# Cerebellum and Cognition

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**Abstract**

Despite the idea that cerebellar input into cognition is a new concept, looking back in history one can see that this function of the cerebellum has long been discussed and was merely forgotten in the middle of the last century! Over the last several decades, the importance of the cerebellum in cognitive development has been shown in many areas. Children who suffer from congenital cerebellar malformations such as cerebellar hypoplasia or Joubert syndrome experience, in addition to motor problems, marked cognitive deficits. The degree of congenital or early acquired cerebellar damage is related to the degree of developmental problems later, as shown for preterm babies. There are many childhood developmental problems, such as fragile X syndrome, ADHD, dyslexia, and autism, where it can be shown that the degree of cerebellar structural abnormalities relates to cognitive deficits. In later acquired problems, such as infratentorial brain tumors or strokes, and late-onset cerebellar disorders, such as Friedreich's ataxia or Louis-Bar syndrome, data show the importance of an intact cerebellum for the normal development of children. The degree of cerebellar atrophy in children after brain trauma or oncological treatments is a prognostic signpost for cognitive problems.

Recent functional neuroimaging data support these clinical observations: the posterior lobe and lobule VI of the cerebellum seem to be involved in higher-level tasks such as verbal and working memory and executive functions. There are also data supporting a lateralized function: logical reasoning and language processing on the right side and visuospatial and attentional skills on the left side of the cerebellum.

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In summary, normal development of cognition seems to depend on an active interplay between cerebrum and cerebellum. The earlier in life and the more pronounced the disturbance of this interplay, the more the cognitive development of these children is hindered.

## Introduction

For centuries, functions of the cerebellum were thought to be limited to several aspects of motor coordination. During the last two decades, there have been important discoveries of additional cognitive functions.

There is an assumption that these cognitive aspects have only been recognized as recently as the end of the last century. However, going back in the literature, the knowledge of cerebellar contribution to cognitive functions has been under consideration much farther in the past.

Andreas Vesalius (1514–1564) wrote in one of his essays: "Anatomists describe the site of the cerebellum as if it stuffed the whole region of that prominence of the occiput, that swelling which the mass of people consider a measure of the power, of memory and talent. . ..," pointing to early beliefs about cerebellar cognitive functions. Early scientific knowledge on cognitive functions of the cerebellum was discovered by Malacarne (1744–1816), an Italian researcher, who stated that healthy humans have 500–780 cerebellar folias, but that in the cerebellum of "cretins'" folias are reduced to the number of about 340. He came to the conclusion that intelligence of human beings depends on cerebellar structures (Glickstein et al. 2009). One of the earliest reports of a patient with cerebellar agenesis and cognitive problems is likely that from Combette in the year 1831 (Schmahmann 2010). However, during the last century, several case reports were published supporting the assumption that a normal life without cerebellum was possible (Anton and Zingerle 1914; Tennstedt 1965; Boyd 1940); but, on closer examination, the patients in all three of these publications had some level of cognitive problems. Recently, Caroppo et al. (2009) reported a patient with partial cerebellar agenesis who had minimal motor but severe neuropsychological impairments. Functional imaging in this patient revealed activation and a symmetrical perfusion of the cerebellar remnants, which the authors attribute to residual cerebellar motor function. Left frontal and parieto-temporal cortex hypoperfusion are interpreted to be associated with disruption of cerbello-cortical connections – leading to cognitive problems.

There were many scientists in the second half of the last century who believed that there is more to cerebellar function than just motor behavior and coordination. Following anatomical studies, there were increasing reports also describing clinical functional inputs. The emotional and behavioral function of the cerebellum became evident first, as early as 1950. Snider and colleagues worked out the connection of cerebellar nuclei to the limbic system and deduced from this physiological study the input of the cerebellum on psychiatric problems (Snider 1950; Snider and Maiti 1976). The cognitive aspects of the cerebellum emerged some decades

later, starting in 1980s, with several different research groups working apart (Botez et al. 1985; Botez-Marquard and Botez 1993; Leiner et al. 1986, 1987; Schmahmann 1991).

These ideas were supported by early publications on investigations of humans during cognitive tasks by PET scans (Fiez et al. 1992) and functional MR (Kim et al. 1994). At the end of the last century, Schmahmann and Sherman coined the term "cerebellar cognitive and affective syndrome" in several papers on non-motor function of the cerebellum (Schmahmann and Sherman 1997, 1998), which was a significant step forward in the acceptance of the cerebellum processing cognitive functions.

## Evolution

During the evolution to the modern human, there was a remarkable increase of volume, not only in the frontal lobe, but also in parallel of the cerebellum, especially the hemispheric neocerebellum. In early humans to the Neanderthals, the cerebrum was more prominently increasing in volume, but in the further evolution this relationship changed and the increasing volume of the cerebellum became more prominent. This increase is most important in the neocerebellum and is more pronounced in humans than in apes (MacLeod et al. 2003). Compared with Macaque monkeys, humans have a large prefrontal contribution to the human cortico-ponto-cerebellar system. These findings support the selective evolution of prefrontal inputs to the human cortico-pontocerebellar system (Ramnani et al. 2006).

Today, we know that the cerebellum contains more neurons and cells than the cerebrum, and that they are more densely packed. The cerebellum has 40 million nerve fibers for connections to neocortical areas, which is remarkable compared with the one million nerve fibers of the visual system (Leiner 2010). These connections go to many neocortical centers via the ventrolateral thalamus to areas in the frontal, prefrontal, posterior parietal, and temporal cortex. It is known that in the dentate nucleus motor output is located more dorsally, and cognitive output is located in the ventro-caudal part (Strick et al. 2009).

Critics note that the enlargement of these tracks during evolution might be causal for improved motor and ocular motor functions and that the cortical areas connected to the cerebellum are not solely for cognitive functions, but are also important for ocular movements. They state that the cerebellum is the single most important link between the visual and motor system (Glickstein 2007).

## Congenital Malformations of the Posterior Fossa

The cerebellum seems to have a very important function during development of cognitive abilities. Usually, children with congenital cerebellar malformations have serious cognitive problems. These neuropsychological impairments cannot be explained by motor and oculormotor dysfunctions alone. Motor disabilities have a tendency to improve with development, whereas cognitive problems become

more apparent. Similar to cerebellar cognitive affective syndrome in adults, malformations affecting the cerebellar vermis are causal for affective and social behavior disorders and often evolve towards more unfavorable presentations associated with autistic symptomatology. Malformations of cerebellar hemispheres are frequently associated with selective neuropsychological deficits involving mainly executive functions, visuospatial and linguistic abilities (Tavano and Borgatti 2010). These children frequently have a typical behavior pattern: they are not disturbed or challenged by their disabilities but rather accept them. Supporting therapies (physiotherapy, occupational therapy) can provide significant stimulation and improve development. However, this stimulation needs much repetition and reinforcement by parents and therapists and thus is a real challenge for all involved individuals.

Children with *cerebellar hypoplasia* are known to have, besides ataxia, cognitive developmental problems from mild to severe degree (Shevell et al. 1996; Steinlin et al. 1998; Ventura et al. 2006). In one group of patients, more detailed neuropsychological examination revealed IQ values ranging from 30 to mild decreased values (Steinlin et al. 1999). These children had significant problems in attention, processing speed, and visuospatial functions, problems that were not paralleled by the degree of their motor problems. The neuropsychological asymmetric profile (better verbal functions) suggests that visuospatial deficits during learning and the influence of disturbed procedural learning might be important (Steinlin et al. 1998). Although less severely affected, autosomal dominant cerebellar hypoplasias, such as Gillespie syndrome, also show cognitive problems resembling the cognitive affective syndrome of Schmahmann (Mariën et al. 2008).

In a group with the so-called *molar tooth sign*, developmental problems seem to be the rule. In a group of children with *Joubert syndrome* on a long term follow-up, IQ ranged between 35 and 85 (Steinlin et al. 1999), results that have since been confirmed by other authors (Bolduc and Limperopoulos 2009; Fennell et al. 1999). Although cognitive problems are present in the majority, there are rare reports of patients with Joubert syndrome who show normal cognitive development (Ziegler et al. 1990; Poretti et al. 2009a; Tavano and Borgatti 2010).

There is only one report on cognitive functioning of children with *rhombencephalosynapsis* (Poretti et al. 2009b). In this paper, in 3 of 5 children, IQ values were below 85. Similar to the patients with cerebellar hypoplasia, these children had higher verbal than performance IQ. Despite better verbal functions, these children still have problems in verbal fluency. In addition, attention and executive dysfunctions as well as problems in memory and processing speed are common.

*Dandy-Walker malformation* seems to be the exception from a posterior fossa syndrome and accompanying cognitive developmental problems: About 50% of children with the diagnosis of Dandy Walker show normal cognitive performance (Gerszten and Albright 1995), However, Boddaert et al. (2003) showed that abnormal lobulation of the vermal remnants was related to IQ values below 70. These data point to the great importance of the vermis for the early cognitive development.

For all the above-mentioned malformations, best shown in Joubert syndrome (Poretti et al. 2007; Senocak et al. 2010) and rhombencephalosynapsis (Pasquier et al. 2009), additional brainstem (and supratentorial) abnormalities might also have an influence on cognitive development. Thus, the cerebellar role for cognitive development in these children seems to be important, but additional brainstem and/or supratentorial inputs might reinforce the problem.

## Abnormalities of Cerebellar Volumes and Structure

Structural imaging studies, especially volumetric studies in several disorders, such as fragile X syndrome, attention deficit disorder, and autism, further support the assumption of an input of the cerebellum in cognition.

In *fragile X syndrome*, there is a decrease in size of the posterior vermis. In females and in male premutation carriers, these vermal abnormalities are related to their cognitive problems (Mostofsky et al. 1998).

Children with *Down syndrome* have smaller brain volumes than their healthy peers. Interestingly, for these children the decrease of the volume is significantly more pronounced in the cerebellum than the cerebrum, and mouse models of Down syndrome point to the fact that trisomy 21 may be mainly a cerebellar problem (Moldrich et al. 2007).

Dysfunctions are not only related to decreases of size or volume. Children with *Williams syndrome* have a megacerebellum. In a magnetic resonance study, the Cho/NA and Crea/NA content was related to verbal and performance IQ (Jones et al. 2002; Rae et al. 1998). This points to the importance of normal structure and also normal content of neurons for function.

There are very prominent connections from the cerebellum to the frontal lobes. Thus, it is not surprising that in *attention deficit disorders* changes of the cerebellum are also detectable. Vermal volume was found to be smaller and, compared with healthy controls, boys with ADHD have abnormalities in posterior lobules (Berquin et al. 1998; Mackie et al. 2007). A clue that these abnormalities are not just transsynaptic effects are findings of baseline activity in functional MR investigations. Baseline activity of vermis was more reduced than parallel reduction of frontal and parietal activities (Zang et al. 2007).

Interestingly, reports discussing "*cerebellar dyslexia of Nicolson*" suggest that cerebellar deficits during development lead to phonological, processing speed, and literacy problems by problems of articulation and working memory (Nicolson et al. 2001). These findings are supported by Stoodley et al. (2006), who show dyslexic adults to have an implicit learning problem, a primary cerebellar function. In addition, the cerebellum is the most consistent location for structural differences between dyslexic and control participants in imaging studies. Cerebellar dysfunctioning as a potential influencing factor for dyslexia is supported by a study of Moretti et al. (2002). They showed that in patients with acquired vermian or paravermian lesions, increased reading mistakes are present. In the

pathophysiology of dyslexia, visuomotor problems are also discussed. The influence of cerebellar coordination of eye movements on the problem of dyslexia and reading after acquired vermal lesion cannot be ruled out.

Last, but not least, is the role of the cerebellum in *autism*. Different aspects of changes of size in cerebellum compared with cerebral lobes are discussed (Hallahan et al. 2009; Amaral et al. 2008). Some studies suggest an immunological influence on pathophysiology of autism (Wills et al. 2008). Routt and Dhossche (2008) suggest a hypothetic model where antiglutamate acid decarboxylase antibodies against Purkinje cells might be an important trigger for autism.

Critics point out that, in recent years, more attention has been drawn to cerebellar than cerebral alterations in the above problems. The abnormalities of the cerebellum might just be a transsynaptic effect induced by undetected and therefore unanalyzed abnormalities of the cerebral lobes. In addition, parallel abnormalities of cerebrum and cerebellum might be easier to delineate in the cerebellum, as neurons/cells are more densely packed.

## Pre- and Perinatally Acquired Cerebellar Problems

*Prenatal exposure to alcohol* is known to have a negative influence on the development of the brain. These children typically present with failure to thrive, microcephaly, and typical dysmorphic symptoms such as small upper lips, missing philtrum, or low-set ears. Moreover, prenatal alcohol exposure leads frequently to a smaller brain, which is thought to be the underlying reason for various developmental, cognitive, and behavior problems. O'Hare et al. (2005) analyzed the cerebellar volume of children suffering from fetal alcohol syndrome. The researchers could show that the vermis as a whole is too small, but typically it is the size of the anterior vermis that is related to cognitive problems of these children.

Also, in *premature children*, the diminished growth of the cerebellum is an important marker for future cognitive problems. The first to point to this relationship, in 1999, was Kraegeloh-Mann and her group, reporting on a group of children with severe cognitive problems, who showed no or only minimal periventricular leucomalacia but had significant cerebellar atrophy. Several groups confirmed these findings over the last decade (Allin et al. 2001; Bodensteiner and Johnsen 2005; Inder et al. 2005).

Messerschmidt et al. (2008) showed that cerebellar volume predicts cognitive developmental problems in children with similar amounts of supratentorial lesions/abnormalities. Furthermore, in premature children, impaired growth of specific cerebral regions after cerebellar lesions have been reported by Limperopoulos et al. (2010). Their conclusion was that regional cerebral growth impairment results from interruption of cerebello-cerebral connectivity and loss of neuronal activation, which is critical for development. Thus, the cerebellum might contribute to cognitive development by its own functions, but also by influencing the cerebrum in its development.

## Acquired Problems During Childhood

The findings in congenital malformations and in premature acquired cerebellar lesions open the discussion to whether the cerebellum itself or its influence on the development of the cerebrum are more important for the cognitive abilities of these children. The fact that acquired lesions during childhood also have a significant impact on the cognition of these children supports the idea that these two mechanisms act in parallel.

*Infratentorial tumors* are the best-known acquired cerebellar lesions leading to cognitive problems. Additional treatments such as radio- and/or chemotherapy worsens the effect significantly. However, over the last decades, several publications concentrate on the effect on cognition of cerebellar tumors that had isolated surgery as treatment. The groups of Levisohn et al. (2000) and Steinlin et al. (2003) showed a similar pattern of neuropsychological problems after resection of infratentorial tumors during childhood: Most affected was memory, visuospatial, and verbal functions. In the second group, a negative relationship of full-scale intelligence quotient and amount of cerebellar abnormalities (normal versus atrophy and resection) was demonstrated. Beebe et al. (2005) confirmed these findings in a large group of 103 children after "resection only": Affected areas were full scale and verbal IQ, but spelling functions were also significantly hampered. In contrast to the results of Scott et al. (2001), the Beebe's group did not find any localization-related dysfunctions, despite the large cohort.

*Cerebellar mutism* is a postoperative dysfunction that is related to resection of infratentorial tumors (Gudrunardottir et al. 2011). The exact pathophysiology is unknown, but there are data to support the idea that bilateral lesions of dentate nuclei are the underlying structural abnormality (Kusano et al. 2006). Catsman-Berrevoets and Aarsen (2010) report on children with mutism in the frame of a posterior fossa syndrome; in these children, SPECT scans showed secondary hypometabolism in several cerebral brain regions. These findings seem to support the idea that cerebellar neuronal activity seems to influence not only development but also activity of cerebral neurons. Luft and colleagues (2005) pointed to the possibility, that the most important influence is generated by the nuclei interpositus. The idea that isolated affection of the cerebellum might lead to mutism is supported by case reports with transient mutism during parainfectious acute cerebellitis, especially after rotavirus infection (Papavasiliou et al. 2004; Shiihara et al. 2007) and also by the observation that in cerebellar acute demyelinating episodes in childhood, mutism might be present (Parrish et al. 2010). Cerebellar mutism is one of the symptoms in the spectrum of the posterior fossa syndrome; its phenomenological similarity to autism is discussed by Tasdemiroğlu et al. (2010). Wells et al. (2008) review underlying pathophysiological mechanisms of cerebellar mutism and draw attention to the fact that cerebellar mutism is, in many aspects, similar to the cerebellar cognitive affective syndrome described in adults.

*Ischemic and hemorrhagic infarctions* restricted to the cerebellum are thought to be good models to study the effect of cerebellar dysfunction. Cerebellar ischemias are responsible for about 10% of ischemic stroke in childhood. Kossorotoff et al. (2010)

report on five boys with posterior fossa arterial ischemic stroke – all five presented with an affective posterior fossa syndrome and, in addition, had persistent cognitive deficits of planning abilities, visuospatial organization, and attention – a neuropsychological profile that is also seen in other etiologies. Wingeier et al. (2010) reported the neuropsychological long-term sequelae of eight patients after hemorrhagic cerebellar stroke in childhood. These children had disabilities in semantic and phonemic word fluency. A dysexecutive syndrome was diagnosed in one patient. These patients had only minor problems in learning and memory.

*Ataxia telangiectasia (Louis-Bar* syndrome) is a disorder that affects primarily the cerebellar Purkinje cells. These patients are shown to have, early in the disease course, neurocognitive problems with reduced verbal IQ and disturbed judgment of time (Mostofsky et al. 2000).

Last but not least, it is shown in several reports that in children after *brain trauma* (Braga et al. 2007; Soto et al. 2001) or *leukemia* (Ciesielski et al. 1994), residual cerebellar atrophy is a marker for the degree of neurocognitive problems. In children with brain trauma, more specific results revealing problems of visual memory and dyscalculia are reported (Braga et al. 2007).

## Late-Onset Cerebellar Problems

It has become increasingly evident that patients with disorders like *Friedreich's ataxia* and *sporadic cerebellar ataxias* have mild neuropsychological difficulties. Friedreich's ataxia patients have a neuropsychological profile with impaired concept formation, visuospatial reasoning, and reduced speed of information processing and learning. Personality profile may be affected, with reduced defensiveness (Mantovan et al. 2006).

Children with the hereditary slowly progressive forms of ataxia ocular motor apraxia type 2 are shown to have neuropsychological problems (D'Arrigo et al. 2008). Sporadic ataxias during childhood are rare, and their cognitive problems mostly manifest only during adulthood.

## Functional Neuroimaging

In many cerebellar disorders, structural and functional magnetic resonance abnormalities have been detected and linked to the clinical neurocognitive problems of these patients. These data from patients with cerebellar disorders is supported by functional imaging studies in healthy volunteers, revealing cerebellar activities for many non-motor tasks. Stoodley and Schmahmann (2009) showed, in a meta-analysis of functional imaging data, that there seems to be a functional organization of the cerebellum: motor and sensorimotor tasks activated the anterior lobe, adjacent parts of lobule VI, and lobule VIII. In contrast, the posterior lobe (lobules VI and VII, in particular) was involved in higher-level tasks for language, verbal working memory, and executive tasks. Language was right lateralized and spatial

function left lateralized. These data have been largely confirmed in a study performed by the same group (Stoodley and Schmahmann 2010). In another study, lateralized function of the cerebellum was suggested: the right cerebellum being associated with logical reasoning and language processing and the left cerebellum mediating visuospatial and attentional skills (Baillieux et al. 2010). These data support the concept of cerebello-cerebral diaschisis. The cerebellum and the cerebrum seem to be interlinked with each other by closed-loop circuits. The information transferred by these loops provides the cerebellum with the information to influence control not only of movement but also cognition (Strick et al. 2009).

**Conclusion**

Reports both from patient studies and functional imaging experiments in healthy volunteers underscore the importance of the cerebellum in cognitive functions. There are a number of theories regarding the precise nature of cerebellar input into cognition. One is that the cerebellum supports the cerebrum by timing processes and temporal regulation. Another is the notion that the cerebellum provides an excitatory impulse from deep cerebellar nuclei to different cortical areas sub-serving cognitive processes (Baillieux et al. 2008), an idea supported by SPECT and PET studies. The fact that congenital and early acquired cerebellar problems have a more pronounced effect on cognitive functioning than lesions acquired later in life supports the idea that the cerebellum has an important influence on the developing structures and function of the supratentorial brain, enabling the perfection of its higher-level functions.

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