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Prognostic biomarkers in primary progressive multiple sclerosis: Validating and scrutinizing multimodal evoked potentials

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HIGHLIGHTS

- Combination of motor EP (MEP) from upper and lower limbs and somatosensory EP (SEP) after tibial nerve stimulation carries the main prognostic information predicting 32% of EDSS-change over two years in primary progressive multiple sclerosis (PPMS).
- Current results replicate and corroborate the previously reported prognostic value of multimodal EP in PPMS.
- Quantitative scoring outperforms ordinal scoring to prognosticate EDSS-change.

ABSTRACT

Objective: To validate the prognostic value of multimodal evoked potentials (mmEP) in primary progressive multiple sclerosis (PPMS) and to determine the most predictive EP-modalities.
Methods: Thirty-nine patients with PPMS (expanded disability status scale (EDSS): 2.0–6.5; mean clinical follow-up: 2.8 years) had visual (VEP), upper and lower limb somatosensory (SEP) and motor EP (MEP) at baseline. Quantitative EP-scores for single (qVEP, qSEP, qMEP) and combined modalities were correlated to EDSS and compared to previously published data of 21 PPMS patients. Predictors of EDSS-change were analyzed in pooled data by linear regression.
Results: Samples were comparable. Except qVEP, all EP-scores were correlated to EDSS at baseline (Rho: 0.45–0.69; $p < 0.01$) and follow-up (Rho: 0.59–0.80; $p < 0.001$). Combined EP-modalities significantly predicted EDSS-change (R^2_{adj}: 0.24), while EDSS and age did not. Tibial qSEP (R^2_{adj}: 0.22) and qMEP (R^2_{adj}: 0.26) were the best single modality predictors, outperformed by their combination (R^2_{adj}: 0.32).
Conclusions: Quantitative EP-scores predict up to 32% of EDSS-change over three years. Modalities representing motor and long tract function carry the main prognostic information.
Significance: Replication of previous results corroborates the use of mmEP as a prognostic biomarker candidate in PPMS.

Abbreviations: mmEP, Multimodal evoked potentials; VEP, Visual evoked potentials; SEP-M, Median nerve somatosensory evoked potentials; SEP-T, Tibial nerve somatosensory evoked potentials; MEP-UL, Motor evoked potentials from upper limbs; MEP-LL, Motor evoked potentials from lower limbs; qVEP, quantitative VEP-score; qSEP, quantitative SEP-score (from SEP-M and SEP-T); qMEP, quantitative MEP-score (from MEP-UL and MEP-LL); qEPS, quantitative EP-score (qVEP, qSEP and qMEP combined); mqEPS, modified quantitative EP-score (qSEP and qMEP combined); q3EPS, quantitative EP-score from 3 bilateral tests (qSEP-T and qMEP combined); o3EPS, ordinal EP-score from same tests as q3EPS.

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1. Introduction

Primary progressive multiple sclerosis (PPMS) is characterized by an insidious accumulation of disability (Miller and Leary 2007) and predominant neurodegeneration rather than inflammation (Mahad et al. 2015). Disease course shows considerable heterogeneity; some patients remain stable for quite some time, while others experience a rapid progression (Koch et al. 2009, Harding et al. 2015). Better prognostic biomarkers may help to select patients for clinical trials and may improve counselling of patients.

Recent research focused on development of biomarkers for progressive MS (Moccia et al. 2017, Barro et al. 2017). On magnetic resonance imaging (MRI), brain gray and white matter as well as cervical cord atrophy is moderately associated with disease progression (Rocca et al. 2017, Moccia et al. 2020). Using MRI activity to enrich trial populations, may overestimate anti-inflammatory therapeutic effects (Pardini et al. 2019). Neurofilament light chain levels are associated with brain and spinal cord atrophy as well as disability progression and reflect neuro-axonal damage (Barro et al. 2018); however, they covary with inflammatory activity and may be confounded by comorbidities (Kapoor et al. 2020).

Evoked potentials (EP) provide complementary information on function in the main tracts of the central nervous system and are closely related to clinical symptoms (Smith and McDonald 1999). Disturbed signal propagation is probably due to both, demyelination as well as axonal damage, and as such close to the neurodegenerative aspects of MS pathology, except of conduction block in the case of acute demyelination (Waxman et al. 2006).

Several prospective and retrospective studies have shown that multimodal EP-scores at baseline are significantly related to future EDSS and EDSS change over two up to twenty years in cohorts with clinically isolated syndrome (CIS; Pelayo et al., 2010), relapsing-remitting MS (RRMS; (Jung et al., 2008), in mixed cohorts of CIS and RRMS (London et al., 2017), RRMS and secondary progressive MS (SPMS; Kallmann et al. 2006), RRMS, SPMS and PPMS (Leocani et al. 2006) as well as in PPMS (Schlaeger et al. 2014a), for review see (Hardmeier et al. 2017). Various approaches regarding EP modalities and EP scoring have been used. Visual EP (VEP) were part of all and somatosensory EP (SEP) of nearly all scores, while motor EP (MEP) were included in 70% of scores. Ordinal and quantitative scores have similar cross-sectional correlations to EDSS (Canham et al. 2015) while the quantitative approach has a higher sensitivity to change (Schlaeger et al. 2016). However, the lack of a common standard for the choice of modalities may be an important obstacle for including multimodal EP (mmEP) in larger studies so far.

As chronic demyelination and axonal loss are probably the main drivers of disease progression in PPMS, mmEP may serve as a relative specific biomarker for neurodegeneration. However, EP data in PPMS patients is sparse and our previous report by Schlaeger et al. has been the only longitudinal study exclusively including patients with PPMS (Schlaeger et al. 2014a). It showed, in a small sample, that a quantitative EP score (qEPS) combining VEP, SEP and MEP predicted EDSS after 3 years.

In the current study, we sought to replicate our previous findings in an independent and multicenter cohort of PPMS patients and to assess systematically which modality or combination of modalities provides the best prediction of change in EDSS over three years.

2. Methods

2.1. Subjects

The current sample (sample 1) was recruited from the Swiss Multiple Sclerosis Cohort study (SMSC; n = 30) and additionally included nine participants of an EP sub-study within the Phase III trial on Ocrelizumab (Oratorio; Hoffmann-La Roche Inc.). Thirty-one subjects were followed prospectively and eight subjects were retrospectively identified in the SMSC database. Clinical and EP exams were performed at three university centers (Basel, n = 31; Geneva, n = 4; Lugano, n = 4). All subjects gave written informed consent in accordance with the Declaration of Helsinki. Studies were approved by the local ethic committee. Sample 2 comprised 21 subjects with PPMS, from a previously published prospective cohort with mmEP assessment and a three-year clinical follow-up (Schlaeger et al. 2014a).

Inclusion criteria in sample 1 were age > 18 years, expanded disability status scale (EDSS) of 2.0–6.5 and a primary progressive disease course (Thompson et al. 2018); sample 2 included patients with age > 18 years, EDSS 2.0–6.5 and definite PPMS (Thompson et al. 2000). Exclusion criteria comprised contraindications to MEP (epilepsy, moveable metal implants, pacemaker, pregnancy), inability to provide informed consent, and presence of other diseases than MS interfering with EP recording.

Subjects were examined clinically at least once a year by certified neurologists using the EDSS (Kurtzke 1983) as defined in Neurostatus (Kappos et al. 2015). EDSS was checked for consistency with functional system scores. EDSS change was calculated as the difference between EDSS at last follow-up and EDSS at baseline. Disease duration was defined as the time from symptom onset.

Treatment with CD20 depleting agents (Rituximab or Ocrelizumab; CD20Tx) was only used in sample 1 and off-label in the beginning. Treatment exposure was operationalized as the time on treatment during the observation period. Other therapies were not taken into account.

2.2. Evoked potentials

The recording of the single EP modalities followed closely the recommendations of the International Federation of Clinical Neurophysiology, details have been published previously (Schlaeger et al. 2014a, Hardmeier et al. 2019). Slight deviations according to local standard operating procedures were allowed. The recording protocol was the same for both samples and for prospectively and retrospectively included subjects.

VEP were recorded from each eye separately using full-field checkerboard stimulation with Fz as the reference and Oz (or O1, Oz and O2) as active electrode. LED monitors were used in sample 1 in Basel and Geneva, CRT monitors were used in sample 2 in Basel and in Lugano. Cortical and spinal SEP responses were elicited by electrical stimulation above motor threshold of median (SEP-M) and posterior tibial nerve (SEP-T) and recorded from C3′/C4′ and CV7 as well as Cz' and LV1, respectively. MEP were recorded from upper and lower limbs bilaterally with facilitation by slight contraction of the target muscle. Stimulation was delivered using a round coil over the respective cortical motor area and spinal nerve roots.

EP curves were exported from the local recording machines, coded and uploaded to a custom software application (EPMark; Hardmeier et al. 2019). All curves were evaluated by an experienced neurophysiologist (MH) blinded to clinical details. Markers were set manually for the peaks of the main cortical responses in VEP (P100) and SEP (N20, P40), for the cervical (N13) and lumbar (N22) responses in SEP, and for cortico-muscular (CxM) and spino-muscular (SpM) latencies in MEP. P100-, N20-, P40- and CxM-latencies as well as central conduction times calculated as the difference between N20 and N13 for SEP-M (CCT) and the difference between CxM and SpM for upper and lower limb MEP (CMCT) were used for analysis. In cases, where latency could not be determined reliably due to severe pathology, the most abnormal measured value of the respective modality was imputed. All EP-

latencies were z-transformed in reference to normative values of healthy controls and corrected for height in lower limbs (see Supplementary Material). For VEP, a respective set of lab-specific normative values was used for z-transformation for each site and screen. Two subjects refused to record SEP-T as stimulation provoked painful spasms; SEP-M was missing in one subject.

For calculation of EP-scores, each EP of one eye or one limb in one modality is referred to as a test. Quantitative EP-scores equal the sum of z-transformed latencies across all included tests divided by the number of tests (Schlaeger et al. 2014a). Quantitative EP-scores are dimensionless. An EP-score of zero indicates that the compound score does not deviate from its normal mean, whereas an EP-score of two indicates an average deviation by two units from the normal mean. A one-unit change in an EP-score means that the average change per included test was one reference standard deviation (SD).

Single modality EP scores comprise P100-latencies (qVEP), N20- and P40-latencies (qSEP-M and qSEP-T, respectively; combined as qSEP) and shortest CxM-latencies for upper and lower limbs (qMEP-UL and qMEP-LL, respectively; combined as qMEP). The quantitative EP score (qEPS) includes P100- and P40-latencies (qVEP, qSEP-T), CCT (SEP-M) and CMCT of upper and lower limb MEP (Schlaeger et al. 2014a), the modified quantitative EP-score (mqEPS) is based on qSEP and qMEP (Hardmeier et al. 2019) and the new q3EPS on qSEP-T and qMEP. In addition, we calculated an ordinal EP score (o3EPS) as the proportion of pathological tests in SEP-T, MEP-UL and MEP-LL. A pathological test result was defined as lying at least three SD above the mean of the reference values.

2.3. Statistical analysis

Statistical analyses were conducted using SPSS Version 25 (IBM Corporation, Armonk, NY, USA) and Stata release 15 (College Station, TX: Stata Corp LLC).

Clinical characteristics and EP scores were compared between samples by Mann-Whitney-U test, EDSS at baseline and at last follow-up by Wilcoxon-signed rank test. Correlation analysis was done using Spearman's rank correlation coefficient rho. Statistical significance was defined as $p < 0.05$.

As previously (Schlaeger et al. 2014a), we used multivariable linear regression to predict EDSS at follow-up in both samples separately. Then, data was pooled as samples were comparable or the difference (time of follow-up: 0.3 years, $p < 0.01$) clinically not relevant. A second multivariable linear regression with backward elimination of variables (exclusion if $p > 0.1$) was run to predict change in EDSS. This model is mathematically equivalent to the first but explicitly shows the influence of baseline EDSS on subsequent change. As only qEPS survived as predictor, we run in a third step univariable regression models using single and combined modality EP-scores as predictors. The distribution of residuals was visually checked using Q-Q-plots, and these showed only minor deviations from linearity.

The 95%-confidence interval for the change in q3EPS associated with a one-unit increase in EDSS was obtained using Monte-Carlo simulation by sampling regression parameters from the 2-dimensional normal distribution defined by the parameter estimates of the intercept and the slope and their covariance matrix.

3. Results

Sample 1 consisted of 39 subjects (18 female; mean age: 52.3 years, SD: 9.6; mean disease duration: 8.0 years, SD: 7.8). Median EDSS was 4.0 (range: 2.0–6.5) at baseline and 5.0 (2.0–8.0) at last follow-up (mean follow-up: 2.8 years, SD: 0.38). Two subjects were already on CD20Tx for 1.4 years at study inclusion, 14 started therapy shortly before or within the first 6 months, 7 later, and 16 subjects had no CD20Tx during the study period.

Sample 2 has been published previously (Schlaeger et al. 2014a). All 21 subjects (3 female) with a clinical follow-up at year 3 were included (mean age: 53.8 years, SD: 9.0; mean disease duration: 9.0 years SD: 7.0; mean follow-up: 3.1 years, SD: 0.14). Median EDSS was 4.0 (2.5–6.5) at baseline and 5.0 (2.5–7.5) at last follow-up. No subject was on CD20Tx.

EDSS increased significantly from baseline to last follow-up in both samples, while they did not differ in clinical measures or change in EDSS except in time of follow-up (difference: 0.3 years). Means of quantitative EP-scores ranged from 2.2 to 6.4 averaged SD. Scores of mqEPS, q3EPS and qMEP were significantly higher in sample 2, the o3EPS-score showed a strong trend ($p = 0.06$), while the qVEP-score was significantly lower (Table. 1).

3.1. Correlation analysis

Correlations of multimodal EP scores with EDSS at baseline and follow-up for samples 1 and 2 are given in Table. 2. All associations of EP-scores with EDSS were significant and numerically stronger with EDSS at follow-up than with EDSS at baseline, except for o3EPS in sample 2. The gap between the cross-sectional and the predictive correlation was numerically bigger in sample 1 than in sample 2. Analyses for single EP modalities showed comparable results, except for qVEP, for which correlations were not significant (Supplementary Material, Table S1). In the pooled sample, intercorrelations between qSEP and qMEP were strong (rho = 0.602, $p < 0.001$), but weak between qVEP and qSEP (rho = 0.241, $p = 0.07$) as well as qVEP and qMEP (rho = 0.09, $p = 0.48$).

3.2. Validation of the quantitative EP score (qEPS)

Multivariable regression of EDSS at last follow-up replicated the main findings from our smaller previous cohort in the current sample (sample 1): baseline qEPS was again an independent predictor of EDSS three years later and contributed considerably to explained variability as indicated by the standardized coefficient (Table. 3). However, age at baseline was no longer significant. Treatment exposure was tested in a separate model in sample 1, but was not predictive either ($p = 0.74$). In a second multivariable regression model with stepwise backward elimination on the pooled dataset, qEPS remained the only significant predictor explaining 24% of variability in EDSS change (Table. 4).

3.3. Comparison of single and differently combined multimodal EP scores

In univariable regression of EDSS change in the pooled dataset, qVEP did not show any and qSEP-M only a weak association, while qSEP-T, qMEP-UL and qMEP-LL had significant associations (R^2_{adj}: 0.22, 0.19 and 0.21, respectively; Supplementary Material, Table S2). Combined MEP (qMEP) and combined qMEP and qSEP (mqEPS) were even better predictors (R^2_{adj}: 0.26 and 0.30, respectively), while combined qMEP and qSEP-T (q3EPS) performed best (R^2_{adj}: 0.32). The performances of qEPS (R^2_{adj}: 0.24) and o3EPS were lower (R^2_{adj}: 0.23), results are given in Table. 5.

The association between q3EPS and EDSS-change is displayed in Fig. 1, showing that a one-step change in EDSS is estimated for a q3EPS-score lying 6 units above normal (95% CI: 4.41–7.62). When simplified to an ordinal scale, a one-step EDSS change is estimated if four out of six tests are pathological.

Table 1
Median EP-scores in samples 1 and 2 (interquartile range) and median proportion of pathological tests for o3EPS. qEPS: quantitative EP-score; mqEPS: modified quantitative EP-score; q3EPS: quantitative EP-score from tibial SEP and upper and lower limb MEP; o3EPS: ordinal EP-score from same tests as for q3EPS; qVEP: quantitative VEP-score; qSEP: quantitative SEP-score; qMEP: quantitative MEP-score; see methods for definitions.* p < 0.05; ** p < 0.01 for comparison between samples.

	qEPS	mqEPS	q3EPS	o3EPS	qVEP	qSEP	qMEP
Sample 1	4.7 (2.4–6.6)	3.0 (1.8–5.0)	3.5 (1.8–5.6)	0.5 (0.33–0.83)	6.4 ** (3.5–10.1)	4.1 (2.1–5.5)	2.5 (1.1–5.3)
Sample 2	5.9 (4.3–7.2)	4.7 * (3.4–6.3)	6.2 * (4.0–7.7)	0.67 (0.5–0.96)	2.2 (1.2–5.1)	4.5 (2.2–6.1)	4.5 * (3.0–7.3)

Table 2
Spearman's Rho correlation coefficients for associations between multimodal EP scores and EDSS at baseline (bs) and at last follow-up (fu) in samples 1 and 2. EDSS: expanded disability status scale; qEPS: quantitative EP-score; mqEPS: modified quantitative EP-score; q3EPS: quantitative EP-score from tibial SEP and upper and lower limb MEP; o3EPS: ordinal EP-score fromsame tests as for q3EPS; see methods for definitions. * p < 0.05; ** p < 0.01; *** p < 0.001.

	Sample 1 (n = 39)				Sample 2 (n = 21)			
	qEPS	mqEPS	q3EPS	o3EPS	qEPS	mqEPS	q3EPS	o3EPS
EDSS bs	0.47**	0.48**	0.45**	0.38*	0.69**	0.61**	0.68**	0.70**
EDSS fu	0.59***	0.68***	0.67***	0.67***	0.80***	0.74***	0.78***	0.68**

Table 3
Prediction of EDSS at last follow-up in samples 1 and 2 by multivariable linear regression with qEPS as predictor adjusted for age and EDSS at baseline in samples 1 (n = 39) and 2 (n = 21). EDSS: expanded disability status scale; qEPS: quantitative EP-score; see methods for definition.

	Predictor	Coefficient (95 %CI)	Standardized coefficient	p-value	R^2_{adj}
Sample 1	intercept	0.67 (-1.84–3.19)		0.591	0.571
(n = 39)	qEPS	0.14 (0.04–0.24)	0.371	0.007	
	EDSS	0.87 (0.52–1.21)	0.578	<0.001	
	age	0.00 (-0.04–0.04)	−0.003	0.979	
Sample 2	intercept	1.14 (-3.08–0.81)		0.234	0.836
(n = 21)	qEPS	0.20 (0.10–0.29)	0.445	<0.001	
	EDSS	0.69 (0.44–0.95)	0.590	<0.001	
	age	0.04 (0.01–0.07)	0.230	0.026	

Table 4
Prediction of EDSS change from baseline to last follow-up by multivariable linear regression with stepwise backward elimination in the pooled dataset (n = 60) with qEPS as predictor, initially adjusted for age and EDSS at baseline. EDSS: expanded disability status scale; qEPS: quantitative EP-score; see methods for definition.

	Predictor	Coefficient (95 %CI)	standardized coefficient	p-value	R^2_{adj}
Model 1	intercept	0.00 (-1.62–1.61)		0.999	0.257
(n = 60)	qEPS	0.16 (0.09–0.23)	0.625	<0.001	
	EDSS	−0.20 (-0.42–0.02)	−0.221	0.079	
	age	0.01 (0.01–0.04)	0.131	0.294	
Model 2	intercept	0.73 (-0.12–1.57)		0.089	0.255
	qEPS	0.15 (0.09–0.21)	0.566	<0.001	
	EDSS	−0.17 (-0.39–0.04)	−0.191	0.118	
Model 3	intercept	0.14 (-0.27–0.56)		0.492	0.236
	qEPS	0.13 (0.07–0.19)	0.499	<0.001	

Table 5
Prediction of EDSS change from baseline to last follow-up by univariable linear regression in the pooled dataset (n = 60) using single EP modalities and differentially composed multimodal EP scores as predictors (see Supplementary Material for upper and lower limb SEP and MEP, Table S2). EDSS: expanded disability status scale; qVEP: quantitative VEP-score; qSEP: quantitative SEP-score; qMEP: quantitative MEP-score; qEPS: quantitative EP-score; mqEPS: modified quantitative EP-score; q3EPS: quantitative EP-score from tibial SEP and upper and lower limb MEP; o3EPS: ordinal EP-score from same tests as for q3EPS; see methods for definitions.

Predictor	Intercept	Coefficient (95 %CI)	p-value	R^2_{adj}
qVEP	0.77	0.02 (-0.04–0.08)	0.465	−0.008
qSEP	0.32	0.13 (0.07–0.19)	<0.001	0.213
qMEP	0.34	0.13 (0.07–0.18)	<0.001	0.255
qEPS	0.14	0.13 (0.07–0.19)	<0.001	0.236
mqEPS	0.16	0.16 (0.10–0.23)	<0.001	0.299
q3EPS	0.15	0.14 (0.09–0.20)	<0.001	0.316
o3EPS	0	0.16 (0.08–0.23)	<0.001	0.227

4. Discussion

In the current study, we showed in a sample of patients with PPMS that multimodal EP scores are moderately associated with change in EDSS over a three-year period, explaining 20–32% of variability. The components carrying the main prognostic information were tibial SEP and MEP to upper and lower limbs bilaterally. An average deviation of 6 units over normal in the combined score

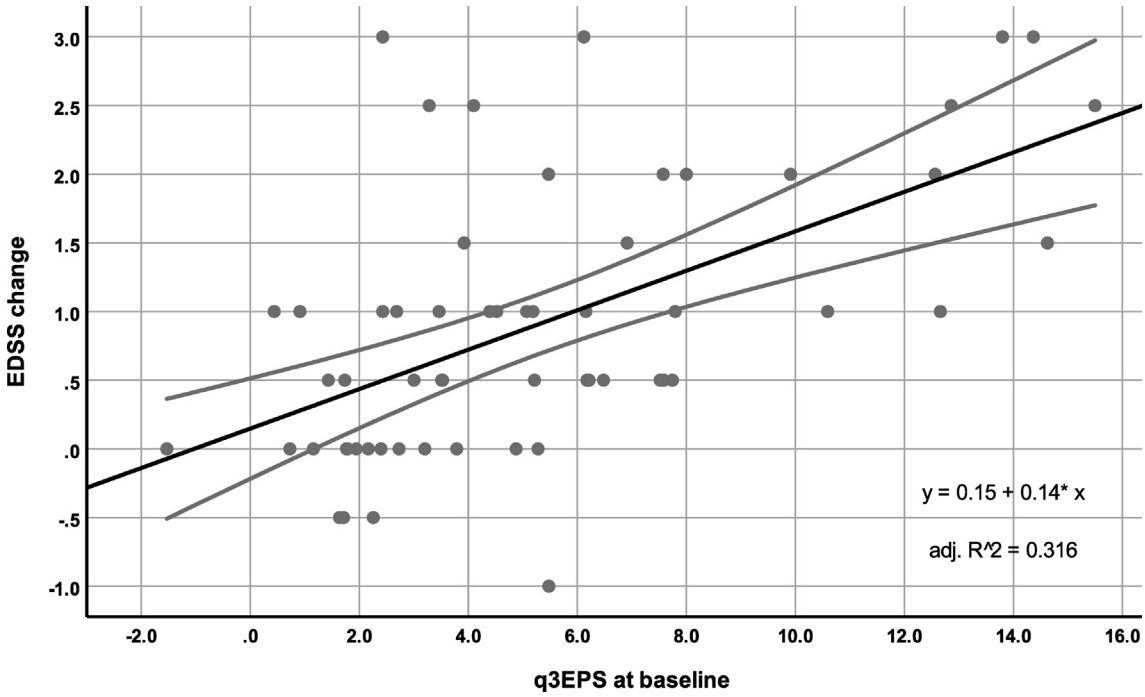

Fig. 1. Association of q3EPS baseline value with change in EDSS from baseline to last follow-up according to univariable linear regression with regression line and 95% confidence intervals. q3EPS: quantitative EP-score from tibial SEP, upper and lower limb MEP bilaterally. EDSS: expanded disability status scale.

of these six tests (q3EPS) predicts a mean change of one EDSS step after three years, as four pathological tests out of six do when referring to ordinal scoring (o3EPS). Exposure to CD20-depleting treatment had no prognostic value for change in EDSS in the current cohort.

Our findings in sample 1 replicate the results of our previous study in an independent cohort (Schlaeger et al. 2014a). While small studies frequently fail to be confirmed, the current results validate the prognostic value of mmEP in patients with PPMS, which is in line with several other EP-studies in various MS phenotypes (review in Hardmeier et al. 2017).

Conceptually, it would be expected that examining the visual, somatosensory and motor system by EP yield the most comprehensive information to quantify the degree of disability. However, concerning the EDSS, the analysis of single modalities showed that the VEP component did not add to the prognostic value and was only weakly associated with SEP and MEP scores. While the visual system is not well represented in the EDSS, this finding does not support the view, that dysfunction in the visual system is an indicator of dysfunction in other systems. However, VEP correlate well with structural measures of the optic system (You et al. 2020) and they have been used as a response biomarker in clinical trials (Green et al., 2017, Cadavid et al. 2017).

SEP abnormalities correlate to sensory deficits in upper and lower limbs (Leocani et al. 2003) and most likely reflect posterior column dysfunction. Tibial SEP better explain balance problems than MEP and add independent information to spinal cord MRI (Capone et al. 2019). In the current study, tibial SEP showed the closest association with EDSS and improved prediction as an additional component to qMEP in the combined score (q3EPS).

Several studies have shown that MEP correlate with clinical disability as well as with lesions and atrophy located in brain and spinal cord (review in Simpson and Macdonell 2015, Pisa et al. 2020). CMCT is the most frequently used quantitative measure and the standard for diagnostic evaluation of the pyramidal tract in single patients. However, CMCT has a lower test–retest reliability and lower sensitivity to change than the corticomuscular latency (Hardmeier et al. 2019, Hardmeier et al. 2020). In the current study, the qEPS based on CMCT performed below the mqEPS and q3EPS, which both contain the corticomuscular latency instead.

Most mmEP-studies have included MEP in ordinally scaled EP-scores (Hardmeier et al. 2017). The combination of VEP, lower limb MEP and tibial SEP has the highest reported prognostic correlation to change in EDSS (Kallmann et al. 2006). This correlation was only significant in the RRMS but not in the more advanced SPMS subgroup. Similarly, in a different cohort of advanced patients with progressive MS and MEP, lower limb MEP reached a ceiling effect, while upper limb MEP were still informative (Pisa et al. 2020).

As clinical symptoms in progressive MS may follow a pattern of a length dependent axonopathy (Giovannoni et al. 2017), the selection of limbs to record from should be adapted to patient sample and study objective. While the EDSS range of our patients is comparable to the two studies mentioned above (Kallmann et al. 2006, Pisa et al. 2020), about two thirds of their patients had SPMS. In these, a higher proportion of EP may not be recordable, as persistent conduction block caused by focal inflammation is more likely. In contrast, the predominantly neurodegenerative pathology in PPMS probably causes a more diffuse alteration of signal propagation.

As in other studies, the prognostic correlation of mmEP to future EDSS was higher than to baseline EDSS. This gap most likely reflects the amount of clinical silent dysfunction already detectable by mmEP at baseline. Hence, the combination of low EDSS and high EP-score may indicate a high risk for EDSS progression. In support of this hypothesis we detected a negative association between baseline EDSS and change in EDSS in the multivariable analysis, which, however, was non-significant.

Exposure to CD20-depleting therapy in sample 1 had no influence on EDSS change at last follow-up. As treatment was off-

label in the beginning of the study, an indication bias towards more active patients may have occurred.

There are some limitations related to the concept of using mmEP for prognostication. As the established EP modalities do not cover cerebellar function, a considerable amount of EDSS relevant disability is not captured. The same applies for fatigue and cognitive dysfunction. Moreover, in the case of inflammatory activity, an acute conduction block may occur, which alters signal propagation reversibly, but resulting EP-changes may not be associated with long-term outcome (Schlaeger et al. 2014b). However, in our PPMS cohort, acute conduction block is unlikely.

A technical limitation relates to VEP assessment. As clinical routine set-ups were used, screens for stimulus presentation differed between centers and between samples 1 and 2. Transformation in z-space by lab-specific normative values may not be sufficient to correct for such differences. These factors may explain the significant difference between qVEP values in samples 1 and 2.

Other limitations include the relatively small sample size and the partly retrospective assessment. Furthermore, EP-reading of sample 1 and sample 2 was performed at different time-points and by different raters. This may partly explain the significant differences in qMEP scores between the two samples in addition to the fact, that small samples may considerably deviate from the population mean in any direction. Nonetheless, to the best of our knowledge, the current study comprises the largest published cohort of patients with PPMS and EP-assessment, and the findings regarding prognostic value of EP-scores are well comparable in the two independent subsamples.

5. Conclusion

EP-scores, particularly the combination of MEP and tibial SEP representing long tract function, were moderately prognostic for EDSS change over three years in PPMS patients within an EDSS-range at baseline of 2.0 to 6.5. As EP measure signal propagation, they yield information, which is unique and complementary to other measures. Quantitative EP-scores have higher prognostic power than ordinal EP-scores, which, however, can be used as a short cut in a clinical setting. Nonetheless, EP-assessment has a blind spot for cerebellar dysfunction as well as cognitive dysfunction and may be complemented by body fluid biomarkers and advanced imaging to improve prognostication.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

Barro C, Benkert P, Disanto G, Tsagkas C, Amann M, Naegelin Y, Leppert D, Gobbi C, Granziera C, Yaldizli Ö, Michalak Z, Wuerfel J, Kappos L, Parmar K, Kuhle J. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. Brain. 2018;141(8):2382–91. https://doi.org/10.1093/brain/awy154.

Barro C, Leocani L, Leppert D, Comi G, Kappos L, Kuhle J. Fluid biomarker and electrophysiological outcome measures for progressive MS trials. Mult Scler. 2017;23(12):1600–13. https://doi.org/10.1177/1352458517732844.

Cadavid D, Balcer L, Galetta S, Aktas O, Ziemssen T, Vanopdenbosch L, Frederiksen J, Skeen M, Jaffe GJ, Butzkueven H, Ziemssen F, Massacesi L, Chai Yi, Xu L, Freeman S. RENEW Study Investigators. Safety and efficacy of opicinumab in acute optic neuritis (RENEW): a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2017;16(3):189–99. https://doi.org/10.1016/S1474-4422(16)30377-5.

Canham LJW, Kane N, Oware A, Walsh P, Blake K, Inglis K, Homewood J, Witherick J, Faulkner H, White P, Lewis A, Furse-Roberts C, Cottrell DA. Multimodal neurophysiological evaluation of primary progressive multiple sclerosis - An increasingly valid biomarker, with limits. Mult Scler Relat Disord. 2015;4(6):607–13. https://doi.org/10.1016/j.msard.2015.07.009.

Capone F, Capone G, Motolese F, Voci A, Caminiti ML, Musumeci G, Di Lazzaro V. Spinal cord dysfunction contributes to balance impairment in multiple sclerosis patients. Clin Neurol Neurosurg. 2019;184:105451. https://doi.org/10.1016/j.clineuro.2019.105451.

Giovannoni G, Cutter G, Sormani MP, Belachew S, Hyde R, Koendgen H, Knappertz V, Tomic D, Leppert D, Herndon R, Wheeler-Kingshott CAM, Ciccarelli O, Selwood D, di Cantogno EV, Ben-Amor A-F, Matthews P, Carassiti D, Baker D, Schmierer K. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. Mult Scler Relat Disord. 2017;12:70–8. https://doi.org/10.1016/j.msard.2017.01.007.

Green A, Gelfand JM, Cree BA, et al. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial.. Lancet Neurology 2017;390:2481–9.

Harding KE, Wardle M, Moore P, Tomassini V, Pickersgill T, Ben-Shlomo Y, Robertson NP. Modelling the natural history of primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2015;86(1):13–9. https://doi.org/10.1136/jnnp-2014-307791.

Hardmeier M, Jacques F, Albrecht P, Bousleiman H, Schindler C, Leocani L, et al. Multicentre assessment of motor and sensory evoked potentials in multiple sclerosis: reliability and implications for clinical trials. Mult Scler J Exp Transl Clin. 2019; 5:2055217319844796. doi: 10.1177/2055217319844796.

Hardmeier M, Leocani L, Fuhr P. A new role for evoked potentials in MS? Repurposing evoked potentials as biomarkers for clinical trials in MS. Mult Scler. 2017;23(10):1309–19. https://doi.org/10.1177/1352458517707265.

Hardmeier M, Schindler C, Kuhle J, Fuhr P. Validation of Quantitative Scores Derived From Motor Evoked Potentials in the Assessment of Primary Progressive Multiple Sclerosis: A Longitudinal Study. Front Neurol. 2020;11:735. https://doi.org/10.3389/fneur.2020.00735.

Jung P, Beyerle A, Ziemann U. Multimodal evoked potentials measure and predict disability progression in early relapsing-remitting multiple sclerosis.. Mult Scler 2008;14:553–6.

Kallmann BA, Fackelmann S, Toyka KV, Rieckmann P, Reiners K. Early abnormalities of evoked potentials and future disability in patients with multiple sclerosis. Mult Scler. 2006;12(1):58–65. https://doi.org/10.1191/135248506ms1244oa.

Kapoor R, Smith KE, Allegretta M, Arnold DL, Carroll W, Comabella M, Furlan R, Harp C, Kuhle J, Leppert D, Plavina T, Sellebjerg F, Sincock C, Teunissen CE, Topalli I, von Raison F, Walker E, Fox RJ. Serum neurofilament light as a biomarker in progressive multiple sclerosis. Neurology. 2020;95(10):436–44. https://doi.org/10.1212/WNL.0000000000010346.

Kappos L, D'Souza M, Lechner-Scott J, Lienert C. On the origin of Neurostatus. Mult Scler Relat Disord. 2015;4(3):182–5. https://doi.org/10.1016/j.msard.2015.04.001.

Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of primary progressive multiple sclerosis. Neurology. 2009;73(23):1996–2002. https://doi.org/10.1212/WNL.0b013e3181c5b47f.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444.

Leocani L, Martinelli V, Natali-Sora MG, Rovaris M, Comi G. Somatosensory evoked potentials and sensory involvement in multiple sclerosis: comparison with clinical findings and quantitative sensory tests. Mult Scler. 2003;9(3):275–9. https://doi.org/10.1191/1352458503ms908oa.

Leocani L, Rocca MA, Comi G. MRI and neurophysiological measures to predict course, disability and treatment response in multiple sclerosis. Curr Opin Neurol. 2016;29:243–53. https://doi.org/10.1097/WCO.0000000000000333.

London F, Sankari SE, van Pesch V. Early disturbances in multimodal evoked potentials as a prognostic factor for long-term disability in relapsing-remitting multiple sclerosis patients.. Clin Neurophysiol 2017;128:561–9.

Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015;14(2):183–93. https://doi.org/10.1016/S1474-4422(14)70256-X.

Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol. 2007;6(10):903–12. https://doi.org/10.1016/S1474-4422(07)70243-0.

Moccia M, de Stefano N, Barkhof F. Imaging outcome measures for progressive multiple sclerosis trials. Mult Scler. 2017;23(12):1614–26. https://doi.org/10.1177/1352458517729456.

Moccia M, Valsecchi N, Ciccarelli O, Van Schijndel R, Barkhof F, Prados F. Spinal cord atrophy in a primary progressive multiple sclerosis trial: Improved sample size using GBSI. Neuroimage Clin. 2020;28:102418. https://doi.org/10.1016/j.nicl.2020.102418.

Pardini M, Cutter G, Sormani MP. Multiple sclerosis: clinical trial design 2019. Curr Opin Neurol. 2019;32:358–64. https://doi.org/10.1097/WCO.0000000000000697.

Pelayo R, Montalban X, Minoves T, et al. Do multimodal evoked potentials add information to MRI in clinically isolated syndromes? Mult Scler 2010;16:55–61.

Pisa M, Chieffo R, Giordano A, Gelibter S, Comola M, Comi G, Leocani L. Upper limb motor evoked potentials as outcome measure in progressive multiple sclerosis. Clin Neurophysiol. 2020;131(2):401–5. https://doi.org/10.1016/j.clinph.2019.11.024.

Rocca MA, Sormani MP, Rovaris M, Caputo D, Ghezzi A, Montanari E, Bertolotto A, Laroni A, Bergamaschi R, Martinelli V, Comi G, Filippi M. Long-term disability progression in primary progressive multiple sclerosis: a 15-year study. Brain. 2017;140(11):2814–9. https://doi.org/10.1093/brain/awx250.

Schlaeger R, D'Souza M, Schindler C, Grize L, Kappos L, Fuhr P. Electrophysiological markers and predictors of the disease course in primary progressive multiple sclerosis. Mult Scler. 2014a;20(1):51–6. https://doi.org/10.1177/1352458513490543.

Schlaeger R, D'Souza M, Schindler C, Grize L, Kappos L, Fuhr P. Prediction of MS disability by multimodal evoked potentials: investigation during relapse or in the relapse-free interval? Clin Neurophysiol. 2014b;125(9):1889–92. https://doi.org/10.1016/j.clinph.2013.12.117.

Schlaeger R, Hardmeier M, D'Souza M, Grize L, Schindler C, Kappos L, Fuhr P. Monitoring multiple sclerosis by multimodal evoked potentials: Numerically versus ordinally scaled scoring systems. Clin Neurophysiol. 2016;127(3):1864–71. https://doi.org/10.1016/j.clinph.2015.11.041.

Simpson M, Macdonell R. The use of transcranial magnetic stimulation in diagnosis, prognostication and treatment evaluation in multiple sclerosis. Mult Scler Relat Disord. 2015;4(5):430–6. https://doi.org/10.1016/j.msard.2015.06.014.

McDonald WI, Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. Philos Trans R Soc Lond B Biol Sci. 1999;354(1390):1649–73. https://doi.org/10.1098/rstb.1999.0510.

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73. https://doi.org/10.1016/S1474-4422(17)30470-2.

Thompson AJ, Montalban X, Barkhof F, Brochet B, Filippi M, Miller DH, Polman CH, Stevenson VL, McDonald WI. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. Ann Neurol. 2000;47(6):831–5.

Waxman SG. Axonal conduction and injury in multiple sclerosis: the role of sodium channels. Nat Rev Neurosci. 2006;7(12):932–41. https://doi.org/10.1038/nrn2023.

You Y, Barnett MH, Yiannikas C, Parratt J, Matthews J, Graham SL, Klistorner A. Chronic demyelination exacerbates neuroaxonal loss in patients with MS with unilateral optic neuritis. Neurol Neuroimmunol Neuroinflamm. 2020;7(3):e700. https://doi.org/10.1212/NXI.0000000000000700.