ACCIDENTAL FALLS AND IMBALANCE IN MULTIPLE SCEROSIS: DIAGNOSTIC CHALLENGES, NEUROPATHOLOGICAL FEATURES, AND TREATMENT STRATEGIES

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Università degli Studi di Roma Sapienza

Relatore:

Chiar.mo Prof.

Carlo Pozzilli

Correlatore:

Chiar.ma Prof.sa

Patrizia Pantano

Candidato:

Dr. Luca Prosperini

MATR. 935295

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ABBREVIATION LIST

25-FWT	25-foot walking test
95% CIs	95% confidence intervals
AD	axial diffusivity
ANOVA	analysis of the variance
AP	antero-posterior
APAs	anticipatory postural adjustements
BBS	Berg balance scale
BHs	black holes
BMI	body mass index
BOS	base of support
BPF	brain parenchymal fraction
CCC	concordance correlation coefficient
CELs	contrast enhancing lesions
CIS	clinically isolated syndrome
cm	Centimeters
CNS	central nervous system
COG	center of gravity
COM	center of mass
COP	center of pressure
CSF	cerebro-spinal fluid
DEB	Delos equilibrium board®
DHI	dizziness handicap inventory
DIR	double inversion recovery
DPA	Delos postural assistant®
DPPS	Delos postural proprioceptive system®
DTI	diffusion tensor imaging
DVC	Delos vertical controller®
EC	eyes closed
EDSS	expanded disability status scale
EO	eyes open
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
FOV	field of view
FP	force platform
FRES	fall risk estimation score
FSS	fatigue severity scale
FSST	four-square step test
FWE	family-wise error
GM	grey matter
HCs	healthy controls
ICC	intraclass correlation coefficient
ICCSA	intracranial cross-sectional area
ICPs	inferior cerebellar peduncles
ICV	intracranial volume

KFS	Kurtzke's functional score
kg	Kilogram
m	Meters
MCPs	middle cerebellar peduncles
MD	mean diffusivity
ML	medio-lateral
mm	Millimeters
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MS	multiple sclerosis
MSCA	mid-sagittal cerebellum area
MSIS-29	29-item multiple sclerosis impact scale
MSQoL-54	54-item multiple sclerosis quality of life
N/A	not applicable
NABT	normal-appearing brain tissue
NPV	negative predictive value
OR	odds ratio
PD	proton density
PP	primary progressive
PPV	positive predictive value
PwMS	patients with multiple sclerosis
RD	radial diffusivity
ROI	region of interest
RR	relapsing-remitting
s	Seconds
SCPs	superior cerebellar peduncles
SD	standard deviation
SE	standard error
SMD	standardised mean differences
SP	secondary progressive
SSBMs	static standing balance measures
T1-LV	hypointense lesion volume on T1-weighted sequences
T2-LV	hyperintense lesion volume on T2-weighted sequences
TBSS	tract-based spatial statistics
TE	time of echo
TFCE	threshold-free cluster enhancement
TR	time of ripetition
TUG	Timed "up-and-go" test
UCCA	upper cervical cord atrophy
VBM	voxel based morphometry
VEL	Velocity
WBBS	Wii balance board system®
WM	white matter

KEYWORDS

balance, postural control, accidental falls, multiple sclerosis, static posturography, magnetic resonance imaging, rehabilitation, virtual reality/visual feedback

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Davide Cattaneo & Johanna Jonsdottir (LaRiCE: Gait and Balance Disorders Laboratory. Don Gnocchi Foundation IRCCS, Milan)

CHAPTER 1

HUMAN BALANCE

Human balance can be defined as the ability to maintain the body's center of gravity (COG) within the base of support with minimal sway [1], by means of postural control. In an uniform gravitational field, the COG is located at precisely the same point as the centre of mass (COM); consequently, these two terms can be used interchangeably. Postural control refers to the ability to maintain equilibrium of COG by counteracting the constant destabilising forces that challenge it. Body posture is the product of several assembled segments and their masses held together by flexible joints and controlled by the central nervous system (CNS) [2]. In order to maintain upright stance, the body is continuously performing a subconscious function of returning the equilibrium of the body's COG vertically above the base of support (BOS) (i.e. the area of each foot and the ground space between them). This represents a complex task which is controlled by a combination of central and peripheral components including spinal reflexes, supra-spinal commands, and the integration of afferent and/or efferent signals of the visual, vestibular and somato-sensory systems respectively. Although many systems are involved in postural control, balance is primarily a sensory function rather than a motor function.

Postural correct is assured by an uninterrupted flow of afferent signals reaching the CNS from the muscle, tendon and joint proprioceptors, skin exteroceptors and vestibular and visual inputs [3]. Visual and vestibular systems provide information regarding spatial orientation and perception of motion, while the somato-sensory system refers to the proprioceptors within muscle spindles, Golgi tendon organs and joints, along with the mechanoceptors and gravity receptors responsible for interpreting pressure or shear induced by the body's motion on its supporting surface. Collectively, sensory inputs contribute to orientating postural segments with respect to each other and the external environment (vertical gravity vector). The coordinated motor outputs from several joints produce reactions to changing posture and act in response to aforementioned incoming sensory information.

Postural reactions can be divided into two principle modes: (i) the feed-back mode, that compensates for any movement away from that of the desired posture; and (ii) the feed-forward mode, responsible for the anticipatory postural adjustments (APAs) that counteract any

destabilising consequences of voluntary movement [2]. If the body's COG goes outside the BOS, instability starts in 100 ms. Since CNS requires longer than 100 ms to detect instability [4] and then make postural compensation (feedback mode), well-organized balance corrections have to be initiated in advance (feed-forward mode).

1.1 - Human bipedalism and balance control: an evolutionary approach

Bipedalism, as a descriptive term for the use of two legs for standing and locomotion, can be applied to a variety of animals, even to extinct reptiles (e.g. Tyrannosaurus rex). However, as for language, dexterity and complex culture, only humans are obligate, habitual and diverse in their bipedalism [5]. Humans have a proficient bipedality (i.e. ability to walking, running, jumping, etc.) and the capability of superimposing upon the gait other secondary movements of upper part of body. Different from other primates, there is no locomotive use of holds in humans. Lower limbs, in contrast, are exclusively adapted for plantigrade walking (human toes are, for instance, the only primate ones which are not opposable). In humans, upper limbs are specialized for power grips and finger thumb pinches.

When erect, humans stand taller than most other primates and do so upon a narrow BOS, with respect to height. As a result, humans stand on a particularly slender foot support. Further, the COM is usually high due to human legs taking up a large percentage of total height. The disadvantage of height is further increased in humans by short arms that are far off the ground (arms are roughly 70% leg length, whereas chimps are 10% longer), and lack the robustness to safely break falls [6]. However, human bipedalism results not only from the aforementioned anatomical features, but also from more sophisticated balance skills

Since the risks of falls is related to both extent of BOS and distance between the COM and ground, the demands made upon balance skills is relevantly increased in humans [7]. These anatomical and postural traits exist due to the human CNS capacity to make appropriate stabilizing skeleton-muscular balance adjustments. Albeit complexes, these adjustments occurred spontaneously and without awareness [2].

Bipedal walking can be done in two biomechanical ways: compliant gait (also known as "bent-hips, bent- knees"), and stiff gait (also known as "inverted pendulum") [8]. Compliant walking is how non-human primates walk bipedally, while stiff gait is typical of humans. Compliant walking maintains the body's COM in a constant position and so makes the body posturally stable. Stiff

gait by creating a postural instability with its constant raising then lowering of the body's COM. From the human evolution standpoint, whether the stiff gait walking goes back to Australopithecine species is still controversial [9]. Even assuming that they were stiff walkers, from a balance perspective they would have faced fewer problems than later humans due to the lower COM of their bodies, due to by their smaller statue and shorter legs (**FIG. 1.1**). The Australopithecus afarensis individual AL-288-1 (Lucy) was 1.05 m tall, while the Homo erectus individual KNM-WT 15000 (Nariokotome Boy) would have been as an adult 1.85 m. Therefore, walking by Home erectus, and its descendent Homo species including modern humans, created a need for a capacity for reliable and robust balance that was not present, or at least not so important, for earlier australopithecine species.

The skull size and, consequently, brain size expansion (encephalization) occurred in Homo erectus (**FIG. 1.2**) can explain the enhanced balance skills arose at this level of evolution, by means of: (i) enlarged size of vestibular canals [10]; (ii) increased numbers of cortical circuits able to integrate afferent signals, especially in the parietal cortex (processing egocentric, allocentric, earthcentric relationships) and pre-frontal and motor cortex (forecasting the consequence of motor actions) [11,12].

1.2 - Postural control mechanisms

Postural control serves two main functions: (i) integration of the antigravity and balance functions of the body, by using joint stiffness and muscle tone (especially extensor muscles) to maintain the COG within the BOS; (ii) reference framework for calculating target locations in the external environment and organization of movement toward these targets [13].

Although the ideal posture occurs when all body segments are aligned vertically and the line of gravity passes through all joint axes, this is impossible to obtain. Therefore, even the ideal posture is accompanied by a fluctuation of the COG around an ideal postural set point.

Typically, the body's COM lies at approximately two thirds the body height, at about the level of the second sacral vertebrae (**FIG 1.3**), making it inherently unstable during upright stance unless the postural control system is continuously functioning. During bipedal stance, sagittal and/or coronal sway occurs spontaneously as a result of this instability and the continual presence of internal and external destabilising perturbations [2]. Commonly, sagittal sway is larger than sway in a coronal plane with a ratio of approximately 1.5 during both vision and non-

visual conditions [14]. The sum of all these oscillations is termed postural sway, that can be measured through the change in center of pressure (COP) positioning over time [14].
The terms COG and COP are often confused and used as if they are or mean the same. The COP is the point location of the vertical ground reaction force vector. It is the calculated as the average of all pressures lying within the surface area in contact with the ground. In quiet stance, the COP is estimated as compatible with the centre of gravity at about 97%; this compatibility diminishes in dynamic condition [14]. In fact, in dynamic condition, the COP and COG are inversely proportional [15]. For instance, as the COG deviates anteriorly, the COP will move posteriorly in order to control and maintain the COG positioning during stance. Movements of the COP must always be greater than that of the COG in order to maintain equilibrium; otherwise, stepping is necessary to prevent falling [16].

1.3 - Ankle and hip strategy models (the “inverted pendulum” theory).

Even during controlled stance, a small amplitude slow speed sway occurs as a result of the interplay between destabilising forces acting upon the body and the actions of the postural control system. Healthy individuals generally portray a slow speed and slow amplitude sway, which indicates an efficient postural control system. To maintain stance, muscles are recruited from distal to proximal to ensure body movement is simultaneous with the head.
Ankle strategy is primarily used in quiet stance and small perturbations [14]. According to the ankle strategy theory, the ankle joint acts as the fulcrum of an “inverted pendulum” (**FIG. 1.4**), and it is responsible for maintaining equilibrium of the COM [17]. When the body is faced with a perturbation beyond which the ankle can compensate, and as a consequence the COG edges towards the outer limits of the BOS, the hip strategy is employed. Muscles are recruited from proximal to distal to encourage redirection of the COG in the opposite direction of the trunk deviation. Major perturbations to the feedback system may encourage additional strategies including knee or arm movement. Failing this, stepping is the last resort utilised to prevent falling. Interestingly, the roles of the ankles and hips reverse while in tandem stance (one foot in front of the other) [16].

1.4 - Implications for understanding imbalance due to multiple sclerosis

Deficiency in any one of the multiple sensory or motor mechanisms of the postural system (as aforementioned) can produce dramatic effects on postural stability and motor performance. Numerous factors including biometric factors, physiological functions, cognitive processing, visual feedback and cerebellar activity have shown to influence postural sway. As a consequence, numerous disorders including injury, aging or neurological / otological / orthopaedic pathologies can adversely affect postural sway by altering the ability of the body's control system to adapt to changing stimuli, thus increasing both sway and the energy expenditure necessary to maintain upright stance. The interruption of balance can bring about a sense of instability, vulnerability, as well as predispose falls and further injury [18].

Multiple Sclerosis (MS) is the most common cause of non-traumatic, progressive disability in young adults [19]. Also known as "disseminated sclerosis", MS is an inflammatory disease in which the myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring, thus affecting the ability of neurons to communicate with each other effectively. Therefore, it has been suggested that MS can be a "multiple disconnection syndrome" leading to a variety of neurological and neuropsychological deficits [20]. The deficient integration of neural pathways, due to the widespread and variable distribution of CNS damage in patients with MS (PwMS), can also affect postural control and the ability to maintain adequate balance [21]. Balance impairment is frequently observed in these patients, and it is among the most disabling symptoms, since it reduces mobility and independence, leads to falls and injuries, and impacts upon overall quality of life [22,23]. Fatigue, muscle weakness and spasticity further contribute to compromise adequate balance and predispose PwMS to accidental falls [24]. Fall tendency may occur early in the course of the disease, even before walking and balance impairment become clinically evident [25]. Imbalance (and its consequences) in MS remains incurable, with major burden on the society [26].

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Figure 1.1

Stiff gait (also known as “inverted pendulum”) and Compliant gait (also known as “bent-hips, bent- knees”) in Australopithecus afarensis (left) and chimpanzee (right).

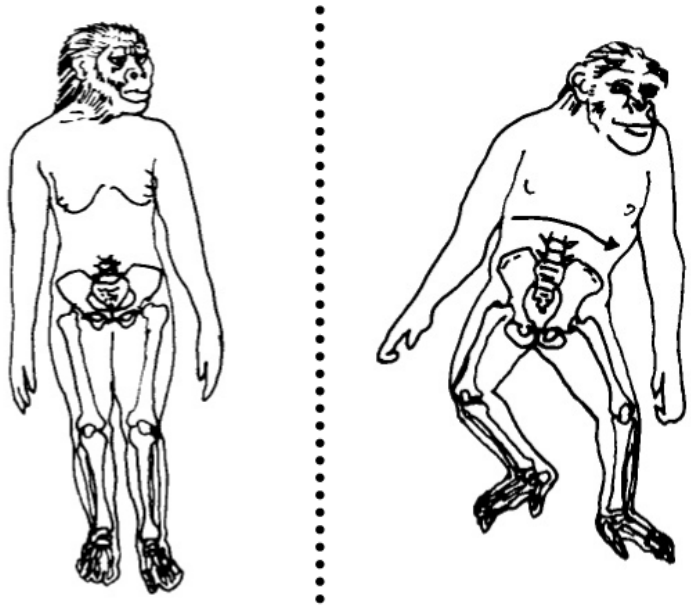


Figure 1.2

Encephalization quotient of animals, hominids and humans (i.e. the ratio between actual brain mass and predicted brain mass for an animal of a given size).

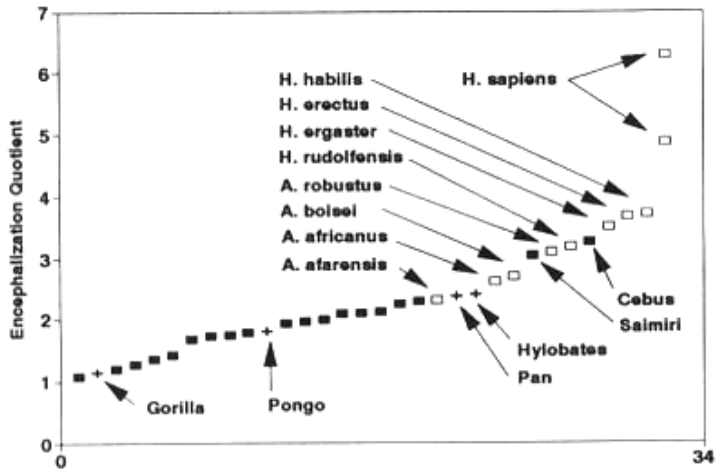
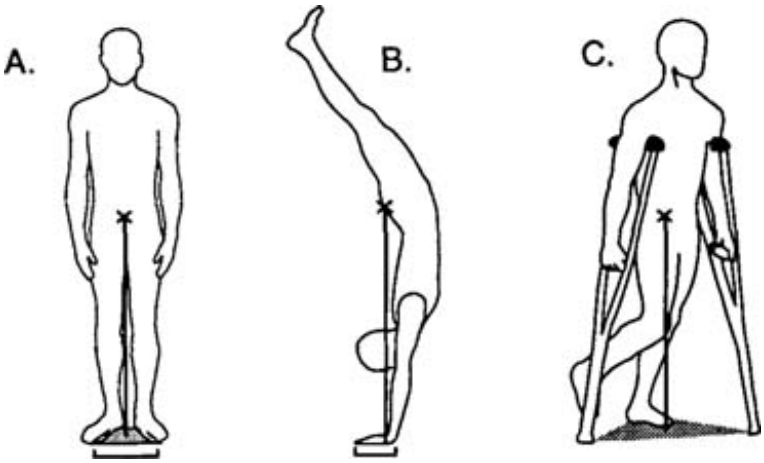


Figure 1.3

Body's COP as resultant of the vertical ground reaction force vector.



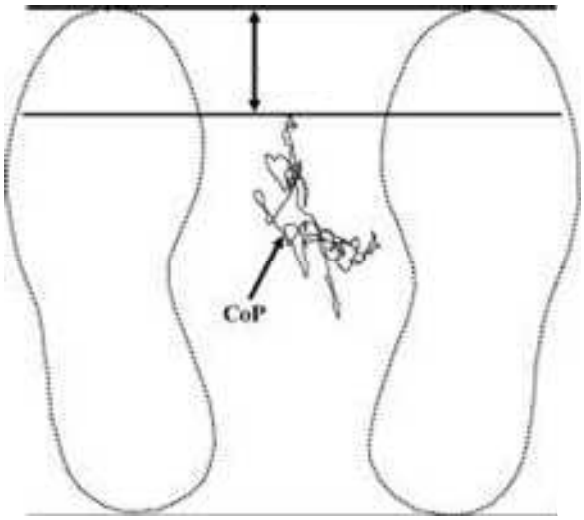
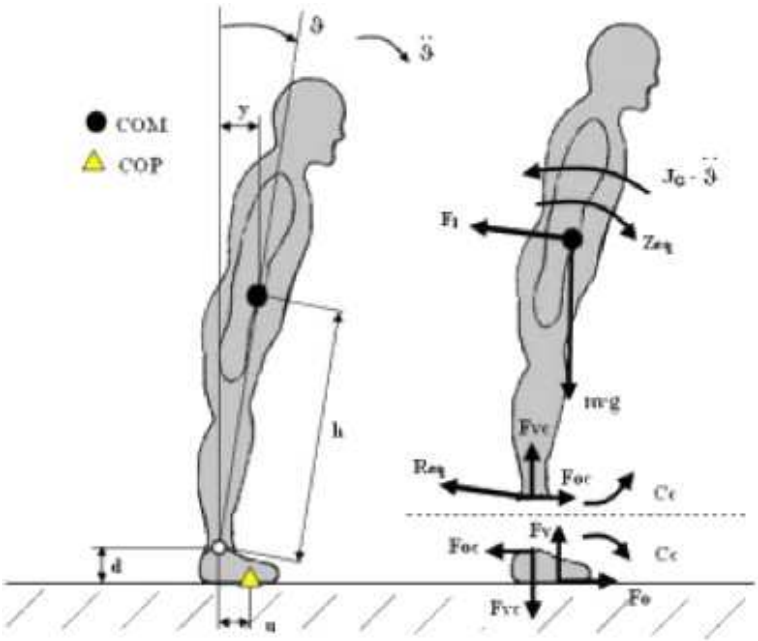
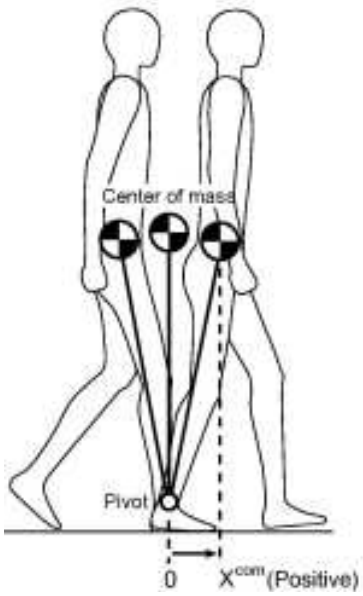


Figure 4

The biomechanical model of the simple inverted pendulum and stiff gait.





CHAPTER 2

ACCIDENTAL FALLS IN MULTIPLE SCLEROSIS: INCIDENCE AND RISK FACTORS

Reduced mobility, especially in walking, is probably the commonest impairment compromising daily living activities in PwMS [1]. According to natural history, about one half of them copes with a limited walking ability in a median time of about 10 years, and about one third copes with the need of assistance to walk in a median time of 20 years [2].Recently, it has been reported that difficulty walking was the most challenging aspect for 70% of PwMS and, more impressively, only 34% of those having difficulty walking were employed [3]. Lack of balance and coordination is reported among the most common symptoms affecting mobility of PwMS (67%), together with weakness (81%) and fatigue (73%) [4]. Although reported as symptoms onset only in about 20%, imbalance may affect about three-quarters of PwMS over the course of the disease [5]. Balance impairment not only reduces mobility and independence, but also leads to falls and injuries, and impacts upon overall quality of life, with major burden on the society. The high incidence of falls increases the risk of fracture in people with MS, especially in those suffering from osteoporosis [6-9]. In fact, the risk of injurious falls has been reported as increased in people with MS [10,11]. Additionally, fear of falling may also lead to activity curtailment and subsequent deconditioning [12,13], which, in turn, can increase the fatigue level and even the extent of other symptoms [14].

Different risk factors have been associated with fall status, such as imbalance [15-22,25], gait and walking impairment [15,16,18,21,22,26,27], use of walking aid [15-17,19,21], male gender [16], progressive disease course [16], bladder dysfunction [16], attention or cognition problems [16,24], spasticity [17], disability level [17,18,20,21,25-27], fatigue [19,23], older age [21], longer disease duration [25]. However, studies conducted so far are methodologically heterogeneous and have provided incomparable, and partially conflicting results [28].

2.1 - Objective

The main purpose of the present study is to determine, by means of a meta-analytic approach, whether there are demographic and clinical variables useful for detecting the fall status of patients .

2.2 - Methods

Article search. According to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [29], Pubmed was searched for abstracts using the terms ("multiple sclerosis" [All Fields] AND "falls" [All Fields]). No limitations or time period restrictions were applied and the latest search was undertaken on January 2013, the 10th. The Cochrane Library was explored for systematic reviews using the same key terms. Both prospective and retrospective studies were encompassed. We were not familiar with any study currently in progress that could be considered for inclusion. Published conference abstracts, articles not available in English, and studies including also patients affected by neurological conditions other than MS were excluded. Studies in which there was not a clear distinction between fallers (i.e. PwMS experiencing one or more accidental falls in a pre-specified timeframe) and non-fallers, or studies where measures equated to falls were adopted as outcomes, were also excluded. Abstracts of resulting articles were then hand-searched in order to select studies which met eligibility criteria. Attempts to identify further articles were done by searching for the references of the studies.

Data extraction. Data on number of fallers and non-fallers were obtained from included articles. For the purpose of this meta-analysis, we considered fallers as the "exposed" group and non-fallers as the "control" one. Each demographic and clinical variable considered in different studies was evaluated as potential risk factor for accidental fall, but it was inserted in meta-analyses only after a quality check by the agreement of the authors. Self-reported symptoms were not considered, unless they were collected by means of validated instruments. To be included in the meta-analysis process, a variable had to be considered in at least three different

studies conducted by three different authors. When applicable, authors of articles were contacted to request supplementary data for inclusion in the meta-analysis.

Statistical analysis. A generic inverse variance with fixed effect models in RevMan 5.2.3 was carried out to calculate the weighted effect of demographic and clinical factors on fall status (i.e. being classified as fallers or non-fallers). Results are presented as odds ratio (OR) and standardised mean differences (SMD), with their 95% confidence intervals (CIs), for dichotomous and continuous variables, respectively.
The OR compares the relative likelihood that a factor occurring between two groups, while the SMD compares the size effect of a given factor in two groups. In this context, an OR<1 indicates the considered factor more common in non-fallers; an OR>1 indicates the considered factor more common in fallers; an OR=1 indicates no difference between fallers and non-fallers; a SMD<0 indicates the value of the considered factor increased in non-fallers; a SMD>1 indicates the value of the considered factor increased in fallers; a SMD=1 indicates no difference between fallers and non-fallers. For each variable of interest, a forest plot was also generated. Heterogeneity of studies was addressed by the estimation of Tau^2 and I^2, considering an I^2 value <40% as an indicator of marginal heterogeneity. Potential publication biases were determined by Egger p-value and by checking Funnel's plots [30].

2.3 - Results

Included studies. Pubmed search initially yielded 115 studies, as shown in the flow diagram (**FIG. 2.1**). In total, 15 studies were selected for inclusion [15-27,31,32], yielding a total of 2,425 PwMS, 1,260 (52.0%) fallers and 1,165 (48.0%) non-fallers. Two study classified as fallers only PwMS who reported at least 2 falls in the pre-specified timeframe [15,26]. According to different studies, the timeframe in which occurrence of falls was collected ranged from 1 to 12 months, with a median timeframe of 4.5 months. Notably, one study [24] did not report the timeframe in which the occurrence of accidental falls was considered, while 7 studies [16,22-24,27,31,32] did not report the proportion of recurrent fallers. Out of 897 PwMS yielded from the remaining 8 studies [15,17-21,25,26] 352 (39.2%) were defined as recurrent fallers (i.e. fell twice or more in the considered timeframe). Lastly, only 3 studies relied on prospectively collected reports of

accidental falls [17,18,25], while other 2 studies were conducted as mail surveys [16,19]. Detailed information about included studies are shown in **TABLE 2.1**.

Identification of potential risk factors. Variables across studies which were included in meta-analyses were:
(i) gender (male *versus* female); age [***demographic variables***];
(ii) disease duration; progressive disease course, i.e. secondary progressive (SP) or primary progressive (PP) *versus* relapsing-remitting (RR) [33]; use of assistive walking device (any type versus none); Expanded Disability Status Scale (EDSS) [34]; walking speed, as assessed by the 25-foot walking test (25-FWT) [35] [***disease related variables***]
(iii) Berg Balance Scale (BBS) [36], Timed up-and-go test (TUG) [37], force platform measures, i.e. COP sway in standing stance with eyes open (EO) or closed (EC) [38] [**balance-related variables**].
No identification of significant publication bias was found for each analysis (Egger p-values ranged from 0.13 to 0.75).

Demographic variables

Gender - Similar proportions of males were found in fallers and non-fallers. The overall OR upon inclusion of 11 studies [15-17,19-21,23-27] was 1.14 (95% CIs 0.88 to 1.47, p=0.31) (**FIG. 2.2/A**). The proportions of males ranged from 16% to 50% and from 5% to 78% in fallers and non-faller ones, respectively, according to different studies. No significant study heterogeneity was identified (I^2=14%, p=0.31).

Age - There were no differences in terms of age between fallers and non-fallers. The overall SMD upon inclusion of all 15 studies [15-27,31,32] was 1.04 (95% CIs -0.28 to 2.35, p=0.18) (**FIG. 2.2/B**). The mean age ranged from 37.2 to 63.6 years and from 38.5 to 64.0 in fallers and non-faller ones, respectively, according to different studies. Only a marginal and not significant study heterogeneity was identified (I^2=32%, p=0.11).

Disease-related variables

Disease duration - Fallers had a slightly longer disease duration than non-fallers. The overall SMD upon inclusion of 12 studies [15,16,19-25,27,31,32] was 0.14 (95% CIs 0.02 to 0.30, p=0.02) (**FIG. 2.3/A**). The mean disease duration ranged from 9.1 to 28.5 years and from 8.5 to 28.3 in fallers and non-faller ones, respectively, according to different studies. No significant study heterogeneity was identified (I^2=25%, p=0.20).

Disease course - Fallers were more likely than non-fallers to have a progressive course (primary or secondary) of the disease. The overall OR upon inclusion of 7 studies [16,17,19,22,24,25,27] was 2.02 (95% CIs 1.65 to 2.47, p<0.0001) (**FIG. 2.3/B**). The proportions of patients having a progressive course ranged from 22% to 52% and from 15% to 39% in fallers and non-faller ones, respectively, according to different studies. No study heterogeneity was identified (I^2=0%, p=0.63).

Use of assistive devices - Fallers were more likely to use assistive devices for walking (unilateral, bilateral, cane or crutch) than non-fallers. The overall OR upon inclusion of 9 studies [15-17,21,22,26,31,32] was 3.16 (95% CIs 2.53 to 3.95, p<0.0001) (**FIG. 2.3/C**). The proportions of patients who used an assistive device for walking ranged from 30% to 91% and from 13% to 70% in fallers and non-faller ones, respectively, according to different studies. No significant study heterogeneity was identified (I^2=0%, p=0.60). Notably, one study [23] considering only PwMS who used bilateral support for gait (as per inclusion criteria) was removed from analysis.

EDSS score - The disability level, as assessed by means of EDSS score, was significantly greater in fallers than non-fallers. The overall SMD upon inclusion of 8 studies [17,18,20-22,24-27] was 0.74 (95% CIs 0.57 to 0.91, p<0.0001) (**FIG. 2.3/D**). Mean EDSS scores ranged from 3.6 to 5.4 and from 2.6 to 4.7 in fallers and non-faller ones, respectively, according to different studies. No study heterogeneity was identified (I^2=3%, p=0.41).

Walking speed - Fallers had worse performance than non-fallers in the 25-FWT. The overall SMD upon inclusion of 4 studies [21,24,26,32] was 0.45 (95% CIs 0.20 to 0.70, p=0.0005) (**FIG. 2.3/E**). Mean 25-FWT time ranged from 6.9 to 8.4 s and from 5.8 to 6.9 s in fallers and non-faller ones, respectively, according to different studies. No study heterogeneity was identified (I^2=0%, p=0.52).

Balance-related variables

Berg Balance Scale - Fallers had worse balance performance than non-fallers, as assessed by means of BBS. The overall SMD upon inclusion of 5 studies [17,22,23,25,31] was -0.48 (95% CIs -0.78 to -0.19, p=0.002) (**FIG. 2.4/A**). Mean BBS scores ranged from 28 to 48 and from 30 to 52 in fallers and non-faller ones, respectively, according to different studies (lower scores indicated worse balance). Albeit not significant, a moderate heterogeneity was identified (I^2=47%, p=0.11).

Timed up-and-go test - There was only a marginal difference between fallers and non-fallers in this test. The overall SMD upon inclusion of 3 studies [21,31,32] was 0.31 (95% CIs 0.01 to 0.60, p=0.04) (**FIG. 2.4/B**). Mean TUG scores ranged from 2.7 to 12.5 s and from 2.5 to 11.4 s in fallers and non-faller ones, respectively, according to different studies. Data from one study was not considered because referring to “cognitive” TUG [17]. No heterogeneity was identified (I^2=0%, p=0.74).

Force platform measures - Fallers had significantly wider postural sway, as measured in static stance, with EO and EC. The overall SMD upon inclusion of 4 studies [20-22,25] was 0.71 (95% CIs 0.21 to 1.21, p=0.006) (**FIG. 2.4/C)** and 0.83 (95% CIs 0.19 to 1.46, p=0.01), for eyes open and closed, respectively (**FIG. 2.4/D**). A relevant heterogeneity was identified (I^2=64%, p=0.04 and I^2=77%, p=0.004). Notably, different measures of postural sway were adopted in these studies, such as sway path [20-22] and sway area [25].

2.4 - Discussion

Studies included in this meta-analysis report a proportion of fallers ranging from 30% to 63% in a median timeframe of 4.5 months (ranging from 1 to 12 months) [15-27,31,32]. Moreover, recurrent fallers accounted for about 29-45% of PwMS considered, although their proportion is omitted in some studies [16,22-24,27,31,32]. Healthcare providers should consider these data as a major concern for several reasons.

Firstly, frequency of accidental falls in PwMS is fairly greater than general population, about 30% of community-dwelling healthy adults over 65 years fall in a 12-month period, and only 10% are recurrent fallers [39].

Secondly, it has been documented a 2-fold increased risk of injurious falls in PwMS compared with sex/age-matched veterans without MS [10]. PwMS had a 4- and 2-fold increased risk of hip and osteoporotic fractures than controls [9], especially when there was a concomitant history of recent falls [11]. A relevant difference was also documented between PwMS and controls in terms of 5-year incidence of fractures (2.4% *versus* 1.8%) [9]. Tendency to falls occurred even in 20% of subjects at first demyelinating event suggestive of MS confronted with 3% of healthy controls [8].

Lastly, fear of falling (often associated with a recent fall experience) may lead to activity curtailment that can produce, in turn, deconditioning and relevant decrease in daily living activities. [12,13]

Therefore, we strongly agree with the suggestion of developing algorithms to predict faller and guidelines aimed to manage PwMS at risk of falls [19], similarly to what has been done for the geriatric population [40].

In the present paper, we aimed to identify demographic and clinical characteristics related to a higher risk of accidental falls in PwMS, by meta-analyzing previously published studies on this topic. While demographic characteristics such as gender and age seem not have any influence on fall status, a longer disease duration, a progressive disease course, a greater disability level and a slower walking speed were found in fallers more frequently than in non-fallers. Likewise, balance tests, such as BBS, TUG and static posturography, revealed worse performance in fallers than non-fallers.

Although EDSS was reported as consistently related with fall status, it exhibit a poor sensitivity (48%) when a score ≥5.5 was applied as cut-off value [17]. A non-linear relationship between fall status and disability level (which is, in turn, related with disease duration and progressive course) may be also hypothesized, since a strong correlation between fall status and EDSS can be found only at intermediate levels of the scale, but not at the lower and upper extremities. In other words, fallers are mainly present in EDSS score between 3.5 and 6.0, rather than between 0 and 3.0 or 6.5 and 9.5. Therefore, EDSS score alone might be not sufficient to estimate the risk of falls, for at least three reasons: (i) reliability is substantially lower on the first portion of the scale (i.e. EDSS less than 3.0), with a 40% variability level even allowing a 1-point difference [41]; (ii) EDSS scores of fallers and non-fallers can be overlapped (from 3.6 to 5.4,

and from 2.6 to 4.7, respectively), as per data of included studies [17,18,20-22,24-27]; PwMS essentially restricted to wheelchair (i.e. EDSS equal or above 7.0) may have a reduced risk of accidental falls simply because they are not ambulatory [13,16]. Similarly, even if a strong correlation between EDSS score and mineral density relationship has been reported, fracture risk appeared to be higher in patients with moderate rather than severe disability [9,42,43].

In this regard, clinical [17,21,22,23,25,30,31] or computer-based assessments of balance [20-22,25] could be useful for enhancing our diagnostic ability. Also walking speed could be considered as an important factor related not only with overall mobility, but also with fall status in PwMS [21,24,26,32].

Surprisingly, patients using an assistive device for walking were prone to accidental falls. Although it may sound as paradoxical - the use of a cane or crutch should represent a strategy to avoid falls - it has been already reported that use of an assistive device is associated with risk for falls even in older adults [44]. Some authors have suggested that assistive device are not only associated with increased metabolic and strength demands, but also they can interfere to compensatory reactions while balance loss occurs [45] Another possible explanation could encompass the failure to correctly prescribe or use walking and mobility aids [16,46]. Finally, the possibility of a spurious relationship might be considered, i.e. assistive device were mainly adopted by PwMS whit higher level of disability and mobility impairment, which in turn are two risk factors for accidental falls.

Study strengths and limitations. To our knowledge, up to now there is only a meta-analysis investigating the risk factors for falls in PwMS [28]. This latter study provided quantitative analyses only from 6 studies, including a total of 1929 PwMS, while our quantitative analyses comprised 15 studies (most of them published on 2012), for a total of 2425 PwMS. The larger sample size, and the increased number of potential risk factors considered in our study should have enhanced the validity of our results, also considering the multifactorial causes leading to accidental falls in PwMS.

However, the results from this meta-analysis have to be interpreted cautiously, since we considered studies which differ from each other in terms of sample size, setting, design, and reporting (retrospectively) or collecting (prospectively) the occurrence of falls. In this regard, future efforts should be made to adopt a shared definition of the optimal timeframe for reporting falls.

While we did not explore specifically these aspects, it is also remarkable that cognitive impairments [17,19,24,47-49], fatigue [14,16,23,47] and concern about falls [12,13,47] have been found to be associated with an increased risk of accidental falls in PwMS.

Despite the aforementioned limitations, our work could contribute to elucidate which variables are associated with accidental falls. In this regard, worse EDSS scores, progressive course, use of walking aid resulted strongly associated with fall status, thus reinforcing the concept that preventing accumulation of irreversible disability should be the ultimate goal in rehabilitation of PwMS. The importance of enhanced accuracy in distinguishing PwMS who are at risk of accidental falls from those who are not, should be emphasized by means of clinical or instrumental tools.

Well-designed, prospective, diary-based studies [17,50] avoiding recall bias in occurrence of falls and establishing which clinical variable is the most able to predict future falls are warranted to allow a better management of symptoms increasing fall tendency.

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Table 2.1

Information about included studies.

Study (year)	Ref. no.	Sample size	Design	Timeframe (months)	Fallers (%)	Recurrent Fallers (%)
Cattaneo D (2002)	15	50	Retrospective	2	54.0	34.0
Cattaneo D (2006)	31	51	Retrospective	1	39.2	N/A
Finlayson M (2006)	16	1089	Retrospective (mail survey)	6	52.5	N/A
Nilsagard Y (2009)	17	76	Prospective	3	63.1	43.4
Kasser SL (2011)	18	99	Prospective	12	48.5	32.3
Matsuda PN (2011)	19	473	Retrospective (mail survey)	6	54.7	42.3
Prosperini L (2011)	20	31	Retrospective	6	45.2	29.0
Sosnoff JJ (2011)	21	52	Retrospective	12	55.8	44.2
Cattaneo D (2011)	22	37	Retrospective	2	29.7	N/A
Coote S (2012)	23	111	Retrospective	3	50.4	N/A
D'Orio VJ (2012)	24	81	Retrospective	N/A	55.5	N/A
Nilsagard Y (2012)	32	84	Retrospective	2	36.9	N/A
Prosperini L (2012)	25	100	Prospective	3	41.0	19.0
Socie MJ (2012)	26	47	Retrospective	12	53.2	N/A
Sosnoff J (2012)	27	75	Retrospective	12	49.3	N/A

Fallers: patients with MS who reported at least 1 fall in the considered timeframe; recurrent fallers: patients with MS who reported 2 or more falls in the considered timeframe; N/A: not applicable.

Figure 2.1

Flow diagram mapping the review, according to PRISMA statement [29].

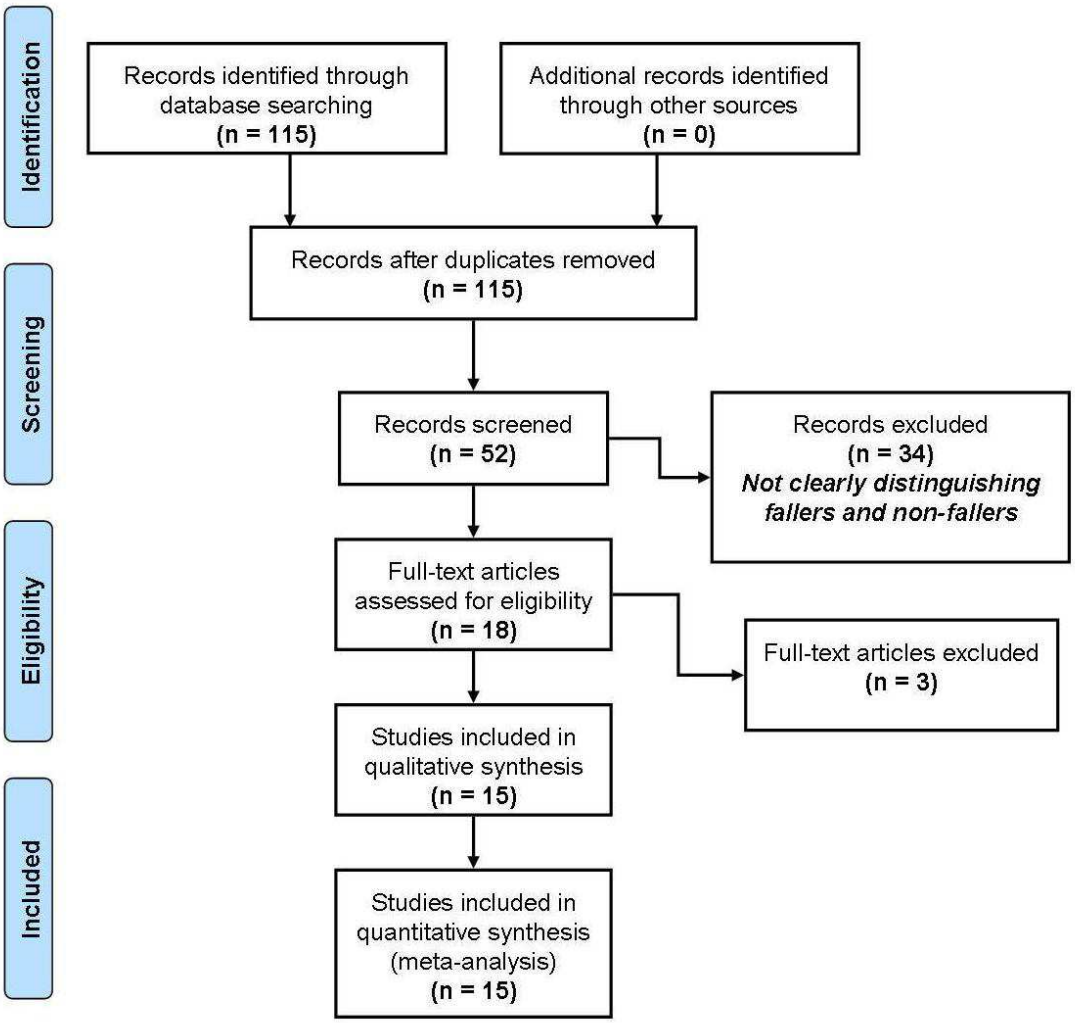
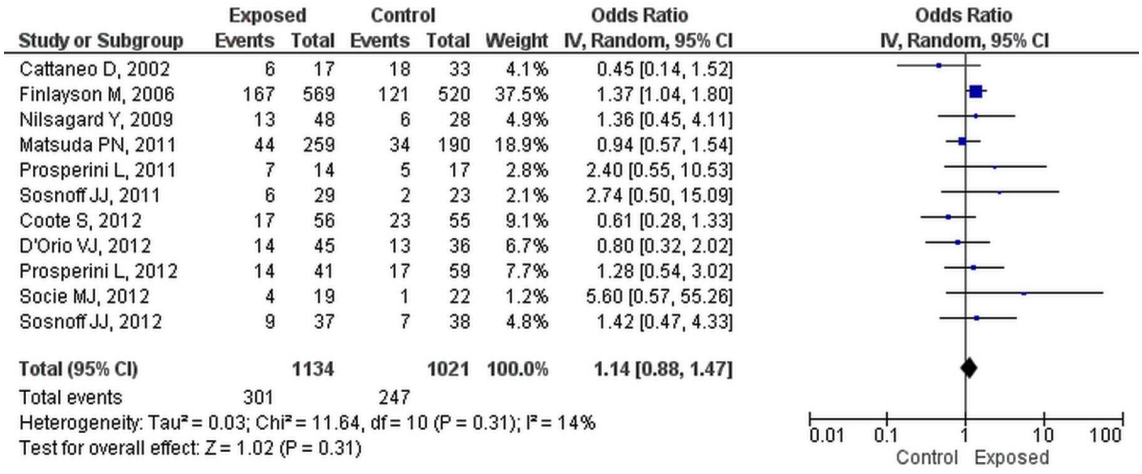


Figure 2.2

Forest plot of comparisons: fallers *versus* non-fallers; demographic variables: male gender (A), age (B).

A



B

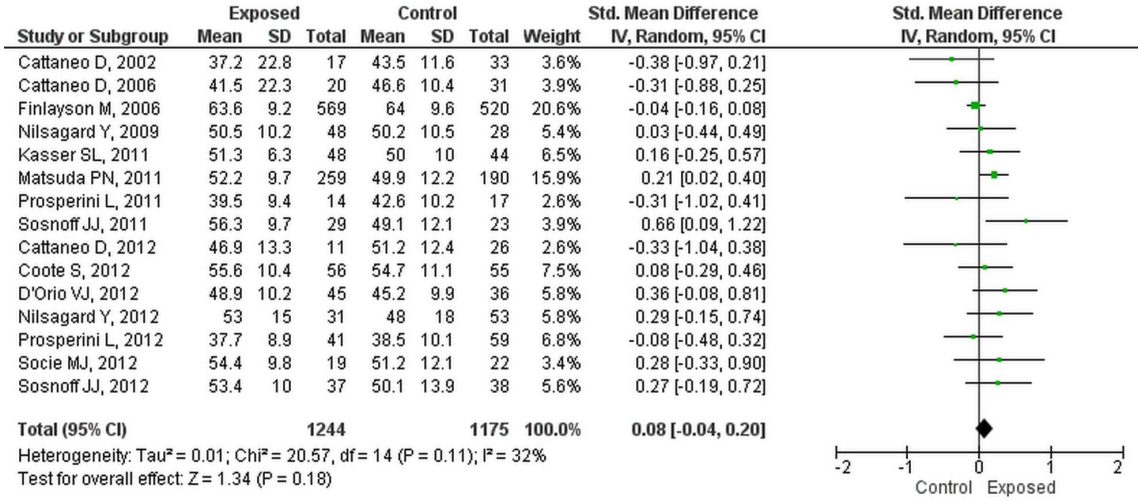
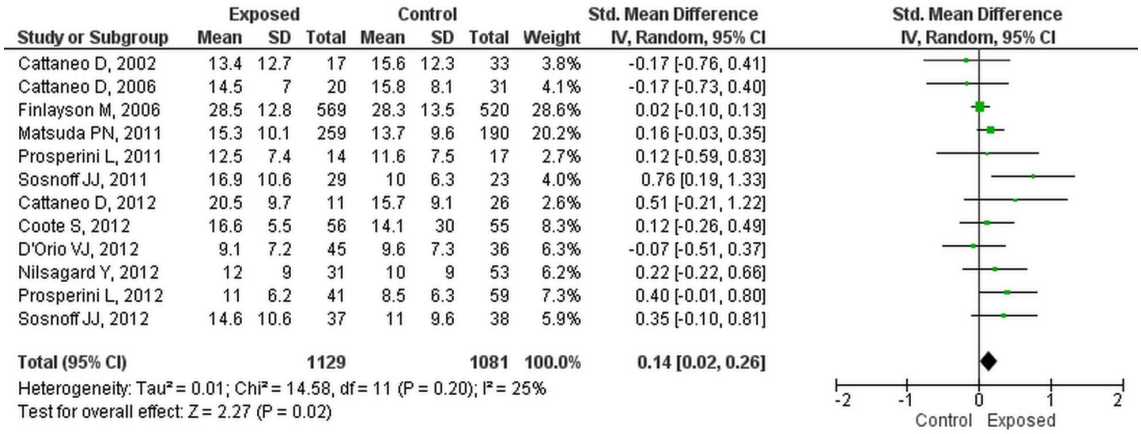


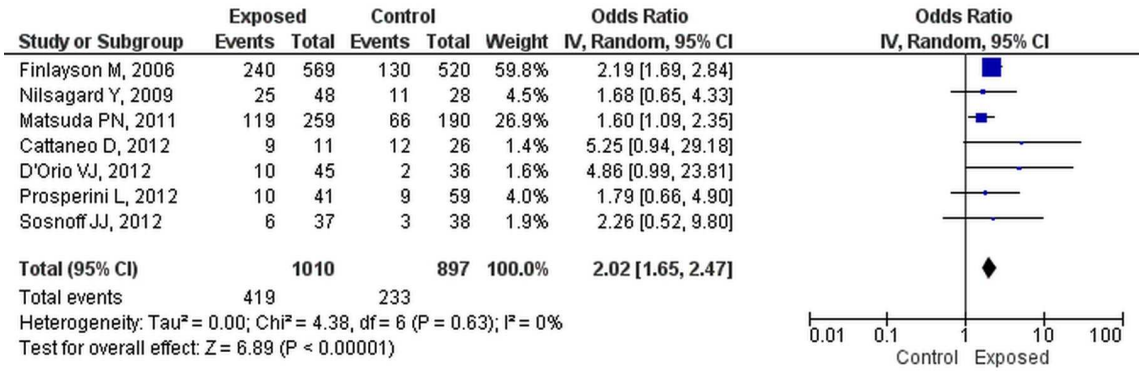
Figure 2.3

Forest plot of comparisons: fallers *versus* non-fallers; disease-related variables: disease duration (A), PP/SP course (B), use of assistive device for walking (C), EDSS score (D), walking speed (as evaluated by means of 25-FWT) (E).

A



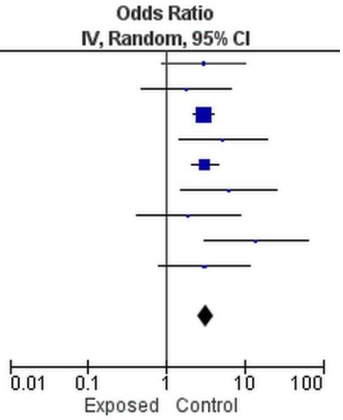
B



C

Study or Subgroup	Exposed Events	Exposed Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Cattaneo D, 2002	9	17	9	33	3.3%	3.00 [0.88, 10.18]
Cattaneo D, 2006	6	20	6	31	2.9%	1.79 [0.48, 6.60]
Finlayson M, 2006	499	569	367	520	50.5%	2.97 [2.17, 4.07]
Nilsagard Y, 2009	44	48	19	28	3.0%	5.21 [1.43, 19.02]
Matsuda PN, 2011	142	259	53	190	30.9%	3.14 [2.10, 4.68]
Sosnoff JJ, 2011	14	29	3	23	2.5%	6.22 [1.51, 25.62]
Cattaneo D, 2012	4	11	6	26	2.1%	1.90 [0.41, 8.80]
Nilsagard Y, 2012	29	31	27	53	2.1%	13.96 [3.02, 64.53]
Socie MJ, 2012	9	19	5	22	2.7%	3.06 [0.80, 11.73]
Total (95% CI)		**1003**		**926**	**100.0%**	**3.16 [2.53, 3.95]**
Total events	756		495			

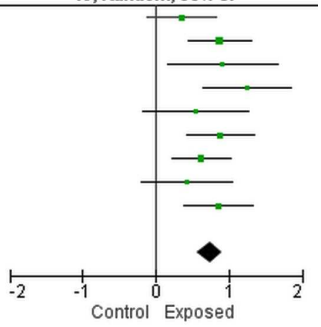
Heterogeneity: Tau² = 0.00; Chi² = 6.38, df = 8 (P = 0.60); I² = 0%
Test for overall effect: Z = 10.13 (P < 0.00001)



D

Study or Subgroup	Exposed Mean	Exposed SD	Exposed Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nilsagard Y, 2009	4.9	1.8	48	4.3	1.5	28	13.2%	0.35 [-0.12, 0.82]
Kasser SL, 2011	3.7	1.2	48	2.6	1.3	44	15.8%	0.87 [0.44, 1.30]
Prosperini L, 2011	3.7	0.8	14	3	0.7	17	5.3%	0.91 [0.17, 1.66]
Sosnoff JJ, 2011	4.5	1.3	29	3	1	23	8.1%	1.25 [0.65, 1.86]
Cattaneo D, 2012	5.4	1.4	11	4.7	1.2	26	5.8%	0.54 [-0.17, 1.26]
D'Orio VJ, 2012	4.2	1.1	45	3.3	0.9	36	13.8%	0.88 [0.42, 1.34]
Prosperini L, 2012	3.6	0.9	41	3	1	59	17.3%	0.62 [0.21, 1.03]
Socie MJ, 2012	4.5	1.6	19	3.8	1.6	22	7.7%	0.43 [-0.19, 1.05]
Sosnoff JJ, 2012	5	2.9	37	3	1.5	38	13.0%	0.86 [0.39, 1.34]
Total (95% CI)			**292**			**293**	**100.0%**	**0.74 [0.57, 0.91]**

Heterogeneity: Tau² = 0.00; Chi² = 8.21, df = 8 (P = 0.41); I² = 3%
Test for overall effect: Z = 8.35 (P < 0.00001)



E

Study or Subgroup	Exposed Mean	Exposed SD	Exposed Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Sosnoff JJ, 2011	7	2.3	29	5.8	2.9	23	20.6%	0.46 [-0.10, 1.01]
D'Orio VJ, 2012	7.4	3.8	45	5.4	2.2	36	31.4%	0.62 [0.17, 1.07]
Nilsagard Y, 2012	6.9	2.7	31	6.3	3.5	53	32.1%	0.18 [-0.26, 0.63]
Socie MJ, 2012	8.4	2.5	19	6.9	2.1	22	15.9%	0.64 [0.01, 1.27]
Total (95% CI)			**124**			**134**	**100.0%**	**0.45 [0.20, 0.70]**

Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0005)

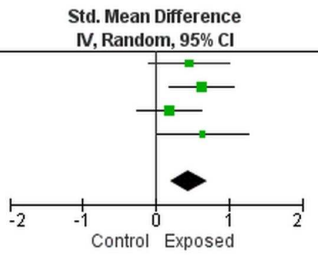
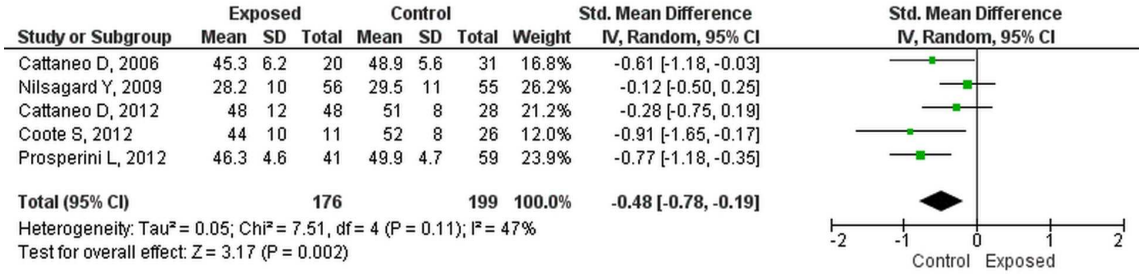


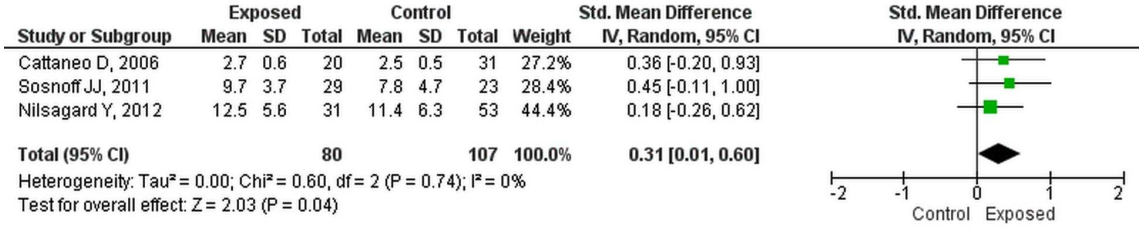
Figure 2.4

Forest plot of comparisons: fallers *versus* non-fallers; balance-related variables: BBS (A), TUG (B), COP postural sway as evaluated in standing stance with EO (C) and EC (D).

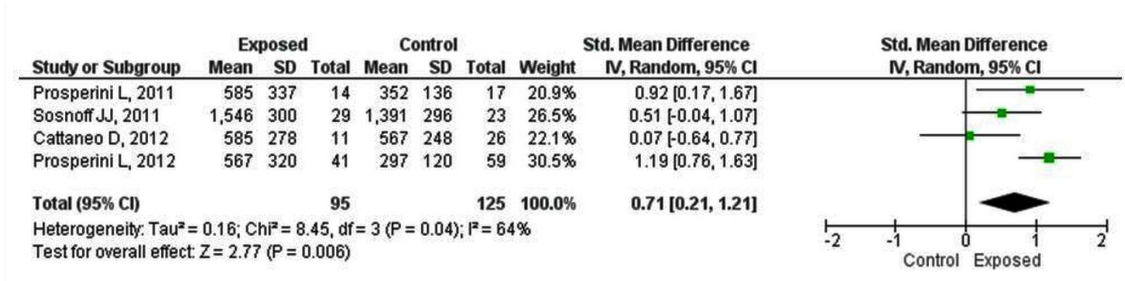
A



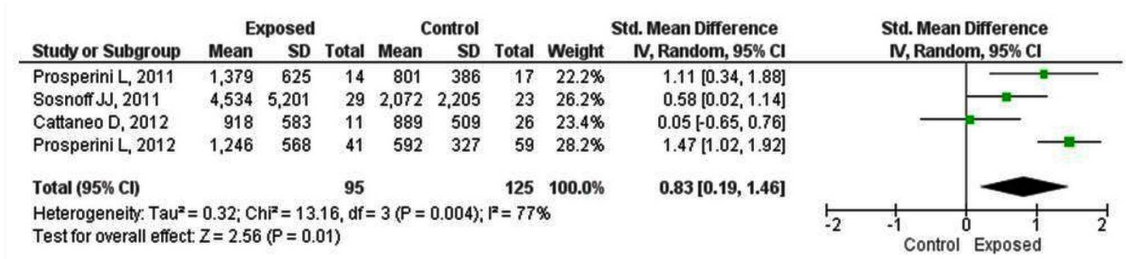
B



C



D



CHAPTER 3

DIAGNOSTIC CHALLENGES IN DETECTING PATIENTS WITH MULTIPLE SCLEROSIS AT RISK OF FALLS: CLINICAL MEASURES *VERSUS* FORCE-PLATFORM MEASURES

Studies investigating demographic and clinical characteristics related to a high risk of accidental falls in PwMS are quite heterogeneous in terms of sample size, setting, design, and for reporting (retrospectively) or collecting (prospectively) the occurrence of falls [1-15]. Studies relying on retrospectively collected patient report of falls at the inclusion are prone to recall bias [4,6], although a good correlation (r=0.82) between prospectively and retrospectively collected falls has been demonstrated [4]. In addition, even if prospectively collected, falls resulting in injury are more likely to be reported, and cognitive or memory impairment may further decrease the accuracy of their recall [6,16]. From a clinical point of view, reliably discriminating fallers between non-fallers is crucial for the development of a program aimed at fall prevention. Potentially, force platform measures may provide an objective, reliable, and accurate and tool for this purpose. Moreover, they may be useful for documenting not only deficits, but also improvements of balance skills after specific intervention.

3.1 - Background

Clinical scales to assess balance. Clinical tests usually rate balance performance on a set of motor tasks. Scoring is based on the sum of ordinal item scores or stop-watch measurements. Ideally, an evaluation of postural balance should include clinical scales that are: practical, sensitive and selective, reliable and valid. Although some clinical scales are easy and relatively quick to use, they are hampered by their variable execution and by the room left for evaluator judgment in the scoring system [17,18]. The **TABLE 3.1** summarize the most commonly used clinical scales to assess balance in PwMS and their main psychometric properties.

So far, few studies provided data on diagnostic accuracy of clinical scales in detecting PwMS prone to accidental falls. These studies showed conflicting results, probably due to different cut-

offs established. Cattaneo and coll. [2] showed that clinical balance scales exhibit good specificity (i.e. performance in detecting non-fallers), but low sensitivity (i.e. performance in detecting fallers). Although other authors found differences between fallers and non-fallers in clinical scale scores of balance and even mobility [8-10,13], they did not provide data on sensitivity and specificity. Nilsagard and coll. [4] suggested a combination of patient variables and selected clinical scales to predict the risk of falls, but failed to identify the "best candidate" to apply in the daily setting. More recently, it has been suggested that the BESTtest was 92% accurate in identifying fallers and non-fallers among PwMS [19]. Despite this high accuracy, the BESTest is time-consuming and requires a lot of tools. The use of a short version (mini-BESTest), having only a 10-minute administration time, could be more useful in clinical practice, but it needs to be validated in PwMS [20]. Lastly, D'Orio and coll. [11] also suggested that cognitive impairment, especially impaired verbal memory, predicted an increased risk of recurrent falls.

Force platform measures: basic principles. Force platforms are instruments that measure ground reaction forces generated by a body standing on or moving across them, to quantify biomechanical parameters of human balance control. Force platforms are also used for gait analysis. Posturography is the general term encompassing all the techniques used to quantify postural control in upright stance, in either static or dynamic conditions, by means of a force platform [18].

The term static posturography refers to the characterization of postural sway of the COP during quiet standing on a fixed support surface (i.e. a relatively unperturbed state). Variations in the instant positions of the COP during a 30 or 60-second test are used to calculate time-domain measures, including the velocity of the COP on the antero-posterior (AP) or medio-lateral (ML) axes (mm/s), the sum of the displacements (path) of COP (mm), the 95% confidence ellipse area of COP (mm^2). From a biomechanical standpoint, the displacement of the COP represents a marker of energy expenditure to maintain balance [21]. Usually, a posturographic assessment consists in two test conditions (EO and EC) and, sometimes, in dual-task condition [22]. This paradigm allows an evaluation of cognitive processing required to maintain standing balance, simply by applying a concurrent cognitive task (e.g. aloud or silent backward counting, Stroop test, paced auditory serial addition test).

Static posturography provides linear, objective and reliable measurements of static balance [18,23-25]. In spite of its reliability and accuracy in PwMS [15,24], the main limitation of static posturography is a lack of standardisation that precludes the possibility to generalize its

application for multicentre purposes [25]. This is due to the fact that different force platform equipment and different test procedures are used in clinical practice. Parameters that should be considered are not well defined (e.g. velocity, path, area, etc.), as well as feet position and test duration [23,26]. Additionally, static posturography evaluates balance control only in the most simplistic condition, thus not reflecting situations occurring in daily-life activities.

Dynamic posturography involves the use of experimentally-induced (external or self-generated) balance perturbation, such as shifting the support surface, using an unstable support surface, moving the visual surround, applying stimuli to upper body parts, performing voluntary weight shift [27]. By manipulating one or more specific inputs (visual, vestibular or proprioceptive) for postural control, a dynamic posturography assessment may provide important data on the motor and sensory contribution to balance control [28]. Thereby, impairments in sensory re-weighing and integrating afferent inputs can be easily detected. Moreover, these data can be combined into composite scores, such as the equilibrium score or the postural stability index [29]. The main advantage of dynamic posturography is the possibility to obtain information on balance control in a variety of conditions simulating situations encountered in daily-life activities [18]. Unfortunately, it requires a long time of administration, and an expensive and bulky equipment. Moreover, subjects cannot maintain balance under the more difficult conditions, especially when they are forced to rely only on vestibular input. A fall frequency as high as 22% has been reported while PwMS performed the more challenging conditions (i.e. surface moving, EO; surface moving, EC; surface and surround moving, EO) [24].

Force platform measures may differentiate balance control between PwMS and HCs. There is a general agreement that PwMS have a postural sway control which is significantly poorer than healthy subjects. PwMS present larger oscillations in the frontal and sagittal planes when compared with healthy controls [15]. By means of posturography, impaired anticipatory postural adjustments have been also described in PwMS [30].

Furthermore, the sensitivity of force platform measures is such that it can detect balance abnormalities even in minimally impaired PwMS (i.e. scoring as normal in clinical balance test) [31,32] or in those presenting a first demyelinating event suggestive of MS [33]. This latter study demonstrated that about 40% of subjects with a clinically isolated syndrome (CIS) suggestive of MS had poor or very poor scores in COP sway rate (i.e. 2-4 or ≥4 standard deviations higher than the mean value of healthy controls, respectively) [33]. Therefore, posturography demonstrates the existence of subclinical balance disorders that cannot be detected by means

of clinical assessment, even in PwMS who did not complain about subjective balance impairment [34].

Another common findings of these studies is that postural stability deficit is increased under more challenging conditions, e.g. reducing the base of support, suppressing visual or vestibular input, generating external perturbations, performing a reach and lean task or a cognitive task [33-38]. It has also been shown that an abnormal performance in quiet standing can be found in 2/3 of PwMS, even when all sensory inputs (visual, vestibular, proprioceptive) are available; the alteration of a single input can lead to an increase in abnormal findings by up to 82% [24].

3.2 - Objective

Quantitative measures as provided by posturography might potentially provide a reliable tool to identify PwMS at risk of falls, but data on its diagnostic accuracy (i.e. the extent to which a measurement is close to the true value) in identifying PwMS at risk of falls are still lacking.

The aims of this study were:

(i) to test the reliability of static standing balance measures (SSBMs) as provided by static posturography;

(ii) to calculate its sensitivity, specificity, predictive values and accuracy for detecting patients at risk of falls.

3.3 - Methods

Participants. PwMS as per McDonald criteria [19], and regularly attending the outpatient MS Centre of S. Andrea Hospital in Rome were consecutively recruited for the present study.

To be eligible each PwMS was required to have: an age from 18 to 55 years; an EDSS score [39] from 0 to 5.5 (inclusive), clinical stability from at least six months (i.e. no relapses, no disability worsening and no other medical complications). As exclusion criteria we considered: pregnancy; severely blurred vision, disease-modifying or symptomatic treatments that began or dose regimen that changed in the previous three months, concomitant otological or vestibular

disease (non-MS related), psychiatric disorders or severe cognitive impairment, cardiovascular and respiratory diseases.

To obtain normative values for SSBMs, gender and age-matched healthy controls (HCs) were also recruited among the students in physiotherapy, residents, nurses and doctors working on the Neurology Unit of S. Andrea Hospital.

This study was approved by Ethic Committee Board of our Institution; inform consents were obtained from each participant before any study procedure.

Study procedures. The assessment protocol consisted of a neurological evaluation, including the EDSS assessment, BBS [40], and static posturography. PwMS were then instructed to report the occurrence of their falls (i.e. an unexpected contact of any part of the body with the ground) over a 3-month follow-up period by means of a daily diary. They were also asked to report the circumstances in which they fell, when occurred. The physiotherapist monthly phoned participants to remind them to record the occurrence of accidental falls on the diary, which was returned at the end of the 3-month follow-up.

The BBS s a 14-item scale exploring the ability to sit, stand, lean, turn and maintain the upright position on one leg [40]; a cut-off score of 45 is an established criterion to identify elderly subjects with high risk of fall [41]. A sensitivity of 40% and a specificity of 90% in predicting fall status has been reported for the BBS in an Italian MS population [2].

Static posturography was carried out by a trained physical therapist unaware of clinical data by a monoaxial force platform (ProKin, Tecnobody, Dalmine, Italy) [42], consisting of three strain gauges set in a triangular position under a surface of 55 cm diameter, with a 20 Hz sampling rate and a sensitivity of 0.1°. Static posturography was performed according to a standardized procedure as follows: each subject was asked to stand barefoot on the ground, in upright static condition, double-leg stance and with arms resting at their sides (**FIG. 3.1**).[24].

The position of the feet on the force-platform was standardized using a V-shaped frame, keeping on a 3-cm distance between the two medial malleoli and an extra-rotation of 12° with respect to the sagittal axis [24].

Stance conditions were tested with EO and EC; each test lasted 30 seconds. The instant positions of the COP on the ground was used to calculate the following time-domain measures: the velocity (VEL) of the COP on the AP or ML axes (mm/s); the sum of the displacements of COP on force-measuring platform (mm), and the 95% confidence ellipse area (COP area) (mm^2).

Variable definition. The target condition was the occurrence of one or more falls (i.e. an unexpected contact of any part of the body with the ground) over the 3-month follow-up period.
The index test was the static posturography; abnormal cut-off values for the SSBMs were set at two standard deviations (SD) above the mean values of the HCs.
The reference test was the BBS; according to a previous study on PwMS, a score ≥44 were considered as abnormal [2].

Statistical analyses. Data are presented as mean (SD), median (range), or proportion, as appropriate. Differences between groups were tested using the Chi-Square test with Yate's continuity correction and Mann-Whitney U tests, for continuous and dichotomous variables, respectively. Relationships between variables were tested using the Spearman Rank coefficient. The normal distribution of the SSBMs was assessed by the Shapiro-Wilk test. Test-retest reliability for SSBMs in MS patients was assessed as concordance correlation coefficient (CCC), and its relative 95% CIs, by comparing the average measures of three consecutive trials from two different evaluations separated by a 30-minute interval.
To test the diagnostic accuracy of static posturography we applied criteria according to the STARD initiative [43]. Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and accuracy, and their 95% CIs, were measured for the presence of the target condition (i.e. being a faller or non-faller in the 3-month follow-up period). Sensitivity was calculated as true-positive/(true-positive + false-negative), specificity as true-negative/(true-negative + false-positive), PPV as true positive/(true-positive + false-positive), NPV as true-negative/(true-negative + false negative), accuracy as true-positive + true negative/(true-positive + false-negative + true-negative + false-positive). Estimates of variability of diagnostic accuracy between subgroups of patients were tested after binning the whole MS population according to EDSS tertiles.
Finally, we evaluated the potential predictors for the fall status (i.e. the dependent variable) computing the OR, with their relative 95% CIs, by a stepwise logistic regression analysis (forward stepwise selection) including as covariates: sex (female or male), age, body mass index (BMI) (calculated as weight/height^2 - kg/m^2), disease duration, MS subtype (RR or SP), EDSS and BBS scores, SSBMs. In each subsequent step, the regression equations comprised those variables reaching specific thresholds of F- and p-values (for variable inclusion: $F \geq 1$ and $p \leq 0.05$; for exclusion: $F < 1$ and $p > 0.05$); interactions terms were also tested, where appropriate. All p-values less than 0.05 (two-sided) were considered as significant.

3.4 - Results

Participants. From September 2010 until April 2011, we consecutively enrolled 100 PwMS (64 females, 36 males) and 50 gender- and age-matched HCs (32 females, 18 males). PwMS had a mean age of 38.0 (9.9) years, mean disease duration of 9.5 (6.4) years and median EDSS score of 3.2 (1.0-5.0). There were no differences as regarding sex, age and BMI between patients and HCs (data not shown).

The **TABLE 3.2** shows the normative values for SSBMs obtained by the sample of HCs; SSBMs of HCs were normally distributed ($p=0.25$), while those ones of PwMS did not satisfied the normality assumption ($p<0.0001$).

Reliability of static posturography. The **TABLE 3.3** shows the test-retest reliability of SSBMs. A better test-retest reliability was observed for the measures recorded in EO than EC. However, the unique SSBM having a substantial CCC (i.e. equal or more than 95%) was the COP path [EO]; hence, we selected this single measure for the diagnostic accuracy analyses. We also observed that all the SSBMs were related each from another, with correlation coefficient ranging from 0.61 to 0.86 (all p-values<0.0001 by the Spearman rank correlation coefficient).

Follow-up data. After the 3-month follow-up a total of 41 (41%) patients reported one or more falls; of them, 22 had one fall, 11 had 2 falls, and 8 had ≥3 falls. Two falls resulted in an injury: a 45-old female with an EDSS score of 3.5 had a hip fracture during her daily living activities, and a 37-old male with an EDSS score of 3.0 had a minor head trauma (without loss of consciousness) while walking in the darkness.

The **TABLE 3.4** shows baseline demographic and clinical characteristics of PwMS according to the occurrence of their falls. Fallers had a longer disease duration ($p=0.02$) and worse EDSS and BBS score than non faller ones ($p=0.001$ and $p<0.0001$, respectively). During the static stance trials the fallers moved faster in the AP and ML directions and had wider displacement of COP path than non fallers, in both EO and EC (all p-values<0.0001). Interestingly, several parameters, especially when measured in EC condition, had mean values larger than the abnormal cut-points not only in fallers, but also in the non-faller group.

Moreover, PwMS who reported multiple falls over the study period had worse BBS and EDSS scores, as well as SSBMs than those ones who reported only one fall over the 3-month study period (p-values≤0.005) (data not shown).

The **FIG. 3.2** shows the differences in the SSBMs among PwMS who reported at least one fall over the 3-month follow-up period (n=41), those who did not (n=59), and the HC group (n=50). As expected, we observed a gradient for worse SSBMs in the three groups (faller > non-faller > healthy controls) ($p<0.0001$ for all between-group comparisons).

Diagnostic accuracy. The **FIG. 3.3** shows the flow diagram regarding the diagnostic accuracy of BBS and the COP path in OE condition. The overall diagnostic accuracy of static posturography in detecting the target condition was better than BBS (75% *vs.* 64%): static posturography had better sensitivity and NPV, similar PPV and slightly worse specificity than BBS (see also **TABLE 3.5**). Moreover, we observed a certain degree of variability in the diagnostic accuracy of static posturography according to the disability level. After binning the whole MS population according to EDSS tertiles (equal or below than 2.0, from 2.5 to 3.5, equal or more than 4.0), we found that worse the disability level, greater was sensitivity; by contrast, static posturography lost specificity in patients with higher EDSS score (data not shown). However, the overall accuracy of static posturography ranged from good to very good (from 71% to 80%).

Although we observed that the number of falls over the 3-month follow-up period, the COP path in EO condition, the EDSS and BBS scores were significantly related each form another (r-values ranging from -0.83 to -0.38 and from 0.54 to 0.36; all p-values<0.0001), the multivariate analysis further confirms that static posturography provided the best predictor of the risk for the occurrence of accidental falls.

According to the stepwise logistic regression analysis, only the COP path [EO] predicted the risk of accidental falls, while the other variables included in the model as covariates (sex, age, BMI, disease duration, MS subtype, EDSS and BBS scores) were excluded from the final model (see also the **TABLE 3.6** for further details). In particular, we found that the risk of accidental falls increased by 8% for each 10 mm-increase in COP path [EO] (OR = 1.08, 95% CIs from 1.04 to 1.12; $p<0.0001$), even after adjusting for other demographic and clinical variables.

This model explains a quite considerable amount of the variance (43%; Nagelkerke pseudo R-square = 0.43) in predicting the fall status.

3.5 - Discussion

In the present prospective study, we demonstrated the high diagnostic reliability and accuracy of static posturography to detect MS people at risk of accidental falls. Among several SSBMs, we adopt the COP path in EO condition as having the best test-restest reliability; but generally, all the measures recorded with EO had CCC values better than those in CE condition. One possible explanation encompasses a greater variability of SSBMs as a source of a major intra-subject variability, especially when the visual input is not available [24,35,38].

In our study, there were significant differences between patients and healthy control regarding the SSBMs, even considering that about one third of our population had only a minimal or none disability as measured by an EDSS lower than 2.5. Accordingly, a recent study demonstrated that about 40% of CIS patients had poor or very poor scores in COP sway rate (i.e. 2-4 or ≥4 SD higher than the mean value of healthy controls, respectively) in open eye condition [33]. Other studies also demonstrated balance deficit in minimally impaired PwMS [31-34], even in those ones with normal clinical balance test, thus suggesting that PwMS may have a sub-clinical balance disorder unrevealed by conventional balance tests [34].

Our study also showed that static posturography was more accurate than BBS, a well-established clinical tool for measuring balance in MS and in different clinical setting. We found that BBS had poor sensitivity although slightly higher specificity than the COP path in EO condition, with more than 10% difference in accuracy favouring of static posturography.

We adopted a cut-off score of 44 for the BBS, since it had been previously determined in MS setting [2]. Accordingly, we found sensitivity and specificity (37% and 83%, respectively) similar to those reported in this latter paper (40% and 90%, respectively) [2]. By contrast, in another MS sample a sensitivity of 94% and a specificity of 32% were found by using a cut-off point between 55 and 56 points (the maximum score of the scale); at this regard, the authors concluded that there was possibly an artefact due to the ceiling effect experienced on the BBS [4]. In our opinion, these two conflicting results further strengthen the *a priori* hypothesis that computer-based SSBMs are more affordable than clinical scales.

It can be argued that the major limits of the static posturography is represented by an overestimation of patients prone to accidental falls (i.e., 34% of false-positive in our study, especially among those patients with greater disability levels). However, in a clinical context it is more convenient having a greater proportion of false-positive than false-negative patients. Moreover, one could speculate that the false-positive group included PwMS having an activity

curtailment driven by the fear of falling [44]. This group of patients may involuntarily adopt a strategy to prevent falls, even paying the price for a reduction in activities of daily living.

According to the guidelines of the STARD initiative [43], we provided estimates of variability of diagnostic accuracy between subgroups of patients after binning the whole MS population according to EDSS tertiles. This allowed us to investigate the relationship between the disability status and the diagnostic accuracy of static posturography. Although sensitivity and specificity in our study were influenced by the patient disability, measuring the COP path in EO condition may ensure an acceptable accuracy regardless to EDSS score. Lastly, the multivariate analysis clearly indicated that the risk of falls was increased in direct proportion to the extent to the COP path in EO condition, irrespective of the other demographic and clinical variables (including MS subtype, EDSS and BBS). Therefore, a gradient of postural disturbance can be hypothesized as follows: PwMS recurrent fallers > PwMS once fallers > PwMS non-fallers > healthy subjects (**FIG. 3.4**). However, this hypothesis needs to further confirmations.

Study limitations. Limits of the present study mainly concern the small sample size and the reliance upon self-reported data; however the prospective design and the collection of patient diaries should be improved the validity of our findings [4].

Although SSBMs of HCs in our study are comparable with those found in a previous report in which the same force-platform and a similar posturometric approach were used [24], the cut-off values for the SSBMs have not still been established in MS population. Furthermore, static posturography instruments are very different each from another, thus precluding the possibility to generalize our results. Up to now, it is not well defined which time-domain parameters of balance (e.g. velocity, path, area, etc.) should be evaluated by static posturography [18,25,29]. A possible solution to standardize the static posturography assessment should be the Balance Board of Nintendo Wii (Nintendo, Kyoto, Japan), that has been recently suggested as an inexpensive and wide available balance assessment system [45]. In fact, it contains four force sensors (located in each corner) which detect subject's COP and weight shifts, and therefeore can be used to collect and analyze COP sway parameters by means of dedicated software [45]. Balance board has not only characteristics similar to the currently used force platform, but it possesses very good test-retest reliability for the COP path, and concurrent validity comparable with a laboratory-grade force platform [45].

Lastly, it has to be consider that falls may be due to the sum of multiple impairments which probably cannot be everyone detected by static posturography [46].

Implications. Despite the aforementioned limitations, we suggest that static posturography may be employed as an useful tool to select PwMS requiring proper rehabilitative interventions (e.g. traditional and novel exercise-based training, torso-weighting, virtual reality, or visuo-proprioceptive training, etc.) that have been proven to be effective in ameliorating balance and reduce the risk of accidental falls.

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Table 3.1

Commonly used clinical scales to assess balance in PwMS.

Tool *Authors* *Journal*	Brief description	Time of administration	Overall Score	Test-retest reliability	Accuracy in predicting fall status in PwMS
Activities-specific Balance Confidence (ABC) *Powell LE, Myers AM* *J Gerontol A Biol Sci Med Sci 1995*	16-item self-administered questionnaire rating the perceived level of confidence in performing daily living activities	15 minutes	0 to 100	92%	SE: 65%, SP: 77% (cut-off: 40)
Balance Evaluation System Test (BESTest) *Horak FB, Wrisley DM, Frank J* *Phys Ther 2009*	36-item physician-rated scale evaluating 6 systems (biomechanical constraints, stability limits/verticality, anticipatory postural adjustments, postural responses, sensory orientation, stability in gait)	30 minutes	0 to 108	88-91%	SE: 86%, SP: 95%
Berg Balance Scale (BBS) *Berg KO, Wood-Dauphinee SL, Williams JI, Maki B* *Can J Public Health. 1992*	14-item physician-rated scale exploring the ability to sit, stand, lean, turn and postural transition	15 minutes	0 to 56	96%	SE: 40%, SP: 90% (cut-off: 44) SE: 94%, SP: 32% (cut-off: 55) SE: 32%, SP: 87% (cut-off: 44)
Dizziness Handicap Inventory (DHI) *Jacobson GP, Newman CW* *Arch Otolaryngol Head Neck Surg 1990*	Multidimensional 25-item self-administered questionnaire quantifying the level of disability in three domains: physical, emotional, and functional	15 minutes	0 to 100	90%	SE: 50%, SP: 74% (cut-off: 59)
Dynamic Gait Index (DGI) *Whitney SL, Hudak MT, Marchetti GF* *J Vest Res 2000*	8-item physician-rated scale exploring mobility function and dynamic balance	10 minutes	0 to 24	85%	SE: 45%, SP: 80% (cut-off: 12)
Four-Square Step Test (FSST) *Dite W, Temple VA* *Arch Phys Med Rehabil 2002*	Stop-watch measurement of the duration of rapidly step over low obstacles in clockwise and counter-clockwise direction	3 minutes or less	N/A	93-98%	SE: 60%, SP: 75% (cut-off: 16.9s)
Functional Reach Test (FRT) *Duncan PW, Weiner DK, Chandler J, Studenski S* *J Gerontol 1990*	Measurement of the maximum distance reached forward while standing in a fixed position	N/A	N/A	85-95%	-
Timed up-and-go test (TUG) *Podsiadlo D, Richardson S.* *J Am Geriatr Soc 1991*	Stop-watch measurement of the duration of stand-up from a chair, walking 3 meters, turn around, walk back and sit down	3 minutes or less	N/A	98%	SE: 73%, SP: 54% (cut-off: 13.6 s)

SE: sensitivity; SP: specificity

Table 3.2

Normative values for SSBMs from a sample of 50 HCs.

	Mean (SD) value	Range	Abnormal value *
VEL AP [EO], mm/s	5.6 (1.8)	4 - 11	> 9.2
VEL ML [EO], mm/s	6.1 (1.9)	3 - 11	> 9.9
COP path [EO], mm	215 (65)	109 - 379	> 345
COP area [EO], mm^2	140 (85)	29 - 479	> 310
VEL AP [EC], mm/s	8.3 (2.9)	4 - 16	> 14.1
VEL ML [EC], mm/s	8.6 (3.2)	4 - 18	> 15.0
COP path [EC], mm	335 (120)	141 - 588	> 575
COP area [EC], mm	290 (205)	45 – 962	> 800

***** *calculated as mean value + 2 standard deviation.*

Table 3.3

Demographic, clinical and posturometric characteristics of PwMS (n = 100) according to fall status at the end of the 3-month observational period.

	Fallers n = 41	**Non fallers n = 59**	**p-value**
Gender (F:M)	25:16	39:20	0.67
Age, years	37.7 (8.9)	38.5 (10.1)	0.74
BMI, kg/mq	22.7 (3.0)	22.8 (4.0)	0.63
Disease duration, years	11.0 (6.2)	8.5 (6.3)	**0.02**
MS subtype (RR:SP)	31:10	9:50	0.25
EDSS score	3.6 (0.9)	3.0 (1.0)	**0.001**
BBS score	46.3 (4.6)	49.9 (4.7)	**<0.0001**
VEL AP [EO], mm/s	16 (4 - 36)	7 (4 - 15)	**<0.0001**
VEL ML [EO], mm/s	14 (4 - 46)	8 (5 - 18)	**<0.0001**
COP path [EO], mm	567 (170 - 1390)	297 (171 - 614)	**<0.0001**
COP area [EO], mm^2	866 (117 - 3646)	241 (58 - 1237)	**<0.0001**
VEL AP [EC], mm/s	36 (8 - 67)	15 (6 - 50)	**<0.0001**
VEL ML [EC], mm/s	32 (8 - 63)	16 (5 - 36)	**<0.0001**
COP path [EC], mm	1246 (509 - 2450)	592 (217 – 1572)	**<0.0001**
COP area [EC], mm^2	4438 (449 - 8304)	807 (80 - 3900)	**<0.0001**

Demographic and clinical values are expressed as mean (SD), unless indicated otherwise; static standing balance measures are expressed as median (range).

Table 3.4

Test-retest reliability for SSBMs, as assessed in PwMS (n = 100), expressed as CCCs.

	EO	EC
VEL AP, mm/s	0.89 (0.78-0.95)	0.77 (0.58-0.88)
VEL ML, mm/s	0.90 (0.81-0.95)	0.58 (0.27-0.78)
COP path, mm	0.95 (0.90-0.97)	0.73 (0.53-0.85)
COP area, mm^2	0.91 (0.84-0.96)	0.64 (0.36-0.82)

Table 3.5

Diagnostic values, and their relative 95% CIs, of index test (i.e the static posturography) and reference test (i.e. the BBS), as assessed in PwMS (n = 100).

	Sensitivity (95% CIs)	Specificity (95% CIs)	PPV (95% CIs)	NPV (95% CIs)	Accuracy (95% CIs)
COP path [OE]	88	67	64	89	75
Cut-off ≥ 345 mm	(74-96)	(53-78)	(50-76)	(76-96)	(66-83)
BBS	32	87	62	64	64
Cut-off ≥ 44	(18-48)	(75-94)	(38-82)	(53-75)	(54-73)

Table 3.6

Statistical score and partial correlation for each variable included in the logistic regression model which was built to predict the fall status over the 3-month follow-up period. At each step, the variables with the largest score whose p-value is less than 0.05 was added in the model. At the last step, the variables which did not contribute to best fitting the model were excluded.

Step 0	**Statistical score**	**Partial Correlation**	**p-value**
Sex	0.276	0.05	0.68
Age	0.165	0.04	0.60
BMI	0.027	0.02	0.87
Disease duration	4.079	0.21	***0.04***
MS subtype	1.312	0.12	***0.25***
EDSS score	11.126	0.33	***0.001***
BBS score	12.235	-0.35	***< 0.0001***
COP path [EO]	28.246	0.54	***< 0.0001***

Step 1	**OR**	**95% C.I.**	***p-value***
COP path [EO]	1.08	1.04 - 1.12	***< 0.001***

Figure 3.1

Force platform equipment **(**ProKin, Tecnobody, Dalmine, Italy) [42].

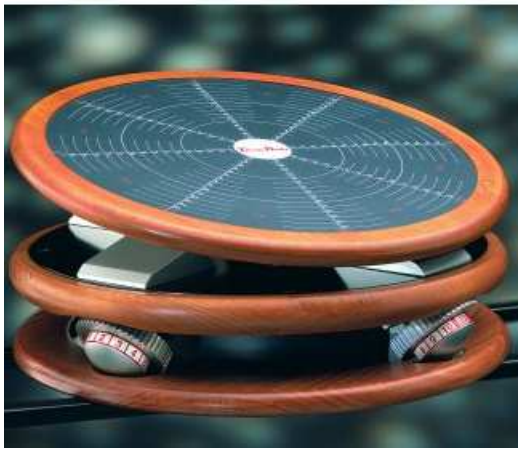
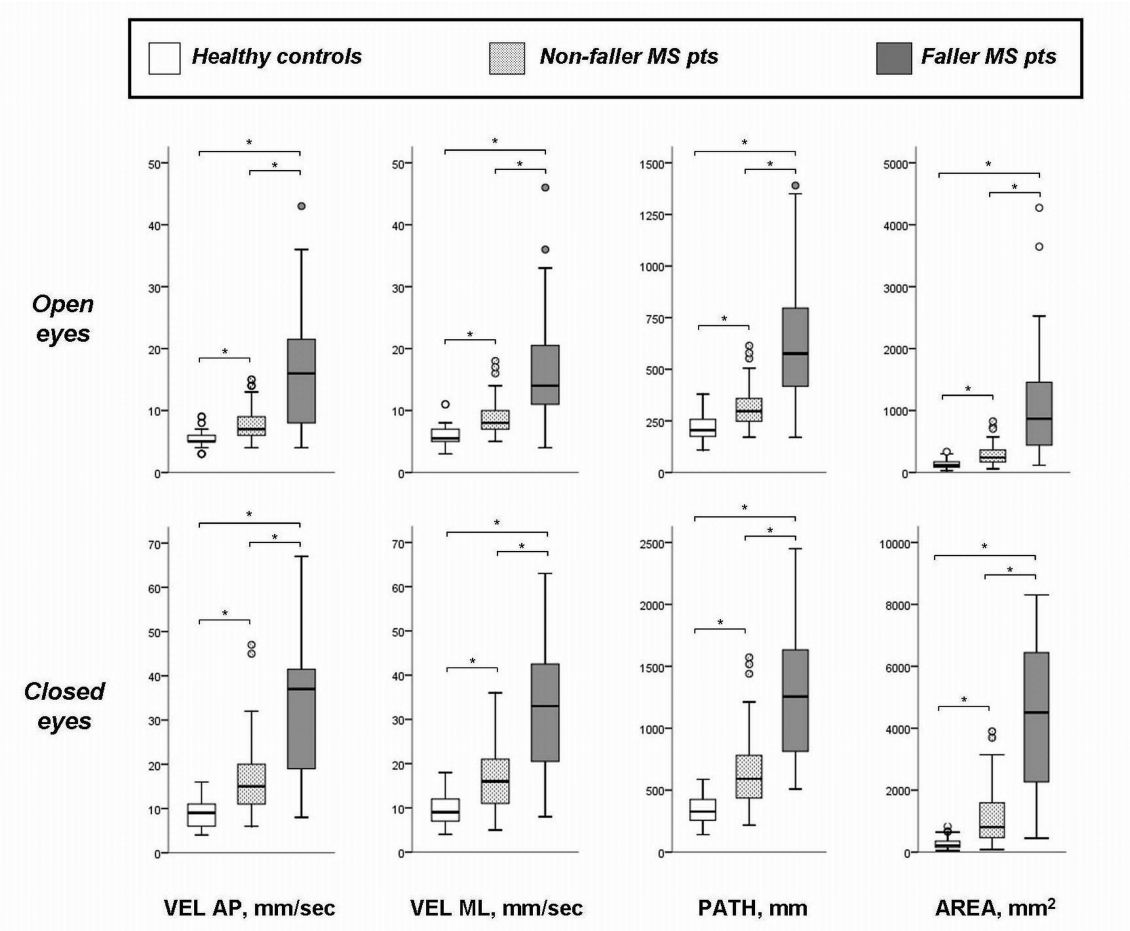


Figure 3.2

SSBMs of HCs (n = 50), non-faller (n = 59) and faller PwMS (n = 41).



***** *p <0.0001 by the Mann-Whitney U test.*

Figure 3. 3

Flow diagram (as recommended by the STARD criteria) showing the number of PwMS undergoing the index test (i.e. the static posturography), the reference test (i.e. the BBS) and their relative diagnosis.

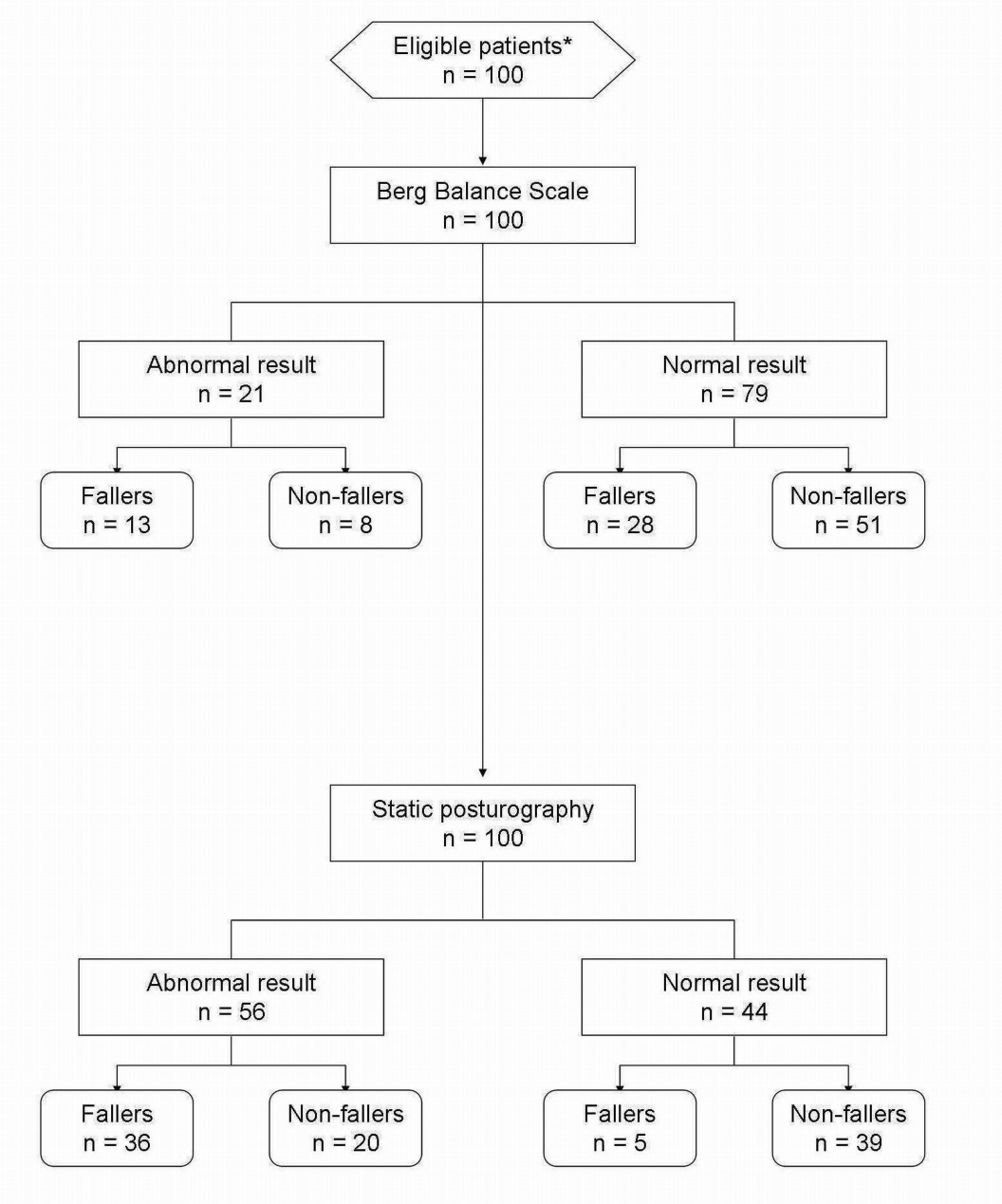
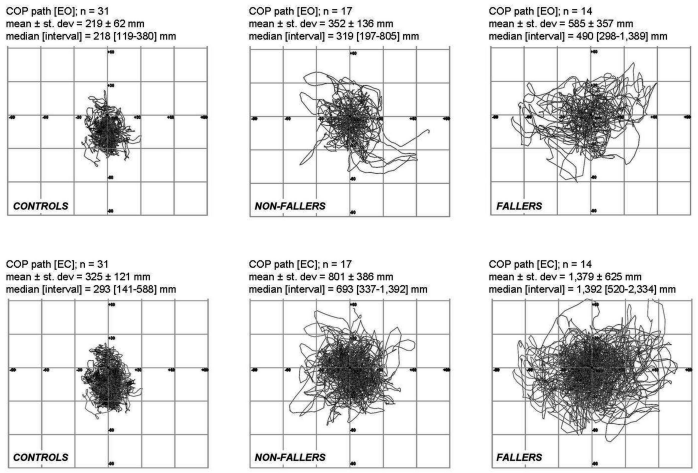


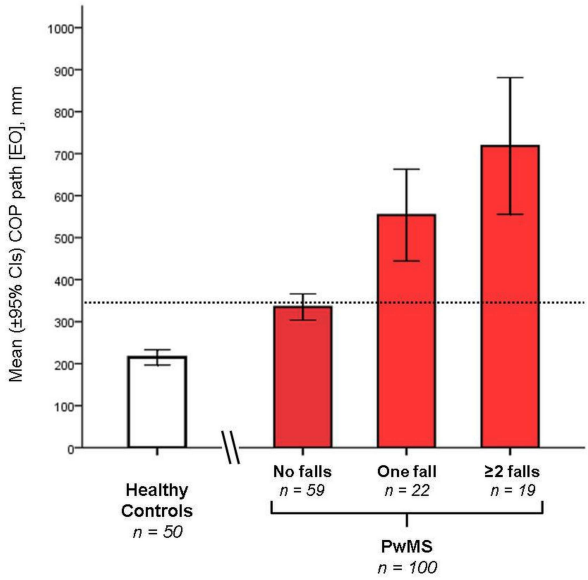
Figure 3.4

A. Superimposed displacements of COP on x-y axes with both EO and EC (upper and lower rows, respectively) of HCs (controls, n = 31), PwMS without a history of falls (non-fallers, n = 17) and those reporting one or more falls in the past 6 months (fallers, n = 14) (adapted from [7]).
B. Means (95% CIs) values of COP path with EO of HCs (n = 50) and PwMS (n = 100) who were divided according to the number of accidental falls (0, 1, ≥2) prospectively collected over a 3-month follow-up period; dotted line indicates two SD above the mean value of HCs.

A



B



CHAPTER 4

NEUROPATHOLOGICAL FEATURES OF IMBALANCE DUE TO MULTIPLE SCLEROSIS: THE ROLE OF MAGNETIC RESONANCE IMAGING

The neuropathological mechanisms leading to balance impairment in people with MS are not yet well determined. The poor postural control in these persons, who have an extensive and variable damage into CNS, may be due to multifactorial causes that differ from one person to the next. It has been suggested that postural balance deficit in patients with MS resulted from impaired central integration of visual, vestibular and somatosensory input [1]. However, it is also possible that lesion in specific locations and their consequent impairment are the primary contributors to imbalance due to MS.

4.1 - Background

The ability of magnetic resonance imaging (MRI) in detecting subclinical MS lesions had led to its widespread acceptance as a tool not only in the diagnostic work-up of subjects who present a first demyelinating event [2], but also in obtaining prognostic information early in the course of the disease [3]. Conversely, in established MS the strength of the relationship between conventional MRI findings and the subsequent clinical manifestations remains modest at best. This is, at least partially, the result of the limited specificity of conventional MRI of the various features (i.e., oedema, demyelination, remyelination, gliosis, and axonal loss) of MS pathology, which can in turn be associated with very different clinical outcomes, and to its inability to detect and quantify the ‘‘occult’’ damage known to occur in the normal-appearing brain tissue (NABT). Moreover, statistical drawbacks of clinical and disability scales should be also considered [4].
In patients with RRMS and SPMS, disease activity is detected 5-10 times more frequently on conventional MRI scans than with clinical assessment of relapses [5]. This, coupled with the fact that conventional MRI provides objective and sensitive measures of disease activity, led to the use of conventional MRI as an established tool for assessing the natural history of MS

progression. Several cross-sectional studies evaluated differences in T2-hyperintense lesion load among different MS phenotypes. T2-hyperintense lesion load is higher in SPMS in comparison to benign MS, RRMS, and PPMS. Moreover, T2-hyperintense lesions were mainly located in the periventricular regions and the posterior fossa in patients with SPMS in comparison with those with PPMS, while PPMS patients had a more diffuse involvement of cortical and subcortical regions [6]. However, in cross-sectional studies the magnitude of the correlation between T2-hyperintense lesion measures and disability has been rather disappointing. Furthermore, a plateauing relationship between T2-hyperintense lesion load may be present for EDSS scores higher than 4.5, which suggests that MRI metrics other than T2-hyperintense lesion loads should be considered when assessing the more advanced phases of the disease [7]. However, it is also noteworthy that Sormani et al. have shown that such a plateauing relationship between T2-hyperintense lesion load and disability is not always present [8]. The lack of a strong relationship between clinical disability and T2-hyperintense lesion load has led to a developing interest in T1-hypointense lesions (comparing with their surrounding tissue), namely “black holes” (BHs). Although they may arise concomitantly in acute contrast enhancing lesions (CELs) - post-contrast T1-weighted imaging visualize disruption of the blood-brain barrier (BBB) and sites of active inflammation - approximately 25% of BHs persist above the CELs resolution [9]. These chronic BHs represent areas of irreversible tissue loss, which can ultimately contribute to disability, thus providing more pathological specificity than T2-hyperintense lesions.

A number of non-conventional MRI techniques have been developed to overcome the limitations of conventional MRI and to define new MRI markers more closely linked to the most disabling pathological features of MS (i.e. irreversible demyelination and neuroaxonal injury). Therefore, metabolic, functional, and structural, MRI-based techniques have recently received considerable attention [10].

Proton MR spectroscopy (MRS) can add information on the biochemical nature of such changes. Functional MRI (fMRI) can provide new insights into the role of cortical adaptive changes in limiting the clinical consequences of MS irreversible structural damage. Magnetization transfer and diffusion tensor imaging (DTI) can quantify the extent and pathological severity of structural changes occurring within and outside T2-hyperintense visible lesions of MS. Diffusion tractography can also provide unique information by means of non-invasive brain imaging data to trace fibre bundles in the human brain *in vivo*.

DTI measures directions of water diffusion in the brain. A tool for voxel based analysis of DTI data, called tract-based spatial statistics (TBSS), was recently developed [11]. DTI

abnormalities, which are already detectable in patients with clinically isolated syndrome [12], become more pronounced as disease duration and neurological impairment increase [13].
Quantification of brain atrophy provides a rather crude, but objective measure of overall tissue loss in MS. Neuronal and axonal damage can occur in the lesions and beyond, thus leading to the concept of the so-called normal appearing white matter (NAWM), even early in the course of the disease. MRI data have also led to the hypothesis that progression of the disease, up to a stage of no return, is dependent on the cumulative effect of axonal damage, which may ultimately result in MRI-visible brain atrophy [4].
The spatial distribution of grey matter (GM) atrophy can be assessed by means of voxel-based morphometry (VBM), which is an operator-independent and unbiased tool used in MRI analysis that reflects the regional GM volume at a voxel scale [14]. Both whole and selective GM measures of brain atrophy have been reported as related to neurologic disability in MS [15].
Non-conventional MRI techniques are usually employed in research studies which aim at understanding the mechanisms of damage and repair in the CNS. These new imaging measures are more sensitive that conventional MRI and therefore they represent a powerful tool for identifying pathological changes which contribute to relevant clinical impairments.

4.2 - Objective

By using MRI techniques, the structure-function relationship mediating postural balance can be extensively investigated, thus providing useful information about the neuropathological substrate of balance impairment.
In the following studies we tried to establish relationship between imbalance (as estimated by force platform measures) and conventional or non-conventional MRI metrics in PwMS, as follows:
(i) a conventional MRI study, mainly focused on lesion volume as seen on T2-weighted images (T2-LV) at infratentorial level ***(→ 4.3);***
(ii) a study integrating conventional MRI features (whole brain and regional T2-LV) and atrophy measurements of cerebellum and spinal cord ***(→ 4.4);***
(iii) a non-conventional MRI study that combined two unbiased (i.e. without any a priori hypothesis) MRI processing approaches (TBSS and VBM) ***(→ 4.5).***

4.3 - The structure-function relationship mediating standing balance: a conventional MRI study

4.3.1 - Methods

Participants. PwMS according to the McDonald criteria and regularly attending the outpatient MS centre of S. Andrea Hospital in Rome were recruited to participate in this independent, single-centre, cross-sectional study. All patients were required to have an objective balance disturbance (i.e. impaired straight line walking, or gait ataxia, or positive Romberg test on neurological examination). Moreover, patients were required to walk without aid or rest for a minimum distance of at least 100 meters. Clinical stability for at least six months (i.e. no relapses and no disability progression) was also required. We excluded patients with PP course and those suffering from severely blurred vision, more than a moderate limb spasticity (i.e. increased muscle tone difficult to overcome and/or impaired full range of motion after a rapid flexion of the lower limbs), concomitant otological or vestibular disease (non-MS related), psychiatric disorders or severe cognitive impairment, cardiovascular and respiratory diseases.
In a single session, each patient underwent a neurological examination with the EDSS assessment, a measurement of SSBMs, and a conventional brain MRI scan. The assessment of the static standing balance was performed with a monoaxial force platfomr according to standardized procedures, as above described (see **Chapter 3, section 3.2, page 32** for more details) [16].

MRI procedures. Brain MRI data were acquired by an expert radiologist using a superconducting 1.5 Tesla magnet (GE Excite) to obtain conventional proton density (PD), T2-weighted spin-echo images, with time of repetition (TR)=2,540 ms, time of echo (TE)=18/105 ms, matrix 320 × 192 mm, field of view (FOV)=250 × 250 mm, 40 axial slices, slice thickness 4 mm, gap 0.4 mm), and T1-weighted images after gadolinium-DTPA injected in a double dose (0.2 mmol/kg) (TR=500 ms, TE=21 ms, matrix 288 × 224 mm, FOV=250 × 250 mm, 40 axial slices, slice thickness 4 mm, gap 0.4 mm). Both T2-LV and hypointense lesion volumes on T1-weighted images (T1-LV) were measured using a local thresholding segmentation technique (Jim 4.0, Xinapse System, Leicester). Regions of interest (ROI) were identified by the agreement of two trained operators unaware of clinical data, focusing on lesions selectively

located at infratentorial levels, according to anatomical boundaries as defined by an anatomical atlas. According to the atlas hallmarks and considering phylogenetic division, we delimited the paleocerebellum (i.e. the anterior lobe, above the primary fissure, including both tonsilles, anterior vermis and paravermis) and neocerebellum (i.e. the posterior lobe, below the primary fissure, including the cerebellar hemispheres and the posterior vermis). The archicerebellum (i.e. the flocculo-nodular lobe) was not considered because its small extent that does not make it easily recognizable with the available sequences. We also delimited the brainstem including medulla oblongata, pons and midbrain. Pons and middle cerebellar peduncles (MCPs) were delimited according to semiautomatic outliners by means of different signal intensities, as seen in T2-weighted sequences, between the pons, vermis, and cerebellar hemispheres (**FIG. 4.1**). The obtained outliners were automatically copied from T2-weighted onto PD-weighted images.

Outcome measures. The instant positions of the COP on the ground were used to calculate the following variables: (i) VEL AP or ML (cm/s): computed as the first time derivative of the COP displacement on the AP or ML axes; (ii) length of COP path (cm): computed as the sum of the displacements of COP on force-measuring platform.
The self-reported number of falls in the past 6 months was also considered. As retrospectively collected at the study inclusion, the self-reported number of falls could be prone to a recall bias; however, it has been demonstrated a good correlation (r = 0.82) between prospectively and retrospectively collected falls [17]. Also, we subdivided patients into two groups: “fallers”, i.e. patients who reported at least 1 fall; and “non-fallers”, i.e. those who did not report any falls in the past 6 months.

Statistical analysis. All values are presented as a mean (standard deviation), or median [range], as appropriate. Differences between groups were calculated using the two-sample Kolmogorov-Smirnov test or the Fisher exact test, as appropriate. Relationships between variables were performed using a non-parametric approach, the Spearman Rank coefficient; a Bonferroni correction for multiple comparisons was applied to set the two-side statistical significance.
Finally, an ordinal regression analysis was run in order to identify variables associated with the number of falls which occurred in the past 6 months. Posturometric and MRI findings showing a statistical significance less than 0.05 (two-sided) in the univariate analysis were inserted in the model as independent variables in a stepwise fashion; the model was also adjusted for gender, age, and BMI.

4.3.2 - Results

Patients. A total of 31 PwMS (19 females, 12 males) affected by RR (n=21) or SP (n=10) course of MS, with a mean (SD) age of 41.2 (9.8) years, mean disease duration of 11.9 (7.4) years, and median EDSS score of 3.5 (range 2.0-5.0) met the eligibility criteria for the present study.
Fourteen (45%) of them reported 1 or more falls over the past 6 months. Among fallers, the median number of falls was 2 (range 1-6). Out of these 14 patients, 9 (65%) were recurrent fallers, i.e. reported more than 1 fall in the past 6 months.
The **TABLE 4.1** shows the demographic and clinical characteristics of the 31 patients according to be fallers or non-fallers in the past 6 months. Fallers had a higher EDSS score (p=0.03) than non-fallers. There were no significant differences between fallers and non-fallers in other clinical variables, such as gender, age, MS duration, BMI.

Posturometric variables. As reported in **TABLE 4.1**, during the static stance trials the fallers moved more and faster in the AP and ML directions (p-values from 0.007 to 0.05), in both EO and EC conditions.

MRI metrics. Disseminate involvement of the periventricular, iuxtacortical and infratentorial white matter was observed in all patients. No MRI images on spinal cord of MS patients were available for the analysis; however, each patient had one or more demyelinating lesion at this level.
Overall, the mean (SD) total T2- and T1-LVs were 10.54 (9.91) and 1.16 (0.99) cm^3, respectively. T2-LVs were predominantly distributed at the sovratentorial (91%) rather than at infratentorial level (9%). At infratentorial level, the T2-LV was higher on brainstem [0.40 (0.32) cm^3] than in cerebellum [0.28 (0.19) cm^3]. Hypointense lesions (i.e. “black holes”) at infratentorial level were detected in 10 patients, and contrast enhancing lesions only in 3 patients, exclusively at supratentorial level.
Whole brain, supratentorial and infratentorial T2-LVs were significantly correlated with each other; T1-LV was associated with whole brain and supratentorial T2-LVs (data not shown). Fallers had greater T2-LVs at brainstem and MCP levels than non-fallers (p=0.01 and p=0.03, respectively). No differences there were between the two groups regarding the whole brain, supratentorial, and infratentorial T2-LVs as measured at paleo- and neocerebellum levels (see also **TABLE 4.1**). Similarly, the two groups did not differ in T1-LV (data not shown).

Relationship between static posturography and MRI metrics. The **TABLE 4.2** shows correlations between variables as measured by the static posturography and conventional MRI metrics. After correction for multiple comparison, brainstem T2-LV was significantly related to VEL ML and length of COP path in EO condition (p=0.001 for both correlations). No significant relationship were found between T2-LVs in other areas and measures from static posturography. Finally, there were no relationship between whole brain T1-LV and static posturography (data not shown).

Identification of patients at risk of recurrent falls. To identify variables associated with the risk of recurrent falls, we carried out an ordinal regression analysis with the number of falls in the past 6 months as dependent variable. According to the model, the independent variables more strictly associated with a higher number of falls in the past 6 months were the MCP T2-LV (Beta=6.2, 95% C.I. 1.5-10.9; p=0.01), the brainstem T2-LV (Beta=5.8, 95% C.I. 2.2-9.5; p=0.001), and the length of COP path in EC condition (Beta=0.02, 95% C.I. 0.01-0.05; p=0.03). These estimates do not change significantly even considering other variables in the model, such as EDSS, length of COP path (EO), and whole brain T1-LV and T2-LV, or T2-LVs at different infratentorial levels (data not shown). The final model explains a considerable amount of the variance (Nagelkerke pseudo R-square=0.71) in the number of the falls which occurred in the past 6 months (**TABLE 4.3**).

4.3.3 - Discussion

The principal findings of our study are that ambulatory MS patients with a history of falls were more disabled, had an impaired static postural balance, and a greater lesion burden on MCP and brainstem than non-faller ones. Recurrent falls were reported by patients who had a greater length of COP path in EC condition, that correspond to an elevated energy expenditure to maintain balance in visual suppression (i.e. more reliance on proprioceptive input), and a prominent lesion burden on MCP and brainstem. These data are consistent with evidences reporting that clinically eloquent sites, such as brainstem and cerebellum, may have major impact on clinical disability in MS [18-23], even in the early stage of the disease [24]. In our study, we also found significant correlations between the velocity on ML axis and length of COP path (both measured with EO) and the brainstem T2-LV. The specific architecture of infratentorial areas, where there are high neural fibre density with a marked

compartmentalisation, may explain the relationship between clinical outcomes and MRI findings stronger than in other brain regions. It may speculate that demyelinating lesions may disrupt white matter pathways of connection between spinal cord, cerebellum, vestibular nuclei, thalami and cortical regions, all of which pass through the brainstem. Also, the involvement of MCPs may lead the disconnection of the cortico-ponto-cerebellar pathway, that has been related with the severity of ataxia in some neurodegenerative disorders [25,26].

The impact of brainstem white matter abnormalities on balance skills has been recently demonstrated even in a sample of older adults without cognitive impairment or concurrent neurological disease [27]. Relevant correlations between the degree of white matter deterioration in specific infratentorial areas (e.g. superior and middle cerebellar peduncles) and balance deficit in young subjects with traumatic brain injuries were also recently reported [28].

Accordingly to previous studies demonstrating a worse postural control in visual suppression [29], we found that the impairment of standing balance in EC condition was an independent predictor of falling. Nevertheless, in our study there were no correlations between posturometric data as measured on the AP axis or with EC and specific infratentorial areas. At this regard, we hypothesized that the damage of dorsal column of spinal cord (not measured in the present study) might contribute to balance impairments, especially when the visual input is unavailable. [30,31].

We did not observe any relationship between disease burden affecting vermal, paravermal, and hemispheric cerebellar areas and balance deficit or risk of recurrent falls. This may have several explanations: (i) cerebellar T2-LV in our sample was only about the 3% of the whole brain T2-LV; (ii) we did not use double-inversion recovery (DIR) sequences, that are leading to better lesion volume measurements, especially at the intracortical level [32]; (iii) balance deficits may be related to disconnection of neural pathway rather than plaques directly located on the cerebellum. At this regard, Derache and coll. observed a cerebellar hypometabolism despite a very low lesion burden on cerebellum (about 2% of the total) in 17 MS patients with mild levels of disability [33]. The authors suggested a functional disruption due to subcortical lesions between cortical areas and cerebellum via thalamus nuclei [33].

Finally, consistent with one study reporting only a little predictive value of BHs in MS [18], we did not observe any relationship between T1-LV, balance skill and accidental falls. Moreover, it is know that shrinkage of tissue in infratentorial areas results in atrophy rather than in development of black holes [34].

Limits of the present study concern a small simple size and lacking of a more specific marker of tissue damage other than the lesion burden on T2-weighted sequences. Non-conventional MRI

techniques [35], including the analysis of the WM white matter tracts using DTI and brain regional atrophy, might provide an anatomical framework for interpreting the pathological ùsubstrate of the balance disorders. Moreover, we did not consider the involvement of the spinal cord, especially dorsal column, which has been documented as having a significant contribution to balance and sensory-motor dysfunctions in patients with MS [30,31].

4.4 - Comprehensive assessment of contribution of cerebellum and spinal cord to imbalance

4.4.1 - Methods

Participants. PwMS according to 2005 revision of McDonald criteria, and regularly attending the MS Centre of S. Andrea Hospital in Rome, and sex/age-matched HCs were recruited in this single centre, cross-sectional study. Approval was obtained from the Institutional Review Board of our Institutions, and written informed consent was obtained from each participant before any study procedure. To be eligible for this study, patients must have: an age ranging from 18 to 55 (inclusive) years; ability to walk without support/aid; an EDSS score ranging from 0 to 5.5 (inclusive). The exclusion criteria were: severe blurred vision, concomitant otological disease, significant cognitive impairment, relapse occurring over the previous six months, initiation of disease-modifying or symptomatic treatments, or any medication change occurred over the previous three months, history of seizures and contraindications to MRI.

Clinical evaluations. Eligible patients underwent a clinical evaluation, static posturography assessment, as above described (see **Chapter 3, section 3.2, page 32** for more details) [16], and MRI scanning in the span of one week. Sex and age-matched HCs also underwent the same static posturography and MRI protocol. Demographic and clinical variables, such as gender (female or male), age and BMI were collected for each subject. Disease duration (i.e. time in years elapsed from disease onset and the study enrolment) was also collected for each PwMS. They also underwent a detailed neurologic examination by the agreement of two board-certified neurologists, including the EDSS score and the 25-FWT to estimate the walking speed (expressed as m/s). The 25-FWT is a stop-watch measurement of time (seconds) to walk a 25-foot (7.6 meters) distance. It has shown good reliability and validity, and represents the most characterised measure of walking speed in PwMS [36].

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: (i) dual-echo turbo spin (PD and T2-weighted) echo axial sequence (TR=5,310 ms, TE=10/103 ms, echo train length=28,

matrix=384x90, FOV=220 mm^2, integrated Parallel Acquisition Technique reduction factor=3, acquisition time=5'04") with 40 slices 4 mm thick and 0 mm interslice gap; (ii) 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^2, acquisition time=3'48"); (iii) T1-weighted spin echo after administration of gadolinium-based contrast agent (TR=550 ms, TE=9.8 ms, matrix=384x90, FOV=220 mm^2, time 2'15") with 40 slices 4 mm thick and 0 mm interslice gap.

Image analyses. Image data processing was performed by an 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, midsagittal cerebellum area (MSCA) and upper cord cross-sectional area (UCCA) at the C2-C3 intervertebral disk level were estimated. To take into account for biological variation in CNS size, both measurements were normalised for intracranial cross-sectional are area (ICCSA).

For each participant, ICCSA was semi-automatically measured on an axial DP/T2-weighted axial slice at the level of inferior margin of corpus callosum, as previously described [37].

MSCA measurements (mm^2) were obtained on 3D-T1-weighted MPRAGE sequences according the following procedure: (i) a slice in which the aqueduct of Sylvius is more clearly visualized was identified among the midsagittal images; (ii) this image was aligned according to a line passing through splenum and genu of corpus callosum; (iii) a ROI was automatically created by means of different signal intensities to outline the boundary between cerebellum and cerebro-spinal fluid (CSF) in the posterior fossa (**FIG. 4.2**). This measure has been reported as highly correlated with cerebellar volume [38]; also, reliability for this measure as been established as very good [39].

UCCA values (mm^2) were quantified on 3D-T1-weighted MPRAGE sequences at the C2-C3 segments using an automatic edge detection technique [40], as follows: (i) images were re-formatted images axially such that the spinal cord was perpendicular to the axial plane; (ii) five contiguous 3-mm pseudo-axial slices were obtained using the centre of the C2-C3 intervertebral disc as a caudal landmark; (iii) a ROI delineating the cord edge was automatically applied to each of 5 axial slices; (iv) the average area enclosed by the five ROIs obtained was then calculated to obtain the UCCA value. Measurement of UCCA has been reported as consistently reliable [40] and clinically relevant in PwMS [37,41].

In patient group, lesion volumes (LV) on axial PD/T2-weighted images were measured, focusing on lesions selectively located at infratentorial level - brainstem, cerebellum, and MCPs - by

means of a semi-automated edge contour technique, as above described (see **section 4.3.1, page 54, and FIG. 4.1, page 84** for more details) [42]. Lesion volumes at different infratentorial levels have been previously reported as related to neurological disability and balance deficit in PwMS [18,20,42].

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

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. Slopes of correlation coefficients between static posturography measurements and radiological features were compared 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 into CNS structures.

Relationships between COP path [EO] and [EC] conditions (as dependent variables) and radiological features (as independent variables) were investigated 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, PwMS 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 of COP path [EC] (pattern B); abnormal values even in 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 (see **Chapter 3, section 3.4, page 32, and TABLE 3.2, page 42** for more details) [16]. These normative values were set at 2 standard deviations above the mean values obtained from 50 HCs sex/age/BMI-matched to a consecutive sample of PwMS [16].

Between-pattern comparisons were carried out by the Kruskal-Wallis test (with Dunn's post-hoc test). To avoid to underestimate the true α-error, p-values equal or less than 0.01 in either direction were considered as significant [43].

4.4.2 - Results

Participants. A total of 50 (37 females,13males) relapsing-remitting or secondary progressive PwMS and 20 (5 females,15 males) HCs were recruited. Demographic, clinical and radiological characteristics of both samples are shown in **TABLE 4.4**.

PwMS and HCs did not differ in terms of gender, age, BMI, and ICCSA. By contrast, displacement of COP path in both EO and EC conditions were wider in PwMS than in HCs ($p<0.001$ for both comparisons). Moreover, MSCA and UCCA values were significantly lower in PwMS than in HCs ($p=0.01$ and $p=0.008$, respectively).

Lastly, the COP path EO and EC were related each with other in both PwMS and HCs ($r=0.84$; $p<0.001$ and $r=0.71$; $p<0.001$, respectively).

Radiological features in PwMS. Disseminate involvement of the periventricular, juxtacortical and infratentorial white matter was observed in all PwMS; furthermore, each patient had at least one demyelinating lesion at spinal cord level.

Overall, the median [range] 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 at infratentorial level (12%).

The **TABLE 4.5** shows correlations between each MRI measurement in PwMS. 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: (i) cerebellar T2-LV ($r=0.70$; $p<0.001$), (ii) MCP T2-LV ($r=0.58$; $p<0.001$). There were no significant relationship between T2-LVs at different infratentorial levels and whole brain T2-LV.

Relationships between balance deficit and radiological features in PwMS. As expected, disease duration, EDSS score and walking speed were related with almost all MRI findings ($p<0.01$ for all comparisons), except for disease duration and walking speed which were not correlated with MCP T2-LV and whole brain T2-LV, respectively (data not shown). Bivariate correlations (adjusted for sex, age, body mass index and ICCSA) between static posturography measures and MRI findings are provided in **FIG. 4.3**. 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 were no relationship between COP path in both EO and EC conditions and whole brain T2-LV or cerebellar T2-LV. Slopes of correlation coefficients did not significantly differ between EO and EC conditions, except for UCCA (see also **FIG. 4.3**); however, from statistical point of view, this figure has to be considered only as marginal (F: 357.3; p=0.042). Multivariate regression analyses (stepwise fashion) showed that MRI findings having the strongest association with COP path OE were MSCA (Beta=-0.58, 95% CIs from -0.97 to -0.20; p=0.004) and MCP T2-LV (Beta=0.59, 95% CIs from 0.23 to 0.96; p=0.002), whereas the COP path EC was most associated with UCCA (Beta=-22.74, 95% CIs from -36.87 to -8.62; p=0.002) and brainstem T2-LV (Beta=0.52, 95% CIs from 0.12 to 0.92; p=0.01). These estimates did not change significantly even after inserting disease duration in the two models, while when EDSS score was inserted as covariate, itself was the only variable which survived the stepwise process (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) (**TABLE 4.6**).

Radiological features underlying to different patterns of balance deficit. After splitting PwMS into the three patterns as above defined, we found no balance deficit in 16 (pattern A), balance deficit only when visual input was lacking in 16 (pattern B), and balance deficit even in EO condition in 18 subjects (pattern C). These three subgroup of PwMS 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<0.0001 for A *vs.* 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<0.0001 for A *vs.* C, and p=0.01 for A *vs.* B), and median speed walking (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<0.0001 for A *vs.* C). The **FIG. 4.4** shows median values of MRI features according to different pattern 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).

4.4.3 - Discussion

The main findings of our study is that damage of both cerebellum and spinal cord contribute to impaired balance in PwMS, thus confirming the hypothesis that multifactorial causes can affect CNS structures controlling the postural balance [29,44]. However, despite their stringent relationship, the COP path in EO and EC can underlie different pathological MRI features.

The assessment of postural balance in upright stance, with EO and after 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) [45]. Although the localization properties of this clinical test has been reported as questionable [46,47], we found the balance deficit resulted mainly related to cerebellum atrophy and demyelinating lesions in the MCPs, when all sensory inputs (visual, proprioceptive and vestibular) were available, while atrophy of spinal cord and demyelinating lesions in brainstem were the principal contributors of a worse postural control when the visual input was lacking, according to the clinical significance of Romberg sign.

Cerebellar dysfunctions may cause the failure of predictive feed-forward control and/or of the estimation of motor command consequences [48]. The role of damage of midline cerebellar structure and/or cerebellar connections in determining balance deficit has been emphasized not only in PwMS [20,23,42], but also in those affected by other neurological diseases [25-28]. Focal and diffuse involvement of the cerebellum, its connections and, more extensively, of infratentorial regions have been also correlated with other clinical measures of disability in PwMS [18-24].

Spinal cord atrophy correlates with neurological disability [37,40,41,49], and damage of this structure has been recently associated with reduced vibration sensation and impaired standing balance in PwMS [30,31]. As regard our findings, we supposed that lesions in brainstem and spinal cord atrophy have worst impact on balance in EC condition probably because when visual input fails there is a greater reliance on other sensory systems, especially proprioceptive and vestibular input.

In our study, impaired standing balance in EC condition was observed in more than 2/3 of PwMS, and in about 1/3 even in EO condition, despite the mild to moderate disability level and the relatively short disease duration of our population. However, this is not surprising, considering that imbalance may occur early in the course of MS, and computer-based measures of balance revealed that deficits in postural control may be detected in mildly disabled patients with MS [50-52], or even after a first demyelinating event [53].

Remarkable differences in terms of cerebellum and spinal cord areas were also found with respect to HCs, as previously reported [37,40,41,49]. Notably, PwMS 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 PwMS. Again, MSCA values in pattern A and B were very close to value of HCs. These findings may suggest that atrophy occurred earlier in spinal cord than cerebellum (and consequently balance impairment occurred sooner in EC than EO), also considering (i) the relevant correlations between MSCA and total/regional T2-LVs (except for MCPs); (ii) the lack of any correlation between UCCA and T2-LVs (except for a weak relationship with cerebellar T2-LV); (iii) the correlations between disease duration and T2-LV, which is usually considered as a marker of the disease burden accrued over time. However, longitudinal data are necessary to definitively confirm this hypothesis.

Limits of the present study concern the small sample size and its observational and cross-sectional design. Albeit static posturography is reliable and accurate, standing balance was evaluated only in the most simplistic condition, thus not reflecting situations occurring in daily-life activities. Another limitation was the lack of measurement in dual-task condition, which potentially can provide further information about the pathological feature underlying to balance deficit in PwMS [53,54].

Taking into account estimations of atrophy of both cerebellum and spinal cord, our findings can provide a comprehensive anatomical framework for interpreting the pathological substrate of the balance disorders. Moreover, it can potentially contribute to develop more tailored rehabilitative programs, focusing on interventions which can restore the function related to the specific structure more involved in balance deficit.

4.5 - White and grey matter damage associated with balance deficit as detected by static posturography in multiple sclerosis

4.5.1 - Methods

Participants. We consecutively recruited PwMS who fulfilled the following inclusion criteria: age ranging from 18 to 50 years, ability to walk without support/aid, RR or SP course of disease, and EDSS score ranging from 0 to 5.5 (inclusive). The exclusion criteria were: severe blurred vision, concomitant otological disease, significant cognitive impairment, relapse occurring over the previous six months, initiation of disease-modifying or symptomatic treatments, or any medication change occurred over the previous three months, history of seizures and contraindications to MRI. Eligible patients underwent clinical assessment, static posturography and MRI in the span of one week. Patients presenting one or more gadolinium-enhancing lesions on MRI scan were not included in the data analysis.
Twenty-five age and sex-matched HCs served as control group.
This study was approved by the Institutional Review Board of our University and complied with the health insurance portability and accountability act. Written informed consent was obtained from each participant before any study procedure.

Clinical Assessments. Demographic and clinical variables, such as age and BMI (kg/m^2), were collected for each participant. PwMS and HCs also underwent the static posturography assessment according to standardized procedures, as above described (see **Chapter 3, section 3.2, page 32** for more details) [16].
Lastly, all PwMS also underwent a detailed neurologic examination by the agreement of two board-certified neurologists, including the measurement of the level of disability, as assessed by the EDSS. The average value of COP path in EO condition, as provided by three consecutive trials, was inserted as dependent variable in the analyses.

MRI acquisition. Patients were imaged with a 3.0T scanner (Verio, Siemens AG, Erlangen, Germany). The body coil was used for signal transmission, and the manufacturer 16 channel head coil designed for parallel imaging (GRAPPA) was used for signal reception. Slice orientation parallel to the subcallosal line was assured by acquiring a multi-planar T1-weighted

localizer at the beginning of each MRI exam. The following sequences were acquired during a single session for all the subjects:
(i) Dual-echo turbo spin (PD and T2-weighted) echo axial sequence (TR=5,310 ms, TE=10/103 ms, echo train length=28, matrix=384x90, FOV=220 mm^2), integrated Parallel Acquisition Technique reduction factor=3, acquisition time=5'04") with 40 slices 4 mm thick and 0 mm interslice gap;
(ii) 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^2, acquisition time=3'48");
(iii) DTI acquired with an axial single-shot echo-planar spin-echo sequence with 30 directions (TR=12,200 ms, TE=94 ms, matrix=96x100, FOV=250 mm^2, b=0 and 1,000 s/mm^2, acquisition time=13'15") with 72 slices 2 mm thick, without gap;
(iv) T1-weighted spin echo after administration of gadolinium-based contrast agent (TR=550 ms, TE=9.8 ms, matrix=384x90, FOV=220 mm^2, time 2'15") with 40 slices 4 mm thick and 0 mm interslice gap.

Image analyses and post-processing. Image data processing was performed by an MR imaging physicist and a neuroradiologist, both blinded to clinical data, on a Linux workstation running Jim 5.0 software (Xinapse System, Leicester, UK; http://www.xinapse.com), the FMRIB Software Library (FSL) 4.1 package (FMRIB Image Analysis Group, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl), MATLAB 7.0 (Mathworks, Natick, Massauchettes, USA) and the Statistical Parametric Mapping 8.0 (SPM8) software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm).
Measurement of T2-LV were obtained using a semi-automated technique based on local thresholding by the Jim software; lesions were segmented on PD images, while T2-weighted images were used to increase the confidence level in lesion identification. The LV yielded the following data for every subject: a quantification of the lesion burden, and a binary lesion mask needed for the volumetric analysis, which is then co-registered to the 3D-T1 sequences.
Maps of mean diffusivity (MD), fractional anisotropy (FA), axial and radial diffusivity (AD and RD, respectively) were computed for all subjects from the DTI, after eddy current correction and automatic brain extraction using FMRIB software library, which is part of the FSL. FA maps were fed into the TBSS tool, which is also part of the FSL. TBSS analysis consisted of four steps: the data of all the subjects were aligned into a common space by non-linear registration, and the mean MD, FA, AD, and RD images were created and thinned to obtain a mean

skeleton. Each subject's aligned DTI data were then projected onto the corresponding skeletons and the resulting data were fed into a voxel-wise cross-subject statistics analysis.

T1 volumetric images underwent automated segmentation in SPM8 to yield GM, WM and CSF images, using the previously created lesion masks to weight the procedure. The VBM protocol consists of an iterative combination of segmentations and normalisations to produce a GM probability map. Normalized GM images were modulated, i.e. multiplied by the local value derived from the deformation field, thereby preserving within-voxel volumes that may have been altered during non-linear normalization. For patients, lesions masks were used to remove lesional tissue in order to avoid erroneous inclusion in the GM volume assessment by the segmentation output. GM, WM and CSF volumes were recorded and used to calculate intracranial volume (ICV) as T2-LV+GM+WM+CSF and brain parenchymal fraction (BPF) as (LV+GM+WM)/(LV+GM+WM+CSF). Data were smoothed using a 12-mm full width at half maximum Gaussian kernel.

Statistical Analysis. Descriptive values are provided as proportion or mean (SD) and median (range), as appropriate. Differences between patients and controls were assessed by the Mann-Whitney U or Fisher Exact tests, as appropriate. P-values less than 0.05 (two-sided) were considered as significant.

Voxel-wise statistical analyses were performed by using a permutation-based inference tool for nonparametric statistical thresholding ("randomise", tool of FSL). The differences in MD, FA, AD, and RD between patients and controls were assessed by an unpaired *t* test, corrected for multiple comparison. The relationships between MD, FA, AD, and RD values and static standing balance measures in patient group were investigated by linear regression. The COP path values were entered in the one-sample *t* test as variable of interest, adjusting for the patient's gender, age, and lesion volume.

The number of permutations was set at 2000. The resulting statistical maps were thresholded at p=0.05, with correction for multiple comparisons based on family-wise error (FWE) at the voxel-level, by using the threshold-free cluster enhancement (TFCE) option in the randomise permutation-testing tool in FSL.

The differences in regional GM volumes between patients and controls were assessed by a covariance analysis unpaired *t* test, adjusting for ICV and subject's age. Correlations between GM regional volumes and COP path values was investigated by the SPM8 software using a one-sample *t* test, adjusting for the subject's gender, age, and T2-LV. P-values less than 0.05 were considered significant at the voxel-level after FWE correction for multiple comparisons.

4.5.2 - Results

Demographic and clinical data. Demographic, clinical and posturometric characteristics of the 45 PwMS and 25 HCs included in the present study are summarized in **TABLE 4.7.**
As expected, PwMS had worse values of COP path when compared to HCs ($p<0.0001$).

Whole brain MRI features. Data on total, supratentorial and infratentorial T2-LV, mean FA, MD, AD and RD (as measured in the TBSS skeleton), whole brain WM and GM volumes and BPF obtained in PwMS and HCs are shown in **TABLE 4.8**. Significantly different values in both DTI parameters (FA, MD, AD, RD), and volumetric measures (WM, GM, CSF, BPF) were found between the two groups (PwMS and HCs).
In PwMS, the total, supratentorial and infratentorial T2-LV were significantly related each to another, with correlation coefficients ranging from 0.57 to 0.99 (all p-values <0.0001). Total T2-LV was related with all DTI parameters, with correlation coefficients ranging from 0.59 to 0.66 (all p-values <0.0001) and with BPF ($r=-0.43$, $p=0.004$); supratentorial T2-LV showed similar correlations (data not shown), while infratentorial LV was related only with BPF ($r=-0.42$, $p=0.005$). All DTI parameters were related with BPF, with correlation coefficients ranging from 0.36 to 0.74 (p-values from 0.021 to <0.0001). Only the mean FA was also related with BPF ($r=-0.38$, $p=0.011$). No other significant correlations were found between conventional and non-conventional MR metrics.
Linear regression analyses investigating the relationships between the COP path and whole brain MRI metrics are shown in **TABLE 4.9**. The infratentorial T2-LV, mean FA and WM volume were significantly associated with the COP path ($p=0.011$, $p=0.045$ and $p=0.034$, respectively).

TBSS. All DTI parameters (MD, FA, AD and RD) were significantly different between PwMS and HCs, showing widespread alterations in most WM bundles (**FIG. 4.5**).
Significant correlations between all DTI parameters and COP values were found in a series of supratentorial and infratentorial WM tracts, as shown in **FIG. 4.6.** The wider the displacement of patients' COP path was, the worse the DTI parameters were in the following brain areas: inferior cerebellar peduncles (ICPs), superior cerebellar peduncles (SCPs) and MCPs, cerebellar WM, pons, thalamus, anterior and middle cingulum, and corpus callosum.

VBM. When compared to HCs, PwMS had lower GM volumes in several brain regions, including cerebellar vermis and thalamus, pulvinar, caudate nucleus, temporal, mesial fronto-parietal and mesial occipital cortex bilaterally (see **FIG. 4.7**).
In PwMS, the whole brain VBM analysis showed a significant indirect correlation between GM volumes and COP path values in several brain regions, mainly located in the cerebellum (see **FIG. 4.8**), indicating that the worse the balance control of patients, the lower were the regional volumes. The **TABLE 4.8** shows the anatomical labels, Montreal Neurologic Institute (MNI) coordinates and Z-scores for all the significant foci; no significant foci were found in the direct correlation.

4.5.3 - Discussion

As previously demonstrated, PwMS showed widespread alterations of both WM and GM brain regions when compared to HCs [12]. The main finding from our study is that the severity of balance impairment due to MS was associated with WM tract damage, including the cerebellar connections and hemispheres, pons, thalamus, and supratentorial associative bundles, as well as with GM atrophy of anterior lobules of the cerebellum (IV, V, VI) and lobule VIII, which are considered as the primary and the secondary somatosensory areas of the human cerebellum, respectively [55].
Interestingly, we also found a remarkable disparity between the widespread WM abnormalities assessed by TBSS and the selective GM damage of the cerebellum assessed by VBM. These findings might suggest a cerebellar atrophy secondary to disconnection from the cerebral cortex and spinal cord in MS,

Anatomical specificity of WM connections involved in balance deficit. The ICP contains most of the cerebellar afferents (dorsal spinocerebellar tracts), which convey inconscient proprioceptive information from lower and upper limbs, trunk and neck to paleocerebellum.
The MCP is by far the largest cerebellar peduncle and contains only afferent fibres (the cortico-ponto-cerebellar tracts).
The SCP contains the majority of the cerebellar efferent fibres, which project to the neocortex through the red nucleus and the ventral intermediate nucleus of the thalamus. Afferents to the cerebellum via the superior peduncle mainly include the ventral spino-cerebellar tract (that conveys proprioceptive information from the ventral horn of the lower spinal cord).

The cingulum is a medial associative bundle that runs within the cingulate gyrus; it is part of the limbic system and is involved in attention, memory and emotions [56]. Recently, it has been proposed as a component of the so-called thalamo-cortical vestibular system [57].
The corpus callosum is the largest bundle of the human brain and interconnects the two cerebral hemispheres [58]. The corpus callosum plays a crucial role in integrating frontal executive functions for the maintenance of gait and balance, as also demonstrated in elderly individuals with abnormal gait who had low FA in the genu of corpus callosum [59].

Anatomical specificity of GM regions involved in balance deficit. The cerebellum plays a major role in motor function, especially in predicting locomotor adjustments, by bringing together motor and sensory information [48].
Previous studies providing functional maps of the human cerebellum indicated two different functional zones in the cerebellar cortex: two somatomotor zones, incorporating the superior lobules V and VI and the posterior lobule VIII, which are interconnected with the primary motor, pre-motor, parietal, visual and auditory cortices; and a secondary supramodal zone, restricted to lobule VII and Crus I and II, having functional connectivity with dorso-lateral pre-frontal and posterior parietal cortices, which are not closely linked to sensori-motor processing [60].

Relating the balance deficit to the damage of the cerebellum and WM connections. In patients with cerebellar dysfunction, the deficits can be attributed to a failure of predictive feed-forward control and/or to accurately estimate the consequences of motor commands [48]. High-resolution structural MRI-based lesion-symptom mapping showed ataxia of stance and gait as correlated with atrophy of the medial and intermediate regions of cerebellum [61]. Abnormal posturometric measurements have been described in patients with different types of cerebellar diseases, particularly when involving the anterior lobe of the cerebellum [46,47], and the cerebellar peduncles [26,28]. Focal and diffuse involvement of the cerebellum, its connections and, more extensively, of infratentorial regions have been shown to correlate with clinical measures of disability also in MS, especially EDSS scores and speed of walking [18-23,42].
So far, few studies have employed instrumental balance measures to identify the anatomical substrates of balance disorders in MS. Some authors hypothesized that the primary cause of imbalance in MS is not cerebellar, but it is rather due to slowed proprioceptive conduction in the spinal cord [30]; however, the aforementioned study did not consider patients' neuroradiological features, but it was based on somatosensory evoked potentials [30]. It has also been reported that standing balance, as measured by force-platform recordings, had a moderate correlation

(r=0.32, p=0.02) with cerebrospinal fluid normalized magnetization transfer signal in the dorsal column of spinal cord [31]. By contrast, in another study it was found a better correlation between impaired balance and T2-lesion volumes (on a 1.5 T MRI scan) in the brainstem (r=0.57, p=0.002) and middle cerebellar peduncles (r=0.38, p=0.05) [42].

The present study extends the findings from this previous study, further developing the hypothesis that the degeneration of specific WM pathways connecting cerebellum, spinal cord, thalami and cortical regions might induce GM atrophy in some cerebellar regions having a crucial role for the balance control.

In addition to the cerebellar damage and its disconnection, the current study indicates also a pathophysiological role for WM associative fibres in determining balance impairments. These associative fibres connect to each other distant areas of the brain, which are implicated in higher level functions. This suggests that balance control is a complex function, requiring an unaffected central integration of different inputs (see **Chapter 1, section 1.4, page 5** for more details) [57,62].

Limitations. We did not consider the involvement of the spinal cord, especially the dorsal column, which has been reported to contribute to balance and sensory-motor dysfunctions in PwMS [30,31]. Nevertheless, as the dorsal column fibers ascend to the spino-cerebellar tracts via the inferior and superior cerebellar peduncles, we believe that their involvement has been indirectly accounted for in this study. Moreover, although our measure of balance is sensitive and reliable, it was evaluated only in static condition; hence, data from dynamic tests exploring aspects of postural control relevant to situations of daily-living activities are not available.

Implications. Balance impairment was associated with both WM alterations of cerebellar connections and GM damage of specific lobules of cerebellum. These findings suggest a cerebellar atrophy secondary to disconnection from the cerebral cortex and spinal cord in MS, but longitudinal data are necessary to confirm this hypothesis. In addition, the reduced integrity of associative WM bundles may result in a deficit of central integration, which is also likely to contribute to imbalance in PwMS. The presents study may have important clinical implications, since it provides an anatomical framework not only for interpreting the pathological substrate of the balance disorders, but also to detect rehabilitation-related changes in disease-modified brain structures. Our findings can also contribute to develop tailored rehabilitative program aimed at ameliorating balance and reducing the risk of accidental falls.

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Table 4.1

Differences between fallers (i.e., one or more accidental falls in the past 6 months) and non-fallers in clinical, posturometric and MRI features.

	Fallers n = 14	**Non-fallers N = 17**	**P-value**
Clinical findings			
Gender, F/M	7/7	12/5	0.29
Age, years	39.5 (9.4)	42.6 (10.2)	0.13
BMI, kg/m^2	22.4 (3.1)	21.9 (3.0)	0.63
MS duration, years	12.5 (7.4)	11.6 (7.5)	0.59
EDSS score	3.7 (0.8)	3.0 (0.7)	**0.03**
Static posturography			
VEL AP [EO], cm/s	1.5 (0.8)	0.9 (0.4)	**0.05**
VEL ML [EO], cm/s	1.6 (1.0)	0.9 (0.4)	**0.01**
VEL AP [EC], cm/s	3.8 (1.7)	2.2 (1.1)	**0.03**
VEL ML [EC], cm/s	3.6 (1.7)	2.1 (1.0)	**0.01**
COP path [EO], cm	58.5 (33.7)	35.2 (13.6)	**0.02**
COP path [EC], cm	137.9 (62.5)	80.1 (38.6)	**0.007**
MRI features (T2-LVs)			
Whole brain, cm^3	13.8 (10.6)	7.8 (3.7)	0.12
Supratentorial, cm^3	12.7 (10.6)	7.2 (3.7)	0.07
Brainstem, cm^3	0.56 (0.45)	0.23 (0.14)	**0.01**
MCPs, cm^3	0.31 (0.23)	0.12 (0.11)	**0.03**
Paleocerebellum, cm^3	0.18 (0.15)	0.19 (0.18)	0.84
Neocerebellum, cm^3	0.16 (0.14)	0.10 (0.08)	0.18

All values are expressed as mean (SD).

Table 4.2

Results of the correlation analyses between MRI metrics and static posturometric measures.

T2-LVs	VEL AP [EO]	VEL ML [EO]	VEL AP [EC]	VEL ML [EC]	COP path [EO]	COP path [EC]
Whole brain	r=0.29	r=0.45	r=0.21	r=0.30	r=0.43	r=0.30
Supratentorial	r=0.24	r=0.42	r=0.20	r=0.27	r=0.40	r=0.26
Brainstem	r=0.40	**r=0.57***	r=0.40	r=0.44	**r=0.57***	r=0.43
MCPs	r=0.27	r=0.31	r=0.05	r=0.13	r=0.38	r=0.16
Paleo-cerebellum	r=0.24	r=0.07	r=0.20	r=0.13	r=0.21	r=0.15
Neo-cerebellum	r=0.26	r=0.31	r=0.19	r=0.22	r=0.36	r=0.21

** p-values remaining significant after Bonferroni correction (p≤0.008).*

Table 4.3

Ordinal regression analysis with number of falls as dependent variables.

Independent variables	Beta	95% CIs	P-value
MCP T2-LV (each cm^3)	6.2	1.5-10.9	0.01
Brainstem T2-LV (each cm^3)	5.8	2.2-9.5	0.001
COP path [EO] (each cm)	0.16 (0.14)	0.10 (0.08)	0.18

Nagelkerke pseudo R-square=0.71

Table 4.4

Demographic, clinical and radiological characteristics of participants.

	PwMS (*n=50*)	**HCs (*n=20*)**	
Sex, F:M	37:13	5:15	
Age (yrs), mean (SD)	34.6 (8.1)	32.3 (5.7)	
BMI, mean (SD)	21.9 (3.5)	22.4 (3.8)	
Disease duration (yrs), mean (SD)	7.5 (6.2)	N/A	
EDSS median (range)	2.5 (1.0-5.5)	N/A	
25-FWT, m/s	1.1 (0.3)	N/A	
COP path [EO] (mm), mean (SD)	**448 (312)**	**221 (58)**	**
COP path [EC] (mm), mean (SD)	**850 (502)**	**335 (120)**	**
ICCSA (mm^2), mean (SD)	16,328 (1,293)	16,785 (1,531)	
MSCA (mm^2), mean (SD)	**1,045 (177)**	**1,198 (102)**	*
UCCA (mm^2), mean (SD)	**68.7 (8.8)**	**78.4 (8.5)**	**
Whole brain T2-LV (mm^3), median (range)	4,335 (20-42,960)	N/A	
Brainstem T2-LV (mm^3), median (range)	181 (0-1,712)	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	

** p ≤0.01*

*** p <0.001*

Table 4.5.

Correlation analyses concerning radiological features of PwMS.

	MSCA	UCCA	Whole brain T2-LL	Brainstem T2-LL	Cerebellar T2-LL	MCP T2-LL
MSCA	–	**0.71 ****	**-0.38 ***	**-0.50 ****	-0.37	-0.26
UCCA	**0.71 ****	–	-0.29	-0.34	-0.36	-0.34
Whole brain T2-LV	**-0.38 ***	-0.29	–	0.25	0.24	0.31
Brainstem T2-LV	**-0.50 ****	-0.34	0.25	–	**0.70 ****	**0.58 ****
Cerebellar T2-LV	-0.37	-0.36	0.24	**0.70 ****	–	0.37
MCP T2-LL	-0.26	-0.34	0.31	**0.58 *****	0.37	–

** p ≤0.01*

*** p <0.001*

Table 4.6

Multivariable stepwise linear regression analyses with COP path [EO] and [EC] as dependent variables of the two models (adjusted for sex, age, BMI, ICCSA).

Dependent Variable	Independent variables	Beta	95% CIs		p-value
			Lower bound	Upper bound	
COP path [EO]	MSCA (each mm^2)	-0.58	-0.97	-0.20	0.004
	MCP T2-LV (each mm^3)	0.59	0.23	0.96	0.002
COP path [EC]	UCCA (each mm^2)	-22.74	-36.87	-8.62	0.003
	Brainstem T2-LV (each mm^3)	0.52	0.12	0.92	0.01

Nagelkerke pseudo R-square=0.47 and 0.41, respectively

Table 4.7.

Demographic, clinical, and posturometric features of study population eligible for the data analysis, consisting of 45 PwMS and 25 HCs.

	PwMS (n = 45)	**HCs (n = 25)**	**P-value**
Gender (*F:M)*	34:11	17:8	0.69
Age, years			
mean (SD)	34.8 ± 7.9	31.7 ± 5.8	0.12
median (range)	34 (18 –- 50)	32 (23 - 42)	
BMI, kg/m^2			
mean (SD)	21.9 ± 3.5	22.4 ± 3.8	0.59
median (range)	21.5 (17.2 - 37.5)	22.7 (18.6 - 38.2)	
Disease duration, years			
mean (SD)	7.6 ± 6.4	N/A	-
median (range)	5 (1 - 20)		
Disease course *(RR:SP)*	32:13	N/A	-
EDSS score			
mean (SD)	2.8 ± 1.1	N/A	-
median (range)	2.5 (1.0 - 5.0)		
Ongoing disease-modifying treatment			
- *Natalizumab*	15		
- *Interferon Beta*	13	N/A	-
- *Glatiramer Acetate*	9		
- *None*	8		
COP path [EO], mm			
mean (SD)	448 ± 312	221 ± 58	***<0.0001***
median (range)	358 (128 - 1350)	195 (110 - 323)	

Table 4.8

Conventional and non-conventional MRI features of study population eligible for the data analysis, consisting of 45 PwMS and 25 HCs.

	PwMS (n = 45)	**HCs (n = 25)**	**P-value**
Whole brain T2-LV, ml *mean (SD)* *median (range)*	 7.58 ± 8.24 4.57 (0.02 - 42.96)	N/A	-
Supratentoral T2-LV, ml *mean (SD)* *median (range)*	 6.91 ± 8.11 3.81 (0.02 - 42.27)	N/A	-
Infratentorial T2-LV, ml *mean (SD)* *median (range)*	 0.57 ± 0.59 0.42 (0 - 3.12)	N/A	-
FA *mean (SD)* *median (range)*	 0.47 ± 0.04 0.48 (0.35 - 0.40)	 0.52 ± 0.02 0.52 (0.49 - 0.56)	***<0.0001***
MD *mean (SD)* *median (range)*	 $7.84E^{-4} \pm 0.67E^{-4}$ $7.61E^{-4}$ ($7.01E^{-4}$ - $10.06E^{-4}$)	 $7.14E^{-4} \pm 0.18E^{-4}$ $7.12E^{-4}$ ($6.79E^{-4}$ - $7.45E^{-4}$)	***<0.0001***
AD *mean (SD)* *median (range)*	 $12.82E^{-4} \pm 1.02E^{-4}$ $12.43E^{-4}$ ($11.58E^{-4}$ - $16.05E^{-4}$)	 $11.81E^{-4} \pm 0.21E^{-4}$ $11.82E^{-4}$ ($11.32E^{-4}$ - $12.16E^{-4}$)	***<0.0001***
RD *mean (SD)* *median (range)*	 $5.56E^{-4} \pm 0.71E^{-4}$ $5.35E^{-4}$ ($4.55E^{-4}$ - $7.86E^{-4}$)	 $4.81E^{-4} \pm 0.20E^{-4}$ $4.79E^{-4}$ ($4.38E^{-4}$ - $5.17E^{-4}$)	***<0.0001***
GM volume, ml *mean (SD)* *median (range)*	 446.6 ± 47.7 447 (344 - 563)	 487.7 ± 47.6 486 (413 - 591)	***0.001***
WM volume, ml *mean (SD)* *median (range)*	 635.5 ± 56.9 628 (542 - 764)	 679.5 ± 63.9 678 (591 - 832)	***0.004***
CSF volume, ml *mean (SD)* *median (range)*	 256.7 ± 40.3 255 (221 - 392)	 299.4 ± 81.7 295 (244 - 375)	***0.005***
ICV, ml *mean (SD)* *median (range)*	 1393.5 ± 120.1 1371 (1214 - 1650)	 1378.8 ± 125.6 1375 (1218 - 1678)	0.64
BPF *mean (SD)* *median (range)*	 0.785 (0.017) 0.788 (0.750 - 0.821)	 0.801 (0.026) 0.805 (0.752 - 0.863)	***0.003***

Table 4.9

Linear regression analyses with the values of COP path [EO] as dependent variable, and whole brain magnetic resonance imaging metrics as independent variables; all models were adjusted for gender, age, BMI and disease duration.

Variable	Adjusted R-square	Beta	p-value
Whole brain LV	0.06	11.45	0.058
Supratentoral LV	0.12	2.44	0.679
Infratentorial LV	0.28	195.02	***0.011***
FA	0.26	-3,384.54	***0.045***
MD	0.25	857.99	0.073
AD	0.25	827.96	0.075
RD	0.26	887,45	0.058
GM volume	0.05	-1.68	0.075
WM volume	0.09	-2.27	***0.034***
CSF volume	-0.02	-0.02	0.988
ICV	0.03	-0.64	0.135
BPF	0.06	-5,649.4	0.057

Table 4.10

Clusters with significantly reduced GM volumes (as assessed by the VBM analysis) correlated with the values of COP path [EO] ($p<0.05$, FWE corrected).

Label	MNI Coordinates x, y, z (mm)	% cluster	Z-score
Vermis IV-V	-2, -54, 2	58.98	4.60
Left lobule HIV-HV		33.33	
Left calcarine sulcus		5.13	
Left lingual gyrus		2.56	
Left lobule HVIII	-18, -63, -51	100.0	4.70
Right lobule HIV-HV	16, -57, -9	65.84	4.74
Right lingual gyrus		21.95	
Right lobule HVI		9.33	
Right fusiform gyrus		1.65	
Vermis VI		1.23	
Right lobule HVI	28, -59, -33	58.96	4.91
Right crus I		41.04	
Right lobule HVIII	32,-65, -54	100.0	4.47

Cerebellar hemispheres are distinguished from vermis by the prefix "H"

Figure 4.1

Boundaries of infratentorial brain structures - brainstem and MCPs, as delineated on T2-weighted images by means of semiautomatic outliners (upper row); boundaries were then automatically transferred onto PD -weighted images where ROIs delimiting MS lesions were automatically outlined by Jim 5.0 (Xinapse) software (lower row).

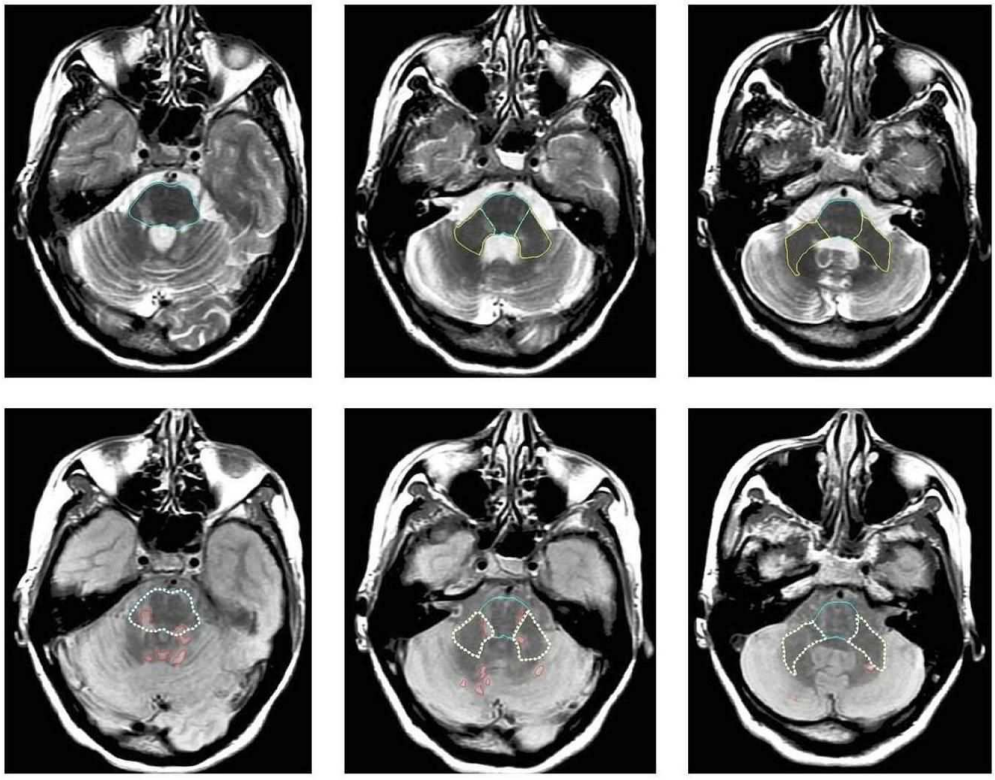


Figure 4.2

Boundaries of cerebellum as delineated on 3DT1-weighted images by means of automatic outliners (A); the cross-sectional area of upper cervical cord at C2/C3 level as outlinead by means of an automatic edge detection algorithm (B).

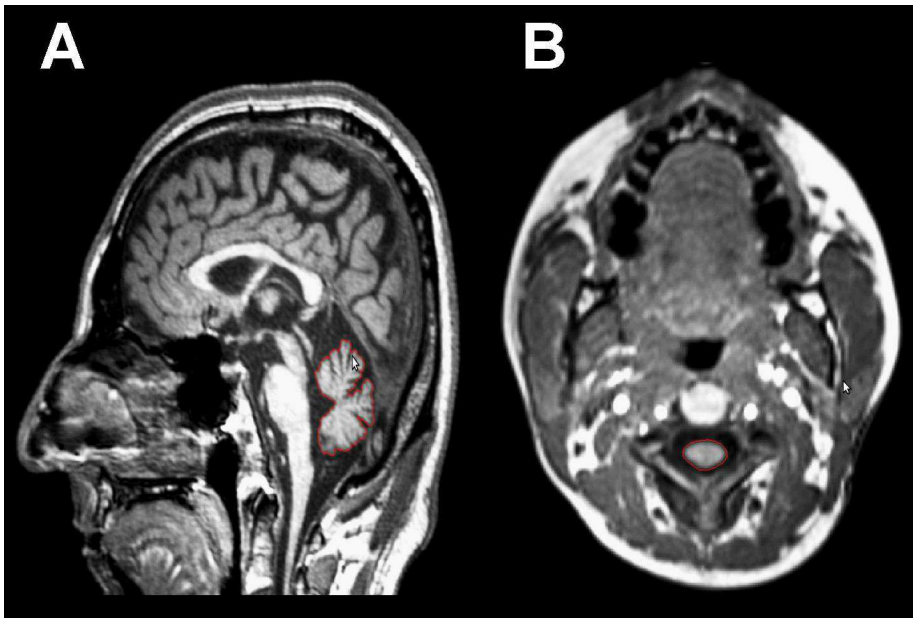


Figure 4.3

Scatterplots showing correlations between radiological features of PwMS and static posturography, i.e. the COP path [EO] (circle) and [EC] (rumbles), with their relative interpolation lines.

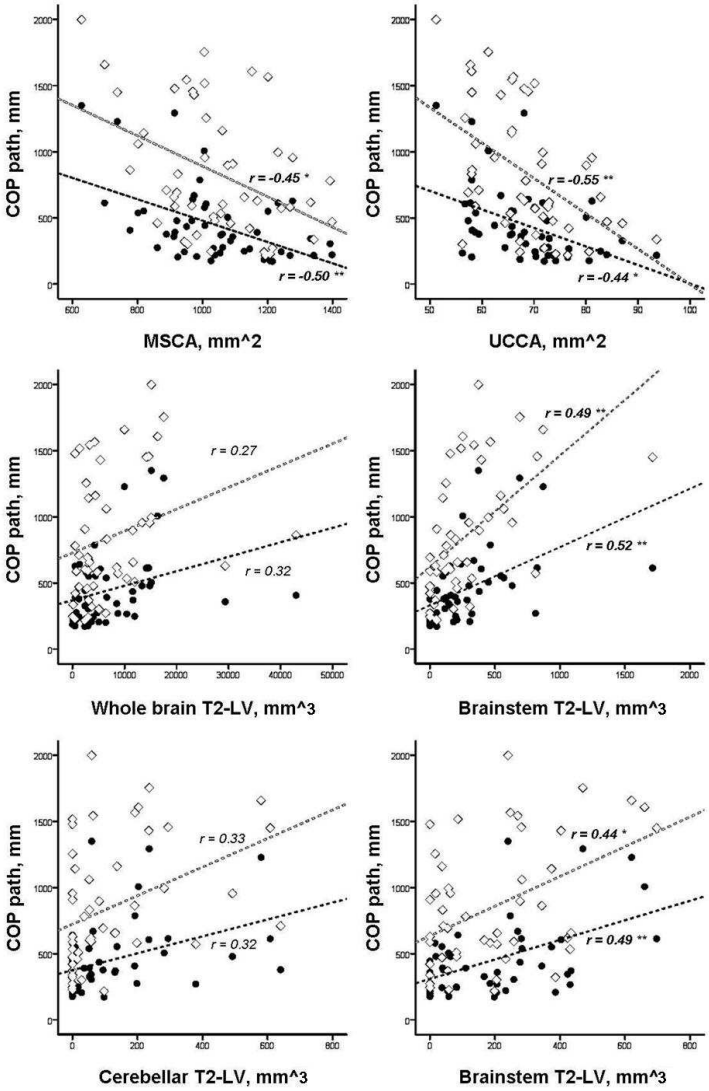
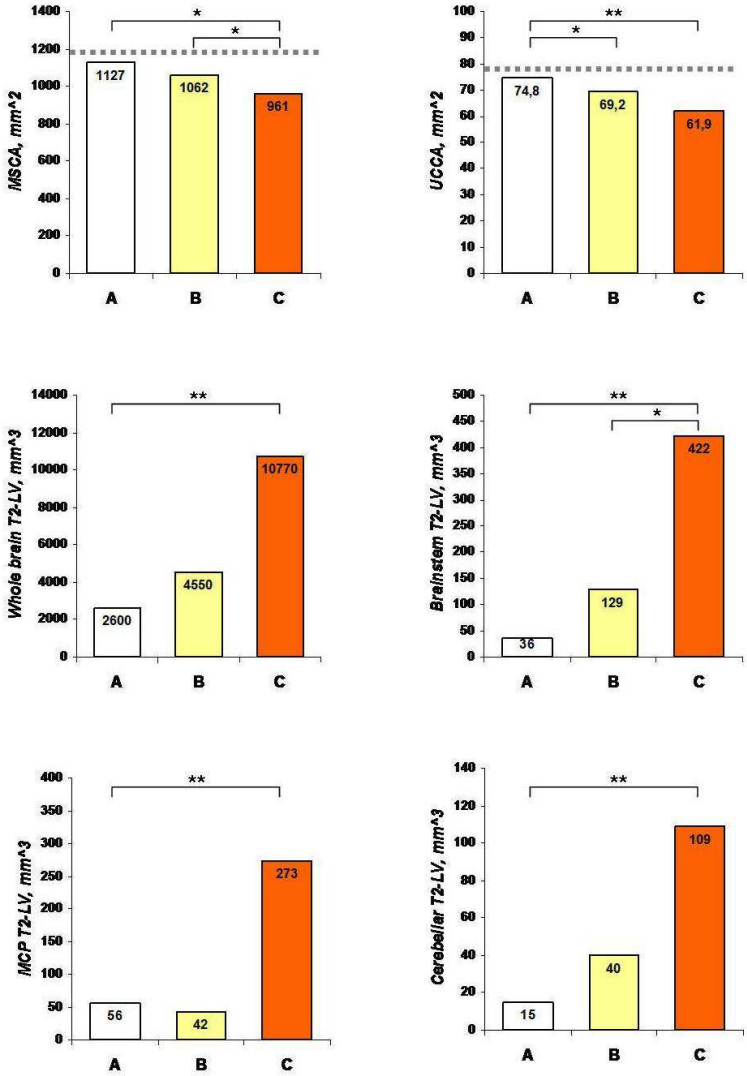


Figure 4.4

Radiological features of PwMS according to pattern of balance deficit, as detected by static posturography according to normative value published elsewhere [16] . Grey dashed lines refer to median values of MSCA and UCCA in sex/age-matched HCs.



Pattern A: normal values in both [OE] and [CE]; Pattern B: normal value of COP path [OE], but abnormal of COP path [CE]; Pattern C: abnormal values of COP path [OE].

Figure 4.5

DTI parameter alterations in PwMS as demonstrated by TBSS. Significantly increased MD (A), reduced FA (B), and increased AD an RD in PwMS (n = 45) as compared to HCs (n = 25) are overlaid on standard coronal T1-weighted template ($p<0.05$, TFCE corrected).

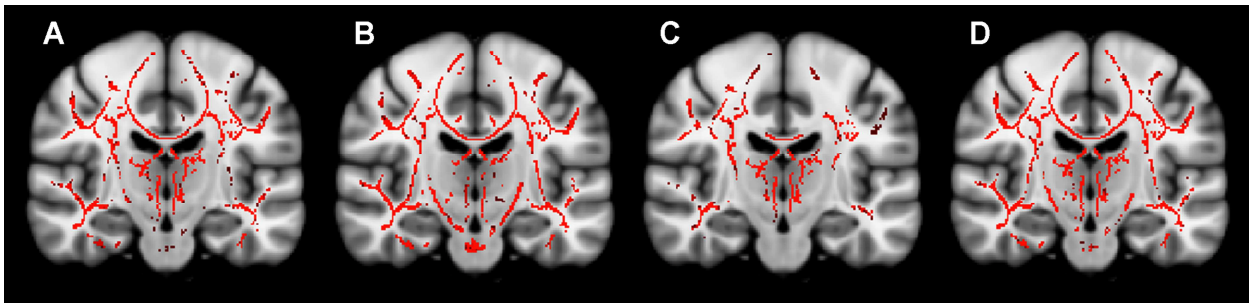


Figure 4.6

Clusters of significant correlations between DTI parameters and COP path [EO] are superimposed on sagittal, coronal and axial standard T1-weighetd template ($p<0.05$, TFCE corrected). Significant clusters (red) of increased MD (A), reduced FA (B), increased AD (C) and RD (4) are located in the SCPs, MCPs, ICPs, pons, thalamic and optical radiations, external capsules, inferior longitudinal fasciculus, fronto-occipital bundles, anterior and posterior cingulate regions, and genu and body of corpus callosum

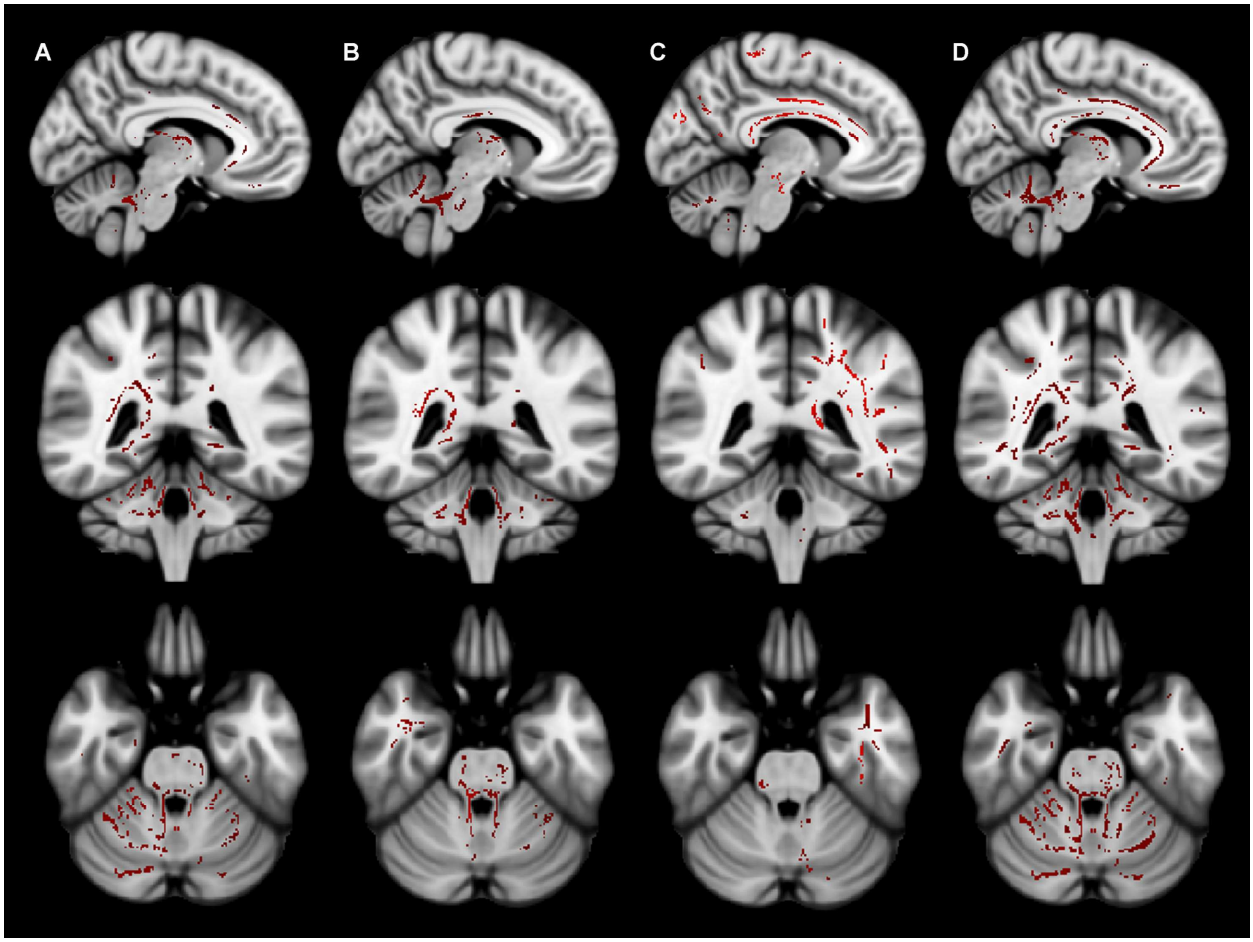


Figure 4.7

Significant reduction in GM volumes in PwMS (n = 45) as compared to HCs (n = 25), as demonstrated by VBM analysis. Significant foci of GM reduction, overlaid on sagittal, coronal and axial slices of the single-subject T1-weighted template provided with SPM8 ($p<0.05$, FWE corrected), are shown in cerebellar vermis; thalamus, pulvinar and caudate nucleus and putamen (bilaterally), mesial fronto-parietal and occipital cortices; temporal cortex (bilaterally).

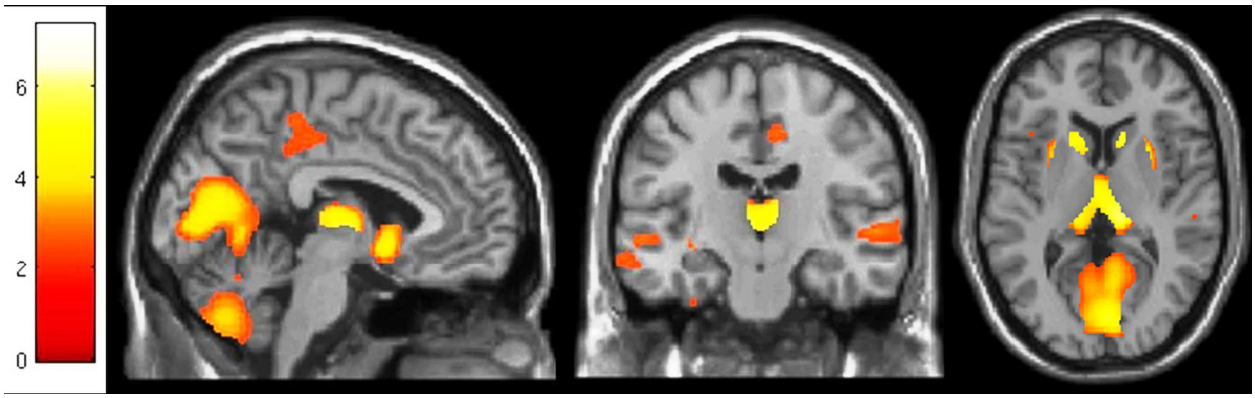
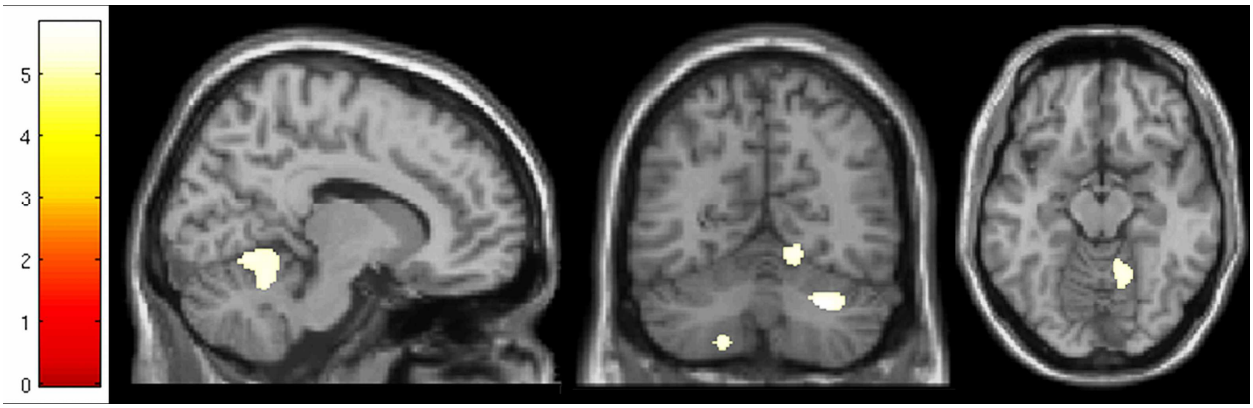


Figure 4.8

Clusters of significant indirect correlation between GM volume and COP path [EO] are superimposed on sagittal, coronal and axial slices of the single-subject T1-weighted template provided with SPM8 ($p<0.05$, FWE corrected). Significant clusters are located in cerebellar vermis (lobules IV, V and VI), left and right cerebellar hemispheres (lobules IV, V, VI and VIII), right Crus I, left and right lingual gyrus (neurological convention).



CHAPTER 5

INTERVENTION AIMED TO REDUCE IMBALANCE AND PREVENT ACCIDENTAL FALLS IN PATIENTS WITH MULTIPLE SCLEROSIS

Recently, there has been a growing interest in investigation and treatment of balance disorders in people with MS. Unfortunately, pharmacological approaches aimed at ameliorating imbalance in patients with MS are often inadequate [1]. It has been also reported that some drugs which are broadly used in neurological setting may affect gait and balance [2]. Therefore, the majority of treatments rely heavily on rehabilitation, that is still considered the only way to improve function in MS [3]. Reducing the risk of falls and improving postural control during ambulation represent the primary targets of balance treatment.

New rehabilitative strategies regarding motor learning and plasticity are mainly focused on high-intensity, repetitive, and task-specific practice [4]. According to these principles, virtual reality and visual feedback training are being used to improve several deficits, such as impaired balance and walking, in both people with MS [5,6] and other populations with neurological disorders [7,8].

5.1 - Objective

Our aims were to investigate the effectiveness of novel visuo-proprioceptive feedback trainings in ameliorating balance and reducing the risk of falls in PwMS having a predominant balance disorder due to cerebellar and/or sensory ataxia, as follows:

(i) a study investigating the effectiveness of a 6-week supervised training by using the Delos Postural Proprioceptive System® (DPPS) (→ ***5.2***);

(ii) a study investigating the feasibility and effectiveness of a 12-week home-based training by using the Nintendo Wii balance board system® (→ ***5.3***).

5.2 - Visuo-proprioceptive training reduces risk of falls in patients with multiple sclerosis

5.2.1 - Methods

Study population. PwMS as per McDonald Criteria referring a history of falls or fear of falling and sex-/age-matched HCs were recruited to participate in this independent, single-centre, pilot study. All PwMS were required to have: an objective balance disturbance (i.e.: impaired straight line walking or gait ataxia or positive Romberg test on neurological examination), walking without aid or rest, and clinical stability from at least 2 months. We excluded patients suffering from severely blurred vision, concomitant otological or vestibular disease (non-MS related), psychiatric disorders or severe cognitive impairment, cardiovascular and respiratory diseases. All patients underwent a neurological examination with the assessment of EDSS and Functional Scores (KFS) [9], 25-FWT [10], Dizziness Handicap Inventory (DHI) [11], Fatigue Severity Scale (FSS) [12], and MS Quality of Life 54-item version (MS QoL-54) [13].
The DHI is a multidimensional self-report 25-item scale quantifying the level of disability and handicap in three subscales (Emotional, Functional and Physical). The final score ranges from 0 to 100, with 0 being the best score. DHI shows good validity and reliability in people with MS [14]; this scale has also been reported more useful than others (i.e.: Berg Balance Scale, Dynamic Gait Index) in discriminate fallers and non-fallers [15].
The FSS is a self-report 9-item scale with 7 levels of agreement with each statement. The final score is derived from the mean of 9 items and may range from 1 to 7, with 1 being the best score. This scale shows sensitivity, reliability and internal consistency in assessment of fatigue and their change over time [12].
The MS QoL-54 is a self-reported 54-item questionnaire providing an MS-specific assessment of health-related quality of life on 12 subscales. It provides two composite scores (physical and mental) with the final score ranging from 0 to 100, with 100 being the best score. All the subscales show good sensitivity, reliability and internal consistency, with physical functions being more disease specific than mental scores [13].

Assessment of postural control. The assessment of postural strategy of patients and controls was performed with the Delos Postural Proprioceptive System® (DPPS, Delos, Turin, Italy) (**FIG. 5.1**) [16] consisting of a Freeman board-like rocking platform (Delos Equilibrium Board -

DEB); a detector of angular velocity (length 7 cm, width 4.5 cm, thickness from 2.5 to 1 cm) applied on the sternum through a belt (Delos Vertical Controller - DVC); an adaptable steel structure for hand support with an infrared sensor (Delos Postural Assistant - DPA). The DVC, once calibrated, detects in real time the oscillations of the COG of the subjects on X-Y axis, with a sensitivity of 0.1 degree. An accurate calibration of DVC was performed for each subject before the diagnostic session. Subject have required to stay in upright static condition for ten seconds, with arms resting at their sides and to stare a point in front of view; their shoulders were blocked by an operator. The x-y values as recorded in these conditions were set at "0" and represented the reference coordinates.

The DPA, located in front of the subject, provides a support for hands to avoid falling; an infrared sensor merged to DPA detected the frequency and duration of the event. All these instruments were connected to a Personal Computer via USB interface to analyse the postural strategies using a dedicated software. In order to evaluate postural strategies, all subjects underwent posturometric tests barefoot on the ground, in upright static condition, both in double- and in single-leg stance. Each test lasted 30 seconds.

The monopodalic test evaluated the stability in single-leg stance and, consequently, provided indirect information of risk of fall during ambulation. Briefly, subjects performed two 30-second trials for each position (left and right alternated), with a rest period of about 30 seconds between each trial. In order to minimize the influence of muscular weakness, we included in the analysis only the values recorded by the best performing limb.

Markers of postural control. The main parameter considered was the fall risk estimation score (FRES), defined as the percentage of time using the hand support to avoid falls both with EO and EC, in both in double- (bipedalic test) and in single-leg stance (monopodalic test)

The degree of trunk sway, defined as the mean error of the COG on the x-y directions in respect to the trunk axis, were also measured in bipedalic stance. The reliance of proprioceptive, vestibular and visual strategy, measured as percentage of time, were evaluated as markers of postural strategy at the monopodalic test. These variables were closely dependent upon each other and derived from an overall evaluation of the test performed with EO and EC. As detected by the DPPS, the FRES in single-leg stance indicate the level of balance impairment, and it is inversely proportional to the other postural strategies. The visual strategy indicates dependence on the visual input and is higher as the postural control worsens with EC. The proprioceptive strategy represents the faster and more accurate reflex correcting the imbalance (i.e. oscillations on the x-y axes less than 2.5 degree, as detected by the DVC). The vestibular

strategy comes into play when the proprioceptive control alone is not adequate; it is activated by a broader degree of sway of the COG and represents an emergency mechanism of postural control in order to avoid the fall; it represents the percentage time with faster and wider position changes. All these values (visual, proprioceptive and vestibular strategies) were calculated after removing the percentage time with the use of handrail support to avoid falls (i.e. the DPA) [16].

Study design. We performed a single group pre/post pilot study (**FIG. 5.2**). Pw MS underwent a first postural strategy assessment (week –6) followed by a run-in 6-week period without any intervention or specific training. Two other assessments of postural strategy with the DPPS were performed before (week 0) and at the end (week +6) of the visuo-proprioceptive training (Figure 2). EDSS score, T25-FWT, DHI FSS and MS QoL-54 were also assessed at week –6, week 0 and week +6 visits.

Training protocol. PwMS were subjected to 12 sessions (twice per week) of visuo-proprioceptive rehabilitation, each lasting 45 minutes. They were tested under the same experimental conditions adopted during the balance training sessions, therefore respecting the principle of specificity between test and training. Each session provided static and dynamic exercises both in double- and in single-leg stance, with and without equilibrium board translating on anterior-posterior, lateral and diagonal (–45°, +45°) way, with a progressive difficult step by step. Training was tailored according to ability level of each patient.
All participants familiarized themselves with the exercises prior to starting the protocol. The training was performed with EO and EC, with and without visual feedback, or with smooth pursuit. During the exercises, a visual trace and a visual feedback (posturogramme) provided by the DEB and the DVC were shown on the PC screen. This visual trace provided information on the rocking of the board (DEB) in real time. While performing exercises, PwMS were asked to maintain balance as longer as possible. In case of imbalance, the visual trace allows a faster reply. Alternatively, PwMS were asked to pursue a virtual itinerary displayed on the PC screen through DEB movements. Rest breaks were provided to avoid early exhaustion of energy.

Statistical analysis. All values are expressed as a mean (SD) or median (range) value, as appropriate. Correlations between variables were performed by the Spearman test. The reliability of measurements was determined as intraclass correlation coefficient (ICC) after a re-test session. As interval data does not satisfied the normality assumption, we used non-parametric tests for the statistical inference. Differences between continuous variables were

calculated using the Mann-Whitney U test for independent samples. The differences in clinical scales and in postural strategies over time were analysed using the Wilcoxon test for related samples. A Bonferroni correction for multiple comparisons was applied to set the two-side statistical significance, according to the number of postural variables (α/10=0.005).

5.2.2 - Results

Baseline data. Forty PwMS were included in the study; the **TABLE 5.1** reports their demographic and clinical characteristics. Twelve HCs (9 females, 3 males) with a mean age ± SD of 35.8 ± 11.0 years were also recruited as the control group. There were no differences in demographic characteristics between PwMS anf HCs (data not shown). ICCs of stabilometric test were: 0.73 and 0.82 for the FRES (EO and EC, respectively) and 0.74 and 0.75 for the degree of trunk sway (EO and EC, respectively). The ICCs of monopodalic test were: 0.90 and 0.84 for the FRES (EO and EC, respectively); 0.89 for the visual strategy; 0.98 for the proprioceptive strategy; 0.92 and 0.89 for the vestibular strategy (EO and EC, respectively).

Follow-up data. Out of 40 enrolled, 31 PwMS (77.5%) accepted to participate to the training protocol. Twenty-eight (90.3%) subjects completed all sessions, while 3 (9.7%) discontinued study protocol due to the lack of compliance (n = 2) and the occurrence of relapse (n = 1).
No changes in both clinical measures and tests of postural control were observed during the run-in period without training (data not shown). After training, we did not observe any changes in EDSS and FSS scores (data not shown). However, a significant improvement in the 25-FWT test performances (7.4 sec. [4.5-13.7] *vs.* 6.3 [4.6-12.7]; p=0.001) and a slight improvement in the DHI score (34 [16-86] *vs.* 30 [0-66]; p=0.05) was observed after the visuo-proprioceptive training. The Mental Health Composite score from the MS QoL-54 also improved after the training protocol, but with a borderline statistical significance (56 [17-92] *vs.* 66 [26-99]; p=0.04). The Overall Quality of Life and the Health Distress significantly increased (75 [0-100] vs. 80 [40-11]); p=0.005 and 60 [18-87] vs. 68 [28-100]; p=0.004, respectively).
After the visuo-proprioceptive training, the performances of PwMS significantly improved (see **TABLE 5.2**). We observed a significant reduction in FRES at the bipedalic test with EC and at the monopodalic test both with EO and EC. Moreover, we found an improvement in visual, proprioceptive and vestibular strategies after the intervention period.

5.2.3 - Discussion

The main finding of the present study is the improvement in the more accurate postural strategies, especially visual strategy, after the visuo-proprioceptive training, that might translate into a reduction in PRES. The improvement in speed walking, DHI and some MS QoL-54 subscales supports the notion that visuo-proprioceptive training has also a role in ameliorating the activity of daily living. The low drop-out rate (less than 10%) indicate that a tailored visuo-proprioceptive training is well tolerated by PwMS. A longer duration of rehabilitation, especially for those PwMS with higher disability level having a greater difficult to perform the training in single-leg stance, is warranted in order to enhance the adherence to visuo-proprioceptive protocol. Alternatively, a simplified exercise protocol may be applied for patients suffering from moderate to severe spasticity and/or weakness of the legs.

Although the double-leg stance has been widely used for measuring postural stability in several studies, periods of single-leg stance occur more frequently within the activities of daily living [17,18]. Since single-leg stance results in a decrease of somatosensory information; postural instability increases most likely as a result of the required reorganization of the COG over a minor base of support [17].

Visuo-proprioceptive training demonstrated its effectiveness in decreasing FRES, with an overall improvement in balance control and a better organization of the postural strategies in single-leg stance. We suggest that the high flow of signals shown on the PC screen, which provided a visual feedback on the rocking of the board, may lead patients to supply adequate postural replies more rapidly. As shown in patients with other neurological diseases (i.e. post-stroke hemiparesis, Parkinson disease and cerebellar ataxia), a visual feedback of COG might improve the postural control, likely enhancing the coupling between perception and action [19-21]. A very recent multicentre study revealed a 63% of prevalence of accidental falls in PwMS and the risk of falling increased with decreased proprioception [22]. The specific retraining of sensory strategies may be an essential component in improving balance and in particular dynamic balance.

This study also shows improvements of walking performance and overall quality of life after the visuo-proprioceptive training. The improvement of speed performance in the 25-FWT is likely explained by an increase of the visual and proprioceptive strategy adopted. The improvements in health distress and overall quality of life (MSQoL-54 subscales) suggest that a better perception of balance can have a positive impact on patient behaviour. It has been previously

reported that balance disorders with fear of falling represents an important problem affecting quality of life even in early and mild stages of MS [23,24].

After training, we did not observe any changes in EDSS and FSS scores. Rehabilitation has been shown to improve the level of functioning, even when neurological status did not change. The main effect of rehabilitation is an improvement in compensation, adaptation and reconditioning. Some studies also suggest the occurrence of cortical reorganisation after rehabilitation [25].

Limits of the present study were the small sample size and the lack of a longitudinal follow-up after the rehabilitation protocol in order to evaluate the maintenance of the beneficial effect over time. Errors in calibration and/or repositioning of DVC may represent potential sources of bias. Moreover, the choice of FRES as outcome measure is something different from the concept of fall, defined as an unexpected contact of any part of the body with the ground. PRES should be considered only a surrogate marker rather than a direct measure of occurrence of falling. Nevertheless, the PRES as assessed in monopodalic stance is comparable to the unipedal stance test [18]. According to the authors, a single-leg stance longer 30 seconds was related with a very low risk of fall; a stance shorter than 5 seconds was, conversely, related to a higher risk of falls [18].

In conclusions, this pilot study indicates that visuo-proprioceptive training is effective in improving balance disorders and, potentially, in reducing risk of accidental falls due to MS. Duration of beneficial effects as well as the exact mechanisms underlying clinical improvement need additional evaluations.

5.3 - Home-based balance training using the Wii Balance Board: a randomized, cross-over pilot study in multiple sclerosis.

The Nintendo ® Wii software/hardware game package (Nintendo, Kyoto, Japan; http://www.nintendo.co.uk/NOE/en_GB/index.html) has recently been included into the definition of visual feedback/virtual reality training [26] and its use in the Neurorehabilitation process is still growing [27-34]. Some Wii videogames require a force-platform (i.e. the balance board) to be played. Once connected to a common home-TV, the Wii Balance Board System (WBBS) provides a constant visual feedback about accuracy of movement patterns by means of pressure sensors and wireless signals.

A WBBS-related improvement in balance has been reported in elderly [31], in people with acquired brain injuries [28], and in Parkinson disease [29]. The WBBS has been recently proposed even for PwMS as a strategy to enhance physical activity behavior [32], and to improve balance and walking ability [32-34]. Thus, WBBS could represent an alternative approach to engage in effective balance training. At the same time, it could allow patients to minimize MS-related barriers to rehabilitation, by means of home-based training programmes [32]. However, so far there are no randomized controlled studies on PwMS investigating the efficacy and safety of WBBS in a home-based setting.

5.3.1 Methods

Participants. PwMS as per McDonald revised Criteria, and regularly attending the MS Centre of S. Andrea Hospital, were asked to participate at this 24-week, independent, randomized, controlled, two-period cross-over pilot study (**FIG. 5.3**). The protocol was approved by the local Ethical Committee; each patient provided written informed consent before any study-related procedure.

Before study enrolment, two expert neurologists screened patients for eligibility criteria, including a neurological examination by means of Neurostatus (www.neurostatus.net/scoring). Inclusion criteria were: an age of 18 to 50 years (inclusive); a RR or SP course of MS; an EDSS score [9] equal or less than 5.5; ability to walk without resting for at least 100 meters; presence of an objective balance disturbance (i.e. impaired straight line walking, gait ataxia or positive Romberg test). Exclusion criteria were: use of assistive device or foot ankle orthosis; relapses occurring over the previous six months; initiation of disease-modifying or symptomatic treatments, or any medication change occurring over the previous three months; seizures; severe blurred vision; concomitant otological or vestibular diseases (non-MS related); psychiatric disorders or severe cognitive impairment; cardiovascular and respiratory disorders.

Patients enrolled in the trial had also to be willing to not change or start any medication for the entire study period, except for steroids required to treat MS exacerbations.

Study design. PwMS who met eligibility criteria were randomly assigned in a 1:1 ratio to two counter-balanced arms by computer-generated random numbers.

Group A started a 12-week period of home-based WBBS training (intervention period), followed by a further 12-week period without any intervention or specific training (observation period). Group B were given the treatment period in reverse order.

PwMS were further re-tested after the first 12-week period (T1), and finally at the end of the 24-week study period (T2). Thus, all patients underwent 12 weeks of WBBS training (active period) and a 12-week observation period. A two-period cross-over study design was adopted for the following reasons: (i) influence of confounding covariates is reduced because each subject serves as his/her own control; (ii) a sample size smaller than a parallel design is required; (iii) carry-over effect is not expected in a chronic disabling condition such as MS; (iv) the impossibility of planning an appropriate wash-out period since the duration of the effect of WBSS training has not been investigated.

Intervention. During the 12-week active period, each patient was submitted to daily sessions (with the exception of the week-end) of home-based training with WBBS, each lasting 30 minutes. Patients were allowed to skip at maximum one session per week, therefore we expected that each patient performed 48 sessions.

Training protocol consisted of repetitions of several games selected from the "Wii Fit Plus" package (http://www.wiifit.com/training/balance-games.html), according to an intervention program published elsewhere [34]. Each game started at basic level and, when a certain score was reached, patients were automatically transferred to a more advanced level by WBBS. Patients were then encouraged to play the next game if they had a level progress; otherwise, 10 minutes were allocated for each game. During the first 4 weeks of WBBS training, they were allowed to play only "Zazen", "Table Tilt", and "Ski Slalom"; thereafter they could add remaining games. In the last 4 weeks of WBBS training, they were allowed to play games that they enjoyed the most. A detailed description of each game is reported in **TABLE 5.3.**

The balance board contains four force sensors (located in each corner) which detect subject's centre of balance and weight shifts. Users can interact naturally with the game by means of weight transferences on balance board, thus constantly having a visual feedback through a sensory-enriched environment. All participants familiarized themselves with the exercises prior to starting the protocol. The device was connected to a common home-TV and balance board located at a distance ranging from 1 to 3 meters, according to TV display size. Home installation of WBBS, detailed explanations of training protocol, and supervision of the first complete training session was carried out by a trained physiotherapist. Engagements with physiotherapists were scheduled every 4 weeks during the intervention period to supervise the

correct execution of games and monitor patients' performance. Phone contacts were also scheduled every week during the intervention period to remind patients to complete the logbook, and encourage them to perform the training.

Study evaluations. The following outcome measures were collected at each scheduled visit (T0, T1 and T2) by two neurologists unaware of the training order allocation: (i) force platform-based measures of static standing balance, providing data on COP path in EO condition, as above described (see **Chapter 3, section 3.2, page 32** for more details) [35]; (ii) the four-square step test (FSST) [36]; (iii) the 25-FWT [10]; (iv) the 29-item MS impact scale (MSIS-29) [37].
Self-reported number of accidental falls (defined as an unexpected contact of any part of the body with the ground) occurred in the 12-week period before randomization was also asked to each patient.
All patients received a logbook describing the training protocol and other additional precautions. This logbook was also used to daily record the log of training (including time and type of game played), and the occurrence of falls (as above defined) or any adverse event (defined as any untoward medical occurrence regardless of its causal relationship to the study intervention) during the 24-week study period. The logbook was given at baseline (T0), was checked at visit T1, and finally was returned to study team at the end of the 24-week follow-up (T2).
Adverse events were graded as mild (minimal or no treatment required and no interference with daily living activities); moderate (may require treatment and cause some interference with functioning); severe (systemic drug or other treatment required, interruption of daily living activities); life-threatening (immediate risk of death) (http://ichgcp.net/12-adverse-event-ae). Patients were also encouraged to contact any component of the study team in case of adverse events, for any question regarding the study protocol or technical problems.

Endpoint definition. The primary endpoint was the mean difference in static standing balance measures (i.e. the COP path) at T1 and T2 visits, as compared to baseline (T0) evaluation.
Secondary endpoints were the mean differences in clinical scales (FSST and 25-FWT), and in self-administered questionnaire (MSIS-29) at T1 and T2 visits, as compared to baseline (T0) evaluation.

Statistical analysis. Given the exploratory nature of this pilot trial, no sample size analysis was performed. Data are presented as mean (standard deviation) or median (range), as appropriate. Well-balancing of two treatment groups after randomization were tested by using the Mann-

Whitney U or the Fisher Exact tests for continuous and categorical variables, respectively. Repeated measures analyses of variance (ANOVAs) with raw values at different time-points (i.e. T0, T1 and T2 visits) as the within-subjects factor and treatment group (A *versus* B) as the between-subjects factor were performed for each of endpoints. A time X treatment interaction analysis was run to evaluate treatment effect on the aforementioned endpoints. Simple contrasts were conducted for each treatment group to determine the source of significant difference with respect to the baseline (T0). This analysis allowed us to determine the maintenance of treatment effect for group A, and the reliability of study measures over time for group B. Finally, a comparison between number of patients free from accidental falls in the12 weeks prior to study enrolment (self-reported at baseline) and number of patients free from accidental falls (prospectively collected) at the end of the 24-week study period was carried out by the McNemar-Bowker test. P-values less than 0.05 in either directions were considered as significant.

5.3.2. Results

From February to June 2011 a total of 45 PwMS were assessed for eligibility; out of these, 36 (25 females, 11 males) with a mean age of 36.2 (8.6) years, mean MS duration of 10.7 (5.8) years, and median (EDSS) of 3.5 (1.5-5.0) were randomized (18 were assigned to group A and 18 to group B). The two treatment groups were comparable in terms of baseline demographic and clinical characteristics (p-values ≥0.15 for all comparisons) (**TABLE 5.4**).

After baseline evaluation, there were two patients who discontinued the study protocol: (i) a 39-year old female patient with an EDSS score of 5.0 and assigned to group A withdrew the inform consent 2 weeks after baseline (T0); (ii) a 54-year old female with an EDSS score of 5.0 and assigned to group B experienced a motor relapse after 5 weeks from baseline (T0), thus becoming unable to accomplish the study protocol. As a consequence, data of these two patients were excluded from the analyses (**FIG. 5.4**). No other patient experienced relapses or EDSS worsening during the 24-week study period in both groups.There was no difference between the two treatment groups in the mean WBBS training time: 27.5 (17.1) hours for group A and 27.1 (15.9) for group B, corresponding to 137 (85) and 135 (79) minutes per week, respectively.

The **TABLE 5.4** shows the results of COP path, FSST, 25-FWT and MSIS-29 for the two treatment groups at baseline (T0), after 12 weeks (T1) and after 24 weeks (T2), including their

relative percentage changes, time effect and time X treatment effect. We did not observe any time effect across groups for all endpoints, while there were significant time X treatment interaction effects in COP path (F=4.608, *p*=0.016), FSST (F=3.745, *p*=0.034), 25-FWT (F=3.339, *p*=0.048), and MSIS-29 (F=4.282, *p*=0.023). These findings indicate significant between-group differences over time favours to WBBS training in static and dynamic balance, walking speed and quality of life (**FIG. 5.5**).

The simple contrast analyses also revealed that WBSS training was effective in all endpoints, regardless of the order of treatment. In group A, there was a significant improvement in COP path, FSST, and MSIS-29 at the end of intervention period, and a trend towards a return to baseline values at the end of observation period. A residual effect on primary endpoint was found in group A even at the end of observation period.

In group B, all efficacy measures remained substantially unchanged during the observation period, while a significant improvement was observed after the intervention period. However, it is noteworthy that in group B the improvement in walking speed after WBBS training reached the statistical significance ($p<0.05$), whilst this did not happen in group A, probably due to the small sample size.

The **FIG. 5.6** shows that proportions of patients who had a ≥30%, 29-20% or 19-10% improvement in all efficacy measures were greater at the end of intervention period than at the end of observation period (all p-values <0.05), regardless group assignment.

At the end of 24-week study period, there was a proportion of non-fallers (n=17, 50%) greater than that one (n=12, 35%) relative to the 12 weeks before the study entry (*p*=0.048 by the McNemar-Bowker test). No accidental falls were reported by patients while performing WBBS training.

During the 24-week study period, 24 (70%) patients reported at least one adverse event. Out of these, five graded as moderate (n=2) and mild (n=3) were considered as attributable to home-based WBBS training (**TABLE 5.5**). The majority of these WBBS training-related adverse events (4 out of 5) occurred after the introduction of the most challenging games.

No extra contacts with the study team were required by patients, except for one patient in group B who needed technical assistance with WBBS after the set-up of device.

4.5.3 Discussion

The main finding of our study is that a 12-week WBBS training improved static and dynamic balance, and reduced the impact of MS on patients' QoL. The use of force-platform based measures [35], which ensure linear, objective and reproducible estimations of balance skills and risk of accidental falls, further strengthens our results.

A possible explanation for the benefits of the WBBS training is that it ameliorated the impairment of proprioceptive signal conduction by providing constant visual information about weight shifting on balance board using the visual display, thus enhancing the coupling between perception and action [19-21,38]. In recent years, the specific re-training of sensory strategies has became an essential component of rehabilitative programmes aimed to improve static and dynamic balance in MS. These interventions could reduce - at least theoretically - the risk of accidental falls while patients perform their daily living activities [19,39].

An alternative hypothesis encompasses the role of mirror neurons [40]. During the WBBS training, patients see an avatar who mimics their movements while they are playing. Some authors suggest that watching your own movements, while executing an action, could facilitate motor re-learning in neurorehabilitation [40-42]. Task-oriented training and rehabilitation can lead to an enhancement of both function and structure of neural mechanisms [40], but future studies are necessary to better examine this theoretical mechanism.

Lastly, improvement in standing balance observed after WBBS training might be even related to enhancement of lower limb strength [32,43], which, in turn, could have improved function of muscles involved in APAs.

We found a 15-17% improvement in force-platform measures after WBBS training. The COP path in open eye condition, which we adopted as primary endpoint, has been recently suggested as reliable (95% concordance correlation coefficient), more sensitive (88% *vs.* 37%) and accurate (75% *vs.* 63%), but slightly less specific (67% *vs.* 81%) than a common clinical test (i.e. the Berg Balance Scale) in predicting accidental falls over a 3-month period [35]. Our findings are even more clinically relevant if we consider that the risk of accidental falls has been reported as increased by 8% for each 10-mm increase in COP path [35].

In our study, we also found a 11-14% improvement in the FSST. This clinical assessment has a sensitivity of 60% and a specificity of 75% in discriminating fallers and non-fallers among people with MS, if scoring above 16.9 seconds is used as a cut-off [44]. After WBBS training, both groups scored below this cut-off, thus suggesting its clinically relevant impact in terms of improved dynamic standing balance and reduced risk of falls.

We observed a slight significant improvement (8-10%) in walking speed after WBBS training. This finding appears to be consistent with studies suggesting that an increase in more accurate postural control strategies lead to clinical improvement not only in balance skills, but also in walking performance [32,38,39]. The improvement in mobility, promoted by practicing high-intensity, repetitive weight shifting exercises, could be explained also by other mechanisms, such as muscle strength reinforcement [32,43], restoration of axial control and APAs [23], or simply enhancement of fitness level [32]. However, the threshold of 20% change, that is considered as clinically meaningful [45], was reached only by about a quarter of patients after the intervention.

The 10-12% improvement in the MSIS-29 confirms previous assumption that balance training can have a positive impact on patients' QoL [38]. After WBBS training, the MSIS-29 scores of both groups were reduced, on average, of 9 or 10 points. This last finding is even more relevant when we consider that a minimal change score of 8 points in the MSIS-29 has been demonstrated as clinically significant [46].

Lastly, after WBSS training, the proportion of non-fallers was increased with respect to the 12-week period before randomization. However, this finding has to be interpreted cautiously because: (i) retrospective self-report of falls is prone to recall bias [44]; (ii) time-frame for optimal reporting of falls is unknown [47]; (iii) comparison was made between a self-reported and a prospectively collected measure.

In our study, we observed a maintained improvement only on the primary endpoint over the 12-week observation period post-intervention (in group A), thus suggesting a stronger benefit of WBBS training on static balance, but not on dynamic balance, walking speed and QoL. Yet, this is not an unexpected results, if we consider that (i) WBBS training is specific for static standing balance rather than dynamic balance or gait; (ii) a previous study demonstrated that benefits gained from rehabilitation are partly maintained until 6 months after the discharge, even despite worsening neurological status [48]. On the other hand, there was a trend towards baseline values in group A after 12 weeks of no longer doing the WBBS. This could suggest the requirement for ongoing WBBS training to maintain benefit. Yet, it is still unclear how long and how often people with MS need to exercise balance with WBBS [32-34].

Although in our study only one patient had to retire from the study due to an adverse event related to WBBS training, further 4 patients reported the occurrence of knee or back pain, graded as mild or moderate. This is not surprising, considering that injuries associated with specific videogames (the so-called "Wii-itis" or "Nintendinitis") have been recently described even in healthy population [49-51] (see also http://www.nintendo.com/consumer/wiisafety.jsp).

In our experience, games requiring body shifts in a fast motion, such as “Soccer Heading”, were more often related to occurrence of knee and back pain.
We scheduled engagements with physiotherapists every 4 weeks during WBBS training, thus leading to a better management of these symptoms. Although it has been reported that patients who have mild balance and mobility deficits can safely use WBBS in their homes [32], no data are yet available on patients with more severe disability. Therefore, a home-based WBBS training is still applicable only to people with MS who are still ambulant (EDSS 5.5 or less).

Limitations. Limits of the present study mainly concern the small sample size, absence of blindness, and the study design lacking of a wash-out period. Data regarding the occurrence of accidental falls prior to study enrolment were not reliably captured, therefore affecting a consistent comparison with respect to study period. Lower extremity strength was not measured, hence we cannot assess whether muscle reinforcement may have play a role in determining the balance improvement. Moreover, although our computer-based measure of balance is accurate and reliable [35], it was evaluated only in the most simplistic condition (static condition, EO). Lastly, an evaluation of sitting balance performance is lacking, although WBBS training also included one game to be played in sitting stance.

Implications. The implications of our study may be significant for PwMS, who are most often neglected for rehabilitation care, especially in early stages of disease. Improvement in balance measures and mobility following the use of WBBS has been also reported in other MS populations [32-34], although one recent study suggests only moderate effect sizes not reaching the statistical significance [33].
According to our findings, WBBS training seems to have a smaller effect than other balance rehabilitation approaches for MS, such as visuo-proprioceptive training [38], sensory strategy re-training [39], hippotherapy [52], vestibular rehabilitation [53], and resistance training [54]. However, the large standard deviations of percentage changes observed in both groups during the intervention period suggest that improvements deeply varied across patients. As a consequence, WBBS cannot yet be considered an alternative to standard rehabilitation.
Owing to the risk of adverse events and its relative effectiveness, we strongly suggest careful monitoring of patients during WBSS training, especially in the first stage and when more strenuous exercises are introduced. Thereafter, patients could be supervised less closely (monthly, for example), and just to verify their progresses over time. In this way, WBBS might potentially offer a cost-effectiveness at least equal than standard care through the reduction in

transport and staffing costs. Unfortunately, we did not carry out a cost-effectiveness analysis to support this statement.

In conclusions, a home-based WBBS training could be considered for PwMS with balance impairment, especially in those ones who have a mild to moderate disability level and still employed. It would permit an inexpensive and pleasant homecare approach, also increasing the openness to rehabilitation. However, it could be used as part of a supervised physiotherapy-based exercise program, in order to minimize risk of adverse events and training-related injuries. Further efforts are warranted to better estimate the risk-benefit ratio (adverse event rate *vs.* efficacy) before the WBBS is used for clinical purposes.

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Table 5.1

Baseline demographic and clinical characteristics of enrolled PwMS.

Gender, *n (%)*	
Females	24 (60)
Males	16 (40)
Age (years), *mean ± SD*	40.3 ± 11.7
MS type, *n (%)*	
Relapsing-remitting	26 (65)
Secondary progressive	14 (32.5)
Primary progressive	1 (2.5)
EDSS score, *median (range)*	3.5 (1.5-5.5)
Functional Scores, *median (range)*	
Piramidal	2 (0-3)
Cerebellar	2 (0-4)
Brainstem	1 (0-3)
Sensory	2 (0-3)
Bowel/Bladder	1 (0-3)
Visual	0 (0-1)
Cerebral	0 (0-2)
Ambulation Index	0 (0-4)

Table 5.2

Pre- and post-visuo-proprioceptive training performances at the bipedalic and monopodalic test.

	Pre-training (week 0)	**Post-training (week +6)**	**P-value***
Stabilometric test			
FRES (EO)	0 (0-25.2)	0 (0-20.4)	0.4
FRES (EC)	0 (0-87.5)	0 (0-37.0)	**<0.001**
Trunk Sway (EO)	1.0 (0.4-6.3)	0.9 (0.4-6.0)	0.1
Trunk Sway (EC)	1.3 (0.7-6.2)	1.0 (0.5-6.5)	0.1
Monopodalic test			
FRES (EO)	39.3 (0-88.4)	15.7 (0-66.3)	**<0.001**
FRES (EC)	67.3 (26.8-99.1)	52.6 (11.0-95.3)	**<0.001**
Vestibular Strategy (EO)	26.4 (4.7-86.2)	26.0 (0-73.2)	0.2
Vestibular Strategy (EC)	19.5 (1.5-49.9)	30.4 (6.7-66.4)	**0.002**
Visual Strategy	0 (0-85.0)	13.4 (0-85.0)	**<0.001**
Proprioceptive Strategy	0 (0-10.0)	2.5 (0-44.4.)	**<0.001**

** Statistically significant by the Wilcoxon test for related samples at a significance level corrected by multiplicity (using a Bonferroni correction) α=0.005.*

All values are expressed as median (range).

Table 5.3

Description of balance games included in the "Wii Fit Plus" package and used for the 12-week WBBS training.

Game	Position	Avatar on display	Aim of the game	Starting message on display
Zazen	Sitting	The flame of a candle	To stand motionless as long as possible avoiding the flame to be extinguished	"A lack of focus will cause the flame to shake. Try to keep your body still"
Table Tilt	Standing	Mobile platform provided by holes	To direct balls into holes avoiding them to go out of the platform	"To guide the balls to the holes, shift to the left, right, front and back"
Ski Slalom	Standing	A ski player	To down the slope as fast as possible avoiding to miss the gates	"Lean left and right to go through the gates"
Penguin Slide	Standing	An iceberg having a penguin on it	To catch as many fish as possible while they jump out of the sea	"Shift your body to the left and right to tilt the iceberg and feed the penguin"
Tightrope Walk	Standing	A tightrope walker	To cross a precipice on the tightrope avoiding to fall down	"Walk in place to cross the tightrope"
Soccer heading	Standing	A soccer player	To hit as many balls as possible avoiding other objects	"Tilt your body left and right to head the soccer balls flying at you"
Balance bubble	Standing	A subject inside a bubble	To go down the river as fast as possible avoiding collisions with borders	"Shift your weight forward to move. You can also shift left and right".

Figure 5.4

Characteristics of study sample at baseline.

	Group A (n = 18)	**Group B (n = 18)**
Gender (F:M)	13:5	12:6
Age, mean (SD)	35.3 (8.6)	37.1 (8.8)
BMI, mq/kg^2	21.8 (3.0)	23.4 (4.7)
Disease duration, mean (SD)	12.2 (6.0)	9.3 (5.3)
EDSS, median (range)	3.0 (1.5 - 5.0)	3.5 (1.5 - 5.0)
Self-reported no. of falls occurred in the previous 12 weeks, n (%)		
0	6 (33)	7 (39)
1	3 (17)	5 (28)
≥2	9 (50)	6 (33)

P-values are ≥0.15 for all the between-group comparisons.

Table 5.5

Summary of study results.

	T0 raw value *mean (SD)*	T1 raw value *mean (SD)*	T2 raw value *mean (SD)*	% change T1-T0 *mean (SD)*	% change T2-T0 *mean (SD)*	Time effect F *p*-value	Time × treatment effect F *p*-value
COP path [OE], mm						F = 0.745 *p* = 0.483	**F = 4.608** ***p* = 0.016**
Group A	597 (370)	487 (319)	485 (330)	–17% (31)	–8% (19)		
Group B	543 (240)	575 (268)	425 (140)	+7% (22)	–15% (27)		
FSST, s						F = 1.423 *p* = 0.256	**F = 3.745** ***p* = 0.034**
Group A	17.5 (12.7)	14.8 (10.1)	15.2 (9.8)	–10% (21)	–5% (18)		
Group B	17.4 (9.7)	17.6 (9.5)	14.4 (10.2)	–1% (16)	–14% (28)		
25-FWT, s						F = 2.036 *p* = 0.147	**F = 3.339** ***p* = 0.048**
Group A	8.5 (2.7)	7.8 (2.8)	8.3 (2.5)	–8% (18)	+1% (15)		
Group B	9.5 (3.3)	8.7 (3.0)	8.3 (2.5)	–2% (14)	–10% (19)		
MSIS-29						F = 0.668 *p* = 0.520	**F = 4.282** ***p* = 0.023**
Group A	81 (24)	69 (21)	76 (22)	–12% (27)	–2% (15)		
Group B	77 (21)	78 (24)	69 (22)	+2% (15)	–10% (22)		

Table 5.6

Summary of the adverse events related to the WBBS training.

ID	Age	Sex	EDSS	Adverse Event	Level	Onset	Action taken
1	18	F	2.5	LOW BACK PAIN	Moderate	After 4 weeks of WBBS training (group A)	1. Interruption of WBSS training; 2. Intramuscular Bethametasone 4 mg/day for 6 consecutive days
2	36	F	4.0	LOW BACK PAIN	Moderate	After 2 weeks of WBBS training	1. WBBS training suspension for 2 weeks; 2. Oral non-steroidal anti-inflammatory drugs upon need for 4 weeks.
3	38	M	2.5	LOW BACK PAIN	Mild	After 6 weeks of WBBS training	1. WBBS training suspension for 2 weeks.
4	32	F	3.0	LEFT KNEE PAIN	Mild	After 8 weeks of WBBS training	1. WBBS training suspension for 1 week 2. Reduction of WBSS training time per day for 2 weeks; 3. Application of dry ice, upon need.
5	33	F	4.5	RIGHT KNEE PAIN	Mild	After 7 weeks of WBBS training	1. WBBS training suspension for 1 week 2. Reduction of WBSS training time per day for 2 weeks.

Figure 5.1

The equipment used to perform the stabilometric and monopodalic test (DPPS®) consisting in: DPA: a handrail support to avoid falls; DEB: a Freeman-like translating board; DVC: an accelerometer applied on the sternum for detecting the degree of trunk sway.

Figure 5.2

Study design (pre/post-intervention pilot trial).

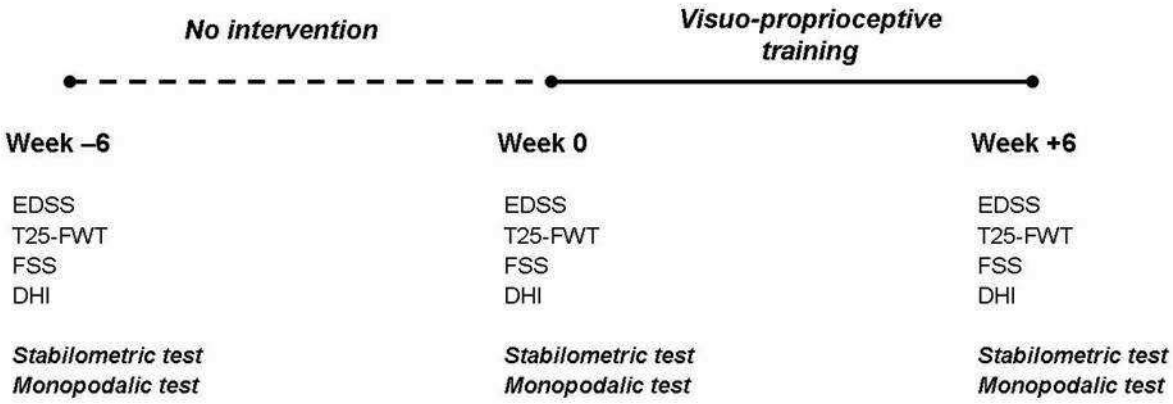
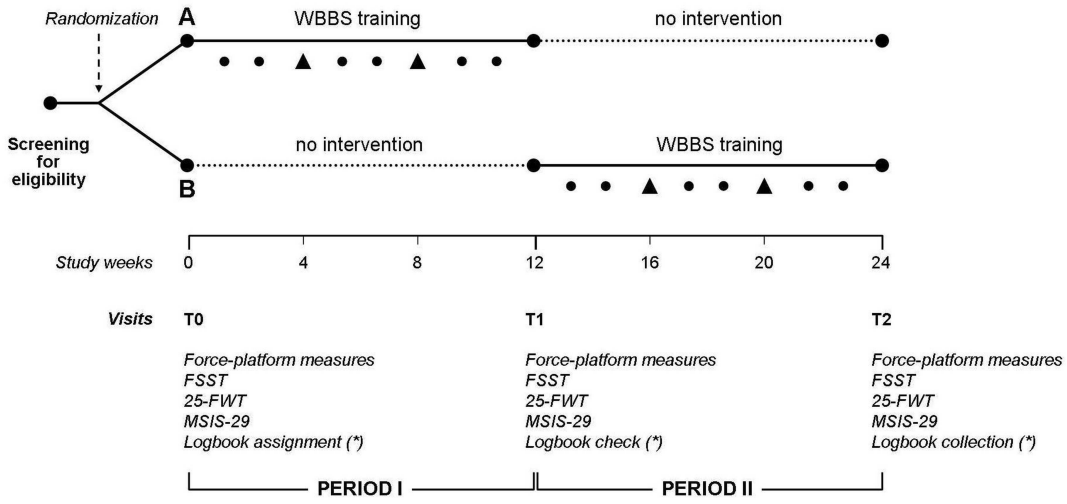


Figure 5.3

Study design. Triangles refer to meetings with physiotherapist, circles refer to phone contacts.



***** *logbooks were given to each patient at baseline (T0); thereafter, they were checked at T1 visit and were returned to study team at visit T2.*

Figure 5.4

Study flow-chart.

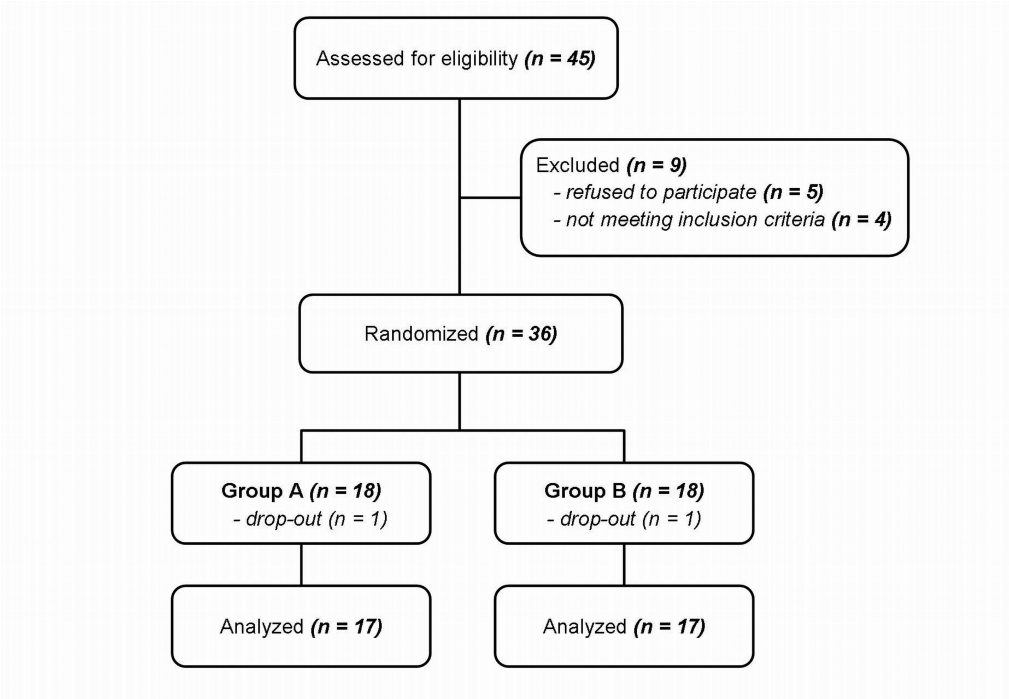
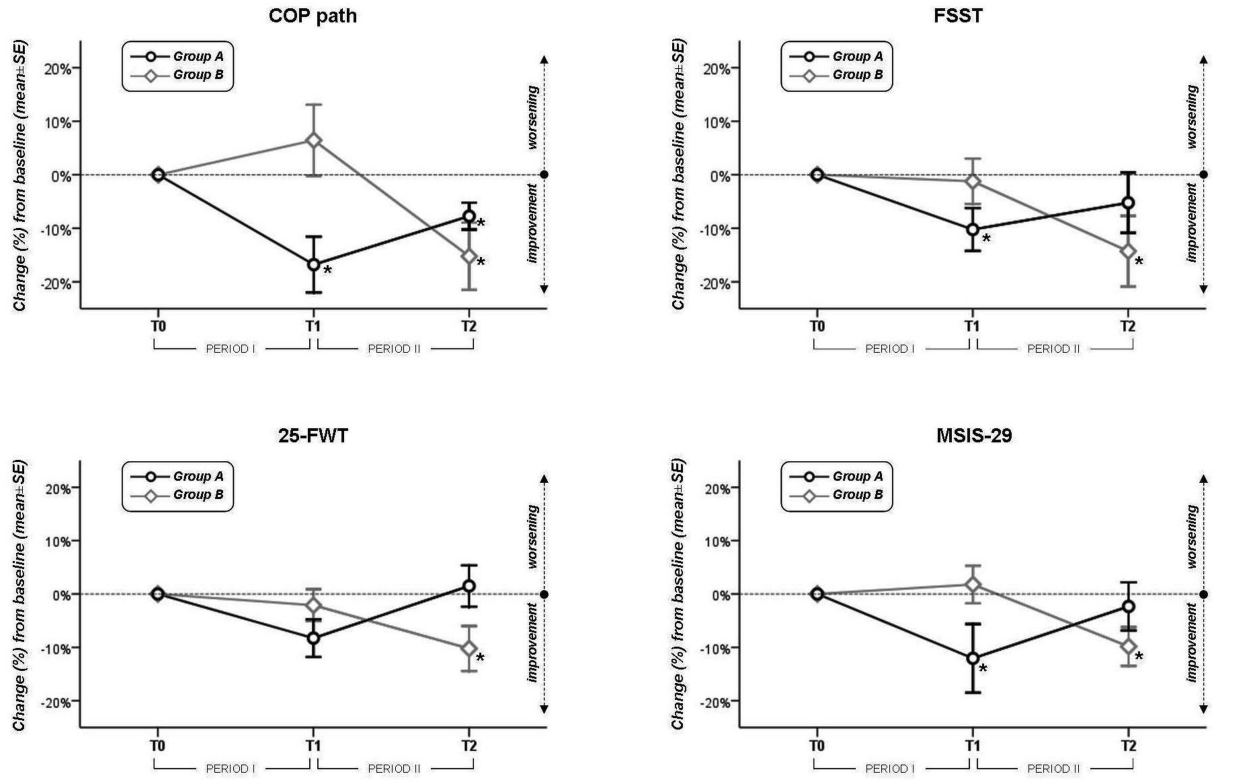


Figure 5.5

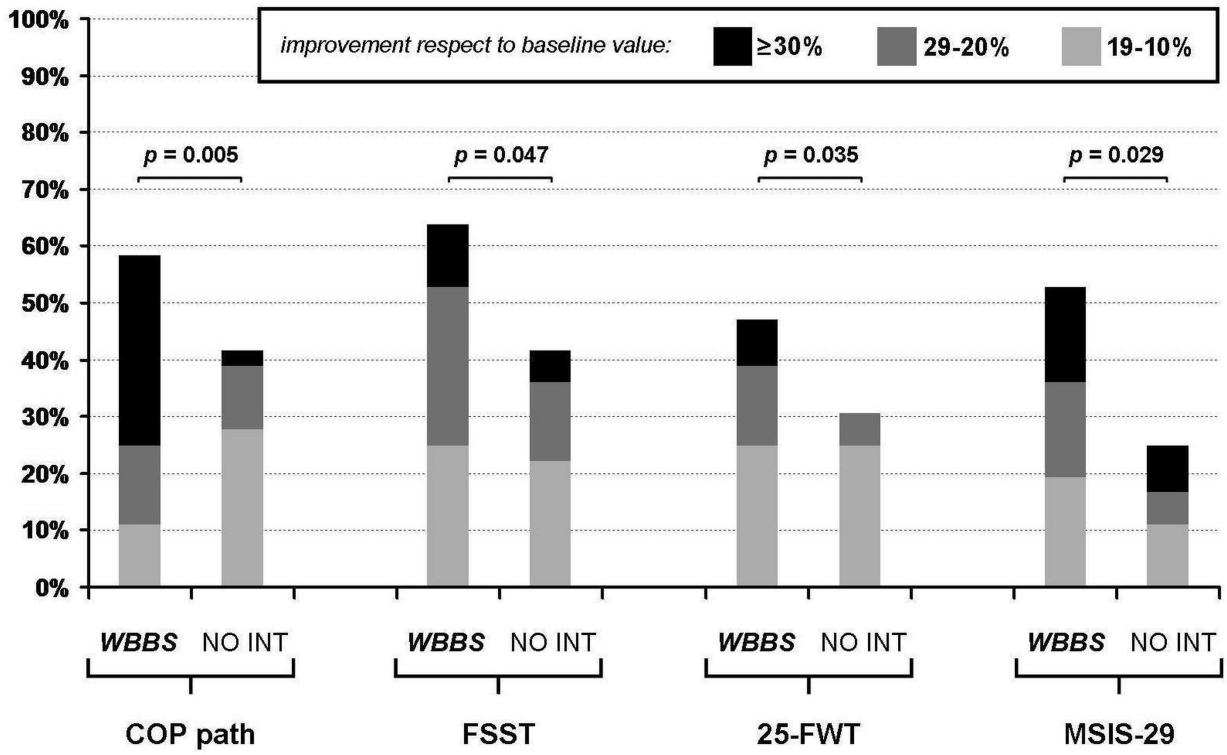
Mean (SE) percentage changes from baseline (T0), as evaluated at 12-week (T1) and 24-week visits in force-platform measures (COP path in EO condition), FSST, 25-FWT, MSIS-29.



** p<0.05 when compared to baseline (simple contrast analysis)*

Figure 5.6

Proportion of patients who had a ≥30%, 29-20% or 19-10%% improvement in all efficacy measures during the active phase of the study (WBBS training) and during the observational phase (NO INT) of the study.



CHAPTER 6

FUTURE DIRECTIONS

Project #1:

"Structural plasticity in MS patients with ataxia: longitudinal changes in brain microarchitecture associated with proprioceptive training"

Funded by FISM grant (2010/R/26)

Principal Investigator: Prof. Patrizia Pantano
Co-investigator: Dr. Luca Prosperini

Project #2:

"Implementation and validation of a portable posturographic system for multi-center studies on patients affected by balance disorders"

Application for FIRB Grant (RBFR131466)

Principal Investigator: Dr. Luca Prosperini
Co-investigator: Prof. Maurizio Patrignani (Dept. of Computer Sciences and Automation, RomaTre University, Rome)

Project #3:

"Longitudinal changes in microarchitecture and neuronal metabolism associated with proprioceptive training to ameliorate balance in multiple sclerosis"

Applicaton for MoH grant (PE-2011-02348795)

Principal Investigator: Luca Prosperini
Co-investigators: Dr. Olga Ciccarelli (Dept. of Brain and Rehabilitation, NMR Unit, UCL Neurology London, UK); Dr. Tatiana Koudriavtseva (Neurology Unit, National Institute for Cancer 'Regina Elena', Rome)