

Deep grey matter involvement and altered sensory gating in multiple sclerosis

Antonella Conte*, Costanza Gianni*, Daniele Belvisi, Antonio Cortese , Nikolaos Petsas , Matteo Tartaglia, Paola Cimino, Enrico Millefiorini, Alfredo Berardelli and Patrizia Pantano

Abstract

Background: Somatosensory temporal discrimination threshold (STDT) is altered in multiple sclerosis (MS). In healthy subjects (HS), voluntary movement modulates the STDT through mechanisms of subcortical sensory gating.

Objective: With neurophysiological and magnetic resonance imaging (MRI) techniques, we investigated sensory gating and sensorimotor integration in MS.

Methods: We recruited 38 relapsing-remitting multiple sclerosis (RR-MS) patients with no-to-mild disability and 33 HS. We tested STDT at rest and during index finger abductions and recorded the movement kinematics. Participants underwent a 3T MRI protocol.

Results: Patients exhibited higher STDT values and performed slower finger movements than HS. During voluntary movement, STDT values increased in both groups, albeit to a lesser extent in patients, while the mean angular velocity of finger movements decreased in patients alone. Patients had a smaller volume of the thalamus, pallidum and caudate nucleus, and displayed higher mean diffusivity in the putamen, pallidum and thalamus. STDT correlated with thalamic volume while mean angular velocity correlated with putaminal volume. Changes in mean angular velocity during sensorimotor integration inversely correlated with mean diffusivity in the thalamus and pallidum. Changes in STDT and velocity were associated with fatigue score.

Conclusion: Altered STDT and sensorimotor integration are related to structural damage in the thalamus and basal ganglia in MS and likely to affect motor performance.

Keywords: Multiple sclerosis, sensory gating, sensorimotor integration, deep grey matter volume, diffusion tensor imaging

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Introduction

Sensory information plays an important role in planning and executing motor action. This process, called sensorimotor integration, requires the correct temporal processing of sensory inputs, which include tactile information.^{1–3} In humans, one of the experimental techniques most commonly used to assess temporal processing of tactile information in the upper limbs is the somatosensory temporal discrimination threshold (STDT). The STDT is the shortest interval at which an individual recognizes paired stimuli as separate in time.^{4,5} The STDT depends on the activation of a subcortical network, in which the basal ganglia and the thalamus are involved, as well as on that of the primary somatosensory cortex (S1), in which inhibitory

interneurons sharpen temporal properties of paired tactile stimuli.⁶

A recent study showed that STDT values are higher in patients with multiple sclerosis (MS), even in those with a mild clinical disability, than in healthy subjects.⁷ The increased STDT in patients with MS may be due to grey matter (GM) involvement of the primary somatosensory cortex and/or involvement of subcortical structures.^{4,6} The possibility that changes in STDT are due to subcortical more than cortical structures is supported by the evidence showing that cortical and subcortical GM damage progresses throughout the disease course, whereas subcortical GM structures are already damaged in the early phases of the disease.⁸

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In healthy subjects, movement execution modifies STDT values according to a specific time course related to movement onset.^{5,9} The STDT increases significantly at movement onset and returns to baseline values towards the end of the movement. STDT modulation during movement execution involves subcortical mechanisms of sensory gating that are mediated by activity in the basal ganglia and thalamus.^{5,9}

Patients with MS may display various types of motor disturbances, including clumsiness and fatigue. An altered sensorimotor integration may be responsible for some of these motor symptoms. Only few neurophysiological studies, however, have investigated mechanisms of sensorimotor integration in patients with MS and these studies have been performed only in the lower limb.^{10,11} It is therefore unknown whether upper limb sensorimotor integration and sensory gating of STDT during movement, which are indispensable for executing accurate movements in daily activities, are altered even in patients with low disability. Hence, our hypothesis is that testing STDT modulation during movement execution in MS patients with low disability will disclose sensorimotor integration failure and a reduced movement efficiency.

This study investigated STDT values in the index finger before and during index finger abductions using a time-controlled experimental paradigm in MS patients. To assess structural and ultrastructural brain tissue damage and identify the brain structures involved in any altered sensorimotor integration detected, patients with MS underwent brain magnetic resonance imaging (MRI).

Materials and methods

Subjects

Thirty-eight patients with relapsing-remitting MS and 33 age- and sex-matched healthy subjects participated in the study (clinical and demographic features are shown in Table 1 and Supplemental Material Table 1). Patients and healthy subjects were prospectively enrolled at the Department of Human Neurosciences, Sapienza University of Rome. Inclusion and exclusion criteria are reported in the Supplemental Material.

MRI was performed in all the participants while the neurophysiological assessment was performed in all the patients and in 27 of the healthy subjects. All the participants gave their informed consent and the experimental procedure was approved by the ethics

Table 1. Subjects' demographic and clinical characteristics.

	Patients with multiple sclerosis	Healthy subjects
Age (years)	40 ± 8	41 ± 10
Female/male	31/7	26/7
Education (years)	13 ± 2	13 ± 3
Disease duration (years)	9.4 ± 8	–
EDSS (median, range)	1.5 (0–3.5)	–
MSFC (z score)	0.01 ± 0.6	–
FSS	34 ± 15	–
SRT-LTS	45 ± 12	–
SRT-CLTR	36 ± 15	–
SPART	18 ± 3	–
SDMT	48 ± 5	–
PASAT3	45 ± 8	–
PASAT2	33 ± 7	–
SRT-D	9 ± 2	–
SPART-D	6 ± 1	–
WLG	25 ± 4	–
BDI	6 ± 3	–

EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; FSS: Fatigue Severity Scale; SRT-LTS: Selective Reminding Test–Long-Term Storage; SRT-CLTR: Selective Reminding Test–Consistent Long-Term Retrieval; SPART: Spatial Recall Test; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Test; SRT-D: Selective Reminding Test–Delayed; SPART-D: Spatial Recall Test–Delayed; WLG: Word List Generation; BDI: Beck Depression Inventory. Values are expressed as mean (standard deviation).

committee of Sapienza University of Rome (CE n 4570) and conducted in accordance with the Declaration of Helsinki.

Clinical assessment

To evaluate the level of patients' disability, we used the Expanded Disability Status Scale (EDSS), the MS Functional Composite (MSFC) Score, including the Paced Auditory Serial Addition Test (PASAT), the timed 25-foot walk at fast speed (T25FW), the nine-hole peg test (9-HPT)¹² and the Fatigue Severity Scale (FSS).¹³

To evaluate possible cognitive impairment in patients, which could have affected the neurophysiological results, patients also underwent the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) for the cognitive assessment¹⁴ and the Beck Depression Inventory (BDI).¹⁵ We excluded patients with even only one impaired cognitive domain, defined as

failure in one test if compared with the performance of the Italian population,¹⁶ as well as patients with a BDI score >10.

Neurophysiological assessment

STDT testing and movement recording

STDT testing was performed according to the experimental procedures used in previous studies^{4,5} (Supplemental Material). Paired stimuli were delivered by starting from an interstimulus interval (ISI) of 0 ms (simultaneous pair) and progressively increasing the ISI in 10-ms steps. The STDT was considered as the first of three consecutive ISIs at which subjects recognized the stimuli as temporally separate.

The functional assessment of the somatosensory and corticospinal pathways was performed by means of somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) (Supplemental Material).

The SMART analyzer motion system (BTS Engineering, Italy) was used to compute mean angular velocity, range of movement and duration of index finger abductions^{17,18} (Supplemental Material).

Experimental paradigm

Subjects were first tested for MEP, SEP and STDT values on the right index finger with the hand at rest. The STDT was also tested during movement execution according to the experimental procedures used in previous studies.^{9,19} Paired stimuli for the STDT were triggered by movement. The movement task consisted in index finger abductions of the dominant hand, with stimuli for the STDT being delivered on the volar surface of the moving finger at three time intervals: 0 ms (concomitantly with movement onset) and 100 and 200 ms after movement onset (Supplemental Material).

MRI

MRI acquisition and analysis

All the participants underwent a standardized MRI protocol on a 3 Tesla scanner (Verio, Siemens AG, Erlangen, Germany) with a 12-channel head coil designed for parallel imaging (GRAPPA, generalized autocalibrating partially parallel acquisition). The following MRI sequences were acquired: (1) high-resolution three-dimensional T1-weighted (T1-3D) magnetization-prepared rapid acquisition with gradient echo sequence; (2) dual turbo spin-echo proton

density and T2-weighted images (DP-T2); (3) high-resolution three-dimensional fluid-attenuated inversion recovery (3D-FLAIR); (4) diffusion tensor imaging (DTI) single-shot echo-planar spin-echo sequence with 30 directions. White matter (WM) areas of hyperintensity compared with the normal appearing WM were detected and segmented on DP-weighted images and considered as WM lesions. GM was segmented with CAT12 (Computational Anatomy Tool; see <http://www.neuro.uni-jena.de/cat/>), a tool running under Statistical Parametric Mapping version 12 (see <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) to estimate the cortical thickness and volume. Cortical thickness analysis has been performed on T1-3D images after hypointense lesion refilling. Volumes of subcortical GM structures were calculated using FMRIB's Integrated Registration and Segmentation Tool (FIRST). DTI fit (see https://users.fmrib.ox.ac.uk/~behrens/fdt_docs/fdt_dtfitt.html) was used to generate whole brain fractional anisotropy (FA) and mean diffusivity (MD) maps for all the subjects. A linear registration was then applied to register T1-3D images to DTI maps, and mean values of FA and MD for each subcortical structure were calculated from the extracted volumes at the subject level. MRI sequences parameters and processing stages are reported in details in the Supplemental Material.

Statistical analysis

We used the SPSS 24.0 toolbox for all but brainwise statistics. Group comparisons were tested by means of the Shapiro–Wilk test to evaluate whether distribution was Gaussian or not, and parametric (unpaired *t* test) or non-parametric tests (Mann–Whitney *U* test) were used accordingly. Gender difference was tested by means of the chi-square test.

To analyse the neurophysiological data, we used between-groups analysis of variance (ANOVA) to compare STDT values at baseline and kinematic parameters in patients with those in healthy subjects. We then compared the percentage changes in the STDT values and kinematic parameters during the sensorimotor integration task using repeated measures ANOVA with factor GROUP (patients vs healthy controls) and factor ISI (baseline, 0 ms, 100 ms and 200 ms after movement onset). We first used correlation analysis (Pearson's *r* and Spearman Rho correlation coefficients) in the patient group alone to evaluate any possible relationship between clinical and neurophysiological variables and between neurophysiological and neuroimaging variables. Clinical variables, which did not correlate with neurophysiological and

neuroradiological variables, were then used for regression analysis.

Effect size was calculated for all the correlations in the patients' group. For a sample size of 38 patients, using a two-tailed $\alpha=0.05$ and $\beta=0.30$, the effect size is $r=0.40$. All the correlations/regressions were thus considered as significant if $r>0.40$.

A general linear model with age as the nuisance covariate was defined to perform a group comparison of cortical thickness and volume between patients and healthy subjects. Moreover, in patients alone, we performed a correlation of the average cortical thickness in the atlas-defined post-central gyrus with neurophysiological variables. This a priori selection is based on the knowledge of the involvement of the primary sensory cortex in the STDT.^{4,20}

All results are reported at $p<0.05$, after false discovery rate (FDR) for multiple comparisons.

Results

Comparison of STDT values and kinematic parameters at baseline between patients and healthy subjects

ANOVA revealed a significant factor GROUP ($F=18.4$, $p<0.001$) for STDT values at baseline. Patients had higher STDT values (84.2 ± 24 ms) than healthy subjects (60 ± 23 ms). The mean angular velocity of index finger abductions at baseline (without paired stimuli delivery) showed that patients were slower than healthy subjects in performing the movement task (patients vs healthy subjects: 73 ± 31 vs 99.4 ± 31 degree/s; ANOVA: $F=11.2$, $p<0.01$).

Percentage changes in STDT and kinematics during sensorimotor integration in patients and healthy subjects

Repeated measures ANOVA for STDT percentage changes revealed a significant factor ISI ($F=59.4$, $p<0.00001$) and a significant GROUP $\times$ ISI interaction ($F=3.4$, $p=0.01$). STDT values during movement increased significantly in both groups, though to a slightly lesser extent in patients than in healthy subjects (patients: $F=25.9$, $p<0.001$; all p values for paired sample t test <0.001 ; healthy subjects: $F=36.8$, $p<0.0001$; all p values for paired sample t test <0.001) (Figure 1).

Repeated measures ANOVA for percentage changes in mean angular velocity of index finger abductions

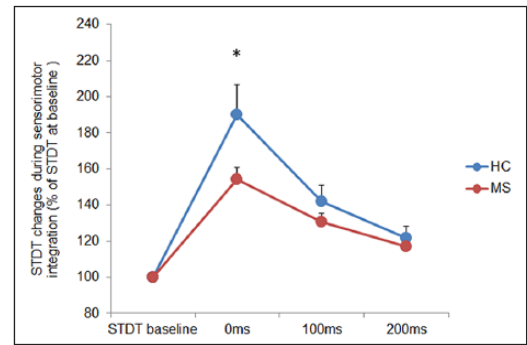


Figure 1. Movement-induced changes in somatosensory temporal discrimination threshold (STDT) values (expressed as percentage of STDT at baseline) at movement onset (0 ms), 100 ms and 200 ms afterwards in healthy subjects and in patients with multiple sclerosis. Bars represent standard error. Note that movement-induced STDT modulation was significantly reduced in patients in comparison to healthy subjects. Repeated measures ANOVA: factor ISI ($F=59.4$, $p<0.00001$) and GROUP $\times$ ISI interaction ($F=3.4$, $p=0.01$). Asterisk represents statistically significant between-groups difference.

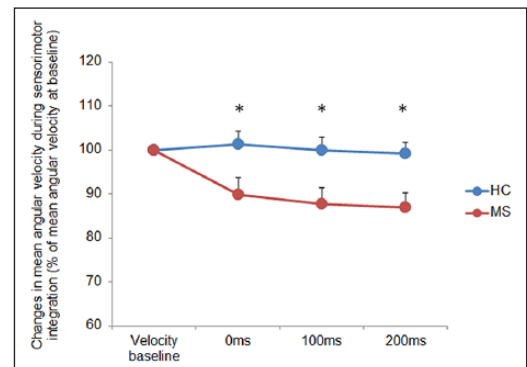


Figure 2. Changes in mean angular velocity of index finger abductions during somatosensory temporal discrimination threshold (STDT) testing in healthy subjects and in patients with multiple sclerosis. Bars represent standard error. Note that movement velocity significantly decreased in patients during STDT testing, whereas it remained substantially unchanged in healthy subjects. Repeated measures ANOVA: factor ISI ($F=2.99$, $p=0.03$), factor GROUP ($F=7.88$, $p=0.001$), GROUP $\times$ ISI interaction ($F=2.7$, $p=0.04$). Asterisk represents statistically significant between-groups difference.

during sensorimotor integration revealed a significant factor ISI ($F=2.99$, $p=0.03$), a significant factor GROUP ($F=7.88$, $p=0.001$) and a significant GROUP $\times$ ISI interaction ($F=2.7$, $p=0.04$). Mean angular velocity decreased significantly in patients ($F=4.52$, $p=0.005$), though not in healthy subjects, at all the time intervals tested (0 ms: $p=0.02$, 100 ms: $p=0.006$, 200 ms: $p=0.001$) (Figure 2).

Table 2. Volumes of subcortical GM structures.

	Multiple sclerosis	Healthy subjects	<i>p</i> ^a
Thalamus	9.710 (7.776)	10.046 (5.811)	0.04
Caudate nucleus	4.282 (3.401)	4.631 (3.962)	<0.001
Putamen	6.241 (5.651)	6.338 (5.375)	>0.05
Pallidum	2.122 (1.51)	2.247 (1.197)	<0.001

GM: grey matter.
Values are expressed in mL as mean (standard deviation).
^a*p* by Mann–Whitney *U* test. Bold indicates statistically significant values.

Table 3. DTI variables of subcortical GM structures.

	Multiple sclerosis	Healthy subjects	<i>p</i> ^a
Thalamus: FA	0.3377 (0.0780)	0.3673 (0.0367)	>0.05
Caudate nucleus: FA	0.2226 (0.0652)	0.2521 (0.0444)	>0.05
Putamen: FA	0.2810 (0.0675)	0.3092 (0.0311)	>0.05
Pallidum: FA	0.3743 (0.0935)	0.4308 (0.0322)	0.02
S1: FA	0.2312 (0.0249)	0.224 (0.0156)	>0.05
Thalamus: MD	9.60179 (0.19855)	8.5732 (0.48831)	0.04
Caudate nucleus: MD	9.86732 (2.77817)	9.62629 (1.10848)	>0.05
Putamen: MD	8.29489 (1.97353)	7.11754 (0.22201)	0.02
Pallidum: MD	7.78714 (2.44267)	6.59104 (0.45723)	0.04
S1: MD	9.9599 (5.590)	8.3477 (2.9355)	>0.05

DTI: diffusion tensor imaging; GM: grey matter; FA: fractional anisotropy; MD: mean diffusivity; S1: primary sensory cortex.
Values are expressed as mean (standard deviation); MD values are reported in mm²/s × 10⁻¹⁰.
^a*p* by Mann–Whitney *U* test. Bold indicates statistically significant values.

SEPs and MEPs

Of the 38 patients enrolled, only 9 had an increased cortical SEP component N20 latency (mean SEP latency 21.2 ± 3 ms), and only 8 had an increased MEP latency (mean MEP latency: 22.2 ± 3 ms) (Supplemental Material Table 1).

MRI findings

WM lesion load. Mean WM lesion volume was 5458.6 ± 4180.6 mm³ in the group of patients. No WM T2-FLAIR hyperintensities were detected in the group of healthy subjects.

Cortical thickness and volume. Two patients and two healthy subjects were excluded from the analysis owing to low GM-WM contrast, technical artefacts or volume outliers (>2 standard deviation). No significant differences in cortical thickness or in cortical volume were observed between patients and healthy subjects.

Subcortical structures volumes. Volumes of the subcortical GM structures are shown in Table 2. Volumes

of the thalamus, caudate nucleus and pallidum were significantly lower in patients than in healthy subjects ($p=0.04$, $p<0.001$, $p<0.001$, respectively). No other significant differences in subcortical volumes were detected between patients and controls.

Diffusion MR imaging. FA and MD values of the subcortical structures are shown in Table 3. Mean MD values were higher in the putamen ($p=0.02$), pallidum ($p=0.04$) and thalamus ($p=0.04$) in patients than in healthy subjects, while the mean FA in the pallidum was lower in patients than in healthy subjects ($p=0.02$). FA and MD values of primary sensory cortex were not different between patients and controls.

Correlations between neurophysiological and clinical variables

Pearson's correlation coefficient did not disclose any significant correlation among the neurophysiological parameters. By contrast, Spearman's correlation coefficient showed that STDT values at baseline significantly correlated with the EDSS score (Spearman correlation

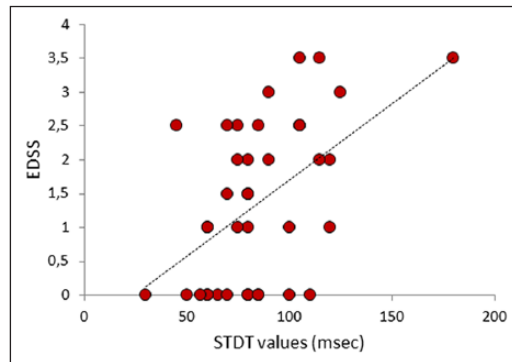


Figure 3. Relationship between somatosensory temporal discrimination threshold (STDT) values and Expanded Disability Severity Scale (EDSS) scores in patients with multiple sclerosis. Spearman's $\rho=0.5$, $p=0.001$.

coefficient=0.50, $p=0.001$; Figure 3) and, specifically, with the sensory subitem of the EDSS score (Spearman correlation coefficient=0.53, $p=0.001$). No other significant correlations were detected between the clinical and neurophysiological variables.

Linear regression analysis revealed that both percentage changes in STDT values during sensorimotor integration at movement onset and concomitant changes in mean angular velocity were significantly associated with FSS scores ($R=0.75$; $t=-4.4$, $p<0.0001$ and $t=3.3$, $p=0.002$, respectively).

Correlations between neurophysiological and neuroradiological variables

In MS patients, neurophysiological parameters (changes in STDT values and mean angular velocity) did not significantly correlate either with WM lesion load or with cortical thickness or volume in the primary sensory cortex.

STDT values at baseline significantly correlated with thalamic volume ($r=-0.47$, $p=0.003$; Figure 4). During sensorimotor integration, the mean angular velocity at the '100ms interval' trial significantly correlated with putaminal volume ($r=0.42$, $p=0.01$; Figure 5). Moreover, the percentage changes in mean angular velocity at the '0ms interval' trial inversely correlated with MD in the thalamus and pallidum (Pearson's correlation coefficient controlled for EDSS: $r=-0.44$, $p=0.008$ and $r=-0.40$, $p=0.01$, respectively).

In healthy subjects, correlation analysis disclosed no significant relationships between neurophysiological and neuroimaging measures.

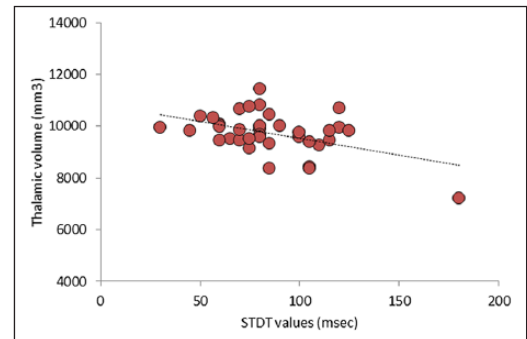


Figure 4. Relationship between somatosensory temporal discrimination threshold (STDT) values and thalamic volumes (expressed in mm^3) in patients with multiple sclerosis. Pearson's correlation test ($r=-0.47$, $p=0.003$).

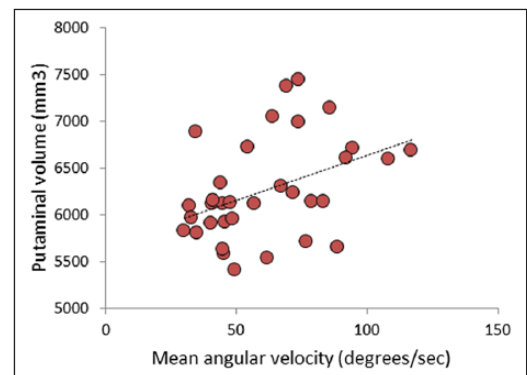


Figure 5. Relationship between mean angular velocity of index finger abductions during somatosensory temporal discrimination threshold testing and putaminal volumes (expressed in mm^3) in patients with multiple sclerosis. Pearson's correlation test ($r=0.42$, $p=0.01$).

Discussion

In this study, we observed an increased STDT and slower index finger movements in MS patients than in healthy subjects. We found a less marked STDT increase during index finger movement and a lower mean angular velocity in MS than in healthy subjects. These findings show that mechanisms of sensorimotor integration during upper limb movement execution are altered in patients with MS. Whereas STDT values were significantly related to the disability score, defective sensorimotor integration was associated with fatigue. STDT alterations and abnormal sensorimotor integration correlated with thalamic volume while the reduced movement velocity during sensorimotor integration correlated with both putaminal volume and ultrastructural damage to the putamen and nucleus pallidus. No correlation was found either between STDT changes and latencies of motor and sensory evoked potentials or between STDT changes

and WM lesion load and cortical thickness of the primary sensory cortex.

Since the order of the trials with the various time lapses between movement onset and paired stimuli for the STDT was randomized, we ruled out the possibility that changes in STDT values and in movement kinematics during sensorimotor integration depended on fluctuating attention levels. Moreover, as an altered cognitive profile or depression may interfere with the neurophysiological assessment, we excluded patients with even only one impaired cognitive domain¹⁶ as well as patients with a BDI score > 10. Since both groups were blinded to the time lapses between movement onset and paired stimuli for the STDT, we ruled out the possibility that the velocity of index finger movements in patients was reduced because the subjects expected the paired stimuli.

The novel finding of this study is that STDT modulation during voluntary finger movements is reduced and is associated with a slower motor performance in patients with MS. These findings point to an altered sensorimotor integration, which might be attributed to temporal dispersion along the central motor and sensory pathways caused by demyelination. This hypothesis is, however, unlikely since the SEP and MEP latencies were increased only in few of the patients in our sample, and we found no correlation between the STDT, mean velocity and SEP and MEP latency. Furthermore, the demyelinating lesion load in the WM did not correlate with changes in either the STDT or mean angular velocity during sensorimotor integration. Since changes in the STDT were unrelated to cortical thickness and cortical volume of the primary sensory cortex, we believe that although the sensory cortex is involved in determining STDT values,^{6,7} it does not play a key role in the STDT-related sensory gating.

One possible explanation for our results is based on the role of the basal ganglia in controlling sensory inputs, which is being increasingly acknowledged. In healthy subjects, the basal ganglia optimize movement parameters and gate irrelevant sensory information.^{5,9,21} Some authors have also identified the thalamic reticular nucleus as an important node between the basal ganglia and the cortex that regulates ascending and descending sensory input.²² The hypothesis we favour is that the altered mechanisms of sensorimotor integration and sensory gating we detected in patients with MS depend on subcortical GM damage and not on WM involvement. In keeping with this hypothesis, we found that STDT values correlated with thalamic volume and that mean angular

velocity of index finger abduction inversely correlated with putaminal volume and ultrastructural damage to the thalamus and nucleus pallidus. Our findings that the STDT and movement velocity changes correlated with MRI parameters of subcortical structures are also in line with previous observations showing that basal ganglia activation during movement execution reflects the velocity of movement, whereas cortical areas control the force and rate of movement.²³ In non-human primates, the movement-related discharge of pallidal neurons correlated with movement velocity^{24,25} and the disruption of normal basal ganglia outflow affected the speed of trained arm movements while preserving the accuracy of the movements.²⁶ In this vein of thought, basal ganglia damage may also be responsible for the slower movement velocity of index finger abductions we observed in patients at baseline.^{27–29} We cannot, however, rule out that slower motor performances at baseline in MS reflect impaired cortical plasticity mechanisms in primary motor cortex^{30,31} or an altered interplay between cortical and subcortical structures due to the disease-related diffuse chronic inflammatory environment.

A growing body of evidence has suggested the importance of GM damage in MS, which occurs independently of WM involvement.^{8,32} Subcortical GM involvement has been shown to be greater than cortical involvement in the early phase of the disease.³³ The abnormal sensorimotor integration we observed is in keeping with recent observations in MS,¹⁰ suggesting that the patients' inability to properly gate sensory activity may give rise to competition for the cortical resources required to generate motor action, thereby limiting motor performance during walking. Using our time-controlled paradigm, we now demonstrate that reduced sensory gating impairs movement performance to varying extents according to the time lapse between the sensory stimuli and movement onset.

Besides, we now suggest that altered sensorimotor integration may also explain fatigue. Fatigue is one of the most disabling symptoms reported in MS. Previous studies have suggested that fatigue may arise in patients with reduced cortical functional resources when concurrent neural processes compete due to disrupted brain networks. The correlation we found between STDT gating, the reduced mean velocity during sensorimotor integration task and fatigue suggests that mechanisms of altered sensorimotor integration may contribute to the pathophysiology of fatigue in MS.³⁴ Our findings are supported by those from MRI studies that did not find any association between fatigue and global brain damage measures

but rather pointed to the association of fatigue with regional damage, specifically of the deep GM, for example, the thalamus, even in patients with early MS.³⁵

Our study has some limitations. First, although the sample size is apparently small, it should be considered that patients who participated in the study underwent several assessments including neuroimaging, neurophysiological and clinical evaluation. Second, we specifically explored the structural and microstructural damage of both cortical and subcortical GM structures, while damage of WM was quantified by T2 lesion load alone. Further studies designed to explore alterations in both structural and functional connectivity between subcortical GM structures and the cortex may shed further light on this issue. Third, the fact that the majority of the patients were taking a range of disease-modifying therapies might have affected the results of the neurophysiological and clinical tests. Finally, fatigue was not measured objectively but was assessed by means of a self-administered scale, which is nonetheless the most widely used tool in both the clinical setting and research studies.

In conclusion, sensorimotor integration and sensory gating are altered in MS, which correlate with functional disability and with basal ganglia and thalamic volumes. These alterations may reflect pathophysiological mechanisms of motor impairment including fatigue. From a clinical perspective, our findings suggest that rehabilitation strategies should be applied from the earliest stages of the disease, even in patients with normal MEPs and SEPs, to compensate for reduced sensory gating mechanisms and optimize the availability of cortical resources during movement.

Declaration of Conflicting Interests

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Supplemental material

Supplemental material for this article is available online.

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