Deep grey matter involvement and altered sensory gating in multiple sclerosis

Antonella Conte, Costanza Giannì, 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

Date received: 11 January 2019; revised: 21 March 2019; accepted: 24 March 2019

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. 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. 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.

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. 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. 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.
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 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

| 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).
failure in one test if compared with the performance of the Italian population, 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 (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 (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. 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_dtfit.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, 0ms, 100ms and 200ms 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 ($84.2 \pm 24$ ms) than healthy subjects ($60 \pm 23$ 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: $73 \pm 31$ vs $99.4 \pm 31$ 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 × 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 during sensorimotor integration revealed a significant factor ISI ($F=2.99, p=0.03$), a significant factor GROUP ($F=7.88, p=0.001$), GROUP × 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).
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 coefficient not provided).
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 ‘100 ms 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 ‘0 ms 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.

**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...
related 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 suggest 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. In non-human primates, the movement-related discharge of pallidal neurons correlated with movement velocity and the disruption of normal basal ganglia outflow affected the speed of trained arm movements while preserving the accuracy of the movements. 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. We cannot, however, rule out that slower motor performances at baseline in MS reflect impaired cortical plasticity mechanisms in primary motor cortex 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. Subcortical GM involvement has been shown to be greater than cortical involvement in the early phase of the disease. The abnormal sensorimotor integration we observed is in keeping with recent observations in MS, 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. 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
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplemental material
Supplemental material for this article is available online.

ORCID iDs
Antonio Cortese https://orcid.org/0000-0003-0803-0004
Nikolaos Petsas https://orcid.org/0000-0001-7150-9697

References
1. Abbuzzese G and Berardelli A. Sensorimotor integration in movement disorders. Mov Disord 2003; 18(3): 231–240.
2. Tomassini A, Gori M, Burr D, et al. Active movement restores veridical event-timing after tactile adaptation. J Neurophysiol 2012; 108(8): 2092–2100.
3. Juravle G, Heed T, Spence C, et al. Neural correlates of tactile perception during pre-, peri-, and post-movement. Exp Brain Res 2016; 234(5): 1293–1305.
4. Rocchi L, Casula E, Tocco P, et al. Somatosensory temporal discrimination threshold involves inhibitory mechanisms in the primary somatosensory area. J Neurosci 2016; 36(2): 325–335.
5. Conte A, Belvisi D, DeBartolo MI, et al. Abnormal sensory gating in patients with different types of focal dystonias. Mov Disord 2018; 33: 1910–1917.
6. Conte A, McGovern EM, Narasimham S, et al. Temporal discrimination: Mechanisms and relevance to adult-onset dystonia. Front Neurol 2017; 8: 625.
7. Rocchi L, Conte A, Bologna M, et al. Somatosensory temporal discrimination threshold is impaired in patients with multiple sclerosis. Clin Neurophysiol 2016; 127(4): 1940–1941.
8. Eshaghi A, Marinescu RV, Young AL, et al. Progression of regional grey matter atrophy in multiple sclerosis. Brain J Neurol 2018; 141(6): 1665–1677.
9. Conte A, Belvisi D, Manzo N, et al. Understanding the link between somatosensory temporal discrimination and movement execution in healthy subjects. Physiol Rep 2016; 4(18): e12899.
10. Arpin DJ, Gehringer JE, Wilson TW, et al. A reduced somatosensory gating response in individuals with multiple sclerosis is related to walking impairment. J Neurophysiol 2017; 118(4): 2052–2058.
11. Crivelli D, Pedulla L, Bisio A, et al. When ‘extraneous’ becomes ‘mine’. neurophysiological evidence of sensorimotor integration during observation of suboptimal movement patterns performed by people with multiple sclerosis. Neuroscience 2018; 386: 326–338.
12. Fischer JS, Rudick RA, Cutter GR, et al. The Multiple Sclerosis Functional Composite Measure (MSFC): An integrated approach to MS clinical outcome assessment. Mult Scler 1999; 5(4): 244–250.
13. Krupp LB, LaRocca NG, Muir-Nash J, et al. The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol 1989; 46(10): 1121–1123.
14. Boringa JB, Lazeron RH, Reuling IE, et al. The brief repeatable battery of neuropsychological tests:
15. Beck AT, Steer RA, Ball R, et al. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996; 67(3): 588–597.

16. Amato MP, Portaccio E, Goretti B, et al. The Rao’s Brief Repeatable Battery and Stroop Test: Normative values with age, education and gender corrections in an Italian population. *Mult Scler* 2006; 12(6): 787–793.

17. LiVoti P, Conte A, Rocchi L, et al. Cerebellar continuous theta-burst stimulation affects motor learning of voluntary arm movements in humans. *Eur J Neurosci* 2014; 39(1): 124–131.

18. Bologna M, Rocchi L, Paparella G, et al. Reversal of practice-related effects on corticospinal excitability has no immediate effect on behavioral outcome. *Brain Stimul* 2015; 8(3): 603–612.

19. Conte A, Rocchi L, Nardella A, et al. Theta-burst stimulation-induced plasticity over primary somatosensory cortex changes somatosensory temporal discrimination in healthy humans. *PLoS ONE* 2012; 7(3): e32979.

20. Colder B. The basal ganglia select the expected sensory input used for predictive coding. *Front Comput Neurosci* 2015; 9: 119.

21. Hintzen A, Pelzer EA and Tittgemeyer M. Thalamic interactions of cerebellum and basal ganglia. *Brain Struct Funct* 2018; 223(2): 569–587.

22. Sadato N, Yonekura Y, Waki A, et al. Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. *J Neurosci* 1997; 17(24): 9667–9674.

23. Brotchie P, Iansel R and Horne MK. Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. *Brain* 1991; 114(Pt4): 1685–1702.

24. Turner RS, Grafton ST, Votaw JR, et al. Motor subcircuits mediating the control of movement velocity: A PET study. *J Neurophysiol* 1998; 80(4): 2162–2176.

25. Mink JW and Thach WT. Basal ganglia motor control. III. Pallidal ablation: Normal reaction time, muscle cocontraction, and slow movement. *J Neurophysiol* 1991; 65(2): 330–351.

26. Berardelli A, Rothwell JC, Thompson PD, et al. Pathophysiology of bradykinesia in Parkinson’s disease. *Brain J. Neurol* 2001; 124(Pt 11): 2131–2146.

27. Michely J, Volz LJ, Barbe MT, et al. Dopaminergic modulation of motor network dynamics in Parkinson’s disease. *Brain* 2015; 138(Pt 3): 664–678.

28. Bologna M, Leodori G, Stirpe P, et al. Bradykinesia in early and advanced Parkinson’s disease. *J Neurol Sci* 2016; 369: 286–291.

29. Mori F, Kusayanagi H, Nicoletti CG, et al. Cortical plasticity predicts recovery from relapse in multiple sclerosis. *Mult Scler* 2014; 20(4): 451–457.

30. Conte A, LiVoti P, Pontecorvo S, et al. Attention-related changes in short-term cortical plasticity help to explain fatigue in multiple sclerosis. *Mult Scler* 2016; 22(10): 1359–1366.

31. Conte A, LiVoti P, Pontecorvo S, et al. Attention-related changes in short-term cortical plasticity help to explain fatigue in multiple sclerosis. *Mult Scler* 2016; 22(10): 1359–1366.

32. Azevedo CJ, Cen SY, Khadka S, et al. Thalamic atrophy in multiple sclerosis: A magnetic resonance imaging marker of neurodegeneration throughout disease. *Ann Neurol* 2018; 83(2): 223–234.

33. Zivadinov R, Havrdova E, Bergsland N, et al. Thalamic atrophy is associated with development of clinically definite multiple sclerosis. *Radiology* 2013; 268(3): 831–841.

34. Finke C, Schlichting J, Papazoglou S, et al. Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. *Mult Scler* 2015; 21(7): 925–934.

35. Nourbakhsh B, Azevedo C, Nunan-Saah J, et al. Longitudinal associations between brain structural changes and fatigue in early MS. *Mult Scler Relat Disord* 2016; 5: 29–33.