Amato et al. Multiple Sclerosis and Demyelinating Disorders (2016) 1:8
DOI 10.1186/s40893-016-0007-x

Multiple Sclerosis and Demyelinating Disorders

RESEARCH ARTICLE Open Access

Stroop event-related potentials as a bioelectrical correlate of frontal lobe dysfunction in multiple sclerosis

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Abstract

Background: Dysfunction of higher cognitive abilities occurs in 40–60 % of people with multiple sclerosis (MS), as detected with neuropsychological testing, with predominant involvement of executive functions and processing speed. Event-related potentials to the Stroop are a bioelectrical correlate of executive function. We tested whether event-related potentials to the executive Stroop test may reflect executive dysfunction in MS.

Methods: 29 MS patients (M/F:14/15; mean age 40 ± 8), and 16 healthy control subjects were included in the study (M/F:7/9; mean age 36 ± 10). Patients underwent a neuropsychological battery and, according to the performance obtained, they were divided in two groups: 13 frontal patients (F-MS; M/F:6/7; mean age: 40 ± 8) and 16 non frontal patients (NF-MS; M/F:8/8; mean age: 41 ± 7). Simple and complex reaction times to the Stroop task were measured using a computerized system. Event-Related Potentials (ERPs) to the same stimuli were obtained from 29 channel EEG, during mental discrimination between congruent and incongruent stimuli. Multivariate analysis was performed on reaction times (RTs) and ERPs latencies; topographic differences were searched with low resolution brain electromagnetic tomography (LORETA).

Results: Significant group effects were found on the percentage of correct responses: F-MS subjects committed more errors than the other two groups. F-MS patients showed delayed P3 and N4 compared to NF-MS patients and delayed P2, N2, P3 and N4 compared to controls. NF-MS subjects showed significantly slower P2, N2 and P3 compared to control subjects. Moreover, frontal score correlated negatively with ERPs' latency and with complex RTs. At source analysis F-MS patients presented significantly reduced activation predominantly over frontal, cingulate and parietal regions.

Conclusions: Taken together, these findings suggest that bioelectrical activity to the Stroop test may well reflect the speed and extent of neural synchronization of frontal circuits. Further studies are needed to evaluate the usefulness of Stroop reaction times and ERPs for detecting frontal involvement early at a subclinical stage, allowing early cognitive therapy, and as a paraclinical marker for monitoring treatment outcomes.

Keywords: MS, Executive function, Stroop task, ERPs, Source analysis

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Background

Cognitive dysfunction is a common finding in multiple sclerosis (MS), being reported in 40–60 % of all patients [18, 58, 62], typically consisting of deficits in attention, memory, executive functions and speed of information processing. This pattern of dysfunctions resembles that typical of subcortical dementia and is considered as mostly dependent on the disruption of connections between cortical associative areas, related to demyelination and/or axonal loss within the white matter immediately underlying the cortex [39].

Several neuroimaging studies investigated these deficits in MS patients trying to establish a relationship to lesion load as detected on MRI; some of these studies proposed that cognitive impairment is better explained by cortical structural abnormalities rather than subcortical white matter lesions [13, 14, 59], other recent studies instead, which compared the role of cortical lesions and white matter lesions in the development of cognitive impairments in MS, documented a higher role of white matter integrity changes than previously assumed [50].

During performance of cognitive tasks, a greater extent of brain activation has been reported in patients compared to healthy subjects, [6, 44, 64] indicating cortical reorganization possibly owing to compensatory mechanisms. Moreover, MS patients with mild cognitive impairment presented increased and additional activation during attention tasks compared to controls, while MS patients with severe cognitive impairments presented no additional activation [53]. These findings suggest that the compensation depends on the possibility to access additional brain structures and the exhaustion of these resources would determine severe cognitive impairment.

Electrophysiological studies have widely examined cognitive dysfunction in MS patients. Coherence analysis is a useful indicator of functional connections between different cortical areas [39], which are disrupted in multiple sclerosis. Cognitive impaired MS patients had a significant increase of theta power over the frontal regions [39] as well as an increase in beta and gamma bends [69] and a diffuse coherence decrease [19, 39].

Event Related Potentials (ERPs) are among the most suitable electrophysiological methods to examine processing speed, which appears to be the most common cognitive deficit in MS [8, 20]. Delayed latency and decreased amplitude of the main ERPs components, particularly of the P3 to oddball paradigm, representing the discrimination of stimuli differing in some physical dimension and whose latency reflects processing speed [36], have been reported in MS [38, 42]. Delayed P3 is associated with higher EDSS scores [22, 67], disease duration [25], low performance on attention and memory tasks and total MRI lesion burden [30, 49, 63]. Previous neuroimaging and neuropsychological studies pointed out the need for early detection of cognitive impairment in MS [1, 46], possibly at the subclinical level. ERPs could be particularly helpful in the early recognition of cognitive dysfunction and have been already successfully used to this end [43]. However, the oddball task, used to evoke P3, is not specifically challenging executive function, which is generally a key feature of cognitive involvement observed in MS [5, 16, 17, 21, 47, 57]. Among the cognitive tests which are suitable for ERPs analysis, the Stroop test [65] can be a good candidate and has been already applied in the study of executive functions in MS patients, in healthy subjects and in other neuropsychiatric disorders [4, 16, 32, 37, 71]. Cognitive control and flexibility are the most impaired in MS among executive functions [16], and the Stroop task is particularly suitable to detect deficits in these components of executive function [26]. We aimed at investigating the electrophysiological correlates of executive dysfunction in MS using ERPs to Stroop stimuli in persons with MS with and without executive dysfunction. As a performance correlate of the ERP task, reaction times to Stroop stimuli were measured.

Methods

Subjects

Twenty-nine patients (15 females; mean age 40 ± 8) with clinically definite multiple sclerosis according to McDonald criteria [45, 55, 56], and 16 healthy controls (9 females; mean age 36 ± 10) were included in the study. Patients with Expanded disability status scale [35] higher than 6.5 or with severe cognitive, motor or visual impairment interfering with task compliance, as well as with steroid or psychoactive drug treatment in the previous 3 months days were excluded from the study. The protocol was approved by the Institutional Ethics Committee at the Hospital San Raffaele and all subjects gave their written informed consent for participation.

Prior to the beginning of the study, patients underwent a neuropsychological battery including: Stroop test [65], Tower of Hanoi [29], Dual task [48], Wisconsin Card Sorting [7, 73], semantic and fonemic verbal fluency tests. According to their performance on these tests, a "frontal score" was assigned to each patient, who were subdivided in two groups: 13 frontal patients (F-MS; 7 females, mean age 40 ± 8 years) and 16 non frontal patients (NF-MS; 8 females, mean age: 41 ± 7).

Computerized Stroop Performance

Reaction times (RTs) in the Stroop task were measured using a computerized version implemented in commercial STIM software (Neuroscan, Herndon, VA, USA). Responses were recorded using a computer mouse with two response buttons. Four colour words (green, red, yellow, and blue) written in congruent (50 %) or incongruent

(50 %) colour were randomly presented (stimulus duration, 200 ms; intertrial interval, 3.5 s) in four different series of 32 stimuli each.

In the first condition (simple RT - SRT), the subjects had to press a button for every stimulus presentation, regardless of stimulus type. The second condition (go/no-go RT) consisted of two series, in which a response was required to either the incongruent (go/no-go I) or congruent (go/no-go C) stimuli. In the third condition (choice RT), the subjects had to press one button after the congruent stimuli (choice C) and the other button after the incongruent stimuli (choice I). For each series, the response latency was measured only for correct responses. Trials with latencies that exceeded 2.3 s were considered omissions and excluded from the calculation of average RTs and accuracy. The latter was calculated in the complex RTs (go/no-go and choice) as the percentage of correct responses.

Event-related potential recording

Twenty-nine EEG channels with binaural reference were recorded using scalp electrodes set on an elastic cap (Electrocap International, Eaton, OH, USA). The EEG signal was amplified (Synamps, Neuroscan, Herndon, VA, USA), filtered (DC–50 Hz), and digitized (sampling frequency, 250 Hz). The electrooculogram and electromyogram of the right and left extensor pollicis brevis were also recorded to detect eye movements and relaxation failure.

A series of 120 of the same Stroop stimuli (stimulus duration, 200 ms; intertrial interval, 6 s) used for the RT measurement were presented using the same computerized version implemented in commercial STIM software (Neuroscan, Herndon, VA, USA). The subjects were instructed to mentally discriminate between congruent and incongruent stimuli. This condition was chosen for ERP recording to avoid movement interference. Attention was monitored every 10–15 trials by randomly asking subjects to verbally define the congruency of the last stimulus presented. Recordings were performed in the morning (8:30–10:00 a.m.) to reduce variability due to circadian fluctuations.

Event-related potential analysis

Epochs from −500 to 1200 ms from stimulus onset were obtained. Linear detrending was performed over the entire epoch to correct for DC drifts. The baseline was then corrected between −500 and 0 ms. Epochs that contained artefacts or muscle relaxation failure upon visual inspection were excluded from the analysis. Initially, separate averages were obtained for congruent and incongruent stimuli. After a preliminary comparison between and within groups, which did not show significant differences between the parameters obtained in the two conditions, data from the congruent and incongruent trials were collapsed into a single ERP for each subject to reduce signal noise.

The latency of the main ERP components (i.e., N1 [O1 or O2 electrode], P2, N2, P3 and N4 [Fz electrode]) was measured for each subject. The amplitude and topographic analysis was performed at time intervals of the same components (time intervals = group mean latency value of each component ± 30 ms) using low-resolution brain electromagnetic tomography (LORETA; [51, 52]; see *Statistical analysis* section below).

Statistical analysis

The significance of group effects with regard to the number of correct responses (in the choice condition, go/no-go C condition, and go/no-go I condition), RT latency in the choice C condition, choice I condition, go/no-go C condition, go/no-go I condition, and simple RT condition, and latency of the main ERP components (N1, P2, N2, P3 and N4) was tested using three separate multivariate analyses of variance (MANOVAs). *Post hoc* tests were performed using Bonferroni correction. Correlations between frontal score and RTs and between frontal score and ERP latencies were also performed using Spearman's coefficient. All of the statistical tests were performed using SPSS 17 software (Technologies, Chicago, IL, USA). Group differences in the amplitude and topography of ERP waveforms were investigated using LORETA with a statistical nonparametric voxel-wise comparison between the F-MS, NF-MS and control groups. The level of significance was set at $p < 0.05$.

Results

Stroop RTs

Significant group effects were found on the percentage of correct responses (Fig. 1) at MANOVA ($p = 0.001$): in

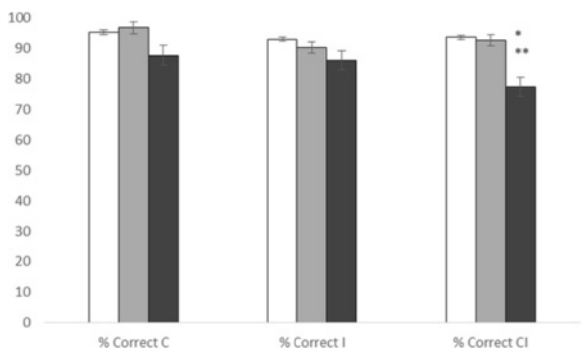

Fig. 1 Percentage of correct responses in the choice condition, the go/no-go condition and the simple reaction time condition, in controls (white), NF-MS (grey) and F-MS (black). F-MS vs CNT: * $p = 0.001$; F-MS vs NF-MS ** $p = 0.001$. Line bars over each column indicate standard error

the choice condition F-MS patients committed significantly more errors than controls ($p = 0.001$) and NF-MS patients ($p = 0.001$).

There were no significant group effects on RTs at MANOVA.

ERPs latency

Significant group effect was found (Fig. 2) at MANOVA ($F = 21.699$; $p = 0.000$); F-MS patients showed significantly delayed P2, N2, P3 and N4 latencies compared to controls (P2: $p = 0.000$; N2: $p = 0.001$; P3: $p = 0.000$; N4: $p = 0.000$) and P3 and N4 latencies compared to NF-MS patients (P3: $p = 0.015$; N4: $p = 0.000$). NF-MS patients showed significantly delayed P2, N2 and P3 latencies compared to controls (P2: $p = 0.007$; N2: $p = 0.021$; P3: $p = 0.033$).

Correlations

There was a negative correlation between frontal score and N1 latency ($\rho = -0.426$, $p = 0.024$), P2 latency ($\rho = -0.643$, $p = 0.000$) and N4 latency ($\rho = -0.566$, $p = 0.002$). Moreover, frontal score correlated negatively with RTs speed in the go/no-go I condition ($\rho = -0.425$, $p = 0.022$) and in the choice C condition ($\rho = -0.381$, $p = 0.042$) (Fig. 3), and correlated positively with the percentage of correct responses in the go/no-go C condition ($\rho = 0.431$, $p = 0.019$) and in the choice condition ($\rho = 0.550$, $p = 0.002$) (Fig. 4).

ERPs amplitude and topography

LORETA statistical non-parametric voxel-wise analysis revealed significant group differences. In the N1 time window (time interval = group mean N1 latency value ± 20 ms), the F-MS group, compared to the other two groups, had a significantly reduced activation of the right supramarginal gyrus, the right inferior parietal lobule, the right middle and inferior temporal gyri and the superior and middle frontal gyri (Figs. 5 and 6). In the P2 time window (time interval = group mean P2 latency value ± 20 ms), there were not significant differences between groups. In the N2 time window (time interval = group mean N2 latency value ± 20 ms), F-MS patients showed a significantly decreased activity in the cingulate gyrus and in the parahippocampal gyrus compared to NF-MS patients (Fig. 7) but not significant differences compared to control subjects; significance was reached vs NF-MS and not *vs* controls, owing to a slight non significant increase in activation in NF-MS vs controls. In the P3 time window (time interval = group mean P3 latency value ± 20 ms), F-MS group presented a reduced activity reaching significance vs controls in the superior and medial frontal gyri, the cingulate gyrus, the precuneus and the precentral lobule (Fig. 8) and vs NF-MS in the anterior cingulate, the medial frontal gyrus and the cingulate gyrus (Fig. 9). In the N4 time window (time interval = group mean N4 latency value ± 20 ms), F-MS patients showed a significant decreased activity compared to healthy subjects in the cingulate gyrus, the paracentral lobule and the precuneus (Fig. 10).

Discussion

Compared to NF-MS patients and control subjects, our sample of F-MS patients showed delayed ERPs' latencies, reduced frontoparietal activity and less accuracy in the execution of the Stroop task. Moreover, frontal score correlated negatively with ERPs' latency and with complex RTs. These findings are discussed in details below.

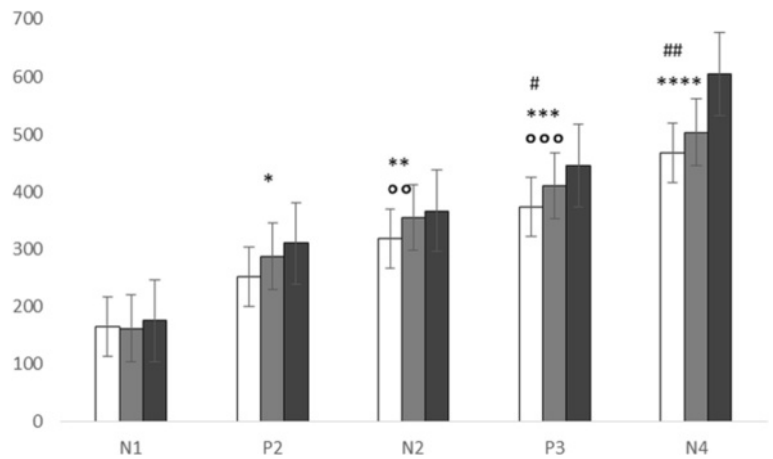

Fig. 2 N1, N2, P3, N4 and P6 latencies in CNT subjects (white), NF-MS patients (grey) and F-MS patients (black). F-MS vs CNT: $_{*}$ $p = 0.000$; $_{**}$ $p = 0.001$; $_{***}$ $p = 0.000$; $_{****}$ $p = 0.000$. F-MS vs NF-MS: $_{\#}$ $p = 0.015$; $_{\#\#}$ $p = 0.000$. NF-MS vs CNT: $_{\circ}$ $p = 0.007$; $_{\infty}$ $p = 0.021$; $_{\infty\infty}$ $p = 0.033$. Line bars over each column indicate standard error

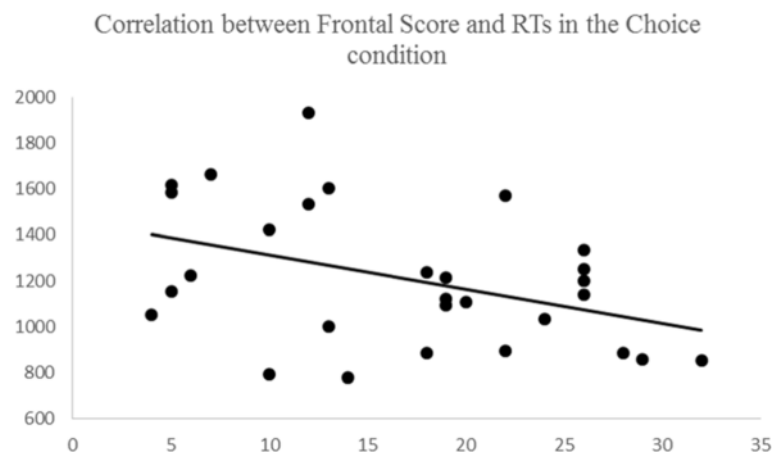

Fig. 3 Correlation between Frontal Score and RTs in the Choice condition ($\rho = -0.381$, $p = 0.042$)

RTs

The lower level of accuracy observed in frontal patients compared with the other two groups, but not in non frontal patients compared with controls, suggests an impairment, in the first group, of conflict monitoring function, necessary to process competing information and select the adequate response, reported to be mediated by frontal structures as the anterior cingulate cortex [10, 12]. Moreover, accuracy and speed in the complex tasks were correlated with frontal score obtained from neuropsychological assessment. Overall, these findings suggest that computerized RTs may provide useful measures for the assessment of executive functions in these patients. Although a learning effect may have certainly occurred during RTs measurements, the tasks were performed in a sequence with increasing difficulty. This choice was made to facilitate learning as much as possible for the subsequent ERPs recordings, to minimize an additional source of between-subject variability across RT tasks and to limit the number of RT exclusions due to errors. However, this methodological choice could not allow us to avoid two possible confounding factors. One is learning itself: subjects with MS-related learning impairment could present slower learning and therefore higher impairment in the most complex tasks because these were performed later, favoring the subjects with faster learning. The second is cognitive fatigue, defined as performance decay with test repetition and reported to affect MS patients to a greater extent than healthy controls [34, 41]. However, performance at the computerized RTs was more impaired in frontal compared with non frontal MS patients and correlated with the frontal score, suggesting that this tools reflects, at least partially, the severity of frontal involvement. To further interpret our findings more studies are needed specifically addressing the issues of whether this impairment is a direct correlate of executive function or it is at least partly mediated by learning difficulties or cognitive fatigue. In any case, both learning difficulties and cognitive fatigue may well represent other correlate of frontal dysfunction,

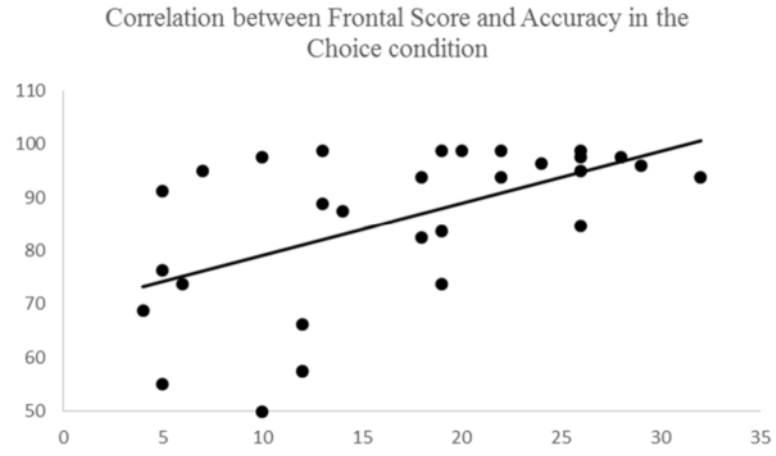

Fig. 4 Correlation between Frontal Score and percentage of correct responses in the Choice condition ($\rho = 0.550$, $p = 0.002$

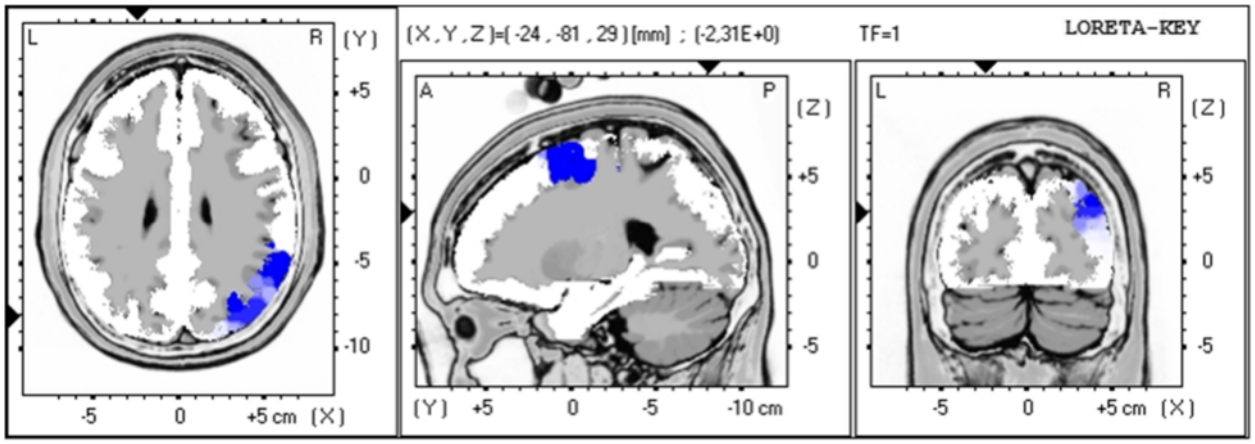

Fig. 5 LORETA non-parametric voxel-wise comparison map between F-MS and controls in the N1 time window. Blue: regions of significant decreased activity in F-MS

needing more work to disentangle the relative contribution of these factors to our findings.

ERPs latency

ERPs latencies were significantly increased in both patients groups compared with controls and in the F-MS group compared to NF-MS group. This finding is consistent with previous studies widely documenting cognitive ERPs latencies' delay in multiple sclerosis [3, 28, 72].

This delay was significant for all components measured but the earliest (N1). This result suggests that in our sample of patients visual discrimination processes, as reflected by the posterior N1 component, were not delayed and that the cognitive ERPs latencies' delay observed cannot be explained only in term of impaired information processing speed since in this case we would have observed a delay also at this earlier level of information processing.

These latter findings point out to the possibility that bioelectrical activity to the Stroop stimuli, particularly the later component, may well reflect the speed of neural synchronization of frontal lobe circuits, being especially involved in patients with frontal dysfunction.

ERPs amplitude and topography

LORETA topographic ERPs analysis showed reduced activity in the N1, N2, P3 and N4 time windows mostly over the frontal, cingulate and parietal regions evident in frontal MS patients compared with controls and with non frontal patients.

N1 is assumed to reflect selective attention to basic stimulus characteristics, initial selection for later pattern recognition, and intentional discrimination processing [70]. Its source is located in the inferior occipital lobe, occipito-temporal junction [31], and inferior temporal lobe [9]. Since the discrimination process, reflected by

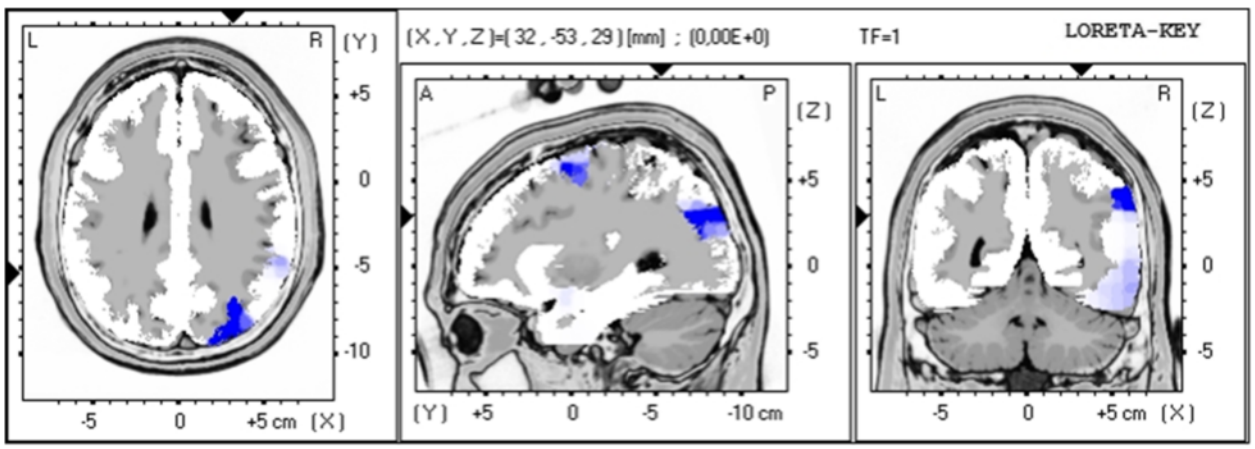

Fig. 6 LORETA non-parametric voxel-wise comparison map between F-MS and NF-MS in the N1 time window. Blue: regions of significant decreased activity in NF-MS

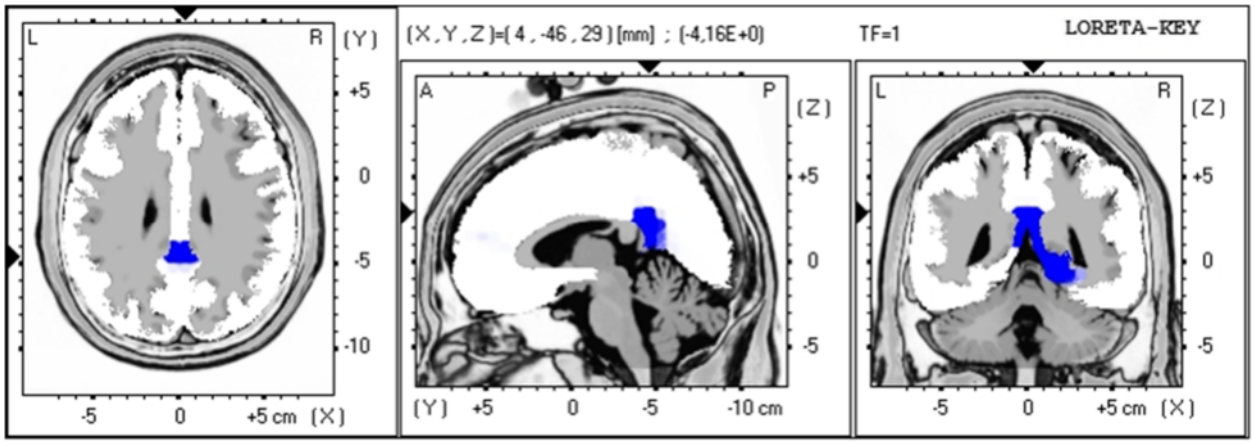

Fig. 7 LORETA non-parametric voxel-wise comparison map between F-MS and NF-MS in the N2 time window. Blue: regions of significant decreased activity in NF-MS

occipito-temporal N1, can be modulated by top-down executive control (the greater the difficulty of stimulus discrimination, the greater the need of top-down executive control modulation and therefore the greater the amplitude of the N1 component, cfr. [23]), the significant reduced activity observed here in the N1 time window in F-MS patients compared to both the other two groups, could be determined by executive control deficits in these patients: control and NF-MS groups would show a greater N1 amplitude, with respect to F-MS group, as a consequence of executive control modulation, which is instead lacking in frontal patients.

The N2 component in go/no-go-like tasks has been attributed to response inhibition mechanisms [27, 33]. However, the N2 component has also been reported to occur in relation to covert responses in the present study and in previous studies [2, 54]. This would indicate that it is not completely attributable to the inhibition of responses and that it may at least partially account for conflict monitoring. N2 is especially pronounced over the fronto-central electrodes and has been proposed to reflect ACC sensitivity to conflict [68].

The P3 component is elicited in tasks related to stimulus differentiation and appears when a memory representation of the recent stimulus context is updated upon the detection of deviance from it [66]. The frontal P300 component in go/no-go-like tasks has been associated with an inhibitory mechanism [24]. However, in the present study, the subjects only had to mentally discriminate between congruent and incongruent stimuli; therefore, conflict did not arise at the response level. Thus, the P3 component observed herein most likely reflects the detection of conflict that arose at the level of the semantic encode.

The N4 component to the Stroop task is supposed to reflect anterior cingulate activity [40], which has been

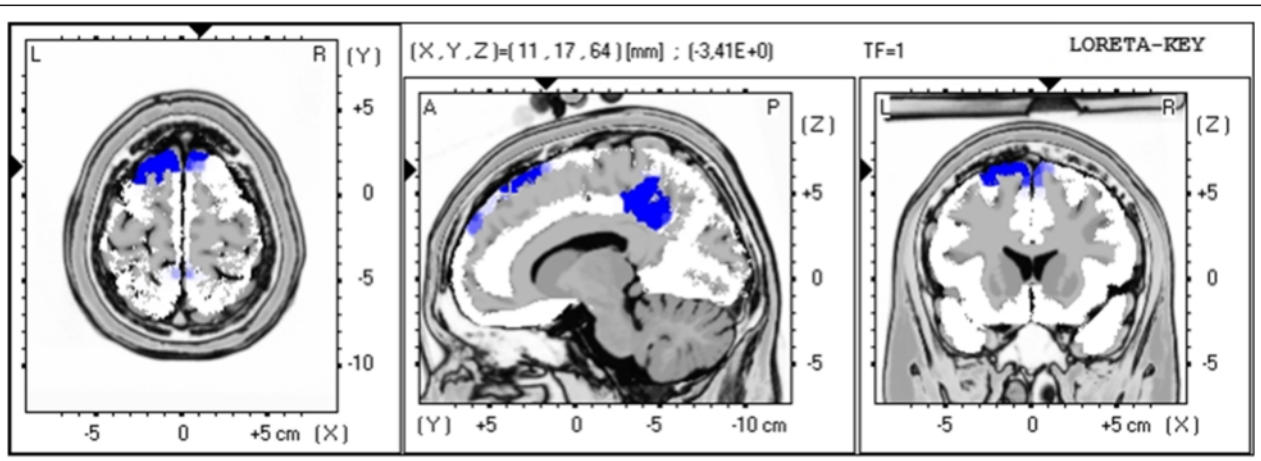

Fig. 8 LORETA Non-parametric voxel-wise comparison map between F-MS and controls in the P3 time window. Blue: regions of significant decreased activity in F-MS

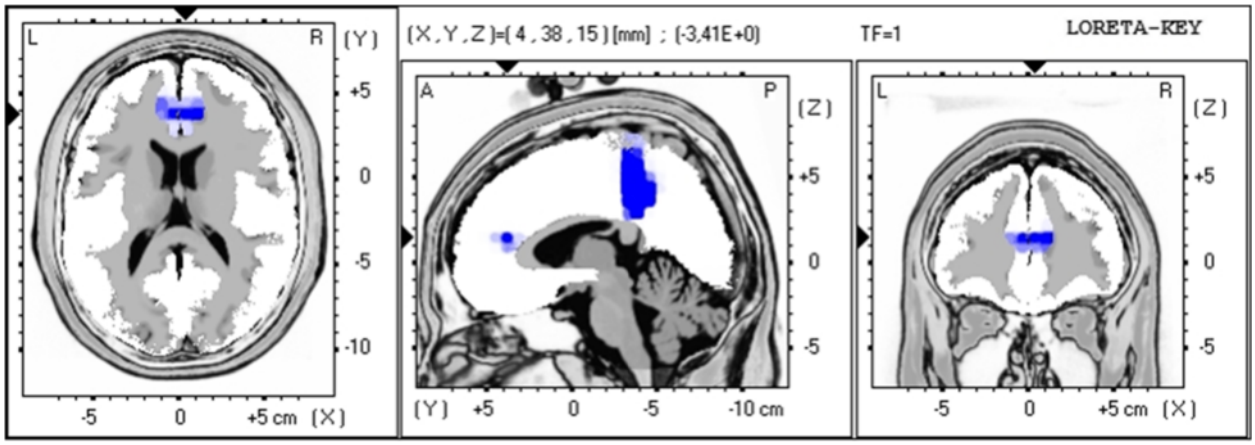

Fig. 9 Non-parametric voxel-wise comparison map between F-MS and NF-MS in the P3 time window. Blue: regions of significant decreased activity in F-MS

widely documented to account for conflict monitoring function and for triggering compensatory adjustment in cognitive control [11, 15, 27].

Taken together these findings reflect cognitive control impairment in frontal involved MS patients.

Previous functional neuroimaging studies to Stroop task [60, 61] showed a greater activation in MS subjects compared with healthy controls in several areas involved in the task execution, which resulted hypo-activated herein in cognitive impaired patients. These findings are only apparently inconsistent; in the studies by Rocca et al., in fact the increase in activation in MS patients, which, although not significant, was reported to occur also herein in NF-MS patients, seems to reflect compensatory mechanisms granting a normal performance, whereas our sample of patients with frontal involvement seems to be too compromised to compensate and just presented reduced activation accompanied by impaired performance at complex tasks. Compensatory mechanisms depend on the possibility to access additional brain structures and the exhaustion of these resources seems to determine severe cognitive impairment, as documented elsewhere [53].

Conclusion

Our finding of decreased accuracy in frontal involved MS group suggests that this approach may provide useful objective measures for the assessment of executive functions in these patients. Topographic analysis of ERPs components to the Stroop stimuli showed predominant involvement of frontal, cingulate and parietal regions, probably reflecting the executive stage of stimulus processing. Also the latency of these components correlated with neuropsychological frontal score. Taken together, these findings suggest that bioelectrical activity to the Stroop test may well reflect the speed and extent of

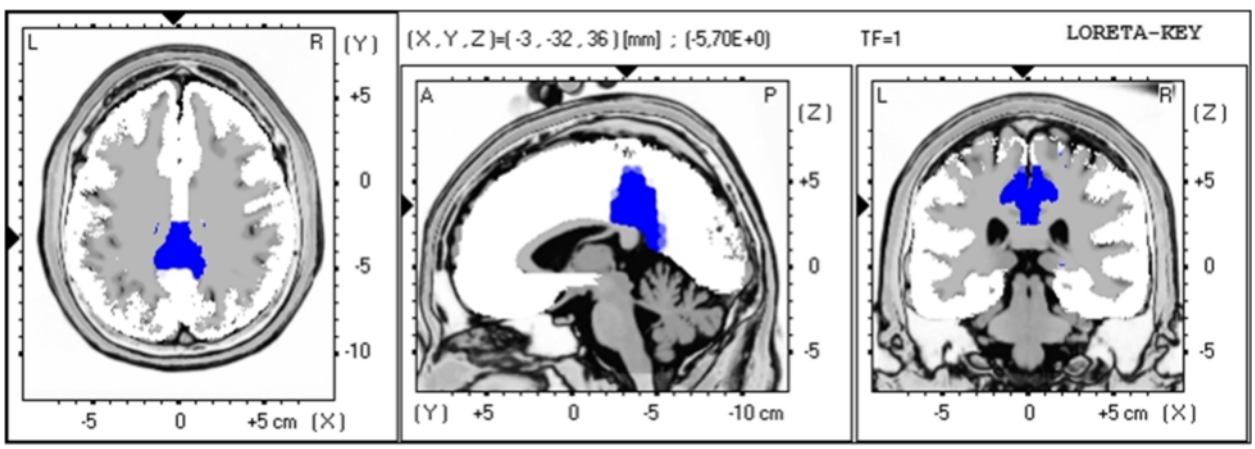

Fig. 10 Non-parametric voxel-wise comparison map between F-MS and controls in the N4 time window. Blue: regions of significant decreased activity in F-MS

neural synchronization of frontal circuits. Further studies are needed to evaluate the usefulness of Stroop reaction times and ERPs for detecting frontal involvement early at a subclinical stage, allowing early cognitive therapy, and as a paraclinical marker for monitoring treatment outcomes.

Competing interests
The authors declare that they have no competing interests.

Authors'contribution
NA data and statistical analysis and interpretation, manuscript draft and revision. MC supervision of source localization, manuscript revision. MR patients recruitment and clinical assessments, manuscript revision. LM patients recruitment and clinical assessments, manuscript revision. BC, patients recruitment and clinical assessments, manuscript revision. MF neuropsychological assessments, manuscript revision. FP neuropsychological assessments, manuscript revision. GC supervision to clinical and neuropsychological assessment, manuscript revision. VM supervision to clinical and neuropsychological assessment, manuscript revision. LL study design, supervision to data collection and analysis, manuscript revision. All authors read and approved the final manuscript.

Acknowledgements
The authors wish to thank A. Nossa, EEG technician, for EEG recordings.

Received: 5 September 2015 Accepted: 18 March 2016
Published online: 01 May 2016

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