

## Cerebellum and neurodegenerative diseases: Beyond conventional magnetic resonance imaging

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### Abstract

The cerebellum plays a key role in movement control and in cognition and cerebellar involvement is described in several neurodegenerative diseases. While conventional magnetic resonance imaging (MRI) is widely used for brain and cerebellar morphologic evaluation, advanced MRI techniques allow the investigation of cerebellar microstructural and functional characteristics. Volumetry, voxel-based morphometry, diffusion MRI based fiber tractography, resting state and task related functional MRI, perfusion, and proton MR spectroscopy are among the most common techniques applied to the study of cerebellum. In the present review, after providing a brief description of each technique's advantages and limitations, we focus on their application to the study of cerebellar injury in major neurodegenerative diseases, such as multiple sclerosis, Parkinson's and Alzheimer's disease and hereditary ataxia. A brief introduction to the pathological substrate of cerebellar involvement is provided for each disease, followed by the review of MRI studies exploring structural and functional cerebellar abnormalities and by a discussion of the clinical relevance of MRI measures of cerebellar damage in terms of both clinical status and cognitive performance.

**Key words:** Cerebellum; Neurodegenerative disease; Ataxia; Multiple sclerosis; Parkinson's disease; Diffusion magnetic resonance imaging; Tractography; Volumetry; Functional magnetic resonance imaging; Alzheimer's disease

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**Core tip:** The cerebellum is involved in movement control and cognition. Conventional and advanced magnetic resonance imaging (MRI) techniques are widely used for the morphologic evaluation and the microstructural and functional investigation of the cerebellum. In this review we show the state of the art of advanced MRI techniques in the investigation of cerebellum alterations, especially in patients affected by neurodegenerative diseases. In particular, we evaluated advantages, limitations and future perspective of these techniques in multiple sclerosis, Parkinson's disease and Parkinsonisms, Alzheimer's disease and hereditary ataxia, highlighting how the investigation of cerebellum may play a key role in the assessment of motor performance and clinical status of these diseases.

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## INTRODUCTION

The cerebellum plays a key role in normal brain function and its structural and functional involvement in several neurological diseases is associated with the impairment of both motor and non-motor functions such as cognition, mood and behavior. Imaging studies have been challenged in the past by the complex cerebellar anatomical structure and by its location in the posterior fossa. The advent of high-field magnets and the development of new algorithms for image acquisition and analysis have, at least in part, improved the study of cerebellar structure and functions. This review provides a brief description of cerebellar macro- and microscopic anatomy and functions and focuses on the imaging methods and segmentation tools for the analysis of the cerebellum with emphasis on each method's advantages and limitations. Further, the clinical implications of the cerebellar involvement in neurological diseases such as multiple sclerosis, hereditary ataxias, Parkinson's and Alzheimer's disease are discussed.

### **Anatomy and function**

The cerebellum is a large folded structure consisting of two cerebellar hemispheres, united by a central part known as vermis located in the posterior cranial fossa, lying dorsal to the brainstem and inferior occipital lobes.

It is separated from the cerebrum by a dura mater layer known as tentorium cerebelli and it is surrounded postero-laterally and infero-medially by venous structures, respectively transverse and sigmoid sinuses. The cerebellar cortex is tightly folded and composed by three layers: Molecular layer, Purkinje cell layer and granular layer. Each ridge or gyrus of gray matter is called folium. Underneath these layer of gray matter there is a central mass of white matter, also called corpus midollare or arbor vitae (tree of life), in which are embedded the three deep gray matter cerebellar nuclei: Fastigial nucleus, interposed nucleus (composed by the emboliform and globose nuclei) and dentate nucleus. Three white matter peduncles (superior, middle and inferior) connect the cerebellum to the brainstem, respectively to the midbrain, pons and medulla oblongata. In addition to the above reported macro- and microscopic description, cerebellar structure can be further characterized from a morphologic, phylogenetic and functional perspective. The morphologic classification describes, without any functional basis, a division into three lobes: Anterior, posterior and flocculonodular lobe, while the phylogenetic classification divides the cerebellum into archicerebellum (the most ancient portion), paleocerebellum (developed after archicerebellum) and neocerebellum (the newest portion). The functional classification divides the cerebellum in three regions: Vestibulocerebellum, spinocerebellum and cerebrocerebellum based on the location of the afferent and efferent neurons<sup>[1,2]</sup>. The vestibulocerebellum corresponds to the flocculonodular lobe, with afferents neurons arising from vestibular nuclei (and some portion of visual cortex) and efferents neurons going to vestibular nuclei. It modulates gait balance and eye movements. The spinocerebellum is formed by the superior and inferior portion of the vermis (with the exception of the nodule) and by a bilateral paravermian portion, located on both sides of the vermis. The vermian part of the spinocerebellum has its afferent neurons arising from the spinal cord, vestibular, visual and acoustic nuclei and has its efferents neurons going through the fastigial nucleus. It modulates head and neck muscle movement as well as trunk and limb proximal portions. The paravermian part of the spinocerebellum has its afferents neurons arising from the spinal cord and trigeminal sensory nuclei, and its efferents neurons going through the interposed nucleus. It completes movement modulation performed by the vermian part, acting on limb distal portions. The cerebrocerebellum is composed by the two cerebellar hemispheres and receives afferent neurons from most of the neocortex (frontal, parietal, temporal, and occipital lobes) through the pons nuclei, sending its efferent neurons to thalamus and cerebral cortex through the dentate nucleus. Functional specificity is granted by the presence of multiple close-loop circuits between cerebral and cerebellar cortex, in which the same brain area that is the major target of output from the cerebro-cerebellar circuit it is also its major source of input<sup>[3,4]</sup>. In each loop, a specific cortical area projects through the pontine nuclei to a distinct region

of the cerebellar cortex. A specific portion of the dentate nucleus projects then to a specific cortical area through a distinct thalamic region, thus closing the cerebro-cerebellar loop<sup>[5,6]</sup>. According to studies conducted on primates, the dentate nucleus is topographically organized in a ventral portion, projecting to the prefrontal and posterior parietal cortex, and a dorsal portion, projecting to the motor cortex<sup>[7]</sup>. Both motor and non-motor domains of the dentate also project to the striatum (input stage of basal ganglia processing), raising the hypothesis that cerebellum could also modulate basal ganglia facilitation of voluntary movements<sup>[8]</sup>. The cerebrocerebellum is the largest part of the cerebellum and accounts for motor planning and motor learning. It is responsible for the transition from controlled to automatic movement: Once motor memories storage has been achieved in the cerebellar cortex, the execution of movements can be triggered by sparse high-level command from cerebral cortex<sup>[9]</sup>. The ability of the cerebellum to adjust performance according to context, automatically integrating interoception with perception and internal models, does not apply only to movements controls but also to cognitive function, as proved by the occurrence of the cerebellar cognitive-affective syndrome following acute cerebellar lesions of the posterior lobe<sup>[10]</sup>. In particular, lesions of the posterolateral hemispheres cause cognitive disturbances, while vermis lesions induce behavioral and affective alterations. Cerebrocerebellum is considered an essential modulator of cognitive abilities, such as language processing and visuospatial perception (respectively lateralized in the right and left cerebellar hemisphere), as well as high order functions as emotions, behaviors and personality. For example, thanks to its connection to the prefrontal cortex, the cerebellum is involved in the execution of abstract rules that govern response selection, regardless of whether they specifically relate to the selection of actions<sup>[11,12]</sup>.

### **MRI of the posterior cranial fossa**

The posterior cranial fossa (PCF) is located between the tentorium cerebelli and foramen magnum and houses the cerebellum and the brainstem. For its peculiar conformation, small dimensions and contained structures, an accurate study by means of computed tomography (CT) and MRI had always represented a great challenge<sup>[13-15]</sup>. However, several progresses have been made in this field to avoid the artifacts related to the X-ray beam hardening and the partial volume effects (which is non-linear) caused by the thickness and the irregularity of the skull-base bones. Specifically, the introduction of thin-section spiral multidetector CT, which allows the acquisition of isotropic voxel scans and the use of MRI scanners which allow the acquisition of multiplanar and multiparametric images have contributed to minimize PCF artifacts<sup>[16-23]</sup>. Most of PCF artifacts are related to blood flow pulsation, inflow/outflow of cerebro-spinal fluid (CSF) and to the brain-bone-air interfaces<sup>[24-30]</sup>.

Artifacts related to vessels blood pulsation generate a signal that is displaced from its correct anatomical

position causing a wrong/inappropriate image, also called "ghost" artifacts<sup>[31]</sup>. Transverse sinuses blood-flow related artifact, which often generate a false image projecting onto cerebellar parenchyma, may lead to an inaccurate or inappropriate interpretation of MR images. Artifacts related to the inflow and outflow of CSF inside PCF from the superior or inferior regions can be minimized by the use of fluid attenuated inversion recovery (FLAIR) images where the CSF signal is nulled out by setting a proper inversion pulse. Unfortunately, these artifacts can still be present if the inversion pulse is spatially selective, allowing a partial suppression<sup>[30,32]</sup>. As shown by Baksi *et al.*<sup>[30]</sup> and Lavdas *et al.*<sup>[33]</sup> this type of artifact may mimic or hide a brain parenchymal lesion due to the presence, along with the phase encoding direction, of a redundant CSF signal.

The brain-bone-air interfaces artifact represents one of the magnetic susceptibility artifacts that are often present on gradient-echo sequences<sup>[28]</sup>, especially in regions like the skull base, petrous temporal bone, paranasal sinuses and orbits<sup>[34,35]</sup>.

It should be noted that some MRI sequences are more prone to specific artifacts than others: *i.e.*, gradient-echo for susceptibility artifacts (since this sequence does not use a refocusing 180° pulse and signal dephases fast due to field inhomogeneity), inversion recovery (*e.g.*, short tau inversion recovery and FLAIR) for pulsatile artifacts, or 2D time-of-flight for slow-flow artefactual gaps in non-dominant transverse sinus<sup>[13,30,33,36]</sup>. Nonetheless, some of these artifacts are routinely exploited for diagnostic purposes: Susceptibility weighted images (and in general T2\*w gradient-echo images) thanks to its capability of being susceptible to paramagnetic molecules, is able to recognize small amounts of blood degradation products better than other sequences and to distinguish between parenchymal calcifications and blood products<sup>[37]</sup>.

Although the combined use of MRI and CT is recommended for the diagnosis of PCF pathologies, MR is preferred to CT in order to evaluate soft tissue structures and to determinate their spatial relationship. While MRI provides higher accuracy in detecting bone marrow changes, brain parenchyma, meningeal infiltration, perineural and perivascular spread caused by tumors<sup>[14,38,39]</sup>, CT is more sensitive for the evaluation of bone structures, PFC tumoral and non-tumoral conditions<sup>[14,40]</sup>.

### **High and ultra-high field MRI**

The possibility to study the brain at high and ultra-high field strength has become quite common after the United States FDA approval of MR magnets up to 4 Tesla (T) for clinical use. Currently, the term ultra-high field is used for MR scanners with a magnetic field strength higher than 3T. The application of high and ultra-high static magnetic field strength can improve the visualization of brain anatomy and the study of changes in brain structure and function in several neuropsychiatric diseases. For example, the higher signal-to-noise ratio (SNR) of 3T scanners allows not only to perform faster imaging compared to 1.5T scanners (doubling the strength of the

magnetic field would theoretically lead to a reduction of acquisition time of a factor of four), but also to acquire images at higher spatial resolution, that turns be very useful in the evaluation of small structures such as the cerebellum and the brainstem. It has been shown that higher spatial resolution is helpful in studying the cerebellar cortex, whose thickness is lower than cerebral thickness (< 0.5 mm vs the 3-4 mm, respectively)<sup>[41,42]</sup>.

In the research field, 7T MR scanners have proven to be of great use for the identification and the study of each cerebellar folia (which are approximately 260)<sup>[43]</sup> and for the study of cerebellar cortical layers. Specifically, the granular and molecular cerebellar layers, whose thickness is approximately 240  $\mu\text{m}$ , are well recognized and morphologically studied at 7T which has the unique advantage to allow an in-plane voxel size of 120  $\mu\text{m}$  not possible at low-field MR scanners<sup>[44]</sup>. It is important to bear in mind that higher magnetic fields bring the inherit heavy burden of several artifacts and limitations. For instance chemical shift imaging and susceptibility artifacts, are only some of the artifacts that will increase with high magnetic field. These phenomena, which may cause images misinterpretation, can also be exploited, leading for example to a better separation of metabolites in spectroscopy, a better performance in perfusion weighted imaging, or a better blood products detection. Further, when using high and ultra-high magnetic fields in humans, the specific absorption rate (SAR) should also be carefully evaluated, since it will be quadruplicate with the doubling of the field strength, limiting the use of some sequences and making some parameter modulation necessary in order not to exceed the SAR threshold limit given by International Electrotechnical Commission<sup>[45]</sup>.

### **MRI techniques available for the study of cerebellum**

#### **Conventional morphologic techniques**

The remarkable wide range of MR sequences available for the study of the PCF and the cerebellum comes with the difficulty of making the optimal selection based on the clinical or research question. In a standard clinical study the MRI protocol should include a turbo spin-echo (TSE) T1weighted (T1w) sequence to assess shape and dimension of the cerebellum and of the PCF, TSE-T2w and FLAIR-T2w sequences to detect potential white matter (WM) lesions. The choice of an isotropic voxel ( $\leq 1$  mm) should always be preferred when available or when a high-resolution multiplanar evaluation is needed. For example, it has been showed that, in comparison to TSE-T2/proton density sequences, isotropic 3D-FLAIR is more accurate in detecting not only white matter lesions but also cortical and infratentorial lesions in patients with multiple sclerosis (MS)<sup>[46]</sup>. 3D FLAIR has advantages even when acquired at ultra-high magnetic field, such as in the study of Kilsdonk *et al*<sup>[47]</sup> in which cortical gray matter (GM) lesions were better detected at 7T with 3D FLAIR than with GM-Specific 3D double inversion recovery (DIR) or with 2D-T2w and 3D-T1w. Finally, quantitative T1 and proton density ( $\rho$ ) magnetic resonance imaging at 3T

provide a good visualization of deep cerebellar nuclei, like dentate nuclei at 1.5T<sup>[48]</sup>. Similarly, susceptibility weighted imaging (SWI) allows a better detection of the dentate nuclei at 1.5T while higher magnetic field allows visualization of the dentate wall corrugation, which is the iron-poorer dorsal portion of it<sup>[49]</sup>.

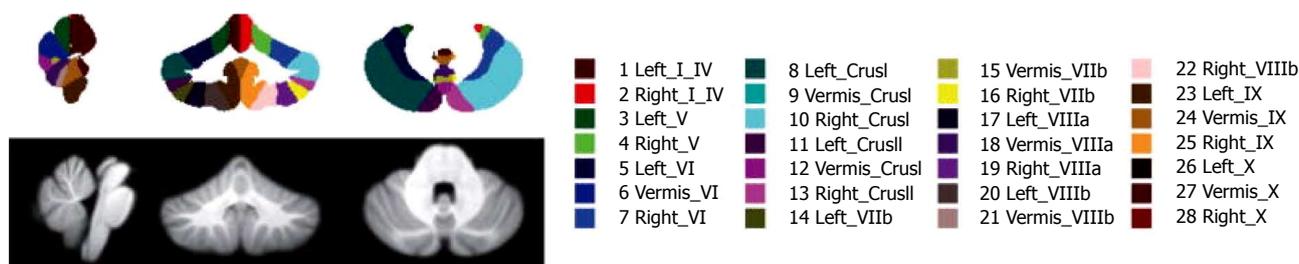
#### **Volumetric techniques**

There is an ever-increasing interest in the evaluation of cerebellar volume as a potential correlate of motor and cognitive performance and as a biomarker of progression and/or treatment outcome in neurodegenerative disorders<sup>[50]</sup>.

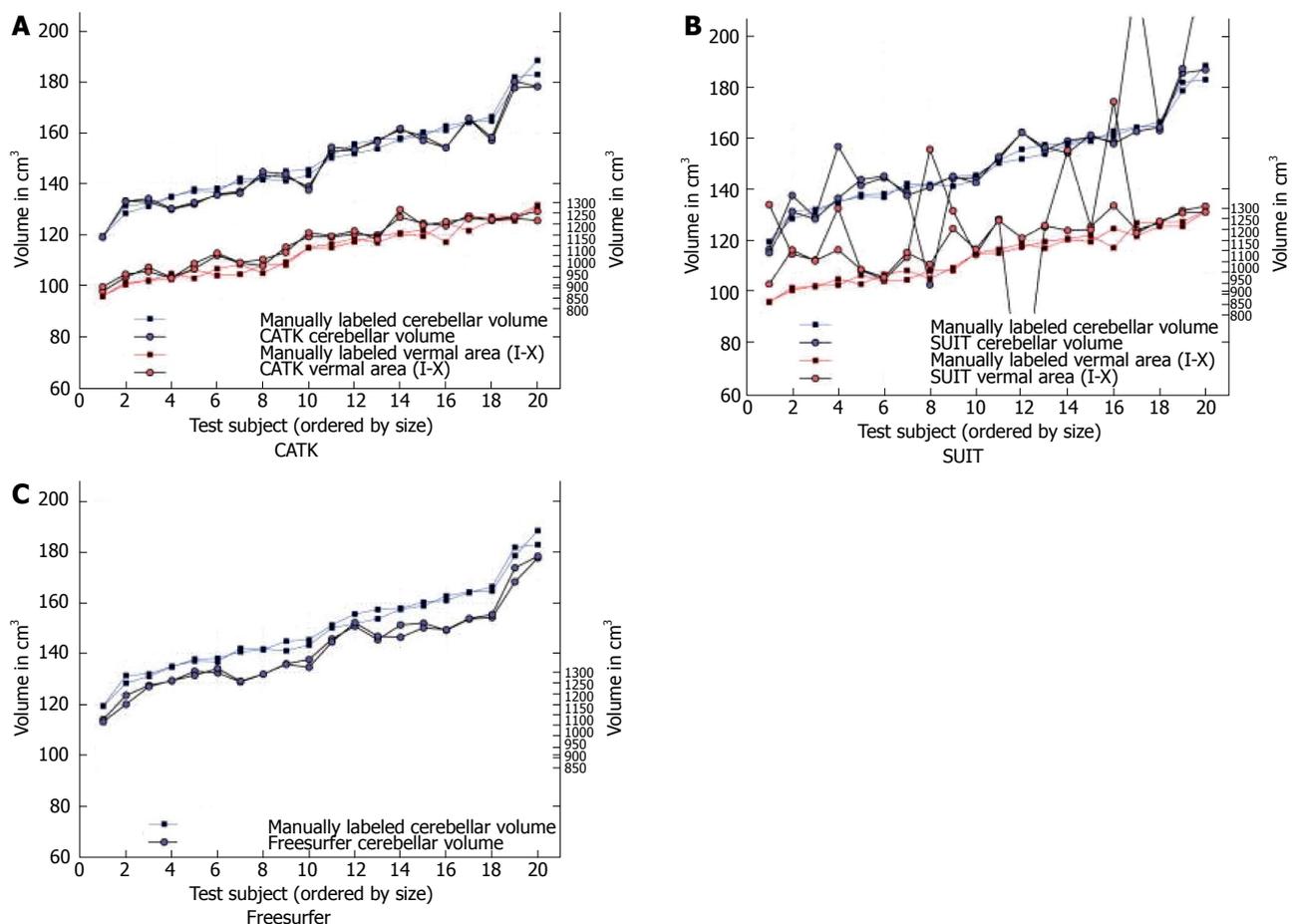
Several computerized methods with specific advantages and limitations are available to perform cerebellar segmentation, lobule parcellation and thus to assess global cerebellar volume, regional or lobular volumes and GM and WM volume. Although manual volume segmentation is considered the "gold standard", this option is extremely time-consuming and its reliability may vary with the experience of the raters<sup>[51]</sup>. Several semi-automatic computerized methods have been developed and validated in order to minimize operator-dependent limitation. We will focus on the methods that have been more extensively applied in clinical studies and will describe each method's advantages and limitations.

SUIT (spatially unbiased atlas template of the cerebellum and brainstem) is a Statistical Parametric mapping software (SPM) toolbox for MATLAB, based on a nonlinear coregistration of MRI images to a high-resolution cerebellum template obtained from images of healthy controls<sup>[52]</sup>. This method allows the parcellation of the cerebellum in at least 28 lobules, thus measuring GM volume for each lobule and the global GM volume as the sum of all lobule volumes (Figure 1). SUIT has been applied to the study of several diseases such as multiple sclerosis (MS), autism spectrum disorder, attention deficit hyperactivity disorder, developmental dyslexia and primary craniocervical dystonia, and it has been shown that it has higher sensibility to volume changes than conventional whole-brain voxel-based morphometry (VBM) methods<sup>[50,53,54]</sup>. The main advantage of SUIT is that it provides an optimal overlap of the cerebellar lobules, preserving anatomical details, and thanks to its cropping step avoids results bias from supratentorial structures<sup>[50,53,54]</sup>. However, Bogovic *et al*<sup>[51]</sup> reported that SUIT accuracy may decrease in patients with severe cerebellar atrophy especially with regard to lobule specific segmentation.

Cerebellar analysis toolkit (CATK) is based on a Bayesian framework of FMRIB's Integrated Registration and Segmentation Tool<sup>[55]</sup>. Using hand-delineated examples, active appearance models are created in order to perform cerebellar labeling and segmentation. CATK has shown a high reliability (Intraclass Correlation Coefficients, ICCs, of 0.96 for test-retest) a good manual segmentation agreement (ICC 0.87) and a better performance than other softwares, such as SUIT (v 2.7) and Freesurfer when compared to manual segmentation



**Figure 1** SUIE atlas (top) and template (bottom) showing the central cerebellar slice in the sagittal, coronal and axial planes. The atlas does not explicitly identify white matter apart from the dentate nuclei (from Ref. [55]).



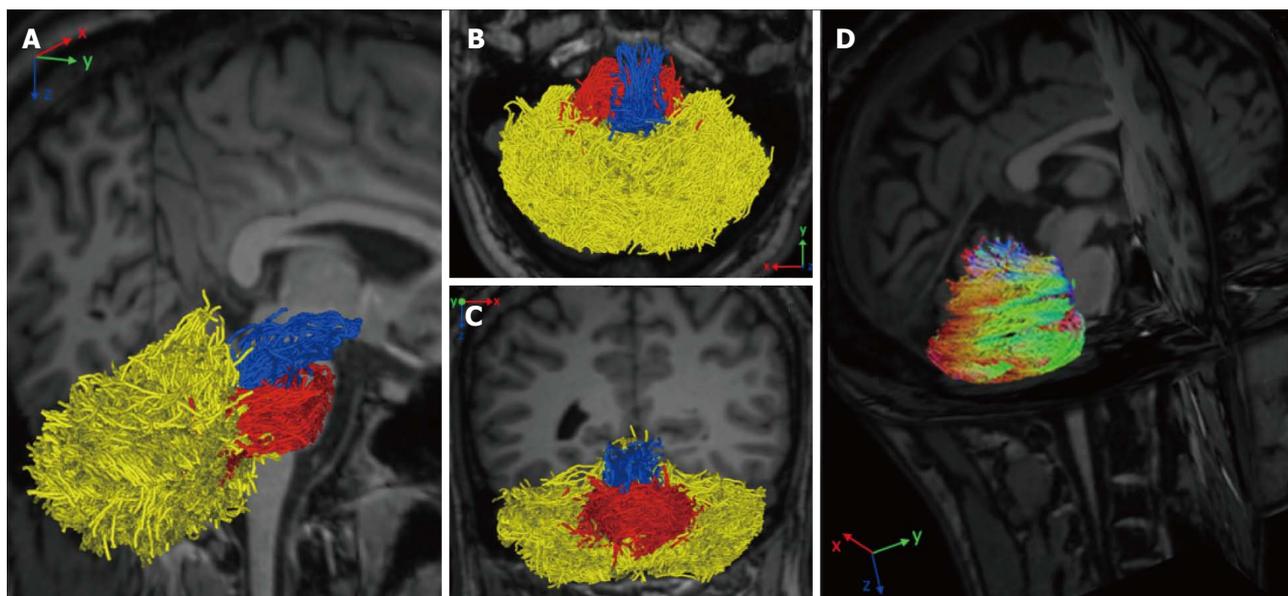
**Figure 2** Comparative plots of total cerebellar volumes and combined vermal areas are shown against manually labeled examples, in 20 subjects with (A) CATK, (B) SUIE and (C) Freesurfer. Both test and retest are plotted, illustrating the repeatability of each method (from Ref. [55]).

(gold standard). However, the main limitation when compared to other softwares, is that CATK does not allow cerebellar hemisphere parcellation, although Price *et al.*<sup>[55]</sup> in their paper stated a pending further improvement which would solve this issue and which would give higher image delineation (Figure 2).

ECCET is a semiautomatic toolkit based on a manually drawn region of interest ROI software. It is able to perform a fast semiautomatic segmentation after a manual outline drawing of few brainstem slices. It allows, when needed, manual editing in a 3D volume rendering mode ([https://www.eccet.de/projects/neuro\\_en.html](https://www.eccet.de/projects/neuro_en.html)). This method has shown a good interobserver (ICC =

0.98, 95%CI = 0.74-0.99) and test-retest reliability (ICC = 0.99, 95%CI = 0.98-0.99) and the capability of avoiding some segmentation errors such as the inclusion of venous sinuses without the need of manual editing<sup>[56]</sup>.

Unfortunately, to date, all the above-mentioned softwares provide pipelines for one time point evaluation (cross-sectional), but not for longitudinal analysis along time. This gap has been fulfilled by Freesurfer, which is a software that allows a reliable automatic whole brain segmentation, with up to 40 subcortical structures, labelling each voxel in a normalized space of the brain volume<sup>[57]</sup>. In addition to the cross-sectional analysis, Freesurfer comprises a longitudinal stream where each



**Figure 3** Reconstruction of cerebellar white matter tracts using constrained spherical deconvolution. Sagittal rotated view (A), superior axial view (B), and coronal view (C) show each fiber bundle manually colored: Superior cerebellar peduncle (blue), middle cerebellar peduncle (red), and hemispheric cerebellar tracts (yellow). The tridimensional sagittal rotated view shows color-coded cerebellar hemispheric streamlines according to the principal eigenvector's direction (with permission of Springer, from Ref. [63]).

time-point is co-registered to a subject-specific template by creating an average segmentation along time points, resulting in volume and GM thickness estimation<sup>[57]</sup>. Although Freesurfer presents this important advantage, it does not allow sub-regional segmentation in cerebellar lobules<sup>[55]</sup>. Moreover, manual editing of segmentation outputs is needed in order to improve volume evaluation reliability<sup>[58]</sup>. Although the editing can be performed manually, resulting in a very time-consuming (up to 4h) and operator-dependent approach, Wang *et al.*<sup>[58]</sup>, in a recent paper, proposed an accurate and efficient new machine-learning based method in order to overcome this issue.

#### **Diffusion weighted imaging and fiber tractography**

Diffusion magnetic resonance imaging (dMRI) is a MRI technique able to detect water molecules diffusion inside brain tissue. While diffusion of water molecules in GM is isotropic, diffusion in WM is anisotropic, *i.e.*, it occurs in one main direction due to the presence of myelin barriers<sup>[59]</sup>. The evaluation of diffusion in a three dimensional space and along at least 6 directions, allows the creation of a diffusion tensor matrix, which provides the bases of tractographic reconstruction of brain neural circuitry<sup>[60]</sup>. Diffusion tensor imaging (DTI) and more advanced approaches (such as diffusion spectrum imaging or constrained spherical deconvolution) have been applied to determine cerebellar pathways and their connection with other supratentorial areas<sup>[61-63]</sup> (Figure 3). Although conventional DTI techniques are the most used technique to reconstruct cerebellar pathways by means of tractography, they are also well known for their limitations in the study of connectivity. DTI, indeed, is limited by the inability to discriminate different fiber

populations with complex configurations at a voxel level (kissing fibers, bridging fibers, merging fibers, crossing fibers), thus leading to artefacts in fiber reconstructions and connectivity evaluations. Methods such as diffusion spectrum imaging and Q-ball imaging have been developed over the last few years to overcome these limitations; however, the more complex hardware set up and the longer acquisition times have limited so far their application in the clinical setting<sup>[64]</sup>. Other promising techniques, such as diffusion kurtosis imaging (DKI), neurite orientation dispersion and density imaging (NODDI) and constrained spherical deconvolution can be performed within clinically feasible acquisition times<sup>[65]</sup> (Figure 3). Moreover, all these techniques can be analyzed with both deterministic and probabilistic fiber reconstruction models. While deterministic models reconstruct streamlines (virtual fiber tracts) taking into account the principle eigenvector of fractional anisotropy (FA) in each voxel, probabilistic models generate a connectivity map from a larger numbers of possible pathways, obtaining the probability of each voxel to be connected to another<sup>[66]</sup>. Regardless of the used approach, tractographic output can be used not only to reconstruct the spatial configuration of fiber tracts but also to measure diffusion parameters (*i.e.*, FA or mean diffusivity) at voxel level. However, it has been proved that, not only parameters' quantification but also the accuracy of tractographic results may be affected by the poor quality of the acquired data that can lead to the detection of false connections or to miss detection of a real connections between structures<sup>[59]</sup>. Therefore, a better data quality, optimized in terms of SNR, spatial resolution, number of diffusion directions, and number and values of *b* values, with the choice of a proper tractography method, may improve the method performance avoiding

inaccuracy in structural connectivity analysis<sup>[67]</sup>. Since cerebellar pathways tracking is particularly difficult due to the presence of sharp turning angles along their crossing, the assessment of cerebro-cerebellar and intra-cerebellar connectivity could especially benefit from data quality improvement<sup>[61,63]</sup>.

### **Resting state and task related fMRI**

Functional MRI (fMRI) is based on the detection of the blood oxygen level-dependent (BOLD) changes that take place as a consequence of neuronal activity. An increase in neural activity leads to an increase in the arterial blood flow, in order to increase the activity itself. To this increase in the amount of oxygenated blood does not correspond a similar increase in oxygen extraction at the level of capillary bed, leading to a relative decrease of deoxyhemoglobin levels, that directly affects the MR signal.

fMRI experiments can be divided in task and rest-related. The first measure brain activity during a task performance, the second evaluate the interaction between different brain regions without the execution of any specific task, in a rest condition (resting-state fMRI - RS-fMRI).

With regard to task-based fMRI studies, two main experimental paradigms are commonly used<sup>[68]</sup>. The first one is the so-called block design experiment, in which stimuli are presented to the subject in blocks of variable length alternated to blocks of rest, in which the stimulus is removed. MRI signals are then compared between the two conditions, in order to extrapolate the areas that show more activation during the execution of the task. The second is the event-related experimental design, in which the stimuli and the resting blocks are not alternated in a set sequence, but the administration, as well as the duration of the stimulus, are randomized.

RS-fMRI experiments can be analyzed using two major approaches. The first one is the seed-based approach, in which a region of interest is selected and the corresponding time-activity curve is extracted. Then, voxels with similar activation are searched whole brain, and are assumed to be functionally correlated to the chosen seed<sup>[69]</sup>. The second method is the independent component analysis (ICA), a mathematical algorithm that allows to subdivide a multivariate and noisy signal in its subcomponents<sup>[70]</sup>. In this approach, no a priori seeds are chosen, but the operator is asked to identify the component of interest, and discard those obtained from noise or physiological signals. ICA analysis has allowed the identification of preferential connections between specific cerebral structures, that take the name of resting state networks<sup>[71]</sup>. Cerebellar lobules are not only hubs of several of these resting state networks (*i.e.*, lobule IX in the default mode network, crus I and II in the executive control network or lobule VI in the salience network)<sup>[72]</sup>, but also an entire and separate cerebellar network is recognized among the major resting state networks<sup>[71]</sup>.

With this knowledge, it is easy to understand how future improvement is warranted to increase the of

functional changes with respect of the cerebellar lobular anatomy. In particular, the possibility of increasing spatial resolution in fMRI experiments is a future challenge for investigating cerebellar functional connectivity due to the characteristic lobular anatomy. The increase in spatial resolution could further help in elucidating the exact functional lobular topography of the cerebellum, with regards to specific motor and cognitive functions<sup>[73]</sup>.

### **Proton magnetic resonance spectroscopy**

Proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) is an analytical method that allows the investigation of brain metabolites. Every metabolite at sufficient concentration level generates a specific peak in function of its resonance frequency<sup>[74]</sup>. Since metabolic abnormalities occur earlier than structural MRI alterations, <sup>1</sup>H-MRS can provide a valid tool for early diagnosis and for monitoring of neurological diseases<sup>[75]</sup>.

The most commonly studied brain metabolites are the N-acetylaspartate, a marker of neuroaxonal integrity, choline containing compounds, a marker of membrane turnovers, creatine/phosphocreatine, a marker of energy metabolism, and myo-inositol, a marker of astroglial activation. From a quantification point of view, metabolites' levels are expressed as absolute quantifications or as ratios where the denominator is the creatine level which is assumed to be stable in normal as well as in many pathologic states<sup>[76]</sup>.

Although the infratentorial structures are often involved in neurodegenerative processes, strong B0 inhomogeneities due to nearby skull bone, scalp lipids and tissue/air interfaces constitute a technical challenge for the <sup>1</sup>H-MRS acquisition. In addition, the small size of cerebellum increases the risk of partial volume effects<sup>[77]</sup>, which can be accounted for by combining spectroscopic data with structural MRI segmentation<sup>[78]</sup>. Nevertheless, <sup>1</sup>H-MRS of the infratentorial fossa is feasible<sup>[79]</sup> and could provide an early biomarker of neuronal damage in cerebellar diseases, with even increased specificity when used in combination with other techniques<sup>[80]</sup>.

### **Perfusion MRI**

Perfusion weighted imaging (PWI) allows the measurement of blood perfusion in brain tissue and it is categorized as: "minimally invasive" if requiring gadolinium injection (*i.e.*, dynamic susceptibility contrast MRI or DSC-MRI and dynamic contrast enhanced MRI or DCE-MRI) or "non-invasive" if no contrast agent is needed (*i.e.*, arterial spin labelling or ASL-MRI)<sup>[81]</sup>. Data from either technique above is subsequently processed and normalized to estimate the well-known perfusion values: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), Ktrans and *etc.*, which are all representable on parametric color maps.

Cerebellar tissue is subject to a great blood supply, and measurement of local variations of blood request/availability is clinically relevant in the assessment of neurodegenerative diseases. Specifically, cerebral blood flow (CBF) alterations (*i.e.*, general or local CBF

reduction) appear to precede structural abnormalities (for example: atrophy). Moreover, the cerebellum has been used as a reference region for intensity normalization of "relative" Cerebral Blood Volume (rCBV), based on the assumption that its CBV is not affected in neurocognitive disorders<sup>[82]</sup>. Although hard to eradicate, this assumption is nowadays obsolete, as alternative reference regions have recently been proposed and validated<sup>[83]</sup>.

With respect to the study of the cerebellum and the PCF, DSC-MRI provides higher spatial resolution, high sensitivity in transit time and whole-brain coverage in shorter scan times, and it is preferred in all situations where a fast assessment is required. DCE-MRI has the advantage of reducing artifacts especially for the measurement of CBV and Ktrans. ASL-MRI is often preferred in the study of neurodegenerative diseases for its complete lack of invasiveness, vessel selective capability<sup>[84]</sup> and the best accuracy in absolute tissue perfusion quantification<sup>[81]</sup>. Particular care in placing the "labeling plane" is essential to avoid artifacts in the lower cerebellar sections<sup>[85]</sup>. Another limit of ASL-MRI is WM assessment, which is particularly challenging due to the low blood transit and the consequent low SNR<sup>[86]</sup>.

Unfortunately, despite the theoretical indications of each method, in the routine clinical settings, is the availability and practicality of the techniques that forces the choice, rather than its potential performance. This could explain the more frequent use of DSC and DCE imaging, faster, easy to perform and widely installed on most clinical scanners, compared to the use of ASL.

## MRI AND CLINICAL APPLICATIONS ON NEURODEGENERATIVE DISEASES

### **Multiple sclerosis**

Multiple Sclerosis (MS) is an inflammatory/demyelinating disease of the central nervous system (CNS) characterized by heterogeneous symptoms and signs that can present a relapsing remitting (RR) or a progressive course. In 1877 Jean Martin Charcot first described the disease as a triad of symptoms consisting of nystagmus, dysarthria and ataxia<sup>[87]</sup>, thus underlining the dominant role of cerebellar deficits. Not only is the cerebellum frequently involved by the disease pathological processes but the presence of MRI visible infratentorial lesions provides high specificity to the diagnostic criteria for MS<sup>[88]</sup>. Indeed, 31% of patients with a clinically isolated syndrome (CIS) present with at least one infratentorial lesion and about 20.5% with a cerebellar lesion. The detection of a cerebellar lesion at onset is associated with an increased risk of conversion to MS<sup>[89]</sup>. In patients with a clinically defined MS, cerebellar lesions have been described in up to 49% of cases and patients with a progressive form have an increased number of PCF lesions when compared to patients with a RR type<sup>[90]</sup>. Disease pathology involves not only the cerebellar WM but also the GM; in fact, cortical cerebellar lesions are

observed in patients with MS, even at the early stages of the disease, and correlate with the cerebellar functional score of the expanded disability status scale (EDSS)<sup>[91]</sup>. Longitudinal studies have shown cerebellar GM volume loss and an increased number of cortical lesions in both CIS, RR and progressive patients<sup>[92,93]</sup>.

### **Volumetry changes**

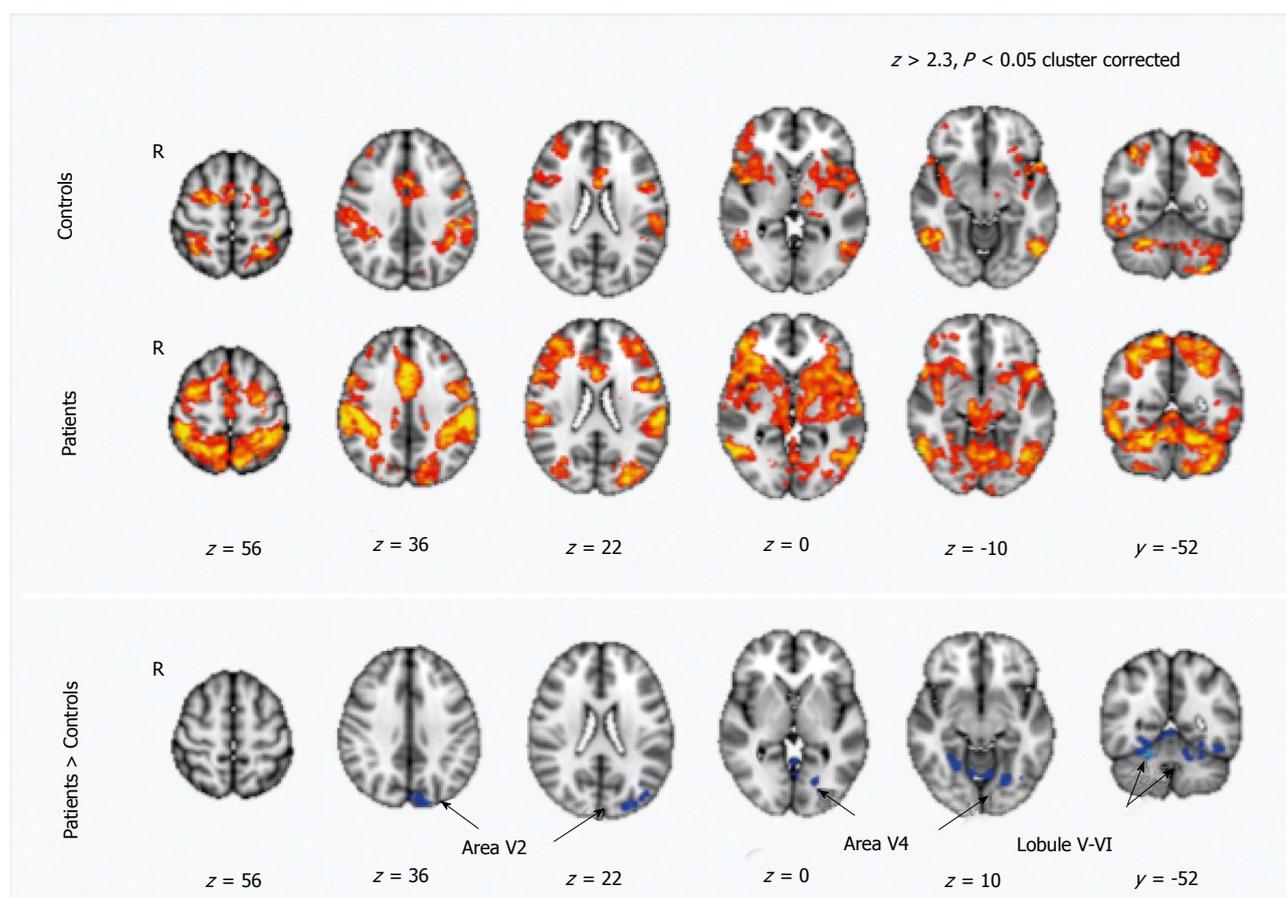
Along with cerebral atrophy, also cerebellar volume loss occurs in patients with MS, at all the disease stages. Edwards and coworkers found reduced global cerebellar volumes in patients with a secondary progressive (SP) form when compared to RR patients, and in both groups when compared to healthy controls<sup>[94]</sup>. However, in a more recent study, when compared to healthy controls only MS patients with a SP form, but not RR or patients with benign MS, showed lower cerebellar volumes<sup>[50]</sup>. When cerebellar WM and GM are considered separately, study results are discordant. Ramasamy *et al.*<sup>[95]</sup> found a reduced cerebellar WM but not GM volume in CIS and MS patients when compared to healthy controls. However, Anderson and coworkers detected a reduced cerebellar GM volume in RR and SP MS patients versus controls and only a trend of significance, when comparing WM volumes, between SP MS and controls<sup>[96]</sup>. In the latter study, cerebellar GM and WM volumes were related with performance at the nine-hole peg test, highlighting the clinical relevance of measures of cerebellar volumes. A greater loss of GM in patients with a progressive course and its correlation with measures of clinical outcome are findings mirroring the process at the whole brain level.

### **Structural connectivity changes**

DTI has been widely used for the study of cerebellar WM, in particular to evaluate the damage of the cerebellar peduncles and its clinical impact. Anderson *et al.*<sup>[97]</sup> found reduced FA and increased radial diffusivity values in the middle cerebellar peduncle in patients with primary progressive (PP) MS; DTI metrics correlated with clinical impairment both of the upper and lower limbs. A study on a cohort of patients at different stages of the disease revealed greater mean, axial and radial diffusivity and reduced FA in MS patients, when compared to healthy controls, at the level of the middle and superior cerebellar peduncles; moreover, when compared to cerebellar peduncles T2 lesion load or atrophy, diffusivity measures better distinguished between patients with a worse EDSS score<sup>[98]</sup>. Disability in RR patients also correlated with the FA values of the cerebellar normal appearing WM<sup>[99]</sup>.

### **Functional MR changes**

MS is characterized by a reorganization of the functional connectivity. Functional MR studies with motor tasks revealed an increased activation in several cortical areas within the sensorimotor network, including the cerebellum, in patients when compared to healthy controls<sup>[100,101]</sup> (Figure 4). The altered functional cerebellar connectivity could represent a compensatory mechanism to WM



**Figure 4** Motor training-dependent functional magnetic resonance imaging signal changes in healthy volunteers and in MS patients. Maps of training-related functional magnetic resonance imaging signal changes are reported in healthy volunteers (indicated as controls) and in patients ( $Z > 2.3$ ,  $P < 0.05$ , cluster corrected). Comparison between patients and controls show a higher signal reduction in the patients in regions corresponding to the secondary visual areas (V2 and V4) and in the cerebellum (lobule V-VI) (from Ref. [100]). V5: Visual cortex; R5: Right hemisphere; fMRI: Functional magnetic resonance imaging.

damage; accordingly, in RR MS patients a damage in the dentatorubrothalamic tract, assessed by means of DTI, was related to an increased functional connectivity between right sensorimotor cortex and cerebellum<sup>[101]</sup>. The cerebellum activation is also increased in patients with greater perceived fatigue where fatigue is conceived as a correlate of an increased resource demand for motor activities<sup>[102]</sup>.

### Cerebellum and cognitive impairment

Besides the classical motor clinical features associated with cerebellar dysfunction, lately more attention has been focused on the role of cerebellum in cognitive impairment. MS patients with cerebellar signs perform worse at the symbol digit modalities test (SDMT) and the paced auditory serial addition test (PASAT); moreover, the PASAT execution is predicted by cerebellar lesion volume<sup>[103]</sup>. In particular the posterior cerebellum has been implicated in cognitive processing; in MS patients, a reduced posterior volume predicted a worse cognitive performance<sup>[50]</sup>. Information processing speed impairment has been associated with GM atrophy of the posterior lobules, especially at the level of the vermis VI<sup>[104]</sup>. As with

motor tasks, a functional reorganization could also occur in response to the impairment of cognitive processes. Recently, a greater functional connectivity of the dentate nucleus with frontal and parietal cortical areas was detected in MS patients versus controls<sup>[105,106]</sup> and the increased connectivity was related to a better cognitive performance. Moreover, an increased connectivity between anterior cingulate cortex and cerebellum was also associated with a better performance at PASAT in CIS, RR and SP patients versus controls and authors suggested an adaptive mechanism<sup>[107]</sup>.

### Dentate nuclei hyperintensity

The hyperintense signal on T1-weighted images at the level of dentate nucleus has been detected in almost 50% of patients with a secondary progressive phase of the disease, in contrast to what found in the RR or PP form<sup>[108]</sup>. Although this change in signal could be related to the reduction in the number and axosomatic synapses in the dentate nucleus as documented by pathological studies<sup>[109]</sup>, an association between the nuclei hyperintensity in T1-weighted images and Gadolinium retention has recently received greater attention<sup>[110]</sup>.

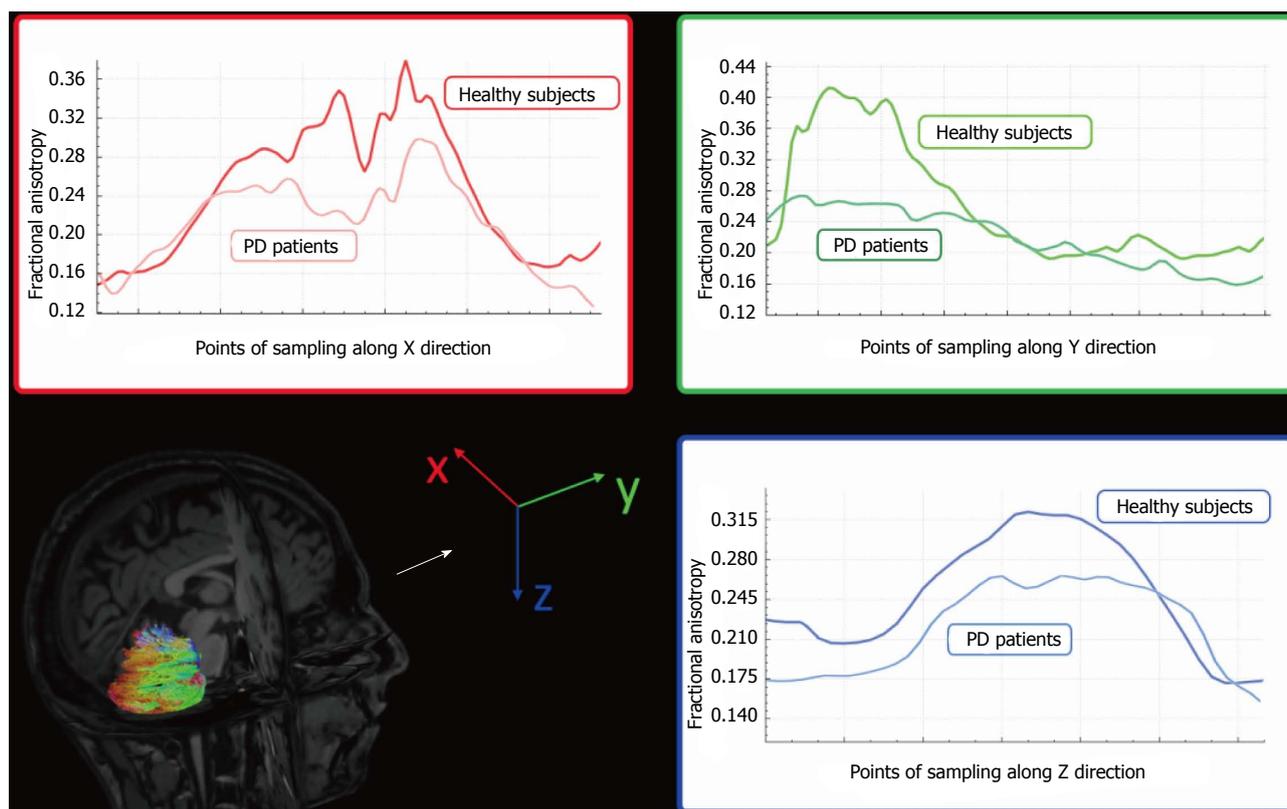


Figure 5 Graphic representations of Fractional Anisotropy mean decrement along X (red), Y (green), and Z (blue) direction samplings of Parkinson's disease patients compared to healthy subjects. Colors follow principal eigenvector's directions (with permission of Springer, from Ref. [63]). PD: Parkinson's disease.

## PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

### Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder pathologically characterized by the loss of dopaminergic neurons of the pars compacta of the substantia nigra; clinical features include motor, in particular rest tremor, bradykinesia and rigidity, and non-motor symptoms. The role of cerebellum in the physiopathology of this frequent neurodegenerative disorder has received increasing interest. Studies on monkeys discovered direct anatomical connections between cerebellum and basal ganglia, in particular with the subthalamic nuclei and the striatum<sup>[8,111]</sup>. Such findings have been confirmed with a DTI study in humans<sup>[112]</sup>. Interestingly, patients receiving deep brain stimulation had a clinical benefit when the electrode was positioned nearby one of these basal ganglia-cerebellum connections, in particular the dentato-thalamic tract.

### Volumetry changes

Cerebellar atrophy has been documented in patients with PD. MRI morphometric studies have shown cerebellar volume loss at the level of the left cerebellum when compared to controls<sup>[113]</sup>, and at the level of the right quadrangular lobe and declive in patients with tremor compared to those without, thus suggesting a possible role of cerebellum in the genesis of rest tremor<sup>[114]</sup>. A more

recent study confirmed cerebellar GM atrophy, which correlated with a reduced connectivity between cerebellum and sensorimotor, dorsal attention and default networks and an increased connectivity with the frontoparietal network<sup>[115]</sup>. Altogether these results confirm the role of cerebellum in the physiopathology of motor symptoms in PD. Atrophy occurs since cerebellum is involved in the neurodegenerative pathological process of the disease, with the accumulation of  $\alpha$ -synuclein and neuronal loss.

### Structural connectivity changes

DTI studies have detected decreased FA in the cerebellar hemispheres of patients with PD when compared to healthy controls (Figure 5)<sup>[63,116]</sup>. Although no differences in DTI parameters in superior and middle cerebellar peduncles have been detected between patients with PD and healthy subjects<sup>[63]</sup>, DTI metrics of the superior cerebellar peduncles could be helpful in differentiating PD and other parkinsonism, such as progressive supranuclear palsy (PSP)<sup>[117]</sup>.

### Functional MR changes

Cerebellar hyperactivation has been showed and confirmed in several studies on patients with PD, both with akinesia-rigidity subtype and with tremor subtype. Whether the contribution of cerebellum is mostly an adaptive mechanism or a primary pathologic change of the disease is still a matter of debate. In a resting-state fMRI study, Wu *et al.*<sup>[118]</sup> observed an increased activation

in the cerebellum in PD patients versus healthy controls; moreover, the altered pattern of activation was normalized after levodopa administration. A substitutive hyperactivity of the cerebello-thalamo-cortical circuit has been proposed as a mechanism to compensate the hypoactivation of the striato-thalamo-cortical circuit in hypokinetic patients; however, for PD tremor subtype, a dysfunction in the cerebello-thalamo-cortical circuit has been advanced as a physiopathologic mechanism for rest tremor<sup>[118,119]</sup>.

### **Multiple systemic atrophy**

Multiple systemic atrophy (MSA) is a movement disorder, with a poor prognosis, which has two clinical phenotypes: one with a prominent akinetic-rigid parkinsonism (parkinsonian variant, MSA-P) and the other with a progressive ataxia (cerebellar variant, MSA-C). It has been suggested that imaging of cerebellum could be useful in the differential diagnosis of MSA. Atrophy of the middle cerebellar peduncles is frequent in patients with MSA and reduced volume of basal ganglia, middle and inferior cerebellar peduncles and pons have been found in the parkinsonian subtype of MSA, when compared with controls and PD patients<sup>[120]</sup>. Moreover, both MSA-P and MSA-C patients were found to have higher MD values in cerebellar hemispheres when compared to PD and PSP patients<sup>[121]</sup>. Brainstem and middle cerebellar peduncles atrophy have also been found to be very specific for the cerebellar subtype of MSA when compared to idiopathic late-onset cerebellar ataxia<sup>[122]</sup>.

### **Dystonia**

Dystonia is a disorder characterized by sustained and abnormal spontaneous muscle contractions. It can be classified according to the etiology (inherited or acquired) or the topographic distribution. Cerebellar dysfunction has been implicated in the physiopathology of dystonia. Morphological cerebellar abnormalities have been reported in 14% of patients with cervical or segmental dystonia<sup>[123]</sup>. Focal cerebellar lesions have been associated with dystonia and cerebellar atrophy has been described in patients with writer's cramp<sup>[124]</sup>. Besides morphological studies, several functional studies have shown an increased activation in cerebellum in patients with writer's cramp<sup>[125]</sup> and in patients with blepharospasm<sup>[126]</sup>.

### **Hereditary ataxias**

Ataxias are an heterogeneous group of conditions characterized by slowly progressive incoordination of gait, often associated with a reduction of coordination of hands, speech, and oculomotor signs<sup>[127]</sup>. Ataxias can be subdivided, basing on the etiology behind the development of the condition, in three major groups: acquired ataxias, nonhereditary degenerative ataxias and hereditary ataxias (HA), which can be further divided in dominant and recessive<sup>[127]</sup>. Spinocerebellar ataxia type 3 (SCA3) is the most frequent type of dominant ataxia, followed by SCA2 and SCA6, while Friedreich Ataxia (FRDA) and ataxia-telangiectasia (AT) are respectively the first and the second most

common type of recessive ataxias, with FRDA that is, independently from the inheritance, the most frequent ataxia in terms of incidence<sup>[128]</sup>.

### **Volumetry changes**

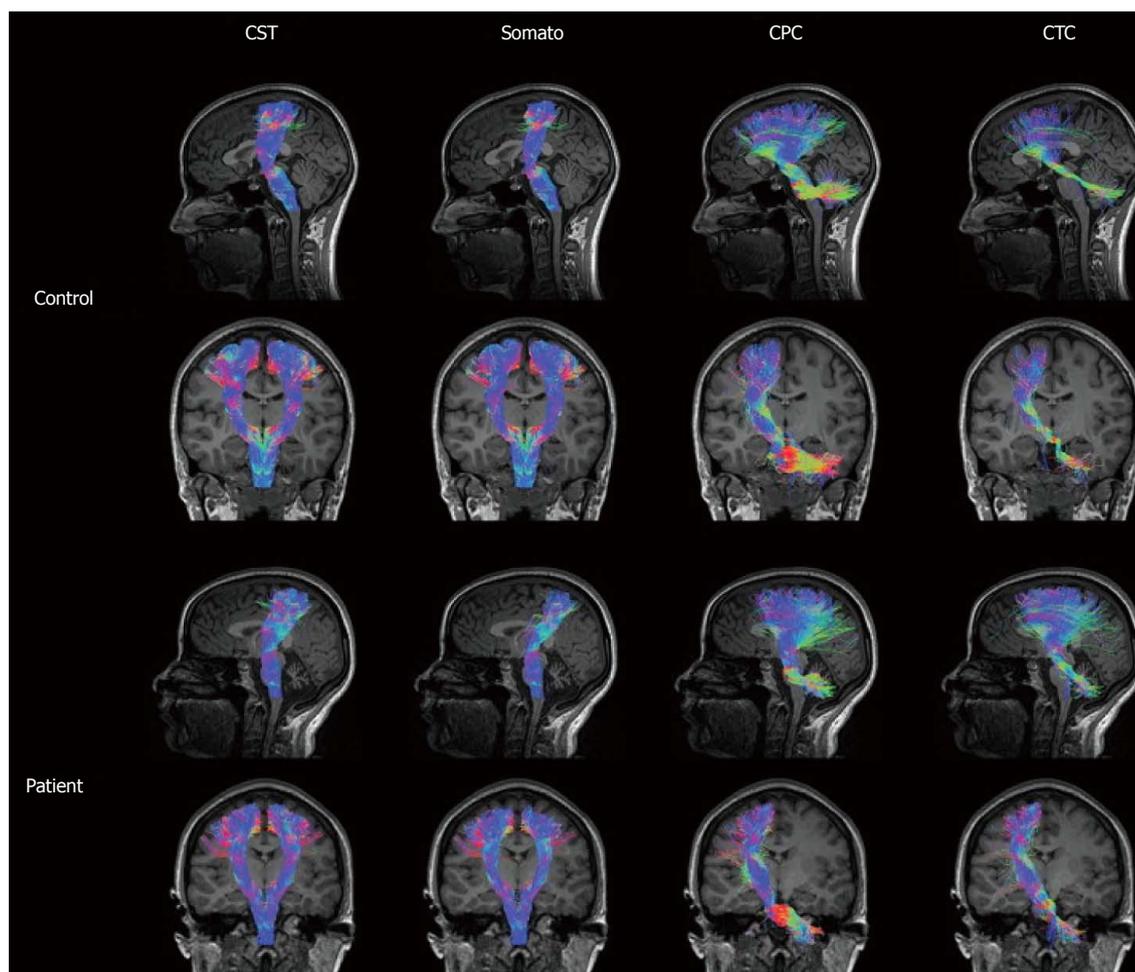
Atrophy of the cerebellar cortex is not a distinguish feature of all the HA. Different patterns of atrophy can be identified, depending on the degree of cerebellar atrophy and the involvement of midbrain structures. In particular, SCA3 and SCA2 are characterized by the presence of cortical, cerebellar and pons atrophy<sup>[129]</sup>. On the other hand, SCA6 shows a pattern of pure cortical cerebellar atrophy, with a relative sparing of midbrain structures<sup>[130]</sup>. With regard to recessive ataxias, FRDA is characterized by a prominent spinal cord atrophy<sup>[131]</sup> compared to cerebellar cortical structures<sup>[132]</sup>, with atrophy that, when significant, affects mainly the lateral cerebellar hemispheres<sup>[133]</sup>. Finally, AT is characterized by superior cerebellar hemispheres atrophy, in particular of the vermis, which appears hypoplastic in its inferior portion<sup>[134-137]</sup>.

### **Structural connectivity changes**

Unlike volumetric measures, almost all the major HA show similar microstructural changes affecting infratentorial WM tracts. Indeed, SCA3 patients showed a significant FA reduction in different cerebellar areas, including both anterior and posterior cerebellar lobes, nodule, culmen, dentate, fastigial, lingual, and all three cerebellar peduncles, as well as in pons and midbrain<sup>[138]</sup>. These abnormalities were correlated with clinical variables, such as scale for the assessment and rating of ataxia (SARA) scores or disease duration<sup>[138,139]</sup>. In SCA2, significant microstructural changes were present in cerebellar WM, brainstem and cerebellar peduncle<sup>[140,141]</sup>, with changes in the mode of anisotropy that were lower in SCA2 patients compared to healthy controls in a longitudinal evaluation<sup>[141]</sup>. Unlike in SCA3, no correlation with clinical variables emerged for these infratentorial clusters of microstructural changes in SCA2. In FRDA, microstructural changes were found to affect predominantly cerebellar peduncles<sup>[142-145]</sup>, as well as cerebellar hemispheres and vermis<sup>[144]</sup> and to be associated with clinical disability<sup>[142-144]</sup>. Finally, in AT patients a reduction of mean diffusivity was reported within cerebellar peduncle regions<sup>[146]</sup> (Figure 6).

### **Functional MR changes**

Similar to structural connectivity, functional connectivity changes are present in almost all HA. However, these modifications are not limited to a somehow expected reduction of FC in HA patients compared to healthy controls, but also increase in FC are reported in some HA, probably due to compensatory phenomena, reflecting the known heterogeneity of this group of conditions. Indeed, a significant increase of activation of the ventral part of the dentate nuclei, but not of the cerebellar cortex, was found during an hand-movement task fMRI experiment in SCA3 patients compared to healthy controls, suggesting a



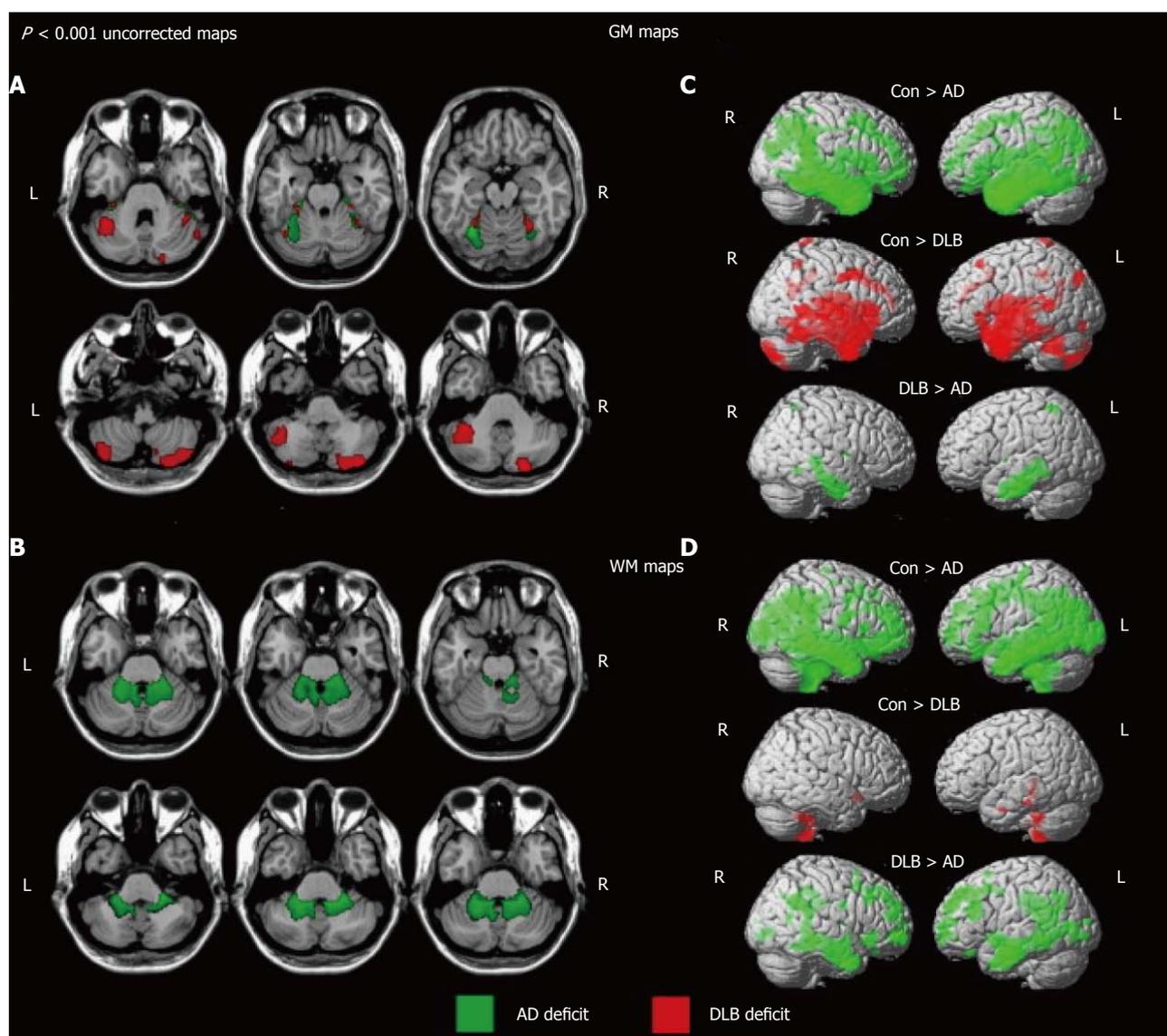
**Figure 6** Somatosensory motor tracts in a representative control and ataxia telangiectasia (A-T) subject (age 23). Control tracts are displayed in the first and second rows comprising the left sagittal (first row) tracts, left and right coronal (second row) corticospinal (CST) and somatosensory tracts, and left coronal (second row) cortico-ponto-cerebellar (CPC) and cerebellar-thalamo-cortical (CTC) tracts. Patient tracts are displayed in the third and fourth rows comprising the left sagittal (third row) tracts, left and right coronal (fourth row) CST and somatosensory tracts, and left coronal (fourth row) CPC and CTC tracts. Tract colors are based on the direction of water diffusion (Blue: Ascending–descending diffusion; Red: Left–right diffusion; Green: Anterior–posterior diffusion). Compared to motor pathways in age matched controls, A-T CST and somatosensory pathways display a morphological thinning of tracts at the level of the thalamus in the coronal view. In addition, A-T CPC and CTC pathways display morphological thinning of tracts in the cerebellum at the position of the medial cerebellar peduncles (from Ref. [147]).

compensatory phenomenon of the *cerebrocerebellum* to a prominent damage of the *spinocerebellum*<sup>[147]</sup>. Moreover, a recent fMRI study, involving a bilateral audiopaced thumb movements paradigm, showed a diminished movement synchronization in SCA3 patients<sup>[148]</sup> that would suggest the presence of functional reorganization of the motor network and a potential role of fMRI as a tool to monitor the disease<sup>[148]</sup>. In SCA2, a seed-based fMRI analysis showed a decreased putaminal connection with the pons, together with a decreased connectivity between the rostral sensorimotor area and both cerebellum and pons<sup>[149]</sup>. Furthermore, a decrease of the functional connectivity of the cerebellar components of the default mode, executive and right fronto-parietal networks was described in SCA2, unrelated to the cortical gray matter volume loss<sup>[150]</sup>, with some authors that showed a significant correlation between both motor and neuropsychological scores and the abnormal cerebellar functional connectivity strength<sup>[151]</sup>. In SCA6 patients, a significantly higher activation at the level of the lobules V and VI, as well as in the dentate

nuclei, was detected compared to controls when performing a hand-movement task fMRI experiment<sup>[147]</sup>. Likewise, in FRDA patients the same motor task showed a higher activation mainly prominent at the level of lobules V and VI and dentate nuclei, compared to healthy control<sup>[147]</sup>. Furthermore, a working memory task fMRI experiment showed that FRDA patients had a decrease functional connectivity between cerebellum and prefrontal areas, with a correlation between disease severity and cerebellar dysfunction<sup>[152]</sup>.

#### Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia and it is preceded by a prodromal phase, called mild cognitive impairment (MCI), characterized by a deficit in one or more cognitive domains. The role of cerebellum involvement in AD is controversial. While a volumetric MRI study in patients with AD, MCI and healthy controls found a volume loss at the level of the posterior cerebellar lobes in AD patients compared to healthy



**Figure 7 Significant cerebellar GM and WM loss in Alzheimer's disease.** A: Significant cerebellar GM loss in Alzheimer's disease (green) and dementia with Lewy bodies (red) relative to healthy older subjects; B: Significant cerebellar WM loss in AD relative to healthy older subjects; C and D: Whole brain maps depicting significant regions of GM (C) and WM (D) loss between groups. Results superimposed on a MRI T1 brain template image (L = left, R = right). AD: Alzheimer's disease; DLB: Dementia with Lewy bodies (from Ref. [154]). GM: Gray matter; WM: White matter.

controls, no significant differences were showed between patients with MCI and healthy controls<sup>[153]</sup>. Another study detected a regional GM atrophy in cerebellar lobule VI in patients with AD<sup>[154]</sup> (Figure 7). These findings were not confirmed<sup>[155]</sup> in a more recent study, suggesting that the decrease of cerebellar volume could be influenced by the patients' age. This is supported by the findings of cerebellar atrophy in patients with a late-onset, but not early-onset AD<sup>[156]</sup> and by the presence of cerebellar atrophy in cognitively preserved old subjects<sup>[157]</sup>.

## CONCLUSION

The cerebellum plays a key role in the control of motor and cognitive functions due to the multiple connections to the forebrain, the thalamus, and the spinal cord. However, the cerebellar complex anatomical structure and its

location in the posterior fossa represent a challenge for *in vivo* structural and cerebellar neuroimaging. The recent advancement in MRI hardware and software and the development of more accurate and robust algorithms for image analysis have improved the structural and functional assessment of the cerebellum. This is of paramount importance due to the frequent and early involvement of the cerebellum in several neurodegenerative diseases. Therefore, MRI measures of cerebellar structure and function could serve as early and sensitive marker of disease progression and help monitor response to current or experimental treatments.

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