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Development of a psychiatric disorder linked to cerebellar lesions

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Abstract

Objectives Cerebellar dysfunction plays a critical role in neurodevelopmental disorders with long-term behavioral and neuropsychiatric symptoms. **Case** A 43-year-old woman with a cerebellum arteriovenous malformation and history of behavioral dysregulation since childhood is described. After the rupture of the cerebellar malformation in adulthood, her behavior morphed into specific psychiatric symptoms and cognitive deficits occurred. **Results** The neuropsychological assessment evidenced impaired performance in attention, visuospatial, memory, and language domains. Moreover, psychiatric assessment indicated a borderline personality disorder. Brain MRI examination detected macroscopic abnormalities in the cerebellar posterior lobules VI, VIIa (Crus I), and IX, and in the posterior area of the vermis, regions usually involved in cognitive and emotional processing. **Conclusions** The described patient suffered from cognitive and behavioral symptoms that are part of the Cerebellar Cognitive Affective Syndrome. This case supports the hypothesis of a cerebellar role in personality disorders emphasizing the importance of also examining the cerebellum in the presence of behavioral disturbances in children and adults.

Keywords: cerebellum, behavioral disorder, artero-venous malformation, tractography, developmental lesions

Introduction

The cerebellum plays a crucial role in motor, cognitive and behavioral development [1]. Abnormal cerebellar development and/or early cerebellar damage could impact a wide range of behaviors via the closed-loop circuits connecting the cerebellum with multiple cerebral cortical regions. Between 20 and 40 weeks of gestation, the cerebellum undergoes a period of rapid growth which is unparalleled by that of any other cerebral structure [2]. This developmental pattern strongly suggests the presence of a critical period of cerebellar vulnerability and the possibility that an early injury disrupts the cerebellar programmed developmental course. In turn, the disruption of cerebellar growth could have significant effects on the structure and function of the cortical regions to which it projects [3].

Based on this hypothesis, there is increasing interest in the study of cerebellar role in developmental disorders. In particular, advances in perinatal care and brain imaging techniques have improved the diagnostic accuracy in detecting cerebellar malformation in infants, suggesting a cerebellar crucial role in typical development [1]. Furthermore, it has been also evidenced that the specific consequences of early cerebellar injury may be predicted on the basis of lesion localization, since a specific cerebellar functional topography has been demonstrated also in childhood [4,5]. These studies are crucial to clarify the cerebellar role in neurodevelopmental disorders such as autism and ADHD and to understand the relationship between localization of the cerebellar lesion and prognosis in pediatric cerebellar damage [5,6].

Moreover, recent evidence in pediatric populations supports the hypothesis that prenatal cerebellar lesions cause changes on distal regions of the brain to which the cerebellum projects, causing long-term effects on behavior, affective regulation [6] and neuropsychiatric symptoms [4,7].

In light of these assumptions, Schmahmann and colleagues [4] reported that adults with cerebellar injury and children who have undergone cerebellar tumor resection experience emotional dysregulation. Specifically, impaired behavioral modulation and flattening or disinhibition of affect are the most prominent manifestation in cases of vermal/paravermal structural abnormalities [4,8].

The authors grouped the neuropsychiatric effects of cerebellar damage into 5 main domains: control of attention, control of emotion, social skill set, psychosis spectrum disorders, and autism spectrum disorders.

Additional evidence of the cerebellar role in psychiatric disorders is provided from the existence of cerebellar abnormalities in various psychopathological disorders, such as schizophrenia, obsessive

compulsive disorder, bipolar mood, and autism [9-11]. Although behavioral impairments after cerebellar damage have been reported, the specific cause-effect relationship between the cerebellar damage and psychiatric disorders remains debated.

In this report, we describe a subject in whom a cerebellar arteriovenous malformation (AVM) occurred with a history of behavioral dysregulation since childhood.

Case

MT, a 43-year-old right-handed woman, was admitted to the Ataxia Laboratory of Fondazione Santa Lucia in May 2015. In July 2014 she suffered from a rupture of a cerebellar MAV which was treated with embolization.

At admission, a neurological examination revealed severe ataxia with a total motor score of 46/100, per the International Cooperative Ataxia Rating Scale (ICARS) [12]. The patient had normal consciousness of her cerebellar diagnosis and she was oriented.

During the clinical interview, MT referred some cognitive problems emerging in the months following the embolization, i.e. poor concentration and some difficulties in finding the meaning of the words.

However, MT's major complaint was her behavioral abnormalities. Specifically, the patient reported disinhibition or inappropriate behavior (e.g., laughter in improper contexts, such as during funerals and work meetings), emotional lability, irritability, aggressiveness, attention disturbances, affective instability, impulsiveness (e.g., spending money irresponsibly), and altered body perception. Moreover, MT complained of transient stress-related psychotic-like symptoms, such as visual hallucinations—she saw fleas, flamingos running around the house, and waterfalls in the kitchen—and dissociative symptoms that were more frequent when she brooded over something, despite more often being in a manic state.

Based on MT's anamnestic reporting, these symptoms were not present before the rupture of the cerebellar AVM and only after the embolization her husband noted deterioration in her impulsiveness and aggressiveness along with the onset of inappropriate behaviors.

To better understand the behavioral profile of the patient we investigated her behavior also in childhood. She described her childhood as happy and peaceful but reported frequent acts of psychological bullying against other children, aggressive and impulsive behaviors with underestimation of her own safety.

These behaviors were underestimated and never been investigated by MT relatives because her cognitive and educational profile had always been normal. She had never taken any psychiatric medication and she had worked as a lawyer until the AVM rupture.

Methods

The cognitive abilities and the behavioral profile of MT were examined extensively through a neuropsychological and a psychiatric assessment.

The experimental procedures were approved by the ethical committee of IRCCS Santa Lucia Foundation and written consent was obtained from all participants according to the Declaration of Helsinki.

Neuropsychological assessment

The neuropsychological protocol covered all cognitive domains including: Intellectual level, Verbal Memory, Visuospatial Memory, Visuospatial Abilities, Language, Executive Functions and Attention (Table 1) [13-30]. Moreover, considering the cognitive problems referred by the patient, attention ability has been thoroughly investigated by the “Test of Attentional Performance” (TAP) [31] (Table 2). To evaluate the attention ability of MT by TAP, five healthy subjects well matched for age, sex and education were enrolled.

The following tests were performed:

Intellectual level: Wechsler Adult Intelligence Scale-Revised Intelligence Quotient (WAIS-r IQ) [13-15]; Raven's Progressive Matrices '47 test [16].

Verbal Memory: immediate and delayed recall of Rey's 15 words [17]; Prose Memory [18]; forward and backward digit span [19,20].

Visuospatial Memory: Rey-Osterrieth Complex Figure Test (recall) [21]; forward and backward Corsi [22].

Visuospatial abilities: Rey-Osterrieth Complex Figure Test (copy) [21].

Language: Naming objects, Naming verbs and Naming objects described by the examiner [23]; Generation of sentences [18]; Token Test [24].

Executive Functions: phonological fluency [25]; verbal fluency [26]; Wisconsin Card Sorting Test (WCST) (number of perseverations and perseverative errors) [27]; Tower of London procedure (TOL) [28]; Stroop Test (“time effect” and “error effect”) [21].

Attention: Multiple Features Target Cancellation task [29]; Trail Making Test B-A (TMT B-A) [30].

In order to further evaluate the MT's attention abilities, four tasks of the TAP battery were used: Flexibility (a "set-shifting" task), Go/NoGo (a selective attention task), Divided Attention and Working Memory.

Psychiatric assessment

The psychiatric assessment comprised the Minnesota Multiphasic Personality Inventory-2 score (MMPI-2) [32], Structured Clinical Interview for DSM IV Axis I Disorders (SCID I) [33], Structured Clinical Interview for DSM IV Axis II Disorders (SCID-II) [34] and Toronto Alexithymia Scale-20 items (TAS-20) [35], while an initial evaluation of her mood was performed by Beck Depression Inventory II Test (BDI II) [36].

Magnetic Resonance Imaging Examination

Advanced MRI data were acquired in order to investigate specific macro- and micro-structural abnormalities associated with patient's cerebellar lesion. Moreover, examination of tomography images (PET) was used to detect possible alterations in cortical or subcortical regions.

Results

Neuropsychological assessment

Despite a normal intelligence quotient (IQ = 105), per the Wechsler Adult Intelligent Scale-Revised (WAIS-R) (short version with four subtests) [13-15], MT showed better performance in Verbal Scale subtests (vocabulary and arithmetic subtests) than those in Non-Verbal Performance Scale subtests (block design and picture arrangement subtests) (Table 1). Considering the cut-off value of the neuropsychological test, attention, visuospatial, memory, and language domains were impaired. Furthermore, in TAP tasks the chi square analysis between MT's and controls' values showed significant differences in Go/NoGo and Flexibility tasks (Tables 1-2).

Psychiatric assessment

The TAS-20 score was within the range of alexithymia and BDI II score indicated a mild (Tables 3). An analysis of MMPI-2 scores demonstrated a tendency to take refuge in strange fantasies and escape from reality and to develop histrionic traits, manic mood, and aggressive behavior with antisocial traits. Overall, the MMPI-2 indicated borderline personality disorder (BPD) with mixed traits, attributed to Cluster B per DSM IV –TR [37]. The use of DSM-IV-TR is linked to the possibility of using the Italian version of the psychiatric scales SCID I and SCID II. Indeed, at the time of MT's psychological assessment the Italian version of these scale related to the new DSM- 5 criteria [38] was not yet available. However, it is worth noting that the diagnostic criteria for MT's specific personality disorder did not change between DSM-IV-TR and DSM- 5.

A personality examination using SCID II confirmed MT's borderline personality organization (Figure 1). Notably, SCID II revealed that MT had suffered from adjustment disorder with a disturbance in conduct since she was a child.

Magnetic Resonance and PET Imaging Examinations

A brain MRI examination that was performed at the time of testing detected macroscopic abnormalities in the left cerebellar hemisphere, the left middle and superior cerebellar peduncles, the superior part of the vermis, and the left portion of the pons (Figure 2). Specifically, the cerebellar lesion, anatomically localized with reference to the SUIF atlas [39], affected lobules VI, VIIa (Crus I), and IX, and the posterior area of the vermis with sparing of the dentate nucleus [39]. By diffusion imaging—a quantitative MR technique that is sensitive to microscopic brain tissue damage—a pattern that was suggestive of demyelination (i.e., impaired radial diffusivity, RD) appeared in the left middle and superior cerebellar peduncles (see Figure 3). VBM did not reveal any regional change (for a detailed description of MRI methods, see Electronic Supplementary Material).

Consistent with the MRI findings, PET imaging showed isolated reduction of glucose metabolism in the left cerebellar hemisphere and a slight decrease in the right cerebellar hemisphere, but no alterations were detected in other cortical or subcortical regions.

Discussion

The described patient suffered from cerebellar hemorrhagic stroke due to a AVM in cerebellar areas that mediate cognitive and emotional processing [51,52].

During cognitive and emotional paradigms, functional neuroimaging activation is localized to the cerebellar posterior lobe in lobules VI and VII, involving Crus I and Crus II, with no anterior lobe involvement [52]. Moreover, damage to the posterior vermis, including parts of lobule IX, is most often associated with emotional lability, flattened affect, and disinhibited behavior [51,53].

The patient's MRI scan showed the lesion extended to the posterior hemispheric regions of the cerebellum, including lobules VI, VIIa (Crus I), and IX, and the posterior area of the vermis (see Figure 2). Consistent with the literature [54] MT suffered from cognitive and behavioral symptoms that are part of Cerebellar Cognitive Affective Syndrome (CCAS) [55].

The presence of behavioral and emotional symptoms when MT was a child could be compatible with the congenital nature of the AVM. Indeed, early cerebellar damage has been often associated with poorer outcomes than cerebellar damage in adulthood, suggesting that the cerebellum is particularly important during development [3].

However, in childhood MT did not show any delays in cognitive domains or academic attainment. Since it has been advanced that specific regions of the cerebellum are more important than others during cognitive development [5,56], the lack of cognitive symptoms (or, at least cognitive symptoms so serious to affect MT's school performance or to worry her family) could be due to the AVM localization before its rupture. Indeed, no data on the extent of the lesion before the stroke are available, because the patient was unaware of her cerebellar malformation before the acute event.

Furthermore, the probable congenital nature of the AVM is compatible with a remodeling of the cerebello-cortical network during development [5]. As suggested by Stoodley and Limperopoulos [6], the cerebellum contributes to typical development by means of the structural and functional optimization of the cerebello-cortical circuits that underlie the acquisition of skills in several domains. Since the cerebellar structure-function relationships change across age in specific regions [5], it is likely that an early cerebellar lesion can affect in a different way cognition and behavior not only according to the localization of the cerebellar lesion but also according to age [5].

Previous studies on pediatric populations have linked an increased GM in the posterior cerebellum (lobules VI through IX) with better cognitive scores [5]. The same regions belong to fronto-parietal cognitive networks [57] and are largely involved in specific abilities [52,58-59]. For example, Stoodley and colleagues [59] found that a lesion of right lobules VII through IX is associated with poorer scores in

a language task (i.e. the Boston Naming Test) while a right lesion in Crus II through VIIIB is linked to a lower score in Rey Figure copy task.

In MT the rupture of cerebellar AVM caused a lesion also involving the cerebellar cognitive lobules, thus justifying the onset of behavioral and cognitive symptoms, both PET and MRI images did not detect any alterations in other subcortical or cortical regions. We advance the hypothesis that the impairments of MT were due to the alterations in the network between the cerebellum and the cerebral regions.

In this regard, the changes in diffusivity in MT's cerebellar peduncles suggest a dysregulation of cerebellar modulation, which consequently affects the cerebello-cortical interplay. Thus, the cerebellum could be prevented from receiving, optimizing, and sending back newly processed information to cerebral cortex regions. Notably, the evident pattern of RD changes in MT is suggestive of demyelination. Myelin allows nerve signals to travel quickly and neural signal transmission to be efficient. Thus, when this transmission is disrupted, long-term alterations in cerebello-cortical circuits arise, significantly impacting behavior [60].

These findings suggest that the lesion of MT in adult age has probably altered the particular stability of the intricate connections between the cerebellum and the cerebral regions that had been structured in early age as consequence of the AVM. Thus, the cerebellar damage of MT in adulthood caused more serious cognitive and behavioral alterations than those present before the rupture of her AVM, worsening the already altered connection between cerebellar output channels and the associative cerebral areas, even without the presence of evident cortical damage. In particular, with regards to the behavioral component of CCAS, after the AVM ruptured, the behavior of the patient morphed into specific psychiatric symptoms, allowing to make a well-defined diagnosis of BPD.

The psychiatric symptoms in our patient are consistent with the classification of neuropsychiatric manifestations described in the presence of cerebellar lesions [4]. Indeed, considering that the cerebellar lesion also involves the posterior vermis, the presence of behavioral dysregulation is in line with an impaired emotional modulation that has been observed in patients with frontal-subcortical network disruption [4]. According with the dysmetria of thought hypothesis [61], the loss of vermal-fastigial influence on cortical component of Papez' limbic ring [62] (i.e. cingulate gyrus, pregenual, retrosplenial and paralimbic neocortical regions) may prevent the individual's ability to give right responses (context dependent) to control the behavior. In fact, this cerebello-cortical network has been proposed to be necessary to support the complex functions inherent in emotion and affect [63,64].

In light of this report and other clinical and neuroimaging findings, the study of the effects of cerebellar lesions should be broadened to include the most complex psychiatric disorders with specific personality examinations of cerebellar patients. We hypothesize that congenital malformations that are confined to the cerebellum can lead to wide-ranging cerebral reorganization that is difficult to predict and might account for the variability in clinical phenotypes.

In conclusion, the present report provides further support to the hypothesis of a cerebellar role in personality disorders and it describes the first case in which the link between cerebellar lesion and well-defined personality disorder, according to the classic psychiatric nosology, seems to be evident. Moreover, it suggests that in presence of behavioral disturbances the existence of a cerebellar pathology should be also considered in both adults and children.

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Conflict of interest

The authors have no conflict of interest to declare.

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Table 1. Patient's cognitive profile

Cognitive Domains	Tests	Raw score	Correct Score	Cut off Normative data
<i>INTELLECTUAL LEVEL</i>				
	WAIS-R IQ ^[13-15] :	113	105	<70
	-Vocabulary	62	14	<7
	-Arithmetic	12	12	<7
	-Block Design	28	8	<7
	-Picture Arrangement	11	9	<7
	Raven Progressive Matrices ^[16]	31	26,2	18,96
<i>VERBAL MEMORY</i>				
	Rey's 15 mots short term ^[17]	50	48	28,53
	Rey's 15 mots long term ^[17]	13	10,6	<4,69
	Prose Memory ^[18]	11,4	9,15	≤4,5
	Forward digit span ^[19-20]	6		7+/-2
	Backward digit span ^[19-20]	4		5+/-2
<i>VISUOSPATIAL MEMORY</i>				
	Rey-Osterrieth figure (recall) ^[21]	14,5	12	9,46≤
	Forward Corsi ^[22]	7		7+/-2
	Backward Corsi ^[22]	5		5+/-2
<i>VISUOSPATIAL ABILITY</i>				
	Rey-Osterrieth figure (copy) ^[21]	29	26,75*	≤28,87
<i>LANGUAGE</i>				
	Naming objects ^[23]	27*		28<
	Naming verbs ^[23]	26		26<
	Naming objects described by the examiner ^[23]	16		14<
	Generation of sentences ^[18]	13	9,25	≤6,25
	Token Test ^[24]	34	31*	<32
<i>EXECUTIVE FUNCTIONS</i>				
	Phonological fluency ^[25]	28	18,3	17,35
	Verbal fluency ^[26]	21	50°perc	<10°perc
	Wisconsin Card Sorting Test ^[27] :			
	Total Number of errors	10	108 PS	<85 PS
	Total Number of perseverative errors	5	100 PS	<85 PS
	Tower of London ^[28]	31	33,2	<32
	Stroop Test ^[21] :			
	Time score	22,5	30,5	≥36,92
	Errors score	2	3,25	≥4,24
<i>ATTENTION</i>				
	Multiple features targets cancellation task- Accuracy ^[29]	0,80*		<0,869
	Trail Making Test –Time ^[30] :			
	Part A	58s	64	>93s
	Part B	70s	99	>282s
	Part B-A	12	35	>186s

Perc= percentile; PS= standard point; s= seconds.

* value under the cut-off normative data

Table 2. Patient and five matched control subjects' performance on the Test of Attentional Performance – TAP (version 2.2) ^[31]

TASK	<i>Patient's score</i>		<i>Control subjects's score</i>	
	N° Errors	Accuracy	N° Errors	Accuracy
Flexibility	6	88%*	1	98%
Go/NoGo	7	78%*	0	99%
Divided attention	3	86%	2	97%
Working memory	3	85%	1	92%

* Performance significantly different between the patient and the control subjects as assessed by chi square analysis $p < 0,005$

Table 3. Patient's scores on the Psychiatric Scales

Test	Raw score	Scoring
TAS-20 ^[35]	72	≤ 51 = non-alexithymia 52-60 = possible alexithymia ≥ 61 = alexithymia
BDI II ^[36]	18	0-13 = no depression 14-19 = mild depression 20-26 = moderate depression 27-63 = severe depression

TAS-20= Toronto Alexithymia Scale-20 items; BDI= Beck Depression Scale.

Fig. 1 The Diagnostic Criteria of DSM IV-TR needed for the diagnoses of BPD are based on the patient's SCID II and for the diagnosis of Bipolar I Disorder on SCID I. The criteria met by the patient are underlined in the figure.

Borderline Personality Disorder :

Characteristics: Pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5)
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Bipolar I Disorder Most Recent Episode Mixed :

Characteristics: it is characterized by one or more Manic or Mixed Episodes, usually accompanied by Major Depressive Episodes.

- A. Currently (or most recently) in a Mixed Episode.
- B. There has previously been at least one Major Depressive Episode, Manic Episode, or Mixed Episode.
- C. The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Fig. 2 Lesion reconstruction and localization of the involved cerebellar structures, as depicted in MRI scans. Lesion reconstruction is presented and superimposed on coronal (=y), sagittal (=x) and axial (=z) slices of the SUIIT atlas template after spatial normalization [39].

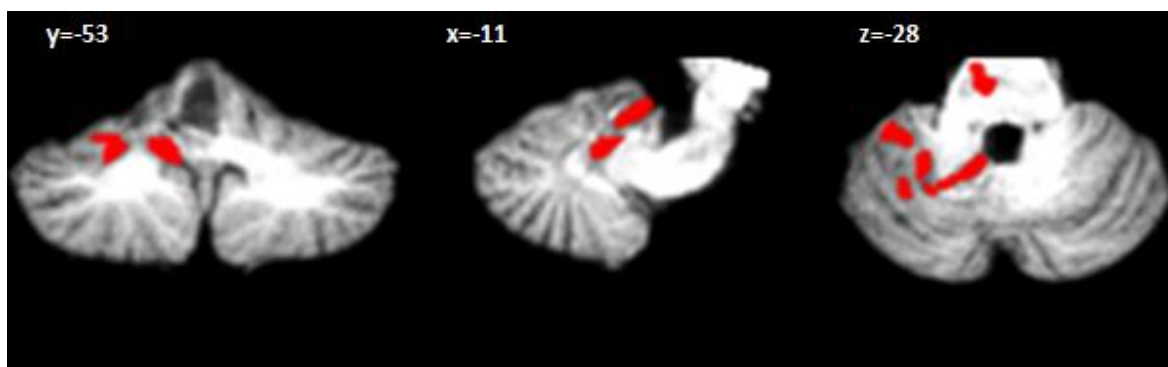


Fig. 3 Regions of Radial Diffusivity (RD) increase in the left middle (a, red) and superior (b, green) cerebellar peduncles of the patient compared to control subjects (FWE $p < 0.05$), presented and superimposed on coronal (=y), sagittal (=x) and axial (=z) slices of the SUIIT atlas template

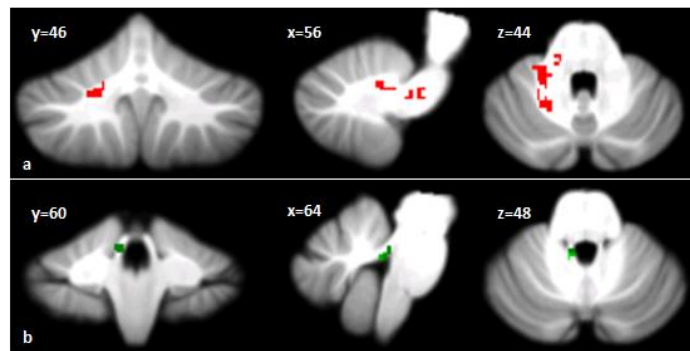
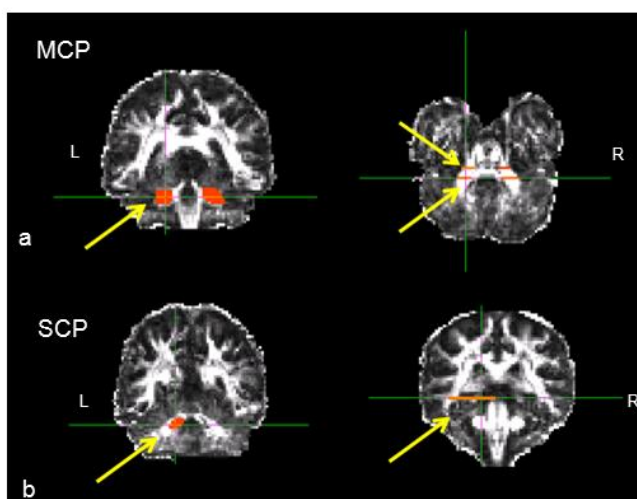


Fig. 4 Anatomical localization of Cerebellar ROIs for tractography of MCP and SCP

ROIs reconstruction is presented on the FA map images for MCP (a) and SCP (b) tracking. For MCP, the coronal seed ROIs (in red) are illustrated (left side of the figure a). In the axial slice (right side of the figure a), cerebellar seed and waypoint ROIs are indicated by the yellow arrows. For the left SCP, the seed region (coronal slice, left side of the figure b) and the endpoint ROI (represented in orange in the axial slice, right side of the figure b) are illustrated (yellow arrows). For the right SCP (ROIs not shown) the same masks were used swapping right and left hemispheres.

ROI= region of interest; MCP= middle cerebellar peduncle; SCP= superior cerebellar peduncle; FA= Fractional Anisotropy.



Supplementary Material

Electronic Supplementary Material

MRI acquisition protocol

As part of the present research study, an advanced MRI protocol was acquired in order to investigate specific macro and microstructural patterns associated with patient's cerebellar damage. A group of 25 healthy subjects (HS) [F/M=19/6] ranging from 40 to 60 years [mean age \pm SD = 53.8 \pm 5.9 years] of age with no history of neurological or psychiatric illness were also recruited for the MRI analysis as controls. Both patient and HS group underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany), including the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); 2) fast-FLAIR (TR = 8170 ms, 204TE = 96 ms, TI = 2100 ms); 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR = 1338 ms, TE = 2.4 ms, Matrix = 256 \times 224 \times 76, in-plane FOV=250 \times 250mm², slice thickness=1 mm); 4) diffusion weighted Spin-Echo Echo Planar Imaging (SE EPI) along 61 non-collinear directions (TR=7 s, TE=85 ms, b factor=1000 s.mm⁻², 45 contiguous slices volumes with a 2.3mm³ isotropic reconstructed voxel size). Information about patient's lesion location was available from previous clinical scans. Nevertheless, the anatomical distribution of tissue damage in terms of cerebellar structures involved and the absence of any extra-cerebellar abnormality were further investigated by an expert neuro-radiologist and performed by visual inspection of the T2-weighted MRI scans acquired as part of this research study. TSE scans were also reviewed to exclude the presence of other remarkable extracerebellar abnormalities in HS assuring that they met inclusion criteria as controls.

MRI image and data analyses

Cerebellar Lesion Assessment

For the patient, a detailed assessment of the macroscopic cerebellar lesion was performed on high-resolution T1-weighted images. The cerebellum was normalized separately to the spatially unbiased infratentorial template (SUIT) atlas of the cerebellum and brainstem [39]. The patient's lesion was manually outlined using the FSL view image viewer from the FMRIB software library (FSL, www.fmrib.ox.ac.uk/fsl/) and anatomically localized with reference to the SUIT atlas. The cerebellar lesions reconstruction and distribution is illustrated in Figure 2.

DTI processing

Correction for eddy currents and small head movements was done on DTI volumes by means of affine registration to the first non-diffusion weighted volume using FSL [40]. After brain segmentation with the BET utility [41] the diffusion tensor (DT) coefficients were computed in Camino [42] to generate whole brain maps of the DTI metrics, including fractional anisotropy (FA), radial diffusivity (RD), mean diffusivity (MD) and axial diffusivity (AD). Each FA volume was registered to the native space MDEFT volume with a linear registration first, followed by a non-linear transformation. The target for the linear registration was the skull-stripped MDEFT, while the original volume (including skull) was the target for the non-linear transformation. The registration was achieved using the tools FLIRT [43] and FNIRT [44] from FSL. This “FA to MDEFT” transformation was combined with each individual “MDEFT to MNI” transformation, obtained by non-linear registration of the MDEFT to the ICBM152 MNI template. This resulted in the final transformation from each participant’s DTI space to the ICBM152 MNI template.

DTI based Tractography

MCP and SCP were reconstructed using tractography based on two multi-fiber models implemented in Camino. Qball [45] was used for MCP, as it provides less false positive fiber components. PAS MRI [46] was used for SCP, as it deals more effectively than QBall with fiber crossing. Once the multi-fiber directions were estimated, probabilistic tractography was carried out based on these data using the PICO algorithm. $N = 10000$ tracking iterations were performed from each voxel of the seed Region of Interest (ROI) with stopping criteria of $FA \leq 0.1$ and curving angle $\leq 80^\circ$. Five ROIs were manually drawn on the FA map images for MCP tracking. A seed ROI was placed bilaterally on a single coronal section, anteriorly to the dentate nucleus of each cerebellar hemisphere, and two coronal waypoint ROIs were located bilaterally and anteriorly to each seed ROIs. Finally an exclusion ROI was placed in axial plane above the pons to prevent fibers not belonging to the middle cerebellar peduncle to be tracked. Left (L-) and right (R-) SCPs were separately reconstructed. For L-SCP, originating from the left cerebellar hemisphere, five ROIs were drawn: one ROI (i.e., “seed” region for tractography) was drawn on a single coronal slice in the dentate nucleus, while two endpoint ROIs were drawn as target points. The first was located posteriorly to the seed to select all extremities going posteriorly, while the second one contralaterally to include the red nucleus and its medial area, where SCP decussates before terminating in the contralateral ventrolateral (VL) nucleus of the thalamus [47-48]. Finally, in order to exclude fibers not belonging to the L-SCP, two ROIs were drawn as exclusion masks and located as follows: the first one

was placed immediately superiorly to the second endpoint ROI on the whole coronal slice, and the second one in a sagittal plane to extend superiorly up to a few voxels below the known SCP decussation. The same procedure was followed for the R-SCP, swapping right and left hemispheres. Cerebellar ROIs for reconstruction of MCP and SCP are illustrated in Figure 4.

In order to obtain a binary map of the “average tract”, every subject’s reconstructed MCP, L-SCP and R-SCP maps were binarised using a probability threshold for probability index of connectivity (PICO) maps computed by in-house software to minimize the amount of tract volume variation with PICO threshold. These images were then warped into standard space using the FA to ICBM152 MNI space transformation previously calculated, and averaged. The resulting maps were thresholded to retain only those voxels that were common to at least 50% of subjects.

Voxel-based morphometry of white matter tracts

A voxel-wise analysis was performed in order to compare diffusivity white matter changes between single case patient and healthy controls, restricting the comparison to the voxels of the MCP and SCP, based on the average tract masks obtained as described above. T -contrasts were evaluated with voxel significance set at $p < 0.0001$ and corrected for family-wise error (FWE) at cluster level with significance level chosen for $p < 0.05$. Multiple diffusion tensor measures were used (in order to better characterize the tissue microstructure [49]). The analysis was adjusted for age and sex.

Voxel Based Morphometry of Cerebral GM

MDEFT volumes were segmented into grey matter (GM) maps and registered to MNI space by means of the “New Segment” and “DARTEL” routines in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>, Wellcome Trust Centre for Neuroimaging, Institute of Neurology University College London, UK) [50]. VBM statistical analysis was performed to compare the GM maps between the patient and HS group entered as independent groups. The analysis excluded voxels in the cerebellum and was restricted to the cerebrum entered as explicit mask. Age, gender and intracranial volume (ICV) were set as nuisance variables. T -contrasts were evaluated with voxel significance set at $p < 0.0001$ and corrected for family -wise error (FWE) at cluster level with significance level chosen for $p < 0.05$.

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