

Multimodal evoked potentials to assess the evolution of multiple sclerosis: a longitudinal study

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J Neurol Neurosurg Psychiatry 2006;77:1030–1035. doi: 10.1136/jnnp.2005.086280

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Received 13 December 2005
Revised version received 19 April 2006
Accepted 27 April 2006
Published Online First 30 May 2006

Background: Evoked potentials are used in the functional assessment of sensory and motor pathways. Their usefulness in monitoring the evolution of multiple sclerosis has not been fully clarified.

Objective: The aim of this longitudinal study was to examine the usefulness of multimodal evoked potential in predicting paraclinical outcomes of disease severity and as a prognostic marker in multiple sclerosis.

Methods: Eighty four patients with clinically definite multiple sclerosis underwent Expanded Disability Status Scale (EDSS) and functional system scoring at study entry and after a mean (standard deviation) follow-up of 30.5 (11.7) months. Sensory and motor evoked potentials were obtained in all patients at study entry and at follow-up in 64 of them, and quantified according to a conventional score.

Results: Cross-sectionally, the severity of each evoked potential score significantly correlated with the corresponding functional system ($0.32 < R < 0.60$, $p < 0.01$, for all but follow-up visual evoked potential) and with EDSS ($0.34 < R < 0.61$; $p < 0.001$ for all but brain stem evoked potential). EDSS significantly correlated with global evoked potential score severity (baseline $R = 0.60$, follow-up $R = 0.46$, $p < 0.001$). Using longitudinal analysis, only changes in somatosensory evoked potential scores were significantly correlated with changes of sensory functional system ($R = 0.34$, $p = 0.006$). However, patients with multiple sclerosis with disability progression at follow-up had more severe baseline evoked potential scores than patients who remained stable. Patients with severe baseline global evoked potential score (higher than the median value) had a risk of 72.5% to progress on disability at follow-up, whereas patients with multiple sclerosis with lower scores had a risk of only 36.3%.

Conclusions: These results suggest that evoked potential is a good marker of the severity of nervous damage in multiple sclerosis and may have a predictive value regarding the evolution of disability.

Evoked potentials have been used for more than 20 years in multiple sclerosis to objectify the involvement of sensory and motor pathways in patients with vague and indefinite disturbances, or to disclose clinically silent lesions.¹ Although evoked potentials allow functional assessment of nervous conduction along clinically eloquent pathways, the pathophysiology of their abnormalities in multiple sclerosis is quite complex and not completely understood. The pathological substrates of functional deficits in multiple sclerosis are mainly represented by demyelination and axonal loss.^{2,3} Demyelination may determine slowing of conduction, failure to transmit impulses at high frequency, partial or complete conduction block and secondary axonal degeneration.⁴ The combination of all these phenomena may account for the pattern of evoked potential abnormalities found in individual patients. The value of evoked potentials in the diagnosis of multiple sclerosis has been greatly reduced after the advent of magnetic resonance imaging (MRI), because of the higher sensitivity of MRI to subclinical lesions.¹ As a matter of fact, although the McDonald criteria for multiple sclerosis diagnosis,⁵ largely based on MRI findings, have been criticised,⁶ only visual evoked potentials are viewed as contributing to the diagnosis of multiple sclerosis.⁵

Although there is a general agreement that evoked potentials correlate with function in somatosensory,^{7,8} visual⁹ or motor pathways¹⁰ and the combination of evoked potential abnormalities correlates with disability,^{11,12} the usefulness of multimodal evoked potentials in monitoring the evolution of multiple sclerosis has not been yet clarified. Conflicting results have been reported on the correlation between clinical and evoked potential changes, which were absent or mild in

some studies^{13–17} carried out on small samples and with short follow-up. A better relationship has been found in other studies,^{11,18–21} mainly because of a higher number of patients studied and longer follow-up duration. Moreover, the use of conventional scores to quantify the severity of neurophysiological abnormalities allows us to combine the results of multimodal evoked potential in a global score, reflecting the global impairment of function.¹² The responsiveness of these scales during the various phases of the disease has yet to be defined. The aim of this study was to evaluate whether neurophysiological abnormalities may parallel the clinical disease evolution in a cohort of patients with established multiple sclerosis, by means of multimodal evoked potentials quantified using a conventional score.

METHODS

Data were collected from patients who referred to the multiple sclerosis centre of our department (Department of Neurology, Clinical Neurophysiology and Neurorehabilitation, University Vita-Salute, Milan, Italy) for routine clinical and neurophysiological evaluations. Inclusion criteria were (1) diagnosis of clinically definite multiple sclerosis²²; (2) complete neurological exam with disability rating using the Expanded Disability Status Scale (EDSS) and Kurtzke's functional system scores²³; (3) multimodal evoked potentials (visual, brain stem auditory, somatosensory and motor to the

Abbreviations: BAEP, brain stem auditory evoked potential; EDSS, Expanded Disability Status Scale; MEP, motor evoked potential; MRI, magnetic resonance imaging; SEP, somatosensory evoked potential; VEP, visual evoked potential

Table 1 Median values (standard deviations) of clinical disability (Kurtzke’s EDSS and functional systems) in the whole multiple sclerosis group and in the different disease courses: primary progressive; relapsing remitting; secondary progressive; progressive

	MS (n=84)	PP (n=13)	RR (n=43)	SP (n=28)	SP v PP	Progressive v RR
Age (years)	37.8 (9.9)	43.8 (6.9)	33.7 (9.4)	41.0 (9.5)	NS	<0.001
F/M	51/33	5/8	28/15	18/10	NS	NS
MS duration (months)	90.1 (77.2)	54.5 (65.4)	85.1 (71.3)	112.7 (85.4)	0.04	NS
EDSS	3.5 (1–8)	5.5 (2–6.5)	3 (1–6)	5 (2.5–8)	NS	<0.001
Pyramidal FS	3 (0–5)	3 (1–4)	2 (0–5)	3 (1–5)	NS	<0.001
Brain stem FS	1 (0–3)	2 (0–3)	1 (0–3)	2 (0–3)	NS	NS
Sensory FS	1 (0–3)	2 (0–3)	1 (0–3)	2 (0–3)	NS	0.03
Visual FS	0 (0–6)	0 (0–3)	0 (0–6)	1 (0–6)	NS	0.03

EDSS, Expanded Disability Status Scale; F, female; FS, functional system; M, male; MS, multiple sclerosis; NS, not significant; PP, primary progressive; progressive, pooled secondary progressive and primary progressive; RR, relapsing remitting; SP, secondary progressive. p Values of differences (right column) represent contrasts by Mann-Whitney U test.

four limbs) separated by an interval of <3 weeks from clinical examination; (4) second clinical examination after 2.5–5 years. Patients with a relapse within 2 months before baseline clinical evaluation were not included. Using these criteria, we selected 84 patients with multiple sclerosis (43 with relapsing remitting, 28 secondary progressive and 13 primary progressive disease course²⁴) with clinical follow-up after a mean (standard deviation (SD)) of 30 (11.7) months. For 64 (76%) patients, a second complete multimodal evoked potential battery within 3 weeks from the second clinical examination was also available.

Multimodal evoked potentials

Multimodal visual, auditory, somatosensory and motor evoked potentials to the four limbs were obtained according to previously published guidelines.²⁵ Somatosensory evoked potentials (SEPs) were obtained on electrical stimulation of the median nerve at the wrist for the upper limb and at the tibial nerve for the lower limb. One patient had median nerve SEP for one limb only. Latencies of the main peripheral, spinal and cortical components were measured, and central conduction time was calculated as the difference between cortical and spinal latencies (for tibial nerve SEP, latencies were corrected by height).

Visual evoked potentials (VEPs) to reversal achromatic checks (each subtending 30 and 15 min of visual angle (min arc)) were recorded over Oz of the 10–20 international EEG system, with Cz as the reference. Latency and amplitude of the P100 component were measured.

Brain stem auditory evoked potentials (BAEPs) to clicks at 85 dB normal hearing level were recorded at the Cz electrode referred to the ipsilateral and contralateral ear. The latency of the main peaks I, III and V and the I:V amplitude ratio were measured.

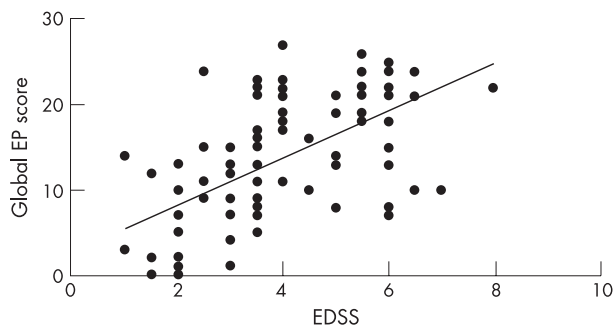


Figure 1 Basal global evoked potential (EP) score versus basal Expanded Disability Status Scale in the whole cohort of patients with multiple sclerosis (n=84). R=0.60; p<0.001 (Spearman correlation coefficient).

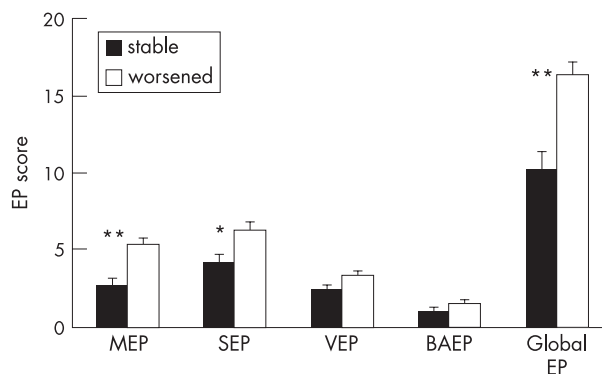


Figure 2 Basal evoked potential (EP) scores in patients with stable (black bars) and worsened (white bars) disability at follow-up. Expanded Disability Status Scale (EDSS) was considered as worsened if increased by 1 point (if basal EDSS <5.5) or increased by 0.5 points (if baseline EDSS ≥5.5). *p=0.01; **p<0.001 (Mann-Whitney test). BAEP, brain stem auditory evoked potential; MEP, motor evoked potential; SEP, somatosensory evoked potential; VEP, visual evoked potential.

Motor evoked potentials (MEPs) to the four limbs were obtained using a Cadwell MS10 magnetic stimulator with a round coil (outer diameter 12 cm). The coil was placed tangentially to the scalp, with its centre over the vertex. Patients were asked to contract slightly the target muscles (abductor pollicis brevis and abductor hallucis) at about 20% of the maximum voluntary effort to facilitate motor responses. Spinal roots were stimulated at C6–C7 and L4–L5 spaces, while recording from the same muscles. Central motor conduction time was measured as the difference between total and peripheral motor conduction time.

Evoked potential analysis

For all evoked potential modalities, latencies (and, where measured, amplitudes) were compared with normative data obtained in our laboratory. Absolute or interside difference values exceeding 2.5 SD from normal values or absence or morphological abnormality of a major component were considered abnormal. Evoked potential abnormalities were quantified according to a conventional 4-point graded ordinal score (0 = normal; 1 = increased latency; 2 = increased latency plus morphological abnormalities of a major component; 3 = absence of a major component) modified from Fukutake *et al.*⁸ For each modality, the evoked potential score was the sum of the scores in the two sides (in the patient with median SEP on one side only, the related score was multiplied by two). We calculated the global evoked potential score as the sum of the left and right BAEPs (from 0 to 6), VEPs (from 0 to 6), and of the left and right upper and lower

Table 2 Percentage frequency of abnormalities of evoked potentials at basal evaluation in the whole multiple sclerosis group and in the different disease courses: primary progressive; relapsing remitting; secondary progressive; progressive

n=84	MS (%)	PP (%)	RR (%)	SP (%)	Progressive v RR
SEP-UL	53.6	69.2	44.2	60.7	NS
SEP-LL	82.1	100	69.8	92.9	0.002
SEP	85.7	100	76.7	92.9	0.02
MEP-UL	72.6	84.6	55.8	92.9	<0.001
MEP-LL	77.4	92.3	60.5	96.4	<0.001
MEP	78.6	92.3	62.8	96.4	<0.001
BAEP	64.0	53.8	41.9	42.9	NS
VEP	77.4	92.3	67.4	85.7	0.03
Any EP	94.0	100	88.4	100	0.02

EP, evoked potential; LL, lower limb; MEP, motor evoked potential; MS, multiple sclerosis; NS, not significant; PP, primary progressive; progressive, pooled secondary progressive and primary progressive; RR, relapsing remitting; SEP, somatosensory evoked potential; SP, secondary progressive; UL, upper limb; VEP, visual evoked potential. p Values of differences (right column) represent Fisher's exact test.

SEPs (from 0 to 12) and MEPs (from 0 to 12) scores. This score ranges from 0 to 36, with higher values representing a more severe evoked potential involvement. Evoked potentials were independently evaluated by two neurophysiologists (LL and SM) blinded to the clinical status of the patients and to the timing of the evaluation; evoked potentials with discordant scoring of morphology (<10%) were reconsidered by the two examiners to reach a consensus.

Statistical analysis

Statistical analysis was carried out by means of non-parametric tests, as ordinal scales were used (EDSS and evoked potential score). Ordinal variables were tested with the Kruskal–Wallis and Mann–Whitney U tests or the Wilcoxon matched pair test; categorical variables were tested with Fisher's exact test or McNemar's paired test. Correlations were tested using Spearman's rank correlation coefficient. A p value of 0.05 was used as cut-off value. SPSS V.10.1 was used.

RESULTS

Table 1 reports the clinical findings in the whole cohort and in the three clinical subgroups. As expected, EDSS did not significantly differ between the primary progressive and secondary progressive groups, whereas it was lower in patients with relapsing remitting disease compared with the whole group of patients with progressive disease.

The percentage frequencies of evoked potential abnormalities (table 2) and the conventional evoked potential scores (table 3) at baseline did not significantly differ between the primary progressive and secondary progressive groups,

whereas they were significantly higher in the progressive compared with the relapsing remitting group (Mann–Whitney; $p \leq 0.03$) except for upper limb SEP and BAEP. A significant correlation (Spearman's rank correlation coefficient; $R = 0.60$, $p < 0.001$) was present between the global evoked potential score and EDSS (fig 1).

Data on follow-up were available for 64 patients. The 20 patients with multiple sclerosis lost at follow-up (8 primary progressive, 3 relapsing remitting and 9 secondary progressive) were significantly older than the remaining patients (mean age (SD) 43.7 (8.6) and 36 (9.7) years, respectively; $p = 0.003$, Student's t test). The correlation between global evoked potential score and EDSS and between the evoked potential score for each modality (except BAEP) with EDSS, and their related functional system was present also at the final evaluation in the 64 patients who completed the follow-up (table 4).

On carrying out the latter analysis on the relapsing remitting and progressive groups separately at baseline and follow-up in the relapsing remitting subgroup the correlation between BAEP and the related functional system was not significant both at baseline and follow-up. In the progressive subgroup, all the correlations between evoked potential and EDSS scores were not significant, with the exception of that between MEP and EDSS score at final evaluation ($R = 0.53$, $p = 0.008$), whereas the correlation between MEP or SEP and the related functional system was significant at final and basal evaluations ($R = 0.53$ and 0.48 , $p = 0.007$ and 0.002 , respectively).

As regards longitudinal analysis, the frequency of abnormalities (table 5) increased from baseline to final evaluations

Table 3 Basal evoked potential scores in the whole multiple sclerosis group and in the different disease courses: primary progressive; relapsing remitting; secondary progressive; progressive

n=84	MS	PP	RR	SP	Progressive v RR
SEP-UL	1.8 (2.1)	2.1 (1.9)	1.7 (2.4)	1.9 (1.9)	NS
SEP-LL	3.4 (2.3)	5.2 (1.4)	2.5 (2.3)	4.1 (2.1)	<0.001
SEP	5.3 (3.7)	7.2 (2.4)	4.2 (3.9)	6.0 (3.3)	0.004
MEP-UL	1.7 (1.4)	2.0 (1.4)	1.2 (1.3)	2.4 (1.2)	<0.001
MEP-LL	2.3 (1.8)	3.3 (1.9)	1.5 (1.6)	3.1 (1.4)	<0.001
MEP	4.1 (3.0)	5.3 (3.2)	2.7 (2.8)	5.5 (2.4)	<0.001
VEP	2.8 (2.1)	3.2 (1.5)	2.3 (2.2)	3.5 (1.9)	0.01
BAEP	1.2 (1.7)	1.5 (1.9)	1.2 (1.8)	1.1 (1.5)	NS
Global	13.4 (7.5)	17.2 (5.5)	10.4 (7.8)	16.5 (6.0)	<0.001

BAEP, brain stem auditory evoked potential; LL, lower limb; MEP, motor evoked potential; MS, multiple sclerosis; NS, not significant; PP, primary progressive; progressive, pooled secondary progressive and primary progressive; RR, relapsing remitting; SEP, somatosensory evoked potential; SP, secondary progressive; UL, upper limb; VEP, visual evoked potential. p Values of differences (right column) represent contrasts by the Mann–Whitney test.

Table 4 Correlation between basal, follow-up and longitudinal delta values (difference between final and basal) of evoked potential scores and their related functional system (visual, somatosensory, pyramidal) and of evoked potential scores and Expanded Disability Status Scale in the whole cohort of patients with multiple sclerosis who underwent both basal and follow-up evaluations

n = 64	EDSS basal	EDSS final	Delta (final–basal)	FS basal	FS final	Delta (final–basal)
SEP	R = 0.55 (<0.001)	R = 0.41 (0.001)	R = 0.15 (NS)	R = 0.46 (<0.001)	R = 0.50 (<0.001)	R = 0.34 (0.006)
MEP	R = 0.50 (0.001)	R = 0.61 (<0.001)	R = 0.13 (NS)	R = 0.55 (<0.001)	R = 0.60 (<0.001)	R = 0.05 (NS)
VEP	R = 0.46 (<0.001)	R = 0.34 (0.006)	R = -0.10 (NS)	R = 0.47 (<0.001)	R = 0.18 (NS)	R = 0.01 (NS)
BAEP	R = 0.10 (NS)	R = 0.06 (NS)	R = 0.09 (NS)	R = 0.32 (0.01)	R = 0.33 (0.007)	R = 0.12 (NS)
Global EP	R = 0.60 (<0.001)	R = 0.46 (<0.001)	R = 0.18 (NS)			

BAEP, brain stem auditory evoked potential; EDSS, Expanded Disability Status Scale; EP, evoked potential; FS, functional system; LL, lower limb; MEP, motor evoked potential; NS, not significant; SEP, somatosensory evoked potential; UL, upper limb; VEP, visual evoked potential. R and p values refer to Spearman's correlation coefficient.

for all the evoked potential modalities, but was significant only for upper limb SEP (McNemar test; $p = 0.03$), whereas the conventional evoked potential scores (table 6) significantly worsened for all modalities (Wilcoxon matched pairs test). At separate subgroup analysis the longitudinal correlation between changes in SEP and the related functional system was significant in the progressive group only ($R = 0.43$, $p = 0.04$).

We also explored the relationship between the severity of evoked potential involvement at basal evaluation and the risk of disability progression at follow-up, defined as an increase of at least 1 EDSS point if baseline EDSS was ≤ 5.5 , and of at least 0.5 point if baseline EDSS was > 5.5 .²⁶ Patients with a more severe evoked potential involvement at baseline, represented by a global evoked potential score ≥ 13 , which was its median value, had a risk of 72.5% for progression to disability at the follow-up examination, whereas patients with multiple sclerosis with less severe evoked potential involvement at baseline, corresponding to a global evoked potential score ≤ 14 , had a much lower risk of 36.3% (table 7), corresponding to an odds ratio (OR) of 4.6 95% confidence interval (CI 1.8 to 11.6). This leads to a positive predictive value of 72.5% and a negative predictive value of 63.6% of the baseline global evoked potential score, categorised according to its median value.

These data were confirmed by the fact that patients with multiple sclerosis whose condition worsened at follow-up had significantly worse somatosensory (Mann–Whitney test; $p = 0.01$), motor ($p < 0.001$) and global ($p < 0.001$) evoked potential scores at baseline compared with patients without clinical worsening (fig 2).

DISCUSSION

Cross-sectional analysis

Consistent with previous literature,^{27–30} VEP, lower limb SEP and MEP were the most frequently involved evoked potentials in multiple sclerosis. These findings may be explained by a higher susceptibility of optic nerve fibres to multiple sclerosis lesions, confirmed by pathological studies,³¹ and by a higher probability of involvement of longer pathways such as sensorimotor projections to the lower limbs. We found more frequent and severe evoked potential abnormalities in progressive forms of the disease compared with the relapsing remitting form; this finding cannot be explained by the older age of patients with progressive multiple sclerosis included in our study, because central conduction time, different from peripheral conduction time, is only mildly affected by age.³² Moreover, according to previous studies,^{8,9,12,33–37} we found a marked correlation between the severity of abnormality of each evoked potential modality (except auditory), reflected by the evoked potential score, and EDSS or the corresponding functional system. These results indicate that evoked potentials in patients with

Table 5 Percentage abnormalities of evoked potential in the whole cohort of patients with multiple sclerosis who underwent both basal and follow-up evaluations

n = 64	Basal (%)	Final (%)	p Value
SEP-UL	51.6	65.6	0.03
SEP-LL	81.3	85.9	NS
SEP	84.4	89.1	NS
MEP-UL	68.8	70.3	NS
MEP-LL	71.9	79.7	NS
MEP	73.4	79.7	NS
VEP	75.0	82.8	NS
BAEP	40.6	50.0	NS
Global EP	92.2	96.9	NS

BAEP, brain stem auditory evoked potential; EP, evoked potential; LL, lower limb; MEP, motor evoked potential; NS, not significant; SEP, somatosensory evoked potential; UL, upper limb; VEP, visual evoked potential. p Values of differences (right column) represent McNemar's test.

Table 6 Evoked potential baseline and final scores in the whole cohort of patients with multiple sclerosis who performed both basal and follow-up evaluations

n = 64	Baseline	Final	p Value
SEP-UL	1.8 (2.2)	2.5 (2.3)	0.007
SEP-LL	3.7 (2.3)	3.8 (2.3)	0.04
SEP	5.0 (3.8)	6.3 (3.9)	0.004
MEP-UL	1.6 (1.4)	2.0 (1.7)	0.003
MEP-LL	2.1 (1.8)	2.9 (2.0)	<0.001
MEP	3.7 (3.0)	4.9 (3.5)	<0.001
VEP	2.7 (2.1)	3.1 (2.1)	0.02
BAEP	1.2 (1.8)	1.6 (1.9)	0.02
Global EP	12.6 (7.6)	15.9 (8.8)	<0.001

BAEP, brain stem auditory evoked potential; EP, evoked potential; LL, lower limb; MEP, motor evoked potential; SEP, somatosensory evoked potential for the lower limb; SEP, somatosensory evoked potential for the upper limb; UL, upper limb; VEP, visual evoked potential. p Values of differences (right column) represent Mann–Whitney test.

multiple sclerosis correlate well with disability and with the severity of involvement of sensory and motor pathways.

Longitudinal analysis

Conflicting results have been reported on the correlation between clinical and evoked potential changes, being absent or equivocal in some studies,^{13–17} whereas a good correlation has been found in others.^{11,18–21}

Such different results can be determined by the use of different measures for quantifying the involvement of evoked potentials, as well as by the type of enrolled patients (whether relapsing remitting or progressive) and by the duration of follow-up.

Table 7 Predictive value of evoked potential global score at basal examination on Expanded Disability Status Scale (EDSS) progression at follow-up, defined as an increase of at least 1 (if baseline EDSS <5.5) and of at least 0.5 (if baseline EDSS ≥5.5)

	EP >13	EP ≤13	Total	PV
EDSS+	29	16	45	0.725
EDSS−	11	28	39	0.636
Total	40	44	84	

EDSS, Expanded Disability Status Scale; EP, evoked potential; PV, predictive value.
The EP global score was categorised into two groups according to the median value: ≤13 (less involved EP) and >13 (more involved EP). χ^2 analysis: $p=0.001$; odds ratio = 4.6 (1.8–11.6).

In our study, the analysis of clinical and instrumental follow-up data has shown a partial correlation between clinical worsening and evoked potential score changes. When assessed in terms of difference between the final and baseline evoked potential and EDSS scores, longitudinal correlation was significant only for SEP, different from previous reports.^{11–16} In 11 patients with chronic progressive multiple sclerosis followed up over 1.5 years, significant changes in VEP latencies but not in BAEP or MRI T2 lesion load were found.¹⁶ In a cohort of patients with relapsing remitting disease followed up for 2 years, a significant correlation between a global measure of evoked potential abnormalities and EDSS, both for cross-sectional and longitudinal evaluations, has been reported.¹² Fuhr *et al*¹¹ found cross-sectional and longitudinal correlations between combined VEP and MEP latency z-score and EDSS in a group of 30 patients with multiple sclerosis (most of whom were relapsing remitting), who had been followed up for 2 years.

The reason why SEPs are most closely related to EDSS change in our study could be that spinal cord involvement is overweighted in EDSS, particularly at scores over 3.5,²⁴ which represented almost half of our patients. In contrast, the lack of longitudinal correlation of the other evoked potentials with clinical disability could be determined by a ceiling effect of evoked potential abnormalities. This is underlined by the fact that in our study, cross-sectional correlations were higher at baseline than at follow-up evaluation, and also by the high proportion of patients with progressive disease, with higher evoked potential scores, of which the highest refers to absence of a major evoked potential component, not susceptible to further worsening. This is also determined by the fact that, in analogy to other studies,^{8,9,37} we used conventional scores taking into account the absence of a major component, thus avoiding excluding from the analysis patients with severe evoked potential abnormalities, which are more likely to present a severe disability. It is, however, worth remembering that the limited sample size of the progressive patient subgroup might be a limiting factor when interpreting the results of the separate correlation analysis carried out in these patients.

However, and consistent with previous reports,¹¹ the global evoked potential score in our study showed a predictive value with regard to future clinical evolution, indicated by a higher risk of disability worsening in patients with higher evoked potentials score, and by more severe basal evoked potential scores in patients with clinical worsening at follow-up compared with stable or improved patients.

It is worthwhile mentioning that our global evoked potential score is weighted towards sensory evoked potentials and MEPs, which count double that of visual and auditory. Moreover, a marked discrepancy between evoked potentials in worsened and stable patients was present for somatosensory

and motor modalities, confirming the importance of spinal cord involvement in the development of disability. Our finding that detection of involvement of eloquent sensory or motor pathways is predictive for the development of future disability in patients with multiple sclerosis is consistent with MRI findings showing continuous optic nerve atrophy after optic neuritis, not evident in the unaffected eye.³⁸ The interpretation of these findings is not unequivocal, because the relationship between inflammation, demyelination and axonal damage in multiple sclerosis still needs to be clarified. Recent pieces of evidence^{39,40} indicate that the use of measures derived from quantitative MRI-based techniques provides useful predictive information for the medium-term clinical disease evolution, most probably because these techniques can quantify the severity of structural and irreversible multiple sclerosis-related tissue damage. Studies incorporating both multimodal evoked potential and quantitative MRI evaluations are, therefore, warranted to clarify whether a multiparametric approach may improve our prognostic ability in the investigation of patients with established multiple sclerosis.

In conclusion, by showing a good correlation between clinical assessment and evoked potential, our results support the usefulness of neurophysiological data both in monitoring the natural history of the disease and in predicting the development of future disability. The integration of MRI and evoked potential data may give us new prospects on the knowledge of pathological processes underlying multiple sclerosis evolution and, if validated, could prove useful in monitoring the effects of symptomatic and disease-modifying treatments.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Istituto Superiore di Sanità (National Ministry of Health, Rome, Italy. Protocol number 96/J/T44)

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Competing interests: None declared.

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