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# Balance deficit with opened or closed eyes reveals involvement of different structures of the central nervous system in multiple sclerosis

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## Abstract

**Objective:** To evaluate whether balance deficit in patients with multiple sclerosis (MS), as assessed with eyes opened (EO) and closed (EC), is associated with damage of different structures of the central nervous system (CNS).

**Methods:** Fifty patients with MS and 20 healthy controls (HCs) underwent static posturography to calculate the body's center of pressure displacement (COP path) with EO and EC. They were scanned using a 3.0T magnet to obtain PD/T2 and 3D-T1-weighted images of the brain and spinal cord. We determined the mid-sagittal cerebellum area (MSCA) and upper cervical cord cross-sectional area (UCCA). We also measured the patients' lesion volumes (T2-LVs) on the whole brain and at different infratentorial levels.

**Results:** MS patients had wider COP paths with both EO and EC ($p < 0.001$), and lower values in both MSCA ($p = 0.01$) and UCCA ($p = 0.008$) than HCs. The COP path with EO was associated with MSCA (Beta = – 0.58; $p = 0.004$) and T2-LV on middle cerebellar peduncles (Beta = 0.59; $p = 0.002$). The COP path with EC was associated with UCCA (Beta= – 22.74; $p = 0.003$) and brainstem T2-LV (Beta = 0.52; $p = 0.01$).

**Conclusions:** Balance deficit in MS was related to atrophy of both the cerebellum and spinal cord, but the extent of COP path under the two different conditions (EO or EC) implied different patterns of damage in the CNS.

## Keywords

Balance, center of pressure displacement, disability, lesions, magnetic resonance imaging, multiple sclerosis, posturography, vision

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## Introduction

Lack of balance is common in patients with multiple sclerosis (MS) and is among the most disabling symptoms, since it reduces mobility and independence, leads to falls and injuries, and impacts overall quality of life.[1–3]

The neuropathological mechanisms leading to balance impairment in MS are not yet well determined. The poor postural control seen in these persons, who have an extensive and variable damage in their central nervous system (CNS), may be due to multifactorial causes that differ from one person to the next.[2] It has been suggested that postural balance deficit due to MS results from impaired central integration of visual, vestibular and somatosensory input;[4] however, it is also possible that lesions in specific locations, and their consequent impairment, are the primary contributors to balance deficit in MS.

The assessment of postural balance in the upright stance, with the patients' eyes opened (EO) and after eyes closed (EC), is usually adopted in clinical practice to distinguish ataxia due to cerebellar damage from a proprioceptive deficit in the lower limbs (Romberg's test);[5] however, the localization properties of this clinical test are reported as questionable[6] and even computer-based force platform measures were not demonstrated to be particularly useful in

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distinguishing among different causes of balance deficit, nor in localizing lesions.[7]

Examining the latency and scaling of automatic postural responses, some authors have postulated that balance deficit in MS is the result of slowed afferent proprioceptive conduction along the spinal cord, rather than cerebellar dysfunction.[8] By using magnetic resonance imaging (MRI) techniques, studies investigating the structure-function relationship report that standing balance, as measured by force platform recordings, can be impaired owing to damage of spinal cord,[9] cerebellar connections (i.e. cerebellar peduncles)[10] or, more extensively, focal and diffuse involvement of the cerebellum, its connections and other associative regions.[11]

So far, none of the aforementioned studies have carried out a comprehensive assessment of the role of both cerebellum and spinal cord damage in causing balance deficit. Potentially, the development of an *in vivo* anatomical framework for interpreting the pathological substrate of balance disorders in MS can be useful in developing tailored rehabilitative programs, focusing on interventions that can restore the function related to the specific structure more involved in balance deficit. Therefore, we aimed to investigate *in vivo*, by means of MRI and static posturography, the association between damage to these two CNS structures and balance deficit in patients with MS.

## Methods

### Participants

We recruited 50 patients diagnosed as affected by MS, according to the 2005 revision of McDonald criteria,[12] and whom regularly attended the MS Center of S. Andrea Hospital in Rome; plus 20 sex/age-matched healthy controls (HCs), for this single-center cross-sectional study. Approval was obtained from our Institutional Review Board (IRB); before any study procedure, each participant signed a written informed consent.

Inclusion criteria were: an age ranging from 18 to 55 (inclusive) years; ability to walk without support/aid; an Expanded Disability Status Scale (EDSS) score[13] ranging from 0 to 5.5 (inclusively). Exclusion criteria were: severe blurred vision, concomitant otological disease, significant cognitive impairment, relapse occurring over the previous 6 months, history of seizures and contraindications to MRI.

Eligible patients underwent the clinical evaluation, static posturography assessment and MRI scanning within the span of 1 week; the HCs also underwent the same static posturography and MRI protocol.

### Clinical evaluation

Demographic and clinical variables were collected for each subject, such as gender (female or male); age; and body mass index (BMI), calculated as weight/height$^2$ (kg/m$^2$). Disease duration was also collected for patients with MS. They also underwent a detailed neurologic examination by the agreement of two board-certified neurologists, including the EDSS score and the 25-foot walking test (25-FWT), to estimate the patients' walking speed (expressed as m/s). The 25-FWT is a stopwatch measurement of time (seconds) to walk a 25-foot (7.6 meters) distance.[14] It has shown good reliability and validity, and represents the most characterized measure of walking speed in patients with MS.[15]

### Static posturography

The assessment of static standing balance was performed using a force-platform (ProKin, Tecnobody, Bergamo, Italy; http://www.tecnobody.it), consisting of three strain gauges set in a triangular position under a 55-cm diameter surface, with a 20 Hz sampling rate and a sensitivity of 0.1°. Room temperature and light were standardized, and all trials were conducted by an experienced operator. Subjects were asked to stand barefoot on the ground, in an upright static condition, double-leg stance and with arms resting at their sides. The position of the feet on the force-platform was standardized using a V-shaped frame, keeping a 3-cm distance between the two medial malleoli and an extra rotation of 12° with respect to the sagittal axis. Displacements of the body's center of pressure (COP path) were recorded for 30 seconds in both the EO and EC conditions, as published elsewhere.[16] It is reported that the COP path not only has very good test-retest reliability, but also that it's more accurate than common clinical tests in discriminating MS patients that are prone to accidental falls over a 3-month period.[17]

### MRI acquisition

Each participant was scanned using a 3.0T magnet (Verio, Siemens AG, Erlangen, Germany) to obtain dual-echo fast spin-echo and 3D-T1-weighted images of the brain and spinal cord. The following sequences were acquired: (a) dual-echo turbo spin (Proton Density (PD) and T2-weighted) axial sequence (repetition time (TR) = 5,310 ms, echo time (TE) = 10/103 ms, echo train length = 28, matrix = 384x90, field of view (FOV) = 220 mm, iPAT reduction factor = 3, acquisition time = 5'04"), with 40 slices 4-mm thick and a 0-mm interslice gap; (b) 3D-T1-weighted MPRAGE sequence with 176 axial, 1-mm slices, with no gap (TR = 1,900 ms, TE = 2.3 ms, flip angle = 9°, matrix = 256x98, FOV = 240 mm, acquisition time = 3'48"); (c) T1-weighted spin echo after administration of gadolinium-based contrast agent (TR = 550 ms, TE = 9.8 ms, matrix = 384x90, FOV = 220 mm, time 2'15") with 40 slices 4-mm thick and a 0-mm interslice gap.

### Image analyses

Image data processing was performed by two experienced operators, both blinded to clinical data, on a Linux workstation running the Jim 5.0 software (Xinapse System, Leicester, UK; http://www.xinapse.com).

In both patients and HCs, we estimated the mid-sagittal cerebellum area (MSCA) and upper cervical cord cross-sectional area (UCCA) at the C2-C3 intervertebral disk level. To take into account biological variation in CNS size, both measurements were normalized for intracranial cross-sectional area (ICCSA). For each participant, ICCSA was semi-automatically measured on an axial T2-weighted axial slice at the level of the inferior margin of corpus callosum, as previously described.[18]

MSCA measurements ($mm^2$) were obtained on 3D-T1-weighted MPRAGE sequences, according the following procedure:

1. A slice in which the aqueduct of Sylvius is more clearly visualized was identified among the midsagittal images;
2. This image was aligned according to a line passing through the splenium and genu of corpus callosum;
3. A region of interest (ROI) was automatically created by means of different signal intensities to outline the boundary between the cerebellum and cerebrospinal fluid in the posterior fossa.

Although some authors suggest this measure correlates with total cerebellar volume in patients with psychiatric disorders,[19] while others do not,[20] it is reported as highly reliable.[20] Moreover, the vermis is specifically activated (together with occipital cortex and anterior lobe of ceberellum) during upright standing, as is demonstrated by nuclear brain imaging techniques.[21]

UCCA values ($mm^2$) were quantified on 3D-T1-weighted MPRAGE sequences at the C2-C3 segments, using an automatic edge detection technique,[22] as follows:

1. Images were re-formatted axially such that the spinal cord was perpendicular to the axial plane;
2. Five contiguous 3-mm pseudo-axial slices were obtained using the center of the C2-C3 intervertebral disc as a caudal landmark;
3. A ROI delineating the cord edge was automatically applied to each of 5 axial slices;
4. The average area enclosed by the five ROIs obtained was then calculated, to obtain the UCCA value.

Measurement of UCCA is reported as consistently reliable[22] and clinically relevant in patients with MS.[18,22]

In the patient group, we measured lesion volumes (LVs) ($mm^3$) on axial PD/T2-weighted images, focusing on lesions selectively located at the infratentorial level (brainstem, cerebellum and middle cerebellar peduncles (MCPs)) by means of a semi-automated edge contour technique, as is described elsewhere.[10] LVs at different infratentorial levels were previously reported as related to neurological disability and balance deficit in MS.[11,23,24]

### Statistical analysis

Data are presented as mean (standard deviation, SD), median [range], or proportion, as appropriate. Differences between patients and HCs were tested using the Fisher exact and Mann-Whitney U tests for dichotomous and continuous variables, respectively.

We determined the inter-rater reliability of MSCA and UCCA measurements as intraclass correlation coefficients (ICCs).

Correlations between demographic and clinical variables, standing balance measures and radiological characteristics were also tested using the Spearman rank coefficient, after controlling for sex, age, BMI and ICCSA. We compared the slopes of correlation coefficients between static posturography measurements and radiological features by means of analysis of covariance, in order to determine whether different test conditions (EO and EC) could be related to different patterns of damage in CNS structures.

We investigated the relationships between the COP path in EO and EC conditions (as dependent variables) and radiological features (as independent variables), by stepwise multivariate linear regression analyses (for inclusion: $F \geq 1$ and $p \leq 0.01$; for exclusion: $F < 1$ and $p > 0.05$). Each model was also adjusted for sex, age, BMI and ICCSA.

Lastly, to verify whether different patterns of balance deficits were associated with different radiological features, patients with MS were divided as follows: no balance deficit, i.e. normal values in both EO and EC (pattern A); normal value of COP path EO, but abnormal COP path with EC (pattern B); abnormal values even in the EO condition (pattern C). Abnormal cut-off values of COP path EO and EC were > 345 mm and > 575 mm, respectively, according to data published elsewhere.[17] These values were set at two SDs above the mean values obtained from 50 HCs.[17] Between-pattern comparisons were carried out by the Kruskal-Wallis test (with Dunn's post-hoc test).

To avoid underestimating the true α-error, $p$-values $\leq$ 0.01 in either direction were considered as significant.[25] Statistical analyses were carried out using the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA).

## Results

### Participants

The demographic, clinical and radiological characteristics of 50 patients and 20 HCs are shown in Table 1. These two samples did not differ in terms of gender, age, BMI and ICCSA. By contrast, walking speed and displacement of

**Table 1.** Demographic, clinical and radiological characteristics of participants.

| | Patients with MS (*n* = 50) | HCs (*n* = 20) |
|---|---|---|
| Sex (F:M) | 37:13 | 15:5 |
| Age (yrs), mean (SD) | 34.6 (8.1) | 32.3 (5.7) |
| BMI (kg/m$^2$), mean (SD) | 21.9 (3.5) | 22.4 (3.8) |
| Disease duration (yrs), mean (SD) | 7.5 (6.2) | N/A |
| Disease course, RR:SP | 35:15 | N/A |
| EDSS median [range] | 2.5 [1.0–5.5] | N/A |
| 25-FWT (m/s), mean (SD) | **1.1 (0.3)** | **1.4 (0.4)**[a] |
| COP path EO (mm), mean (SD) | **448 (312)** | **221 (58)**[b] |
| COP path EC (mm), mean (SD) | **850 (502)** | **335 (120)**[b] |
| ICCSA (mm$^2$), mean (SD) | 16,328 (1293) | 16,785 (1531) |
| MSCA (mm$^2$), mean (SD) | **1,045 (177)** | **1,198 (102)**[a] |
| UCCA (mm$^2$), mean (SD) | **68.7 (8.8)** | **78.4 (8.5)**[b] |
| Whole brain T2-LV (mm$^3$), median [range] | 4,335 [20–42,960] | N/A |
| Brainstem T2-LV (mm$^3$), median [range] | 181 [0–1712] | N/A |
| Cerebellar T2-LV (mm$^3$), median [range] | 52 [0–640] | N/A |
| MCP T2-LV (mm$^3$), median [range] | 138 [0–697] | N/A |

[a]$p \leq 0.01$.
[b]$p < 0.001$.
HCs: healthy controls; BMI: body mass index; EDSS: Expanded Disability Status Scale; 25-FWT: 25-foot walking test; COP: center of pressure; EO: eyes opened; EC: eyes closed; F: female; ICCSA: intra-cranial cross-sectional area; M: male; MS: multiple sclerosis; MSCA: mid-sagittal cerebellum area; UCCA: upper cervical cord cross-sectional area; T2-LV: lesion volumes on PD/T2-weighted images; MCP: middle cerebellar peduncles; N/A: not applicable; RR: relapsing-remitting; SP: secondary progressive.

COP path in both EO and EC conditions were wider in patients than HCs ($p \leq 0.001$ for all comparisons). Moreover, MSCA and UCCA values were significantly lower in patients than HCs ($p = 0.01$ and $p = 0.008$, respectively). Lastly, we correlated the COP path with EO and EC in both patients with MS and the HCs (r = 0.84; $p < 0.001$ and r = 0.71; $p < 0.001$, respectively).

## *Radiological features in patients with MS*

Disseminate involvement of periventricular, juxtacortical and infratentorial white matter was observed in all patients; furthermore, each patient had at least one demyelinating lesion at the spinal cord level. Overall, the median whole brain T2-LV was 4,335 mm$^3$ [20–42,960]. On average, T2-LVs were predominantly distributed at the supratentorial (88%) rather than infratentorial level (12%).

Reliability of MSCA and UCCA was strong, with ICCs of 0.87 and 0.85, respectively (based on 30 subjects measured by each rater).

Table 2 shows correlations between each MRI measurement in the patient group. A strong, direct correlation was found between MSCA and UCCA (r = 0.71; $p < 0.001$). MSCA was found as inversely related to brainstem T2-LV (r = –0.50; $p < 0.001$), and whole brain T2-LV (r = –0.38; $p = 0.01$). The UCCA did not significantly correlate with any of T2-LV measures. Considering only T2-LV measurements, the stronger relationships were found between brainstem T2-LV and (a) cerebellar T2-LV (r = 0.70; $p < 0.001$), (b) MCP T2-LV (r = 0.58; $p < 0.001$). There were no significant relationships between T2-LVs at different infratentorial levels and whole brain T2-LV.

## *Relationships between balance deficit and radiological features in patients with MS*

As expected, disease duration, EDSS score and walking speed were related with almost all MRI findings ($p \leq 0.01$ for all comparisons), except for MCP T2-LV and whole brain T2-LV, which were not related with disease duration and walking speed, respectively (data not shown).

Correlations (adjusted for sex, age, BMI and ICCSA) between static posturography measures and MRI findings are provided in Figure 1. The COP path in both EO and EC conditions was inversely related to MSCA (r = –0.50; $p < 0.001$ and r = –0.45; $p = 0.002$, respectively) and UCCA (r = –0.44; $p = 0.003$ and r = –0.55; $p < 0.001$, respectively). Moreover, we found that the COP path in both EO and EC conditions was directly related with brainstem T2-LV (r = 0.52; $p < 0.001$ and r = 0.49; $p = 0.001$, respectively) and MCP T2-LV (r = 0.49; $p = 0.001$ and r = 0.44; $p = 0.003$, respectively). There was no relationship between COP path in both EO and EC conditions and the whole brain T2-LV or cerebellar T2-LV. Slopes of correlation coefficients did not significantly differ between EO and EC conditions, except for UCCA; however, from a statistical standpoint, this figure has to be considered as only marginal (F = 357.3; $p = 0.042$).

**Table 2.** Correlation analyses concerning radiological features of patients with MS.

| | MSCA, mm² | UCCA, mm² | Whole brain T2-LV, mm³ | Brainstem T2-LV, mm³ | Cerebellar T2-LV, mm³ | MCP T2-LV, mm³ |
|---|---|---|---|---|---|---|
| **MSCA, mm²** | – | | | | | |
| **UCCA, mm²** | **0.71**[b] | – | | | | |
| **Whole brain T2-LV, mm³** | **–0.38**[a] | –0.29 | – | | | |
| **Brainstem T2-LV, mm³** | **–0.50**[b] | –0.34 | 0.25 | – | | |
| **Cerebellar T2-LV, mm³** | –0.37 | –0.36 | 0.24 | **0.70**[b] | – | |
| **MCP T2-LV, mm³** | –0.26 | –0.34 | 0.31 | **0.58**[b] | 0.37 | – |

[a] $p \leq 0.01$.
[b] $p < 0.001$.
MS: multiple sclerosis; MSCA: mid-sagittal cerebellum area; UCCA: upper cervical cord cross-sectional area; T2-LV: lesion volumes on PD/T2-weighted images; MCP: middle cerebellar peduncles.

As seen in Table 3, multivariable regression analyses (stepwise fashion) showed that MRI findings having the strongest association with COP path OE were MSCA (Beta: –0.58; $p = 0.004$) and MCP T2-LV (Beta: 0.59; $p = 0.002$), whereas the COP path EC was most associated with UCCA (Beta: –22.74; $p = 0.003$) and brainstem T2-LV (Beta: 0.52; $p = 0.01$). These estimates did not change significantly, even after inserting disease duration in the two models (data not shown). Both models explain a considerable amount of the variance of COP path (adjusted R-square: 0.47 and 0.40 for EO and EC, respectively).

### *Radiological features underlying different patterns of balance deficit*

After splitting patients with MS into the three patterns defined above, we found no balance deficit in 16 subjects (pattern A), a balance deficit only when visual input was lacking in 16 subjects (pattern B), and a balance deficit even in the EO condition in 18 subjects (pattern C). These three subgroups of patients did not significantly differ in terms of gender, age and BMI (data not shown). By contrast, significant differences were found regarding the median disease duration (A: 3 years [< 1–18]; B: 5 years [< 1–20]; C: 11 years [2–21]; $p < 0.001$ for A versus C), median EDSS scores (A: 1.5 [1.0–3.0]; B: 2.5 [1.0–4.5]; C: 3.5 [2.0–5.5]; $p < 0.001$ for A versus C, and $p = 0.01$ for A versus B), and median walking speed (A: 1.34 m/s [0.69–1.58]; B: 1.15 m/s [0.61–1.55]; C: 0.92 [0.41–1.46]; $p < 0.001$ for A versus C).

Figure 2 shows median values of MRI features according to different patterns of balance deficit. No differences were found between patterns A and B, in terms of MSCA, while pattern C had lower values than B and A ($p = 0.01$ and $p = 0.004$, respectively). By contrast, pattern A had greater values of UCCA than B and C ($p = 0.01$ and $p < 0.001$, respectively). While no other significant differences were found between patterns A and B, pattern B significantly differed from C in terms of brainstem T2-LV ($p = 0.007$). Lastly, there were significant differences between pattern C and A in all the T2-LV measurements, such as whole brain T2-LV ($p < 0.001$), brainstem T2-LV ($p < 0.001$), MCP T2-LV ($p = 0.01$), and cerebellar T2-LV ($p < 0.001$).

## Discussion

The main finding of our study is that damage of both cerebellum and spinal cord are associated with impaired balance in MS, thus confirming the hypothesis that multifactorial causes can affect CNS structures controlling the postural balance;[2] however, despite their stringent relationship, we found different pathological MRI features underlying the extent of COP path in EO and EC. According to the clinical significance of the Romberg sign, when all sensory inputs (visual, proprioceptive and vestibular) were available, the resulting balance deficit related mainly to cerebellum atrophy and demyelinating lesions in the MCPs; while when the visual input was lacking, atrophy of spinal cord demyelinating lesions in the brainstem were the principal contributors of worse postural control.

Cerebellar dysfunctions may cause the failure of predictive feed-forward *control* and/or of the estimation of *motor* command consequences.[26] The role of damage of midline cerebellar structures and/or cerebellar connections in determining balance deficit has been emphasized not only in patients with MS,[10,11,23,24,27,28] but also in those affected by other neurological diseases.[29–31]

Spinal cord atrophy correlates with neurological disability,[18,22,32,33] and damage of this structure has recently been associated with reduced vibration sensation and impaired standing balance in MS.[9,34] As regards our findings, we hypothesized that lesions in the brainstem and spinal cord atrophy have the most impact on balance in the EC condi-

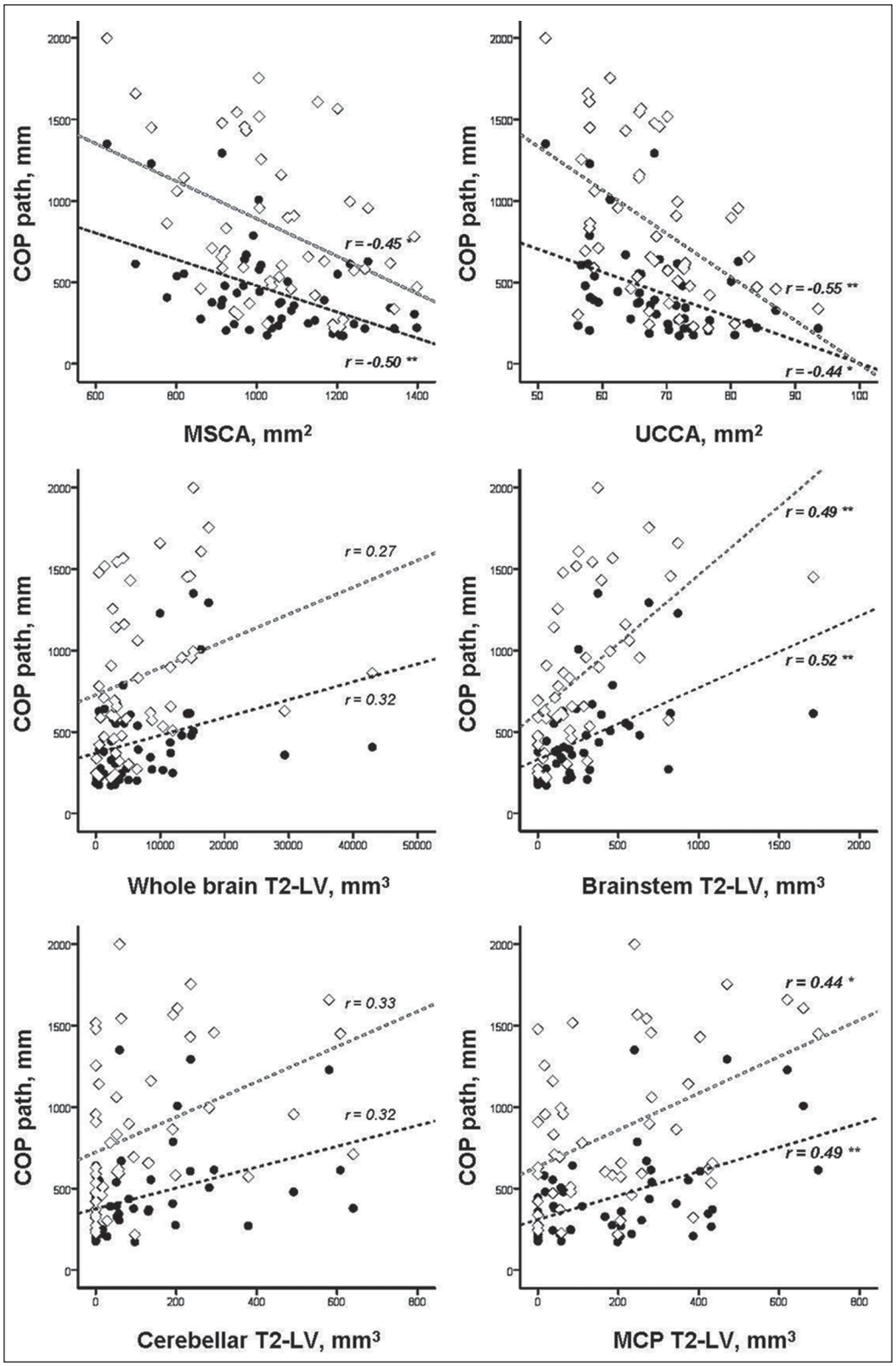


**Figure 1.** Scatterplots showing correlations between radiological features of patients with MS and static posturography, i.e. the COP path with EO (circle) and EC (rumbles), with their relative interpolation lines. *$p \leq 0.01$ **$p < 0.001$.
COP: center of pressure; EO: eyes opened; EC: eyes closed; MS: multiple sclerosis; MSCA: mid-sagittal cerebellum area; UCCA: upper cervical cord cross-sectional area; T2-LV: lesion volumes on PD/T2-weighted images; MCP: middle cerebellar peduncles.

**Table 3.** Multivariable stepwise linear regression analyses with COP path EO and EC as dependent variables of the two models (adjusted for sex, age, BMI and ICCSA). Significance at a level of greater than or equal to 0.01 is bolded.

| Independent Variables | Dependent variable: COP path EO | | | | Dependent variable: COP path EC | | | |
|---|---|---|---|---|---|---|---|---|
| | Beta | 95% confidence intervals | | *p*-value | Beta | 95% confidence intervals | | *p*-value |
| | | Lower bound | Upper bound | | | Lower bound | Upper bound | |
| MSCA | **–0.58** | **–0.97** | **–0.20** | ***0.004*** | –0.60 | –1.31 | 0.12 | 0.10 |
| UCCA | –2.85 | –10.93 | 5.24 | 0.48 | **–22.74** | **–36.87** | **–8.62** | ***0.003*** |
| Whole brain T2-LV | 0.02 | –0.01 | 0.02 | 0.68 | 0.01 | –0.02 | 0.02 | 0.98 |
| Brainstem T2-LV | 0.11 | –0.15 | 0.37 | 0.41 | **0.52** | **0.12** | **0.92** | ***0.01*** |
| Cerebellar T2-LV | –0.10 | –0.69 | 0.48 | 0.72 | –0.12 | –1.05 | 0.81 | 0.79 |
| MCP T2-LV | **0.59** | **0.23** | **0.96** | ***0.002*** | 0.65 | –0.05 | 1.36 | 0.06 |

BMI: Body mass index; COP: center of pressure; EO: eyes opened; EC: eyes closed; ICCSA: intra-cranial cross-sectional area; MSCA: mid-sagittal cerebellum area; UCCA: upper cervical cord cross-sectional area; T2-LV: lesion volumes on PD/T2-weighted images; MCP: middle cerebellar peduncles.

tion, most likely because when visual input fails there is a greater reliance on other sensory systems, especially proprioceptive and vestibular input.

In our population, impaired standing balance in the EC condition was observed in more than 2/3 of the patients with MS, and in about 1/3 of them even in the EO condition, despite the mild-to-moderate disability level and the relatively short disease duration; however, this is not surprising, considering that balance deficit may occur early in the course of MS, and computer-based measures of balance reveal that deficits in postural control may be detected in mildly disabled patients with MS,[35] or even after a first demyelinating event.[36]

Remarkable differences in terms of cerebellum and spinal cord areas were also found with respect to HCs, as previously reported.[11,22,24,32,33] Notably, patients without balance deficit (pattern A) had similar clinical characteristics than those having balance deficit only in EC condition (pattern B). Moreover, the only MRI feature useful for discriminating patterns A and B was the UCCA, while T2-LV measurements were not different in the two subgroups of patients. Again, MSCA values in patterns A and B were very close to the value of HCs (Figure 2). These findings may suggest that atrophy occurred earlier in spinal cord than the cerebellum (and consequently balance impairment occurred sooner in EC than EO). To support the hypothesis of an early involvement of spinal cord and a late involvement of cerebellum in MS, one also should consider: on the one side, the lack of any correlation between UCCA and T2-LVs (except for a weak relationship with cerebellar T2-LV); and on the other, the significant correlations between MSCA and total/regional T2-LVs (except for MCPs). T2-LV represents a marker of the disease burden accrued over time; therefore, its correlation with MSCA, but not with UCCA, is relevant. Although suggestive, this hypothesis needs to be confirmed in longitudinal studies.

The limitations of the present study concern the small sample size; its cross-sectional, observational design; and the estimation of cerebellum area rather than a measure of volume. Although static posturography is reliable and accurate, standing balance was evaluated only in the most simplistic conditions; thus, not reflecting situations that occur in daily-life activities. Another limitation was the lack of measurement in dual-task conditions, which can potentially provide further information about the pathological features underlying balance deficit in patients with MS.

In conclusion, our findings can provide a comprehensive *in vivo* anatomical framework for interpreting the different pathological substrates of the balance disorders in MS. Specific rehabilitative programs aimed at ameliorating balance and reducing risk of falls should be tailored to each patient with MS, according to the specific CNS structure more closely associated with the patient's balance deficit.

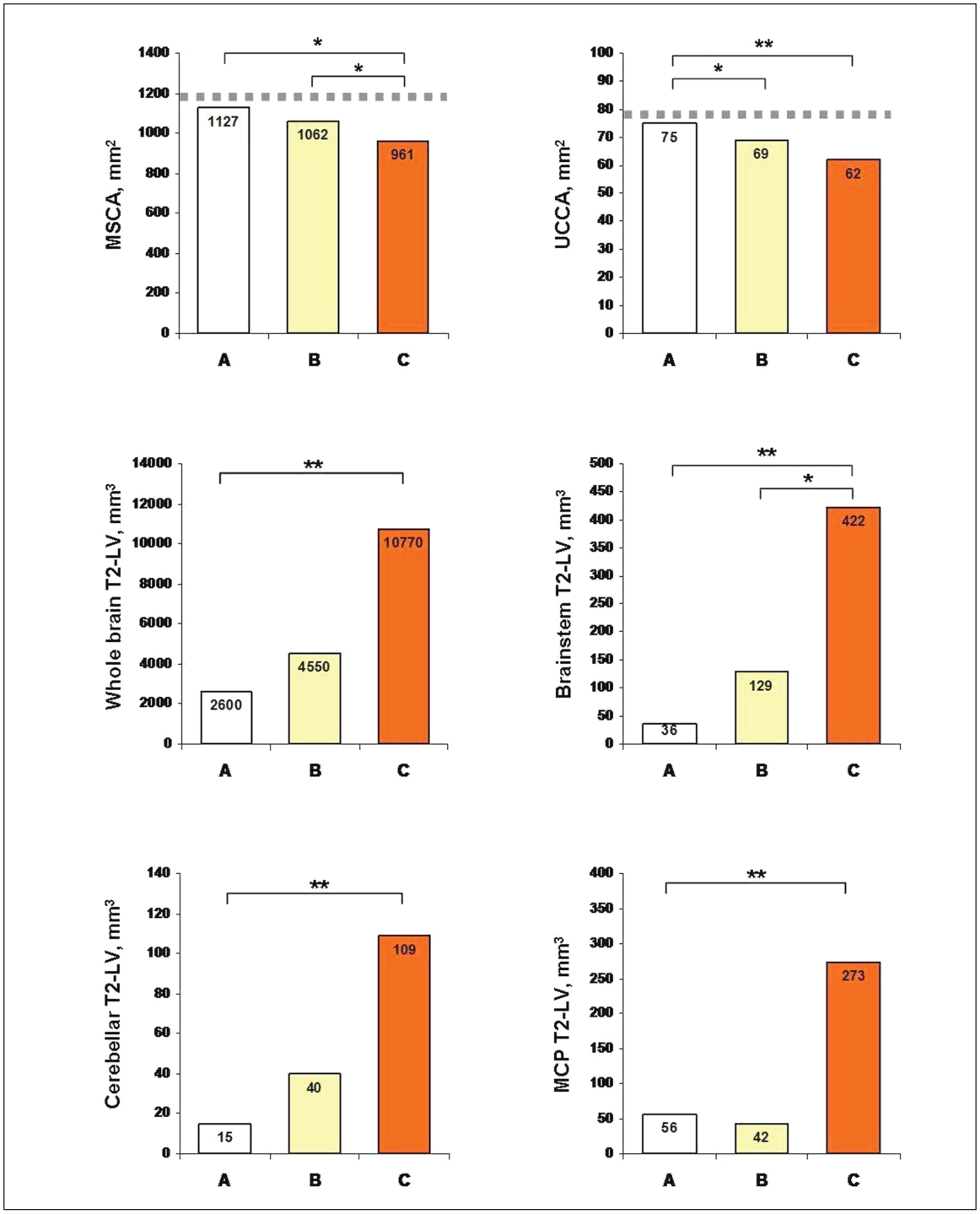


**Figure 2.** Radiological features of patients with MS according to the pattern of balance deficit, as detected by static posturography and according to normative data value of COP path, as published elsewhere.[17] Bars refer to median value of each MRI feature. Grey dashed lines refer to median values of MSCA and UCCA in sex/age-matched HCs.

Pattern A: normal values with both EO and EC (< 345 mm and < 575 mm, respectively).

Pattern B: normal value with EO, but abnormal value with path EC (< 345 mm and > 575 mm, respectively).

Pattern C: abnormal values in both EO and EC (> 345 mm and > 575 mm, respectively).

*$p \leq 0.01$.

**$p < 0.001$.

COP: Center of pressure; EO: eyes opened; EC: eyes closed; HCs: healthy controls; MCP: middle cerebellar peduncles; MRI: magnetic resonance imaging; MS: multiple sclerosis; MSCA: mid-sagittal cerebellum area; T2-LV: lesion volumes on PD/T2-weighted images; UCCA: upper cervical cord cross-sectional area.

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## Conflict of interest statement

The authors declare no conflicts of interest.

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