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The Role of the Cerebellum in Multiple Sclerosis – 150 years after Charcot

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Highlights

- The cerebellum is a prevalent site of Multiple Sclerosis (MS) disease pathology.
- Indication of high connectivity between the cerebellum and other CNS regions.
- Extent of cerebellar MS pathology is comparable to its related network counterparts.
- Proof of ubiquitous cerebellar involvement in MS dysfunction incl. cognitive decline.
- New technologies may overcome limitations in assessment of cerebellar dysfunction.
- Advanced methods are needed to characterize disease dynamics in longitudinal studies.

Abstract

Despite its functional importance and well known clinical impact in Multiple Sclerosis (MS), the cerebellum has only received significant attention over the past few years. It is now established that the cerebellum plays a key role not only in various sensory-motor networks, but also in cognitive-behavioural processes, domains primarily affected in patients with MS. Evidence from histopathological and magnetic resonance imaging (MRI) studies on cerebellar involvement in MS is increasingly available, however linking these pathological findings with clinical dysfunction remains challenging. There are promising advances in technology that are likely to improve the detection of pathological changes within the cerebellum, which may elucidate how pathology relates to disability.

Keywords:

Cerebellum; multiple sclerosis; cognition; atrophy; neurodegeneration; magnetic resonance imaging; depth-sensing computer vision.

Introduction

Simple tasks in daily living such as finding the keyhole, pouring a cup of tea or walking on a narrow path can be a major challenge for patients with multiple sclerosis (MS). The cerebellum is the brain structure primarily involved in such fine motor, coordination tasks. In fact the defining triad of MS recorded by the French neurologist Jean-Martin Charcot (1825–1893), describes three predominantly cerebellar symptoms: tremor, nystagmus and scanning speech (Charcot, 1877). Beyond this triad, many more symptoms related to cerebellar function, in particular cognitive-behavioural dysfunction can be disabling for MS patients impairing their daily routine, and predict poor prognosis and rehabilitation outcome (de Groot et al., 2009; Langdon and Thompson, 1999; Miller et al., 1992). Although cerebellar abnormalities have been known in MS for a long time, the cerebellum has received greater attention by MS researchers only during the past two decades. The aim of this review is to shed light on the distinctive role of the cerebellum in MS. Starting with a review of the complex functional cerebellar anatomy, the histopathological changes in the cerebellum of MS patients, their clinical signs and symptoms, the difficulties in capturing the latter as well as the clinical-radiological correlations and future research directions are then critically discussed.

Functional anatomy of the cerebellum

While the cerebellum represents only about 10% of the size of the whole brain, with more than 100 billion neurons, it comprises the same amount of neural cells as the cerebrum (Voogd, 2003). This is possible through a characteristic structure of tightly folded cortical grey matter, the foliae, which together form the cerebellar lobules of two cerebellar hemispheres including the midline vermis. Larsell, and recently revisited by Schmahmann and colleagues, standardized and shaped a systematic nomenclature of the individual cerebellar lobules (from I – X), which is applied in most magnetic resonance imaging (MRI) studies using cerebellar segmentation techniques (Larsell and Jansen, 1972; Schmahmann et al., 1999). In addition to multiple nomenclatures, there

are various anatomico-functional subdivisions of the cerebellum (Manni and Petrosini, 2004). The hemispheres can be subdivided in the anterior-posterior direction, namely the anterior, the posterior and the flocculonodular lobes. Further distinction is made by afferent sensory input from various cortical, subcortical and also spinal regions projecting to the cerebellar cortex, separating the so-called cerebro-, vestibulo-, and spino-cerebellum. Another longitudinal division was proposed by Jansen and Brodal in a medial, intermediate and lateral zone based on efferent feedback projections connecting via the four cerebellar nuclei, embedded in the medullary core of the white matter, back to cortical, subcortical and spinal regions of the central nervous system (CNS) (Jansen and Brodal, 1954; Voogd, 2003). The fastigial nucleus, most medially located, receives input from the medial cortical zone (the vermis), the interposed nuclei (emboliform and globose) from the intermediate cortical zone (paravermal zone) and the dentate, the largest and most laterally located nucleus is connected with the lateral hemispherical cortical zones.

Functionally, the cerebellum represents an associative center in multi-synaptic, segregated cortico-nuclear-thalamo-cortical circuits, involved not only in motor functions, but also, as recently recognized, in various higher order cognitive and emotional functions (Koziol et al., 2014). In general, lesions in the cerebellum (unlike lesions in the cerebrum) cause a qualitative dysfunction rather than a total loss of function; e.g. movements become disorganized, fine-tuning is lost and the patients' speech becomes incomprehensible. Historically, lesional and anatomical studies in humans and animals contributed to our understanding of cerebellar dysfunction. It was shown that lesions of the cerebellar midline structures (vermis and intermediate zone) predominantly lead to impairment of basic motor functions such as limb coordination and balance, whereas pathology in the lateral cerebellar hemispheres cause dysfunction in higher motor functions and cognitive processes (Konczak and Timmann, 2007; Schmahmann and Sherman, 1998). The precise somatotopic organization of the cerebellar cortex especially regarding higher order functions, has been the subject of an intense discussion and reappraisal over the years. Similar to the functional compartmentalization of the cerebral homunculus, a systematic cortical representation of body

parts is also postulated in the cerebellum (Manni and Petrosini, 2004). Functional imaging studies and intraoperative mapping improved understanding of functional compartmentalization and helped to better understand the cerebellar cortical topography (Buckner et al., 2011; Mottolese et al., 2013; Stoodley and Schmahmann, 2010). Ipsilateral body movements follow a reliable topography mainly, but not exclusively, in the anterior lobe and lobule VI of the cerebellum, where different sectors may represent the same body part or vice versa and the size of the cortical representation is proportional to its functional importance (Mottolese et al., 2013). A second motor cortical–cerebellar loop is represented in lobule VIII with further hand/arm and lower limb representation (Buckner et al., 2011; Mottolese et al., 2013). Situated in between these two motor task-dominated regions, the largest lobule, lobule VII (subdivided in Crus I, II and VIIb), is activated during various language, working memory and executive function tasks (Stoodley and Schmahmann, 2010). Language tasks, e.g. verb generation tasks, further activate parts of the adjacent Lobule VI (Thurling et al., 2011). The latter cerebellar region is proposed to participate in higher-order cognitive networks with at least three cortical regions, including the dorso-lateral prefrontal, inferior parietal and lateral temporal area (Buckner et al., 2011).

Patients with MS suffer not only from the clinically more obvious cerebellar motor dysfunction, e.g. gait ataxia, tremor or ocular motor dysfunction, but also from a specific cognitive deficit profile, likely related to cerebellar dysfunction, which is discussed below.

Neuronal Models of the Cerebellum: From Cells to Neurological Conditions

Since the first description of neurons by Camillo Golgi and Santiago Ramón y Cajal at the beginning of the last century, the cerebellum has been attractive for its regular network structure and clear identification of the different neuronal types. The two main questions that arose at that time and remain under investigation are: (1) how does the cerebellum operate and (2) what is the role of the cerebellum in overall brain functioning. Understanding these points, in turn, brings about relevant consequences for neuropathology (D'Angelo, 2010; D'Angelo et al., 2011).

Intense investigation in molecular, cellular and circuit physiology has revealed relevant properties of cerebellar neurons and synapses (D'Angelo and De Zeeuw, 2009). Moreover, various kinds of mathematical models have been devised to investigate whether the cerebellum microcircuit functions can be explained in terms of its elementary neuronal and synaptic properties. Recently detailed computational models of neurons and synapses based on physiological measurements have been developed to generate a bottom-up reconstruction of the cerebellar microcircuit, showing how spatio-temporal reconfiguration of input signals and internal microcircuit computations take place (D'Angelo et al., 2013; Solinas et al., 2010).

A critical issue is that, whilst it is well known that the cerebellum is involved in learning and memory of sensory motor skills, the way these processes take place is still unclear (D'Angelo, 2014). The initial proposal, drawing on Motor Learning Theory, suggested that learning had to occur at the parallel fiber - Purkinje cell synapse under supervision of climbing fibers (Marr, 1969). However, the uniqueness of this mechanism has been questioned and multiple forms of long-term plasticity have been revealed at various locations in the cerebellar circuit, including synapses and neurons in the granular layer, molecular layer and deep cerebellar nuclei. At present, more than 15 forms of plasticity have been reported. There has been a long debate on which plasticity is more relevant to specific aspects of learning, but this question has been hard to resolve using physiological analysis alone. Recent experiments and models making use of closed-loop robotic simulations are revealing a radically new view: one single form of plasticity is insufficient whilst altogether the different forms of plasticity can explain the multiplicity of properties characterizing cerebellar learning (Casellato et al., 2014; Solinas et al., 2010). These include multi-rate acquisition and extinction, reversibility, self-scalability and generalization. Moreover, when the circuit embeds multiple forms of plasticity, it can easily cope with multiple behaviors, allowing the cerebellum to operate as an effective generalized forward controller.

The functional role of the cerebellum has recently been reassessed using transcranial magnetic stimulation (TMS), showing that it effectively controls both sensori-motor integration (Monaco et

al., 2014) and cognitive processing (Cattaneo et al., 2014). High-resolution MRI tractography has revealed a remarkable connectivity not just with motor but also with associative cortical areas (Palesi et al., 2014) and functional MRI (fMRI) has shown that the cerebellum is part of numerous cognitive resting-state networks (Castellazzi et al., 2014) and in consequence is prominently involved in neurodegenerative pathologies like Alzheimer's Disease (Castellazzi et al., 2014) and in MS.

Pathology of cerebellar abnormalities in MS

The cerebellum is a predilection site for lesion development in MS. Both grey (GM) and white matter (WM) demyelination are observed, the former representing the most prominent pathological feature (Figure 1). Analogous to cortical demyelination in other brain regions (Kutzelnigg et al., 2005), several histopathological studies highlighted the presence of cerebellar cortical demyelination, in particular in progressive MS. Demyelination in the cerebellar GM is more extensive than in the WM, usually affecting one or more cerebellar foliae and comprising, on average, ~14-39% and up to ~80-90% of the total cerebellar GM area (Gilmore et al., 2009; Howell et al., 2014; Kutzelnigg et al., 2007). Morphologically, cortical demyelination presents mainly as confluent lesions affecting all layers of the cerebellar cortex in a band-like subpial manner, yet leukocortical lesions as well as intracortical perivenous lesions have also been described (Gilmore et al., 2009; Kutzelnigg et al., 2007). The extent of cortical demyelination in the cerebellum seems to be related to the extent of overall MS pathology, associated with the amount of cortical demyelination in the forebrain (Kutzelnigg et al., 2007) and the overall proportion of demyelinated GM (Gilmore et al., 2009).

In contrast to late stage MS, cerebellar cortical demyelination in early MS has been described as sporadic in histopathological studies, with a percentage of demyelination in the range of 0-7.5% (Kutzelnigg et al., 2007), thus favoring the view that GM lesions reflect cumulative – or late stage – pathology (Gilmore et al., 2009).

Cerebellar cortical lesions are associated with neuronal loss and axonal damage (Kutzelnigg et al., 2007; Redondo et al., 2014), an attribute common to cortical lesions in other locations in the CNS(Peterson et al., 2001). However, contrary to the brain (Wegner et al., 2006) and hippocampus (Dutta et al., 2011), no differences in the synaptic density were observed between myelinated and demyelinated regions in the cerebellum (Kutzelnigg et al., 2007). It is conceivable, however, that these discrepancies may in part arise from differences in the sensitivity of the methods applied.

Mechanistic considerations also suggest similarities between GM pathology in the brain and cerebellum in late stage MS. In particular, a prominent role for inflammation in GM pathology has been proposed. Similarly to the brain, subpial GM demyelination in the cerebellum has been related to the presence of meningeal inflammation (Howell et al., 2014; Kutzelnigg et al., 2005). The extent of GM demyelination correlated with meningeal macrophage density and microglial activation in the GM (Howell et al., 2014). Interestingly, both demyelination and meningeal inflammation were more pronounced in patients harboring B cell accumulations in forebrain regions. The role of inflammation as a major contributor to cortical cerebellar pathology is further underscored by experimental data. Particularly myelin oligodendrocyte glycoprotein $(MOG)_{1-125}$-induced experimental autoimmune encephalomyelitis (EAE) in the common marmoset has been instrumental in studying the relationship between focal cortical lesions and cortical atrophy in the brain and the cerebellum (Merkler et al., 2006). As in chronic MS, where an overall cortical thinning occurrs independently of focal cortical demyelination (Wegner et al., 2006), marmosets with EAE also show diffuse cortical thinning, diffuse axonal damage and synaptic loss in both demyelinated and myelinated cortex (Pomeroy et al., 2010). The diffuse nature of cortical pathology suggests the involvement of soluble inflammatory factors, a hypothesis that was further substantiated in other experimental models of MS (Pomeroy et al., 2010; Yang et al., 2013). Moreover, inflammation has been shown to induce functional alterations in synaptic input

(Mandolesi et al., 2012) to Purkinje cells and in their ion channel composition, thus leading to changes in their firing properties (Shields et al., 2012).

Altogether, the cerebellum presents itself as a predilection site for focal demyelinated lesions in the white, but also especially in the grey matter. The extent of tissue damage seems to be related to the overall severity of MS-related pathology. However, histopathological reports showing significant widespread neuronal and axonal degeneration in the cerebellum in MS suggest that diffuse generalized cerebellar pathology is at least in part independent of focal lesions. Experimental data support these findings and indicate potential molecular correlates underlying diffuse cerebellar changes. Although there are emerging insights into the mechanisms of cerebellar pathology, further work is needed to fully elucidate the interplay between inflammation, demyelination, and neuroaxonal pathology in MS.

Cerebellar involvement in Clinically Isolated Syndromes - Clinical symptoms and lesional MRI features

Clinically isolated syndromes (CIS) suggestive of MS represent first clinical attacks of MS. These syndromes are usually categorised in terms of topography of the suspected underlying lesion: optic neuritis, myelitis and CIS of the brainstem and/or cerebellum. While features of attacks of optic neuritis and, less so, myelitis are clinically well defined and may be thought to represent a single clinical entity even though lesions may affect distant parts of the optic nerve or spinal cord, clinical manifestations of CIS in the brainstem and/or cerebellum are diverse, and multiple combinations of signs and symptoms are possible (McDonald and Compston, 2006). From a clinical point of view, it is often difficult to differentiate cerebellar from brainstem syndromes and these two topographies are therefore usually considered together.

In a retrospective analysis of CIS with brainstem/cerebellar symptoms (assessed within 3 months of onset) the most common symptoms noted were: diplopia (68%), facial sensory symptoms (32%) and gait disturbance (31%) (Sastre-Garriga et al., 2010). Regarding MRI findings, the

presence of 2 or more infratentorial lesions was related to long-term disability in a small study with 42 patients with CIS followed for 8.7 years (Minneboo et al., 2004). In another large CIS cohort of 146 patients followed for a median of 7.7 years, patients with infratentorial lesions had a higher risk of a second attack and the presence of infratentorial lesions further increased the risk for disability (Tintore et al., 2010). In this regard brainstem rather than cerebellar lesions were responsible for the poor prognosis.

In the 2001 and 2005 MS diagnostic criteria, definition of dissemination in space was based on Barkhof's MRI criteria which have shown a high specificity for predicting conversion to clinically definite MS (CDMS) (Barkhof et al., 1997; Montalban et al., 2010). However, the presence of an infratentorial lesion, one of the four Barkhof criteria, was less specific, compared with specificity in other topographies in CIS (Sastre-Garriga et al., 2004). Because of this lower specificity and because the symptomatic lesion is not in itself demonstrating dissemination in space, the 2010 McDonald criteria foresee that the symptomatic lesions should not contribute to the lesion count (Polman et al., 2011). However, if the symptomatic lesion has to be excluded, CIS patients with one single symptomatic lesion in the brainstem/cerebellum would be seen as CIS patients with zero brain MRI lesions. Tintore et al. showed that, in fact, brainstem/cerebellum or spinal cord syndromes with a unique symptomatic lesion had a higher risk of developing CDMS and disability than patients without lesions (Tintore et al., 2016). Therefore, despite the recommendations of the 2010 McDonald criteria, the symptomatic lesion seems to matter in terms of risk of developing CDMS and should also contribute to dissemination in time (Kang et al., 2014; Tintore et al., 2016).

Automated quantification of cerebellar ~~dysfunction~~ signs and symptoms in multiple sclerosis using depth-sensing computer vision

Motor cerebellar signs and symptoms (e.g. tremor, gait or truncal ataxia, oculomotor disturbance) may be the predominant clinical manifestation in 11–33% of patients with MS (Weinshenker et

al., 1996). It was shown that patients demonstrating cerebellar dysfunction early in the disease course tend to develop severe disability more quickly (Amato and Ponziani, 2000). Especially in progressive disease courses, motor dysfunction, frequently cerebellar in nature, is a major contributor for reduced mobility and quality of life (Feinstein et al., 2015). So far, the Expanded Disability Status Scale (EDSS) assessment remains the most widely used clinical outcome measure and the only scale accepted by most health agencies for approval of MS therapeutics (Cohen et al., 2012; Kurtzke, 1983). However, the EDSS has well-known shortcomings, especially its high inter-rater and intra-rater variability (Goodkin et al., 1992). Higher consistency and potentially higher sensitivity is particularly relevant for detection of subtle changes in patients' neurological performance, e.g. in fine motor tasks related to cerebellar pathology. A promising alternative is offered by the "Assess MS" system, which has been developed as a touch-free, consistent and potentially finer grained tool to measure motor dysfunction - including cerebellar signs - in MS (Kontschieder et al., 2014; Morrison et al., 2015). Based on advanced machine learning algorithms (MLA), "Assess MS" automatically analyzes 3D-depth-sensor (Kinect camera) recordings of patients performing standard tests of motor function. The MLA are trained by Neurostatus-EDSS scorings (Kappos, 2011) performed by trained neurologists. The agreement between the MLA and the neurologists' scores are compared with the neurologists' short- and long-term intra-rater agreement. First results of a proof-of-concept multi-centre study are promising (D'Souza et al., 2016).

To validate future automated assessments, a video-based system has been developed, whereby pairwise comparisons of patient videos assessed by neurologists, can be mapped onto a continuous scale using the TrueSkill™ algorithm (Herbrich et al., 2007). First unpublished results demonstrate that the mapping of comparative assessment scores based on the TrueSkill™ algorithm appear to be much more sensitive to the variability in patients' neurological performance than ordinal measures, resulting in finer increments than the Neurostatus-EDSS subscores, with high intra- and inter-rater consistency on average 80-100%.

Automated computer assisted systems may overcome current problems in the reliable assessment of disability, especially providing a more sensitive (and potentially more specific) tool for measuring cerebellar dysfunction.

The Cerebellum and Cognition in MS

The cerebellar role in cognition has been recognized more recently and was first described as the cerebellar cognitive-affective syndrome (CCAS) (Schmahmann and Sherman, 1998). The CCAS includes, amongst other domains, impairment of executive functions such as planning, verbal fluency, abstract reasoning, working memory, visual–spatial skills and memory, many of which are frequently affected in patients with MS (Chiaravalloti and DeLuca, 2008). Studies on MS patients with cerebellar motor dysfunction showed that these patients may have a different cognitive profile compared to those without cerebellar symptoms, performing less well on tests of information processing speed and verbal fluency (Cerasa et al., 2013b; Valentino et al., 2009; Weier et al., 2014b) and less commonly on memory tasks (Cerasa et al., 2013b) and the Stroop test (Cerasa et al., 2012) (Table 1). In relapsing-remitting MS (RRMS) patients with cerebellar motor signs Symbol Digit Modality Test (SDMT) scores correlated with GM volume in the right dorsolateral prefrontal cortex and verbal fluency correlated with GM volume in the left superior temporal gyrus (Cerasa et al., 2013b). An fMRI group comparison of RRMS with and without cerebellar signs using a Paced Auditory Serial Addition Test (PASAT) paradigm revealed only one difference, which was overactivation in the left cerebellum (Crus I) and reduced connectivity between the left Crus I and the right superior parietal lobule (Cerasa et al., 2012).

In unselected MS groups, higher cerebellar leukocortical lesion load has been linked to poorer PASAT performance, whereas poorer SDMT scores have been linked with greater cerebellar intracortical lesion burden (Damasceno et al., 2014), although not always (Valentino et al., 2009). Lesion occurrence in particular within the middle cerebellar peduncles (MCP) may lead to cognitive impairment by damaging important connecting pathways (Tobyne et al., 2017).

Cerebellar volume has been significantly albeit weakly related to both PASAT and SDMT performance (Weier et al., 2014b). Especially posterior lobe damage was shown to be associated with reduced performance in information processing speed tasks (Moroso et al., 2017).

FMRI experiments have utilised a range of cognitive tasks, which have implicated the cerebellum to varying degrees in particular when testing executive function. The go/no-go task increased cerebellar activation for MS patients (Loitfelder et al., 2014), the Stroop test demonstrated increased connectivity between the right inferior frontal gyrus and the right cerebellum in benign MS patients (Rocca et al., 2009), and the Tower of London paradigm increased activation for MS patients in the cerebellum (Lazeron et al., 2004). Information processing speed tasks have also shown cerebellar involvement. The n-back task demonstrated increased cerebellar activation in cognitively impaired primary progressive (PP) MS (Rocca et al., 2010b). The PASAT demonstrated more right cerebellar activation in patients with CIS who were cognitively impaired (Forn et al., 2012) and also in unselected CIS (Audoin et al., 2003).

Interestingly, in a small trial, rivastigmine improved cognitive performance on the verbal PASAT and increased right cerebellar activation (Huolman et al., 2011). Two studies on the effects of cognitive rehabilitation have concordantly highlighted that cognitive rehabilitation promoted cerebellar recruitment during the performance of cognitive tasks (Cerasa et al., 2013a; Sastre-Garriga et al., 2011), thus linking higher cerebellar recruitment with better cognitive performance (Cerasa et al., 2013a).

Although clearly implicated in cognitive function in MS, the precise processing contribution of the cerebellum is not yet elucidated. It has been suggested that the cerebellum's role is to automate subroutines, thus freeing up the anterior areas of the cerebrum to manage novelty and more elaborate planning. For information processing speed tasks, where learning and efficient processing are essential to support optimal performance, the contribution of the cerebellum is clear. However, recently theories of cerebellar function have started to embrace much broader concepts of internal modelling, which incorporate the formidable processing capacity of the

cerebellum and its ability to co-ordinate many different inputs (Ito, 2008). These internal model theories have mainly concentrated on motor processing, but by extension cognitive internal models could also be hypothesised, providing neural representations of the external world (Koziol et al., 2014). This might explain the ubiquitous involvement of the cerebellum in MS dysfunction, including cognitive decline. It might also help increase understanding of why cerebellar pathology has such a wide-ranging negative impact on the lives of MS patients.

Relation of structural and functional abnormalities of the cerebellum with physical disability in MS

Several structural and functional imaging techniques have been applied to investigate the extent of cerebellar involvement in MS patients and its contribution to the clinical manifestations of the disease (see summary in Table 1). While cerebellar T2 hyperintense lesions are frequent, especially in the progressive disease phenotypes (Ormerod et al., 1987), correlation between the extent of these lesions and disability was relatively modest. More recently, cerebellar T2-hyperintense lesions have been associated with recurrent falls in MS patients (Prosperini et al., 2011). Infratentorial T1 hypointense lesions, which represent areas of severe tissue damage and permanent axonal loss, were frequent in MS patients with chronic cerebellar ataxia and correlated with the severity of disability (Hickman et al., 2001). While histopathological studies have revealed more pronounced demyelination in the cortex than the white matter, current in vivo imaging techniques are very limited in their sensitivity towards cortical lesions. Double Inversion Recovery (DIR) and Phase Sensitive Inversion Recovery (PSIR) MRI sequences may help to better identify cortical lesions within the cerebellum (Calabrese et al., 2010; Favaretto et al., 2016), however a clear distinction between purely intracortical, subcortical or mixed lesions is not (yet) possible. Studies revealed moderate to strong correlations between the cortical lesion burden and clinical measures of cerebellar motor and cognitive dysfunction (Calabrese et al., 2010; Damasceno et al., 2014; Favaretto et al., 2016). Cerebellar GM involvement in MS has also been

investigated in terms of T2 hypointensity (Tjoa et al., 2005) (which are likely to reflect increased iron content) of cerebellar nuclei, in particular the dentate nucleus. These signal abnormalities correlated with the severity of clinical disability (Tjoa et al., 2005).

Several authors applied diffusion tensor (DT) MRI and different methods of analysis to investigate the integrity of cerebellar WM connections and its clinical relevance in MS. Microstructural alterations in the cerebellar WM can already be found early in the disease course and even in absence of focal lesions (Deppe et al., 2016). Using DT tractography, abnormalities of the main cerebellar connections have been found in PPMS patients and were significantly associated with worse upper limb function and walking ability (Anderson et al., 2011).

Investigations on the contribution of structural disconnection between the cerebellum and cerebral hemispheres to clinical outcome using measures of global brain and cerebellar injury as well as DT MRI metrics, showed a higher probability of T2 lesions and more severe diffusivity abnormalities in the MCP and superior cerebellar peduncles (SCP) in MS patients with clinical impairment involving ambulation, and the cerebellar and brainstem functional systems (Preziosa et al., 2014) (Figure 2). More importantly, such diffusivity measures of MCP or SCP damage distinguished clinically impaired from unimpaired patients better than volumetric measures of T2 lesions or cerebellar atrophy (Preziosa et al., 2014). In ambulatory MS patients, balance impairment was correlated with worse DT MRI indices along the cerebellar connections and supratentorial associative WM bundles (Prosperini et al., 2013). In a 12-week intervention trial using visual feedback training with a video game balance board system, improved standing balance at static posturography was correlated with modifications of diffusivity parameters of the SCPs. Unfortunately, both clinical and DT MRI changes did not persist beyond 12 weeks after training, suggesting an impaired structural plasticity in these patients (Prosperini et al., 2014).

The role of cerebellar functional plasticity for disease clinical manifestations has been explored using fMRI during both active tasks or at rest. Abnormal activation and functional connectivity of

the cerebellum has been found in adult MS patients compared to matched healthy controls (Rocca et al., 2007; Saini et al., 2004) and pediatric MS patients (Rocca et al., 2010a) during the performance of motor tasks. The correlation found between these fMRI abnormalities and the severity of structural damage of the underlying WM tracts suggests an adaptive role of functional connectivity changes in limiting the clinical consequences of structural damage in these patients (Rocca et al., 2007). Abnormal cerebellar functional connectivity has also been demonstrated in MS using resting state fMRI and has been correlated with more severe clinical disability and ataxia and was influenced by higher lesion volumes (Dogonowski et al., 2014).

First promising approaches on improving cerebellar motor dysfunction in MS have been shown using transcranial magnetic stimulation in two small studies (Elzamarany et al., 2016; Koch et al., 2008).

Cerebellar atrophy in MS

Progressive brain volume loss is a common feature in MS, occurs early in the disease course, reflects damage in the WM and GM, and has been associated with disability (De Stefano et al., 2014; Filippi et al., 2012). For a long time, cerebellar volume loss was not the primary focus of MRI research, partly due to technical challenges concerning correct segmentation of the thin cerebellar gyri, sulci and cerebellar nuclei and extracting the cerebellar tissue from adjacent infratentorial structures. Whilst commonly used automated segmentation tools (e.g. ANIMAL (Collins et al., 1995), FreeSurfer (Fischl et al., 2002), SPM (Ashburner and Friston, 2005) etc.) for volumetric studies have been primarily developed and validated for the whole brain or supratentorial structures, detailed (semi-) automated methods focusing on the cerebellum as a whole or - even more demanding - allowing segmentation of its individual lobules were developed only recently (Diedrichsen et al., 2009; Park et al., 2014; Weier et al., 2012; Weier et al., 2014a). Few cross-sectional studies have addressed the question of cerebellar atrophy in particular and its clinical relevance in MS up to date (see summary in Table 1). Generally speaking, these studies

show a reduction of the total cerebellar volume in MS patients when compared to healthy controls, more pronounced in the progressive disease forms (Anderson et al., 2009; Davie et al., 1995; Ramasamy et al., 2009; Weier et al., 2012). However, study results are heterogeneous regarding the distribution of the disease burden in cerebellar WM and GM, the different disease courses and in terms of the associated clinical impact of such volume loss. In CIS patients, cerebellar GM volume loss was evident only in one small cohort investigated by Calabrese and colleagues (Calabrese et al., 2010), whereas other groups did not find significant GM volume differences in the cerebellum of CIS and HC (Anderson et al., 2009; Henry et al., 2008). However, Ramasany and colleagues found reduced WM volumes in a cohort of CIS and MS patients (Ramasamy et al., 2009). Comparing patients with benign MS to patients with secondary progressive MS, the cerebellum was the only region showing a reduction of GM in the progressive patients (Mesaros et al., 2008). Anderson and colleagues also found a reduced cerebellar GM volume in SPMS patients when compared to HC and a borderline GM volume reduction in the cerebellum of RRMS patients (Anderson et al., 2009). A reduction of cerebellar white matter volume was only seen in progressive patients. Only cerebellar GM volume was a significant predictor of cerebellar dysfunction, which led the authors to conclude that cerebellar GM atrophy may be related to progressive disability. In contrast, clinical dysfunction during the relapsing-remitting phase rather relates to the accumulation of focal white matter damage within the brain and spinal cord.

Interpretation of these studies must be cautious, because the distinction of “pure” GM and WM in the thin cerebellar foliae is particularly challenging with existing methodologies. Further, cerebellar volume loss in RRMS patients may be more subtle and therefore not be detectable with global segmentation techniques (Figure 3).

Correlations of cerebellar volume with clinical measures such as the EDSS are at best moderate (Calabrese et al., 2010) or not significant (Davie et al., 1995; Mesaros et al., 2008; Ramasamy et al., 2009; Weier et al., 2012). More specific tests - such as the depth-sensing video recordings

with machine learning methods discussed above - may in the future better reflect cerebellar function than global clinical assessments such as the EDSS. This may help to give a clearer picture of the clinical impact of cerebellar damage. Indeed studies using fine motor skills (Anderson et al., 2009; Henry et al., 2008) or cognitive-behavioural dysfunction (Weier et al., 2014b; Weier et al., 2016b) as major outcome measures showed a more robust correlation with cerebellar atrophy.

The application of novel automatic cerebellar segmentation techniques allows lobe- or even lobule-wise determination of volumes and their disease-related changes (Weier et al., 2014a). In a prospective cohort of pediatric patients with monophasic acquired demyelinating syndromes and pediatric-onset MS, a failure of age-expected growth of the cerebellum, in particular of the posterior lobe was found when comparing their cerebellar growth trajectory to healthy children (Weier et al., 2016a). Another matched-control study on pediatric-onset MS patients revealed that smaller cerebellar posterior lobe volume adversely impacts cognitive function, in particular measures for information processing speed and vocabulary (Weier et al., 2016b), underlining the role of cerebellar pathology also in pediatric-onset MS patients. Similar results were found in a study on adult relapse-onset MS patients (D'Ambrosio et al., 2016).

Cerebellar volumes were further analysed with respect to possible secondary degeneration of the spino-cerebellar tract after inflammatory spinal cord pathology in patients with neuromyelitis optica (NMO; an important differential diagnosis to MS) and compared to matched patients with RRMS and healthy controls (Weier et al., 2015). While atrophy seemed to be diffuse in MS patients involving both supratentorial and infratentorial structures (but less so the upper cervical cord), NMO patients presented with a rather localized pattern with predominant involvement of the upper cervical cord, but normal total cerebellar volume.

Conclusions and future directions

This review of the increasing number of basic science, neuropathology and imaging studies clearly emphasizes the cerebellum as a prevalent site of MS disease pathology. The high connectivity between the cerebellum and other CNS regions makes it difficult to be precise about its role in clinical disability and its correlation to pathology, especially in the early phases of the disease. Novel automated depth-sensing computer vision techniques combined with machine learning algorithms may overcome current limitations regarding the reliable clinical assessment of cerebellar dysfunction. First promising results show how cerebellar dysfunction may be successfully treated in the future. Further advances in imaging, e.g. higher field strength combined with multimodal approaches including advanced functional and structural imaging, will help to further improve our understanding of the functional consequences of cerebellar pathology. Reliable and accurate methods are needed to characterize disease dynamics in longitudinal studies and larger patient cohorts to support and extend the results from cross-sectional studies.

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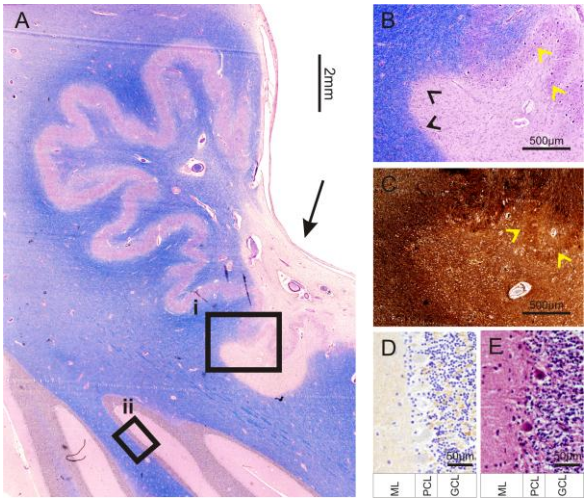
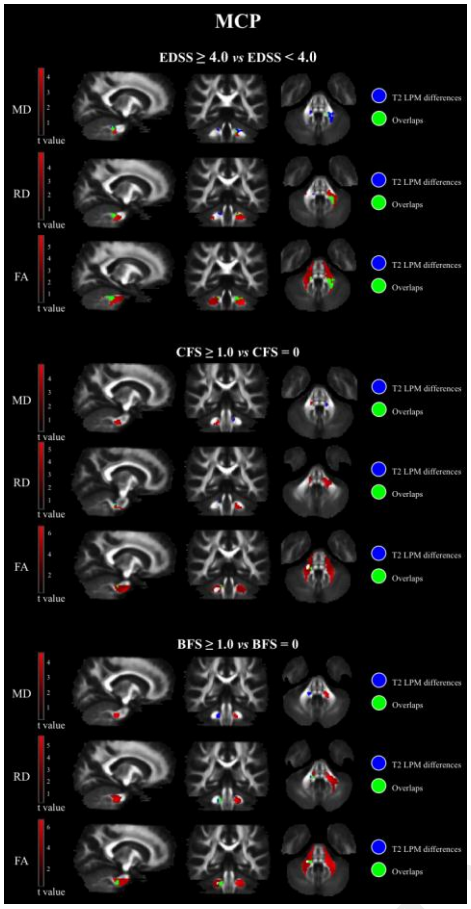
Figure Captions:

Figure 1: *Cerebellar histopathology of MS.*



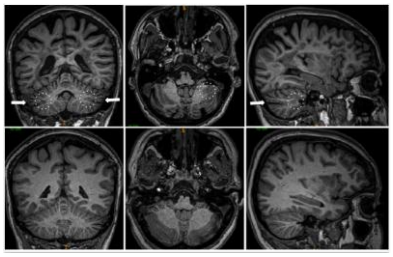
Microphotographs of the dentate nucleus and cerebellar cortex obtained from autopsy material of an MS patient. Demyelinating lesions can be clearly visualized using the Luxol Fast Blue – Periodic acid-Schiff staining (A, *arrow*; B) and often localize to the deep cerebellar nuclei (Ai). Similar to other brain regions, the lesions present clearly delineated borders (B, *black arrowheads*) and a reduction in the axonal density, which becomes apparent in the Bielschowsky silver impregnation (C). Note that the structure of the dentate nucleus is largely preserved (B-C, *yellow arrowheads*). D. Synaptophysin immunhistochemistry of the cerebellar cortex (from the region marked as Aii). Previous studies[3] detected no differences in the density of immunoreactivity between demyelinated and normal areas of the granular cell layer (GCL) in MS. E. Hematoxylin-eosin staining showing Purkinje cells. A reduction in the Purkinje cell density was associated with cerebellar cortical lesions in MS [3,6]. PCL: Purkinje cell layer. ML: Molecular layer.

Figure 2: *Cerebellar pathways damage and clinical disability.*



SPM analysis (red color-coded for t values; p <0.05, corrected for multiple comparisons) of clusters with increased mean diffusivity (MD) and radial diffusivity (RD), reduced FA and increased probability of having T2 lesions (blue) in the middle cerebellar peduncle (MCP) of multiple sclerosis (MS) patients according to the different subgroup dichotomization. Upper rows: patients with Expanded Disability Status Scale (EDSS) score ≥ 4.0 *vs* patients with EDSS < 4.0. Middle rows: patients with cerebellar functional system (CFS) ≥ 1 *vs* patients with CFS=0. Bottom rows: patients with brainstem functional system (BFS) ≥ 1 *vs* patients with BFS=0. Overlap between T2 lesion probability maps and abnormalities of DT MRI indices are also shown in green. Images are in neurological convention. From Preziosa et al. 2014 with permission.

Figure 3: *Macroscopic cerebellar pathology in MS*



T1-weighted images (3D MPRAGE) of a 31 y/o woman with RRMS (upper row) presenting only with mild cerebellar disability (cerebellar FSS 1) after 9 years disease duration and a sex- and age-matched healthy control are displayed in coronal, axial and sagittal view (left to right). Lesional pathology (dashed circle) and macroscopic detectable global volume loss can easily be seen. Cerebellar volume reduction is present with focus of the superior posterior lobe (VI and Crus I; arrows).

Table 1: Studies analysing associations between cerebellar functions and MRI metrics in patients with multiple sclerosis (chronological order).

Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Davie et al. 1995	Cross-sectional	Controls = 11 RRMS "cerebellar impaired" = 11 RRMS "cerebellar non-impaired" =11 (ADCA = 8)	Cerebellar GM and WM volume NA spectroscopy in cerebellar ROI	EDSS Kurtzke functional cerebellar scale	Moderate negative rank correlation of NA-level and EDSS and cFSS in all RRMS	Reduced NA-levels in the cerebellar ROI of impaired RRMS vs non-impaired RRMS RRMS with severe cerebellar dysfunction ("impaired") demonstrated significant reduction of median cerebellar volume and greater posterior fossa LV Positive correlation between NA-level and cerebellar volume
Hickman et al. 2001	Cross-sectional	RRMS = 2 SPMS = 7	Whole brain T2- and T1-LV Infratentorial T2- and T1-LV No. of infratentorial T1-hypointense lesions	EDSS Cerebellar FSS	Moderate positive correlation between EDSS and no. of infratentorial T1 hypointense lesions per patient Strong positive correlation between EDSS and infratentorial T1 LV per patient	No correlation between EDSS and whole brain T1- or T2-LV, or infratentorial T2-LV
Saini et al. 2004	Cross-sectional	Controls = 11 RRMS = 14	Functional connectivity analysis of primary motor cortex; premotor cortex, Crus I and dentate nucleus Whole brain T2-LV Normalized brain volume	EDSS Simple fMRI motor task	No correlation between lateralisation index or regional signal change and EDSS, brain volumes or LV	No "crossed" connectivity between left primary motor cortex and right cerebellar dentate nucleus in patients, but in HC Ipsilateral connectivity between left premotor neocortex and left cerebellar cortex (Crus I) in patients, but not in HC

(Table continues on next page)

Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Continued from previous page						
Tjoa et al. 2005	Cross-sectional	Controls = 15 RRMS = 47 SPMS = 6	Whole brain T2- and T1-LV Whole brain volume (BPF) Subcortical grey matter T2-hypointensity measurements (incl. dentate nucleus)	EDSS 25-FWT	Weak negative correlation between dentate T2-hypointensity and 25-FWT Dentate T2-hypointensity was best MRI correlate of physical disability (EDSS)	T2-hypointensity present throughout subcortical GM in MS vs controls
Measaros et al. 2008	Cross-sectional	Controls = 21 BMS = 60 SPMS = 35	Voxel-based regional GM differences	Neuropsychological tests for: attention and information processing speed, verbal and visual-spatial memory, executive functions, and spatial cognition EDSS	No correlation between EDSS and regional GM atrophy in any group	Significant cerebellar GM loss in SPMS vs BMS was the only distinctive measure; subgroup analysis: results consistent only in a subgroup of non cognitive impaired BMS patients and BMS patients with disease duration >20yrs and EDSS <2.0 No significant WM reduction between groups
Anderson et al. 2009	Cross-sectional	Controls = 25 CIS = 29 RRMS = 33 SPMS = 11	Cerebellar GM and WM volume	EDSS Cerebellar FSS 9-HPT 25-FWT	Cerebellar GM volume: reduced in patients with cerebellar dysfunction (cFSS>0); only significant predictor of cerebellar dysfunction; correlation between 9-HPT and cerebellar GM volume Cerebellar WM volume: borderline reduction in patients with cerebellar dysfunction (cFSS>0)	Cerebellar GM volume: significant reduced in SPMS vs HC; borderline reduced in RRMS vs HC and CIS Cerebellar WM volume: reduced only in SPMS vs HC

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Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Continued from previous page						
Calabrese et al. 2009	Cross-sectional	Controls = 32 CIS = 38 RRMS = 35 SPMS = 27 PPMS = 25	Cerebellar GM and WM volume Cerebellar leukocortical LV Brainstem and cerebellar T2-LV Whole brain cortical GM volume	EDSS Cerebellar FSS	Correlation of cerebellar GM volume and cerebellar cortical LV with clinical disability (cFSS, EDSS)	Evidence of cerebellar GM atrophy and cortical LV in all MS group Weak correlation between cerebellar GM volume and T2-LV Absence of cerebellar WM atrophy in CIS and RRMS patients
Valentino et al. 2009	Cross-sectional	RRMS "cerebellar non-impaired" = 21 RRMS "cerebellar impaired" = 21	Regional T2-LV	Neuropsychological testing for: verbal memory, spatial memory, visuo-spatial skills, sustained attention and processing speed, abstract/conceptual reasoning verbal fluency	No significant between-goup-difference of LV in any brain region no correlation between regional LV and tasks assessing processing speed/attention and language	significant between-group difference on tasks assessing processing speed/attention and language
Rocca et al. 2010	Cross-sectional	Controls = 17 PPMS = 16	Cognitive task based fMRI activity Whole brain T2 LV Normalized brain volume Corpus callosal area	EDSS Maximum finger tapping frequency Neuropsychological testing for: memory, attention and frontal lobe cognitive domains	Increased activity of cerebellum, secondary sensorimotor cortex, and insula in cognitive impaired compared to non-impaired patients and HC Correlation of decreased composite cognitive score with increased activity of cerebellum, insula and secondary sensorimotor cortex in cognitive impaired PPMS	No difference in structural MRI metrics between cognitive impaired and non-impaired patients

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Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
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Rocca et al. 2010	Cross-sectional	Pediatric controls = 10 Pediatric RRMS = 17 Adult CIS = 16 Adult RRMS = 14	Simple motor task based fMRI activity Connectivity analysis between brain regions involved in motor task Whole brain and regional T2-LV DTI measures (FA, MD) of corpus callosum and corticospinal tract	EDSS 9-HPT Maximum finger tapping frequency	Increased intra- and interhemispheric strengths of coefficients of effective connectivity in adult CIS and RRMS Correlation of coefficients of effective connectivity with callosal and corticospinal tract damage, T2-LV and DTI metrics	Coefficients of effective connectivity of the sensorimotor network were similar in pediatric RRMS and HC
Anderson et al. 2011	Cross-sectional	Controls = 16 RRMS = 14 PPMS = 12	Cerebellar GM and WM volume DTI measures (FA, MD, AD and RD) from the SCP and MCP	EDSS Cerebellar FSS 9-HPT 25-FWT	Cerebellar WM volume was associated with worse performance on upper limb tasks in PPMS Significant associations between SCP FA and upper limb function and SCP FA, MD and RD and walking ability in PPMS	FA in MCP of PPMS reduced when compared to HC and RRMS No difference in any MRI measure between RRMS and HC Extent of cerebellar WM damage was independent from GM damage in both groups of patients
Prosperini et al. 2011	Cross-sectional	RRMS = 21 SPMS = 10	Whole brain T2- and T1-LV ROI analysis of supra- and infratentorial LV	EDSS Static posturography Self-report of falling within past 6 months ("fallers" vs "non-fallers")	"Fallers" had higher EDSS, poorer static balance and greater T2-LV at brainstem and MCP level than "non-fallers" Positive correlation between brainstem T2-LV and impaired static standing balance in open eye condition Association of greater MCP and brainstem T2-LV and wider displacement of body center of pressure in closed eye condition with recurrent falls	No difference between "fallers" vs "non-fallers" with respect to whole brain T1- and T2-LV, supratentorial LV and LV of paleo- and neocerebellum

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Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Continued from previous page						
Sastre-Garriga et al. 2011	Longitudinal (10 weeks period)	Controls = 5 RRMS = 15	Cognitive task based fMRI activity at baseline, pre and post rehabilitation Whole brain T2- and T1-LV	Cognitive fMRI task: PASAT Neuropsychological tests: TMT, SDMT and Digit Span EDSS	Detection of increased fMRI activity after rehabilitation in two regions of the right cerebellar hemisphere of cognitive impaired RRMS No correlation between cognitive improvement and regional activity increases	
Cerasa et al. 2012	Cross-sectional	Controls = 16 RRMS "cerebellar impaired" = 12 RRMS "cerebellar non-impaired" = 15	Functional connectivity between cerebellar ROI and other brain regions Supratentorial and cerebellar T2-LV Supratentorial and total cerebellar volume Intracranial volume	Neuropsychological testing for: visuo-spatial skills, executive function, information processing speed and attention, verbal learning, working memory, and verbal fluency Cognitive fMRI task: PVSAT	Greater cerebellar LV in "impaired" vs "non-impaired" patients Lower performance of "impaired" vs " non-impaired" patients in attention/working memory performance, abstract reasoning and verbal fluency task Activation of cerebellar Crus I/Lobule VI in "impaired" patients during PVSAT task Detection of altered connectivity between Crus I and superior parietal lobule in "impaired" patients	No correlation between supratentorial or cerebellar LV and cognitive outcome measures in either group
Weier et al. 2012	Cross-sectional	Controls = 15 RRMS = 15 MS = 15	Cerebellar GM and WM volume Whole brain volume Cerebral and cerebellar lesion load	EDSS Cerebellar FSS	No correlation between EDSS /cerebellar FSS and normalized TCV	Volume reduction of NBV and normalized TCV in MS vs HC
Cerasa et al. 2013	Longitudinal (6 week period)	"Experimental group" MS = 12 "Control group" MS = 11	Cognitive task based fMRI activity Whole brain T2-LV	Cognitive fMRI task: PVSAT FSS MMSE	Association of increased abilities in attention task with increased activity in posterior cerebellar lobe	

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Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Continued from previous page						
Prosperini et al. 2013	Cross-sectional	Controls = 25 RRMS = 48	Whole brain, supra- and infratentorial T2- and T1-LV Whole brain GM and WM volume DTI measures (FA, MD, AD, RD) Voxel-based regional GM differences	EDSS Static posturography	Correlation of severity of balance impairment in MS with worse DTI parameters along cerebellar connections and supratentorial associative WM bundles and with GM atrophy of anterior lobules and lobule VIII of the cerebellum	MS patients had worse postural stability, widespread alterations in most WM bundles, and GM atrophy in several brain regions
Damasceno et al. 2014	Cross-sectional	Controls = 30 RRMS = 42	Cerebellar WM and cortical (intra- and leukocortical) LV Whole brain WM and cortical LV Cerebellar WM and cortical volume Whole brain WM and cortical volume	EDSS / cerebellar FSS 9-HPT 25-FWT SDMT, PASAT	High burden of cerebellar intracortical LV is only predictor for EDSS, cerebellar FSS and arm / leg function Patients with high cerebellar intracortical LV showed higher EDSS and cerebellar FSS, worse performance in 9-HPT, 25-FWT and SDMT Correlation of high cerebellar leukocortical LV with lower PASAT scores	High cerebellar leukocortical LV is only predictor of cerebellar WM volume
Dogonowski et al. 2014	Cross-sectional	Controls = 30 RRMS = 27 SPMS = 15	Resting-state regional functional connectivity analysis (= homogeneity of BOLD-signal fluctuations) Whole brain T2-LV T2-LV in cerebellar peduncles	EDSS Ataxia score of Multiple Sclerosis Impairment Scale	Regional homogeneity decrease in upper left cerebellar hemisphere (lobules V and VI) of MS vs controls Correlation of higher EDSS / ataxia scores and reduced homogeneity in left posterior cerebellum (Crus I, Crus II and dentate nucleus)	Patients with higher LV showed stronger reduction in cerebellar homogeneity

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Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Continued from previous page						
Prosperini et al. 2014	Longitudinal (12 weeks period)	Controls = 15 RRMS = 27 SPMS = 3	Whole brain T2-LV Whole brain GM and WM volume Change of DTI measures (FA, MD, AD, RD) Voxel-based regional GM changes	EDSS Static posturography	Relevant differences between patients and HC in postural sway and DTI parameters Correlation of changes in DTI metrics (FA and RD of SCP bilateral) with balance improvement, however not persistent beyond 12 weeks training period	
Weier et al. 2014	Cross-sectional	MS "cerebellar non- impaired" = 52 MS "cerebellar impaired" = 120	Cerebellar GM and WM volume Whole brain volume Whole brain and cerebellar LV	EDSS / cerebellar FSS 9-HPT Neuropsychological testing (SDMT, PASAT) fatigue testing (FSMC)	Patients with cerebellar dysfunction ("impaired") had lower TCV, NBV, and higher whole brain LV and showed worse performance in SDMT and PASAT Cerebellar metrics explain partial variance of SDMT and PASAT performance	None of the cerebellar metrics contribute to variance in FSMC
Weier et al. 2015	Cross-sectional	Controls = 35 RRMS = 25 NMO = 30	Cerebellar GM and WM volume Whole brain volume Whole brain and cerebellar LV Upper cervical cord volume	EDSS / cerebellar FSS 9-HPT 25-FWT	Association of higher cerebellar LV with worse EDSS and 9-HPT performance in MS patients	Focal atrophy pattern in NMO (upper cervical cord) Diffuse atrophy pattern in MS (incl. cerebellum and whole brain, but not UCV)
Deppe et al. 2016	Cross-sectional	Controls = 26 "early" RRMS = 23 "late" RRMS = 45	Cerebellar GM and WM volume Whole brain GM and WM volume Whole brain LV DTI measures (FA, MD, AD, RD)	EDSS	FA reduction in absence of lesions Correlation of cerebellar FA reduction with EDSS, DD, and reduction in WMV-GMV ratio	

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Author/year	Type of study	No. of subjects per study group	MRI outcome measures	Clinical assessment	Clinico-radiological correlations (main findings)	Additional findings
Continued from previous page						
Favaretto et al. 2016	Cross-sectional	CIS = 10 RRMS = 24 SPMS = 6	cerebellar cortical and WM lesions	EDSS / cerebellar FSS	Correlation of cortical lesions with EDSS and DD	PSIR improves cortcal lesion detection
Weier et al. 2016	Cross-sectional	pediatric cohort Controls = 33 RRMS = 28	Cerebellar regional GM and WM volume Whole brain volume Whole brain and cerebellar LV	EDSS Comprehensive Neuropsychological testing	Cerebellar posterior lobe volume and infratentorial LV accounted for extra variance on measures of information processing and vocabulary	Reduced cognitive and motor performance in patients
Weier et al. 2016	Longitudinal (3.1 yrs)	pediatric cohort monoADS = 56 ADEM = 20 MS = 22 controls = 418	Cerebellar GM and WM volume growth trajectories Whole brain and cerebellar LV	EDSS / cerebellar FSS	No correlation with physical disability	All patient groups failed to reach age-expected cerebellar growth trajectories Reduced cerebellar volumes most notably in the posterior lobes Cerebellar and cerebral volume reduction similar magnitude No decline of cerebellar WM volume in monoADS patients
D'Ambrosio et al. 2016	cross-sectional	Controls = 32 RRMS = 52 benign MS = 20 SPMS = 23	Cerebellar regional GM and WM volume Whole brain volume Whole brain and cerebellar LV	EDSS 9-HPT PASAT SDMT	T2 LV and anterior cerebellar volume as independent predictors of EDSS Anterior cerebellar volume as independent predictor of 9-HPT T2 LV and posterior cerebellar volume as independent predictors of SDMT score and PASAT	
Moroso et al. 2017	Cross-sectional	CIS = 37 RRMS = 32 HC = 36	Cerebellar regional GM and WM volume Whole brain volume Whole brain and cerebellar LV	EDSS / cerebellar FSS Comprehensive Neuropsychological testing	Reduction of cerebellar posterior lobules volume (esp. vermis) was associated with reduced measures of information processing	Significant volume reduction of bilateral lobule VI, left crus I, right VIIb and TCV in patients vs HC
Tobyne et al. 2017	Cross-sectional	MS "cognitive non- impaired" = 16 MS "cognitive preserved" = 15	Cerebellar lesion location Cerebellar GM and WM volume Whole brain GM and WM volume	EDSS Comprehensive Neuropsychological testing	No correlation of cerebellar lesion load with EDSS Correlation of hemispheric lesion load with EDSS	predilection of middle cerebellar peduncle lesion occurence in cognitive impaired MS

Abbreviations (alphabetical order):

ADCA = autosomal dominant cerebellar ataxia; AD = axial diffusivity; ADEM = acute disseminated encephalomyelitis; BMS = benign MS; BPF = brain parynchemal fraction; BRB-N = Brief Repeatable Battery of Neuropsychological Tests; BVC = brain volume change; CIS = clinically isolated syndrome; cFSS = cerebellar Functional System Scale; DTI = diffusion tensor imaging; EDSS = Expanded Disability Status Scale; FA = fractional anisotropy; fMRI = functional magnetic resonance imaging; FSS = Fatigue Severity Scale; 25-FWT = timed 25 foot walk test; GM = grey matter; 9-HPT = 9 hole peg test; HC = healthy controls; LV = lesion volumes; MCP = middle cerebellar peduncle; MD = mean diffusivity; MMSE = Mini Mental Status Exam; monoADS = monophasic acute demyelinating syndrome; MS = multiple sclerosis; NA = N-acetyl group; NBV = normalized brain volume; PASAT = Paced Auditory Serial Addition Test; PVSAT = Paced Visual Serial Addition Test; PPMS = primary progressive MS; RD = radial diffusivity; RRMS = relapsing-remitting MS; ROI = region of interest; SCP = superior cerebellar peduncle; SDMT = Symbol Digit Modality Test; SPMS = secondary progressive MS; TCV = total cerebellar volume; TMT = Trail Making Test; UCV = upper cervical cord volume; vs = versus; WM = white matter; WCST = Wisconsin Card sorting Test.