richter et al. (2004) investigated the longitudinal outcome in 21 patients with cerebellar lesions with an average of 46 months following the onset of a cerebellar stroke. Their results indicated full recovery of cognitive disorders, except for marked impairments in verbal fluency. Schweizer et al. (2008) described a patient with a severe dysexecutive syndrome after a cerebellar arteriovenous malformation rupture. After 1 year of intensive rehabilitation, the patient's executive deficits had completely resolved. However, other studies did not confirm a positive prognosis following cerebellar lesions. De Smet et al. (2013) reported persistent linguistic, cognitive, and behavioral deficits in five children following posterior fossa tumor resection. Similar observations of persistent cognitive deficits were described by Neau et al. (2000), Fabbro et al. (2004), and Baillieux et al. (2006).

Findings suggest that classical language and neuropsychological tests may fail to detect subtle but significant cognitive changes after cerebellar damage (Mariën et al. 2000; Aarsen et al. 2004). Consequently, there is a need to develop more sensitive neuropsychological tools to identify the wide range of subtle neurocognitive repercussions after cerebellar dysfunction.

Refinement of insights into the functional role of the cerebellum in cognition and affect may also be accomplished by means of a close cooperation between the clinical neurosciences (neurology, neurolinguistics, neuropsychology), structural and functional neuroimaging (MRI, SPECT, fMRI, DTI), and neurophysiology (ERP, TMS, tDCS). In order to determine the functional outcome of cognitive disturbances following cerebellar damage and the underlying pathophysiological mechanisms, longitudinal follow-up studies are needed to disentangle the mysteries of this impressively competent structure at the bottom of the brain.

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