Multiple Sclerosis: Changes in Microarchitecture of White Matter Tracts after Training with a Video Game Balance Board[1]

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Purpose: To determine if high-intensity, task-oriented, visual feedback training with a video game balance board (Nintendo Wii) induces significant changes in diffusion-tensor imaging (DTI) parameters of cerebellar connections and other supratentorial associative bundles and if these changes are related to clinical improvement in patients with multiple sclerosis.

Materials and Methods: The protocol was approved by local ethical committee; each participant provided written informed consent. In this 24-week, randomized, two-period crossover pilot study, 27 patients underwent static posturography and brain magnetic resonance (MR) imaging at study entry, after the first 12-week period, and at study termination. Thirteen patients started a 12-week training program followed by a 12-week period without any intervention, while 14 patients received the intervention in reverse order. Fifteen healthy subjects also underwent MR imaging once and underwent static posturography. Virtual dissection of white matter tracts was performed with streamline tractography; values of DTI parameters were then obtained for each dissected tract. Repeated measures analyses of variance were performed to evaluate whether DTI parameters significantly changed after intervention, with false discovery rate correction for multiple hypothesis testing.

Results: There were relevant differences between patients and healthy control subjects in postural sway and DTI parameters ($P < .05$). Significant main effects of time by group interaction for fractional anisotropy and radial diffusivity of the left and right superior cerebellar peduncles were found ($F_{2,23}$ range, 5.555–3.450; $P = .036$–$.088$ after false discovery rate correction). These changes correlated with objective measures of balance improvement detected at static posturography ($r = -0.381$ to 0.401, $P < .05$). However, both clinical and DTI changes did not persist beyond 12 weeks after training.

Conclusion: Despite the low statistical power (35%) due to the small sample size, the results showed that training with the balance board system modified the microstructure of superior cerebellar peduncles. The clinical improvement observed after training might be mediated by enhanced myelination-related processes, suggesting that high-intensity, task-oriented exercises could induce favorable microstructural changes in the brains of patients with multiple sclerosis.

Online supplemental material is available for this article.

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Balance impairment is observed frequently in patients with multiple sclerosis (MS), and it is among the most disabling symptoms because it reduces mobility and independence, leads to falls and injuries, and affects overall quality of life. Lack of balance in patients with MS remains incurable, and validated pharmacologic approaches are not yet available for these patients (1). Moreover, some drugs that are used frequently in neurologic practice may even have detrimental effects on gait and balance (2). Therefore, most treatments rely heavily on rehabilitation, which is still considered to be important for improvement of function in patients with MS (3).

Rehabilitation of balance by using a video game balance board system (WBBS) (Nintendo Wii; Nintendo, Kyoto, Japan; *http://www.nintendo.co.uk/index.html*), and more extensively, visual-feedback and virtual reality training have been reported to be effective in patients with MS (4–6) and in those who have other neurologic diseases (7–10). However, the neurobiologic basis of the observed improvements in balance is still unknown.

Advances in Knowledge

- A medium effect size (Cohen f^2 = 0.161–0.273) of high-intensity, task-oriented visual feedback exercises on diffusion-tensor imaging parameters can be expected.
- Training-induced behavioral changes in standing balance may be accompanied by transient structural white matter plasticity (correlation coefficient, −0.381 to 0.401), specifically involving the superior cerebellar peduncles.
- The observed improvement in fractional anisotropy observed after balance training in 27 patients with multiple sclerosis was mainly due to a reduction in radial diffusivity, suggesting the occurrence of activity-dependent modulation of myelin in partially damaged pathways.

The use of nonconventional magnetic resonance (MR) imaging techniques have added insight about the relationship between structure and function that mediates standing balance in patients with MS, providing an anatomic framework for interpreting the pathologic substrate of balance disorders (11). In comparison with classic MR imaging measures, advanced imaging techniques have improved pathologic specificity and have highlighted the correlations among anatomic damage, clinical impairment, and rehabilitation-related changes in disease-modified brain structures (12). Diffusion-tensor imaging (DTI)–based fiber tracking is a promising technique that allows detailed quantitative analyses of white matter tracts, and it is thought to reflect pathologic processes accurately (13). However, although functional plasticity has been described after motor and cognitive training (14–17), to our knowledge, structural plastic changes induced by rehabilitation have not been investigated in patients with MS.

In this study, we tested the following hypotheses: *(a)* High-intensity, task-oriented, visual feedback training by using the commercial WBBS induces significant changes in DTI parameters of cerebellar connections, whose damage has been related with postural balance deficit in patients with MS (11). *(b)* DTI parameters of other supratentorial associative bundles may change after the intervention. *(c)* DTI changes are significantly related to clinical improvement.

Materials and Methods

Participants

The protocol was approved by the local ethical committee; each participant provided written informed consent before any study-related procedure. From February to June 2011, 45 patients with MS diagnosed on the basis of the McDonald revised criteria (18) were screened for eligibility by two expert neurologists (L.P. and C.P., with 5 and 28 years of experience, respectively) in agreement. Inclusion criteria were age of 18–50 years (inclusive); relapsing-remitting or secondary progressive MS; expanded disability status scale score (19) less than or equal to 5.5; ability to walk without resting for 100 m or more. Exclusion criteria were use of an assistive device or foot or ankle orthosis, relapses during the previous 6 months, any medication initiation or change during the previous 3 months, seizures, severe blurred vision, psychiatric disorders or severe cognitive impairment, and cardiovascular and respiratory disorders. A total of 15 healthy subjects also were recruited and served as the control group.

Study Design

This was an ancillary prospective study of an independent, randomized, two-period crossover pilot study to investigate the effectiveness and safety of

Implication for Patient Care

- Home-based balance training is an effective option to improve balance of patients with multiple sclerosis, but training-induced changes in clinical and diffusion-tensor imaging parameters are not sustained after discontinuation of training.

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Abbreviations:
AD = axial diffusivity
DTI = diffusion-tensor imaging
FA = fractional anisotropy
MD = mean diffusivity
MS = multiple sclerosis
RD = radial diffusivity
ROI = region of interest
WBBS = Wii balance board system

Author contributions:
Guarantors of integrity of entire study, L.P., F.F., F.T., D.F., F.D.A., P.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, L.P., E.S., F.T., E.R., D.F., F.D.A., C.P., P.P.; clinical studies, F.F., F.T., E.R., D.F., F.D.A., C.P., P.P.; experimental studies, N.P., E.S., F.T., E.R., D.F.; statistical analysis, L.P., F.T., E.R., D.F.; and manuscript editing, L.P., N.P., E.S., F.T., E.R., D.F., C.P., P.P.

Conflicts of interest are listed at the end of this article.

Figure 1

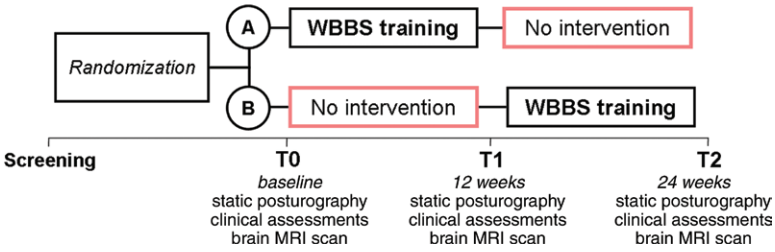

Figure 1: Flowchart shows study protocol.

12-week home-based balance training with the WBBS, as detected at static posturography (6).

Patients who met all eligibility criteria underwent study assessments and were randomly assigned in a 1:1 ratio to two counterbalanced groups (groups A and B) by computer-generated random numbers. Group A started a 12-week period of home-based WBBS training (intervention period), followed by a 12-week period without any intervention or specific training (observation period). Group B was given the treatment in reverse order.

Patients were tested by means of clinical evaluation and underwent brain MR imaging at baseline (T0), at the end of the first 12-week period (T1), and finally, at the end of the 24-week study period (T2) (Fig 1). The healthy control group also underwent MR imaging (only once) and static posturography.

Static posturography was performed with a monoaxial force platform (ProKin PJ-254P, Tecnobody, Bergamo, Italy; *http://www.tecnobody.it*) according to standardized procedures (20). The instant positions of the center of pressure on the ground were used to calculate postural sway (ie, the sum of displacements in millimeters) on the force-measuring platform during a 30-second trial, with the patient's eyes open.

Intervention

During the 12-week active period, each patient committed to five 30-minute sessions (Monday through Friday, with no sessions on weekends) of home-based training with the WBBS. Training protocol consisted of repetitions of several games (selected from the Wii Fit Plus package, Nintendo; *http://www.wiifit.com/training/balance-games.html*) according to rules described elsewhere (6).

MR Imaging Acquisition

Participants were imaged with a 3.0-T imager (Verio; Siemens, Erlangen, Germany). The body coil was used for signal transmission, and the manufacturer's 12-channel head coil designed for parallel imaging was used for signal reception. Section orientation parallel to the subcallosal line was ensured by acquiring a multiplanar T1-weighted localizer at the beginning of each MR imaging examination. At each time point, patients were repositioned in the imager in a consistent way.

The following sequences were performed during MR imaging sessions for all the subjects: *(a)* a dual fast spin-echo proton-density and T2-weighted sequence with 40 axial contiguous sections and integrated parallel acquisition technique (repetition time msec/echo time msec, 5310/10–103; echo train length, 28; matrix, 384 × 384; field of view, 220 mm; reduction factor, three; acquisition time, 5 minutes 4 seconds; section thickness, 4 mm), *(b)* a three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence with 176 axial contiguous sections (1900/2.3; flip angle, 9°; matrix, 256 × 256; field of view, 260 mm; acquisition time, 3 minutes, 48 seconds; section thickness, 1 mm), *(c)* DTI performed with an axial single-shot echo-planar spin-echo sequence with 30 gradient directions and 72 axial contiguous sections (12200/94; matrix, 96 × 96; field of view, 192 mm; b = 0 and 1000 sec/mm^2; acquisition time, 13 minutes 15 seconds; section thickness, 2 mm), and *(d)* a T1-weighted spin-echo sequence with 40 axial contiguous sections after administration of gadolinium-based contrast agent performed only in the patient group (550/9.8; matrix, 320 × 320; field of view, 240 mm; acquisition time, 2 minutes 15 seconds; section thickness, 4 mm).

MR Imaging Data Set Processing

Two operators (N.P. and E.S., with 5 and 4 years of experience, respectively) who were blinded to the clinical data performed the image data processing on a Linux workstation by using FMRIB Software Library 4.1 package (FMRIB Image Analysis Group, Oxford, England, *http://www.fmrib.ox.ac.uk/fsl)*, MATLAB 7.0 (Mathworks, Natick, Mass), Jim 5.0 software (Xinapse System, Leicester, England; *http://www.xinapse.com*), Statistical Parametric Mapping 8.0 software (SPM8; Wellcome Department of Cognitive Neurology, London, England; *http://www.fil.ion.ucl.ac.uk/spm)*, and MedINRIA package 1.9.0 (ASCLEPIOS Research Team, Sophia Antipolis Cedex, France, *http://www-sop.inria.fr/asclepios*).

Lesion volumes were obtained by using a semiautomated technique based on local thresholding with the Jim software (F.T., with 3 years of experience); lesions were identified and delineated on proton-density images, and T2-weighted images were used to increase the confidence level for lesion identification. Volumetric images were segmented automatically in SPM8 to yield images of gray matter, white matter, and cerebrospinal fluid. The voxel-based morphometric protocol consisted of an iterative combination of segmentations and normalizations to produce a gray matter probability map (E.R., with 6 years of experience). Normalized gray matter images were modulated (ie, multiplied by the local value derived from the deformation field), thereby preserving in-voxel volumes that may have been altered during nonlinear normalization. For patients, lesion masks were used to remove lesions from images to avoid

erroneous inclusion in the gray matter volume assessment by the segmentation output. Gray matter, white matter, and cerebral spinal fluid volumes were recorded and used to calculate the intracranial volume and brain parenchymal fraction. Data were smoothed by using a 12-mm full width at half maximum Gaussian kernel.

Streamline Tractography

Eddy-current correction and spatial normalization and realignment into standard space by both linear and nonlinear registration were performed with the DTI datasets of the participants by using FSL tools. The streamline DTI tractographic method requires the manual delineation of regions of interest (ROIs) as constraining areas of obligatory passage in each white matter tract according to a three-dimensional brain atlas for virtual brain dissection (21). To enhance the reliability of this approach, the ROIs were previously identified and outlined on standardized DTI images by two operators (L.P. and P.P., with 5 and 20 years of experience, respectively) in agreement. Thereafter, the ROIs were copied onto standardized DTI images by two operators who were unaware of the clinical results of the pilot study (F.F. and F.D.A., with 2 and 3 years of experience, respectively) by using freeware software for streamline tractography (MedINRIA 1.9.0). The fiber tractographic algorithm implemented in MedINRIA is a modified tensor deflection algorithm that uses a log Euclidean framework for diffusion-tensor estimation (22). This implemented algorithm ensures positive semidefiniteness of the tensor (23) and very good anatomic accuracy (24). The following parameters were set: background removal threshold for images with a *b* value of 0, less than 0.2; minimal length of fibers, 10 mm; and smoothing deactivated during fiber tracking process.

In Figure 2 the dissected fibers with relative ROIs as starting and ending seed points are shown together with their respective standard Montreal Neurologic Institute coordinates: the corpus callosum, left and right inferior cerebellar peduncles, middle cerebellar peduncles, superior cerebellar peduncles, internal capsule and corona radiata, fronto-occipital fasciculi, and inferior longitudinal fasciculi.

The software for streamline tractography also provided data on volume, number of fibers and length of each dissected tract, as well as metrics of directional diffusivity such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in square millimeters per second times 10^{-3}.

Statistical Analyses

All data were analyzed by using software (SPSS version 16.0; SPSS, Chicago, Ill). Differences between the patient and control groups were tested by using the Fisher exact test and unpaired Student *t* test for dichotomous and continuous variables, respectively. Reliability of streamline tractography for each bundle was determined as the intraclass correlation coefficient (two-way random effect model for absolute agreement definition) by comparing the volume, number of fibers, and mean length derived from the three evaluations (T0, T1, and T2).

To assess whether diffusivity parameters (FA, MD, AD, RD) changed significantly after the intervention, repeated measures analyses of variance were performed. We considered FA, MD, AD, and RD as dependent variables, the time (T0, T1, and T2) as within-subject factors and treatment groups (groups A, B) as between-subject factors. All analyses were controlled for age, which is known to influence DTI parameters (25). The main effect of time, group, and time by group interaction, and effects size (estimated by using the Cohen f^2) were also provided. The assumptions of normality and sphericity were satisfied for each DTI parameter of white matter tracts.

The relationship between changes in DTI parameters and static balance (ie, postural sway) was investigated by means of the Spearman rank correlation coefficient (univariate analysis) and linear regression analyses (stepwise fashion) with DTI changes as the dependent variable and age, sex, disease duration, disability level, postural sway, T2 lesion volume and intervention with the use of the WBBS as covariates (multivariate analysis). For each patient, intervention-related changes were calculated as a T0–T1 value (group A) or a T0–T2 value (group B). Changes in postural sway were log transformed because static standing balance measures in patients with MS could be nonnormally distributed (20). The false discovery rate for multiple testing correction (26) was applied to the primary aim of study (ie, to determine whether the 12-week training with the WBBS induces significant changes in DTI parameters of cerebellar connections).

Results

Participants

Of the 45 screened patients, 36 were included in the pilot clinical study (6) (Table E1 [online] shows their baseline characteristics), while five declined to participate and four did not meet inclusion criteria (Fig 3).

Table 1 shows the demographic, clinical, and whole-brain MR imaging characteristics of patients who agreed to undergo the serial MR imaging protocol ($n = 30$) and of healthy control subjects ($n = 15$). We found significant differences in brain parenchymal fraction and global FA, MD, AD, and RD values ($P < .01$ for all). There were no between-group differences in volume, number of fibers, and mean length of each white matter tract. In comparison, significant ($P < .05$) or at least marginal (ie, $P = .05$–$.10$) differences between patients and control subjects were found for FA, MD, AD, and RD of all dissected white matter tracts.

The reliability of streamline tractography was more than acceptable or excellent (27), because intraclass correlation coefficients ranged from 0.804 to 0.987 for volume, from 0.792 to 0.945 for number of fibers, and from 0.738 to 0.932 for length. The highest reliability values were found for callosal fibers, while infratentorial bundles, especially inferior cerebellar peduncles,

Figure 2

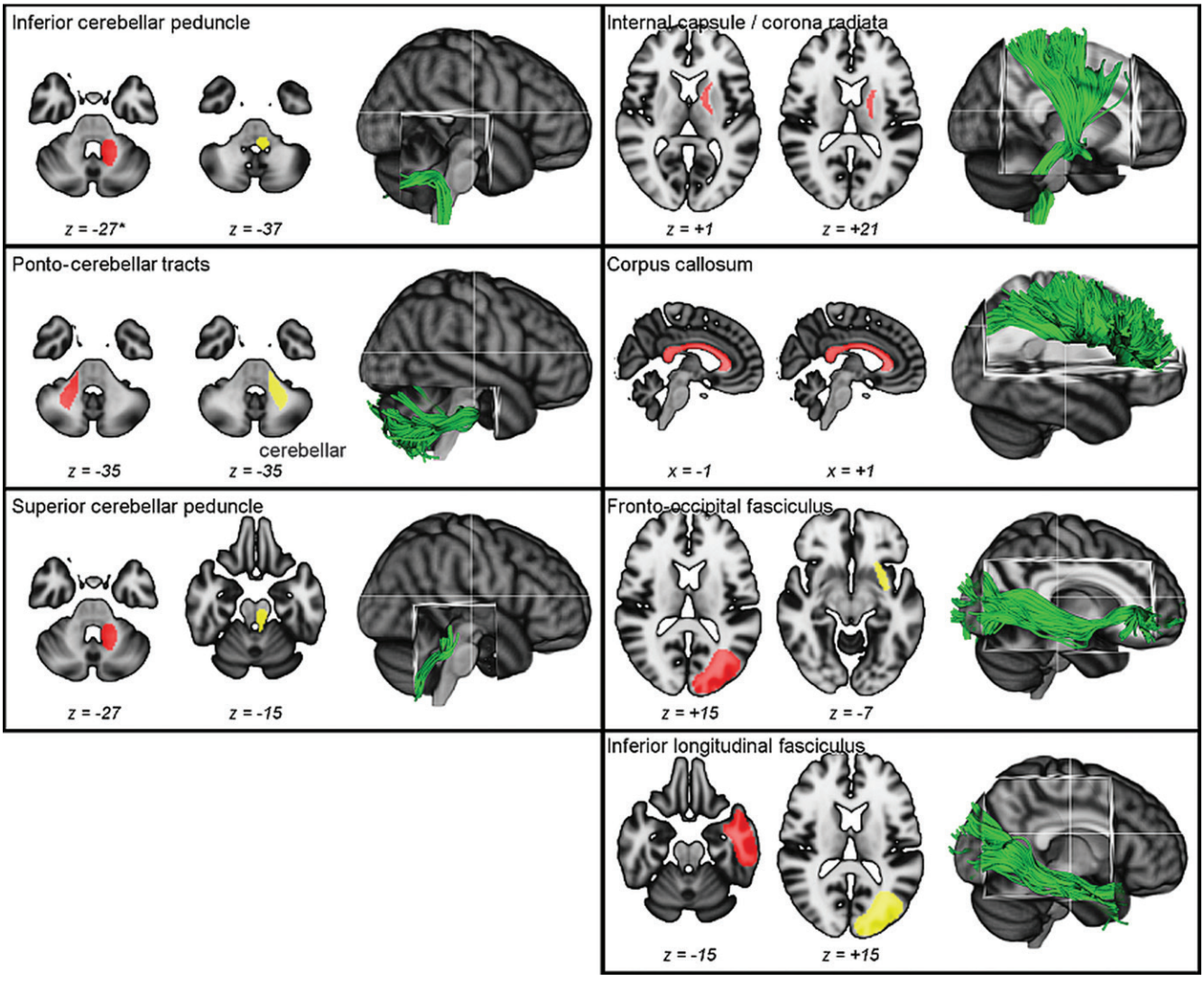

Figure 2: Starting ROI (left image in each section), ending ROI (center image in each section) with Montreal Neurologic Institute coordinates, and their relative dissected white matter tract (right image in each section) are superimposed onto standard T1-weighted template. A two-ROI approach was used to dissect the left and right inferior, middle, and superior cerebellar peduncles, fronto-occipital and inferior longitudinal fasciculi; a one-ROI approach was used to dissect the corpus callosum and left and right internal capsules and corona radiata (21).

had the lowest intraclass correlation coefficients (Table E2 [online]).

Follow-up Data

Twenty-seven patients (13 randomized to subgroup A and 14 randomized to subgroup B) completed the serial brain MR imaging protocol. Three patients were excluded from data analysis: two patients missed the last (T2) imaging examination and one patient's MR imaging acquisition had an error (Fig 3). There were no differences in clinical characteristics, or in T2 lesion volume, brain parenchymal fraction and whole-brain FA, MD, AD, and RD between patients randomized to subgroups A or B ($P > .3$ for all). Relapses and gadolinium-enhancing lesions were not detected in the study. The descriptive summary of the DTI findings of the study is reported in Table E3 (online).

Repeated measures analyses of variance (corrected for age) showed no effect of time, group, and time by group interaction on FA, MD, AD, and RD of middle cerebellar peduncles, and left and right inferior cerebellar peduncles. In comparison, there were significant effects of time by group interaction on FA of the left and right ($F_{2,23}$ = 5.555, false discovery rate–corrected P = .036; and $F_{2,23}$ = 4.198, false discovery rate–corrected P = .047, respectively) superior cerebellar peduncles. There was also a significant effect of

Figure 3

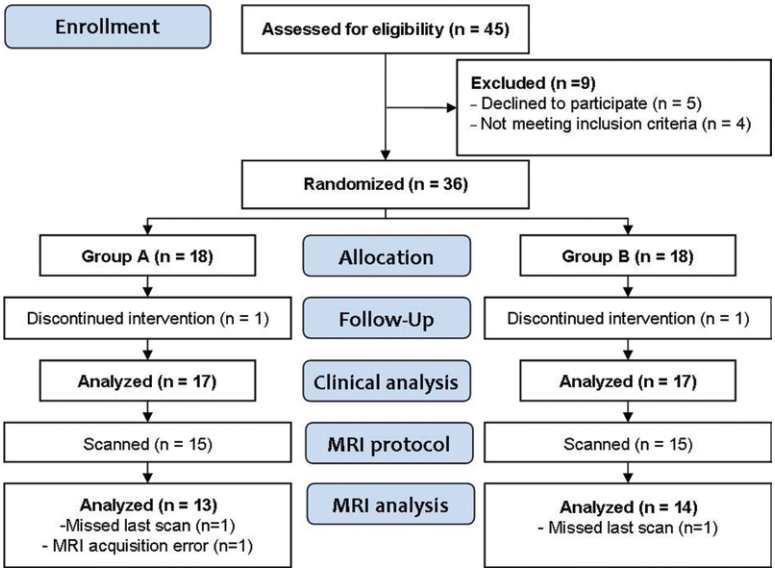

Figure 3: Flowchart shows subject selection.

Table 1

Participants' Characteristics at Baseline

Characteristic	Patients ($n = 30$)	Control Subjects ($n = 15$)
Sex		
Female	18	9
Male	12	6
Age (y)	35.6 ± 7.7	34.8 ± 5.6
Body mass index (kg/mq)	22.9 ± 4.3	23.7 ± 3.9
Phenotype*		
Relapsing remitting	27	NA
Secondary progressive	3	NA
Disease duration (y)	10.5 ± 5.2	NA
Expanded disability status scale score†	3.0 (1.5–5.0)	NA
Postural sway with open eyes (mm)	584 ± 311‡	257 ± 56‡
Intracranial volume (mm^3)	1400 ± 133	1435 ± 125
Lesion volume (mL)†	6.5 (1.5–42.9)	NA
Brain parenchymal fraction	0.781 ± 0.016‡	0.803 ± 0.012‡
Whole brain FA	0.339 ± 0.021‡	0.387 ± 0.011‡
Whole brain MD ($mm^2/sec \times 10^{-3}$)	2.544 ± 0.091‡	2.458 ± 0.056‡
Whole brain AD ($mm^2/sec \times 10^{-3}$)	1.115 ± 0.029‡	1.087 ± 0.021‡
Whole brain RD ($mm^2/sec \times 10^{-3}$)	0.716 ± 0.028‡	0.685 ± 0.022‡

Note.—Unless otherwise indicated, values are means ± standard deviation. NA = not applicable

* Data are number of subjects.

† Data are medians, with ranges in parentheses.

‡ Indicates $P < .05$ (two-sided).

time by group interaction on RD of the left superior cerebellar peduncle ($F_{2,23} = 5.014$, false discovery rate–corrected $P = .042$); moreover, a marginal (just not significant) effect of time by group interaction on RD of the right superior cerebellar peduncle ($F_{2,23} = 3.450$, false discovery rate–corrected $P = .088$) was found. The effect size of training with the WBBS on FA and RD of the left and right superior cerebellar peduncles was medium ($f^2 = 0.161–0.273$, Table 2). On the basis of these findings and with the available sample size, a power of 35% at the two-sided 5% α level was achieved in detecting a significant change in FA of superior cerebellar peduncles after the WBBS training.

Figure 4 shows the effect of WBBS training on FA and RD of both superior cerebellar peduncles. FA and RD changes observed after the training did not persist after the 12 weeks after training, as revealed by simple contrast analyses performed in patients who initially received the intervention first and the observation period second (group A). No significant effect of time, group, and time by group interaction on FA, MD, AD, and RD of the corpus callosum, corona radiata, fronto-occipital fasciculi, or inferior longitudinal fasciculi was found, even without application of multiple testing correction ($P > .05$ for all).

There were strong correlations between changes in postural sway and in FA of superior cerebellar peduncles, which were statistically significant for the left ($r = 0.401$, $P = .038$) and right sides ($r = 0.395$, $P = .042$). We also found weaker but still significant correlations between changes in postural sway and in RD of superior cerebellar peduncles (left: $r = -0.386$, $P = .047$; right: $r = -0.381$, $P = .049$). Scatterplots with log-transformed differences between values before and after intervention in postural sway and in FA and RD of the left and right superior cerebellar peduncles are shown in Figure 5.

In multivariate analyses, we did not identify any clinical or radiologic feature at baseline other than the WBBS training that was associated with changes in DTI parameters, probably because of the small sample size. Linear regressions established that WBBS training was associated with both changes in FA (left side: β = 0.017, $P = .002$; right side: β = 0.008, $P = .037$) and RD (left side: β = −0.024, $P = .006$; right

Table 2

Summary of Study Results (Repeated Measures Analyses of the Variance Corrected by Age)

Brain Area and Diffusivity Metric	Main Effect			Effect Size (Cohen f^2)		
	Time $F_{2,23}$	Group $F_{1,24}$	Time by Group $F_{2,23}$	Time	Group	Time by Group
Left inferior cerebellar peduncles						
FA	0.088	0.175	3.327	0.004	0.007	0.157
MD	0.080	0.041	0.164	0.003	0.001	0.007
AD	0.143	0.034	0.337	0.006	0.001	0.014
RD	0.028	0.057	0.464	0.001	0.002	0.020
Right inferior cerebellar peduncle						
FA	0.191	0.183	1.501	0.008	0.008	0.066
MD	0.017	0.040	0.805	0.001	0.002	0.035
AD	0.231	0.003	2.247	0.010	0.000	0.101
RD	0.007	0.047	0.938	0.000	0.002	0.041
Pontocerebellar tracts						
FA	3.285	0.053	2.605	0.134	0.002	0.104
MD	3.823	1.087	2.067	0.154	0.045	0.079
AD	2.285	1.429	1.063	0.094	0.059	0.042
RD	3.225	0.338	1.071	0.258	0.014	0.036
Left superior cerebellar peduncle						
FA	0.732	0.059	5.555*	0.030	0.002	0.273
MD	1.210	0.175	0.245	0.050	0.007	0.010
AD	0.352	0.001	0.461	0.015	0.000	0.019
RD	1.400	0.122	5.014†	0.058	0.005	0.234
Right superior cerebellar peduncle						
FA	0.298	0.073	4.198‡	0.012	0.003	0.202
MD	0.033	0.199	1.679	0.001	0.008	0.075
AD	0.001	0.001	0.163	0.000	0.000	0.007
RD	0.378	0.166	3.450	0.016	0.007	0.161

* $P = .036$

† $P = .042$

‡ $P = .047$

side: $\beta = -0.016$, $P = .011$) of superior cerebellar peduncles, accounting for 33.1% (left) and 20.8% (right) of the explained variability in FA changes, and for 19.7% (left) 17.6% (right) of the explained variability in RD changes.

Discussion

The main finding of this study is that the microstructural properties of both superior cerebellar peduncles significantly changed after a 12-week intervention aimed at improving balance by using visual feedback training with a WBBS. These DTI changes could be considered clinically relevant because they were correlated with improved standing balance detected at static posturography, further supporting our main hypothesis that high-intensity, task-oriented exercises can induce microstructural changes in the cerebellar connections of patients with MS. Moreover, our findings indirectly reinforce the role of the cerebellum in adaptive mechanisms induced by high-intensity, task-oriented exercises (28–30).

Rehabilitative strategies for motor learning and plasticity are mainly focused on high-intensity, repetitive, and task-specific practice (31), and they can lead to an enhancement of both functional and structural neural circuits (32). The improvement of FA observed in both superior cerebellar peduncles after the 12-week training period was mainly due to a reduction in RD, suggesting an enhancement of myelination-related processes driven by training-induced white matter plasticity after high-intensity, task-oriented exercises. This mechanism might have led to a functional restoration (ie, activity-dependent myelomodulation in partially damaged pathways) of myelin sheaths on demyelinated axons, which, in turn, re-established the saltatory conduction along fibers of superior cerebellar peduncles. Motor training–induced structural plasticity and increases in myelination without generation of new neurons have been described in animal models (33). Motor activity can influence not only the formation of new myelin but also the maintenance and morphology of preexisting white matter by increasing axonal diameter and/or permeability, myelin thickness, packing density, or internodal distance (34).

The use of DTI to determine structural plasticity has been described repeatedly as an experience-dependent phenomenon in healthy adults (35) and in patients affected by neurologic diseases after specific training (36); however, elucidating the cellular or molecular changes that underlie DTI observation is still a challenge (34).

The improvement in clinical balance and the microstructural changes observed in our study did not persist after the discontinuation of the training protocol, suggesting that there was no retention of training-induced balance control restoration. Dynamic structural plasticity without a subsequent consolidation has been observed in healthy subjects after a short learning video gaming session (37). Although the mechanisms behind these findings have not been elucidated yet, an intriguing hypothesis might include the role of reversible molecular changes at the

Figure 4

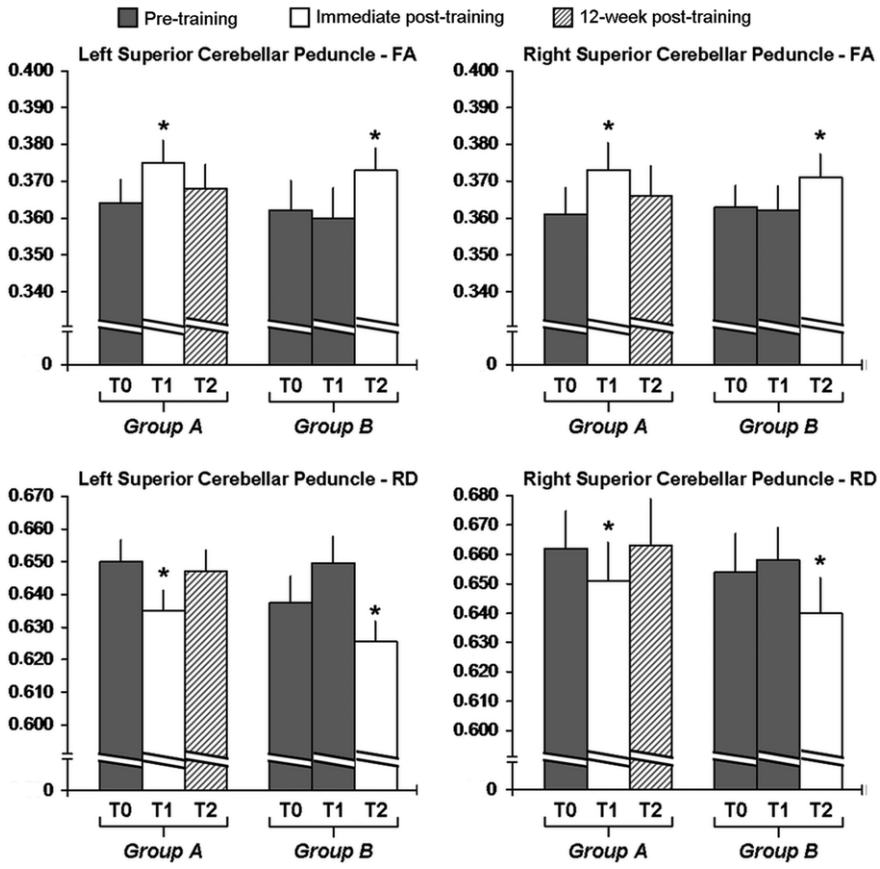

Figure 4: Bar graphs show mean ± standard error of the mean FA and RD in square millimeters per second times 10^{-3} at different time points in group A ($n = 13$) and group B ($n = 14$). * $P < .05$ with respect to baseline.

Figure 5

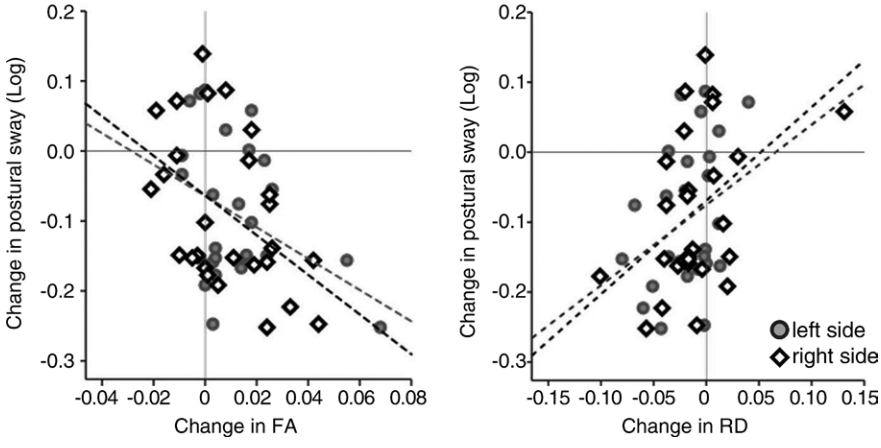

Figure 5: Scatterplots show changes in FA and RD of superior cerebellar peduncles as related to changes in postural sway. Improvements are indicated by positive values for FA changes and by negative values for both RD and postural sway changes.

paranodal level (38) or, alternatively, transient structural changes of glial cells and astrocytes (39,40).

The limitations of our study mainly encompass the small sample size, which resulted in a low statistical power, and the study design, which lacked a control group treated with an intervention other than the balance board training. Moreover, given that the control group was imaged only once, we cannot exclude the possibility that the mechanism underlying the clinical improvement is not MS-specific and could be observed in subjects affected by other neurologic diseases or even in the general population.

In conclusion, we found that training-induced behavioral changes detected with computer-based measures of balance may be accompanied by transient white matter structural plasticity specifically involving the superior cerebellar peduncles. Training-induced balance improvement related to microstructural white matter changes in patients with MS, to our knowledge, has not been well established in the literature. Future studies are warranted to confirm our findings and to better establish the role of MR imaging techniques in the assessment of the neurobiologic basis of effective rehabilitative training.

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