



# Evoked potentials after autologous hematopoietic stem cell transplantation for multiple sclerosis

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## ARTICLE INFO

### Keywords:

Multiple sclerosis evoked potentials  
Autologous hematopoietic stem cell transplantation  
Visual evoked potentials  
Somatosensory evoked potentials  
Motor evoked potentials

## ABSTRACT

**Objective:** To investigate the effect of autologous hematopoietic stem cell transplantation (AHSCT) on functional aspects of the nervous system assessed by visual (VEP), somatosensory (SEP), and motor (MEP) evoked potentials in patients with relapsing-remitting multiple sclerosis.

**Background:** Several studies have demonstrated the efficacy of AHSCT on inflammatory activity and disability progression in patients with multiple sclerosis. However, the impact of AHSCT on evoked potentials has not been evaluated before.

**Methods:** Twelve AHSCT-treated patients from Uppsala University Hospital were consecutively recruited. Evoked potentials (EP) were collected at baseline and two follow-up visits, 3 and 12 months post-AHSCT. We calculated a composite EP score for each participant and compared it between different time points.

**Results:** The median total EP score decreased from 5 at baseline, to 2.5 at 12 months post-AHSCT ( $p = 0.008$ ). A significant improvement in tibial SEP (tSEP) latencies was observed (42.7 vs 41.5 ms,  $p < 0.001$ ), with a similar trend for MEP latencies 12 months post-AHSCT. No significant changes in median SEP or VEP latencies were observed.

**Conclusions:** Treatment with AHSCT was associated with improved transmission in some central nervous system pathways in multiple sclerosis patients.

## 1. Introduction

Evoked potentials (EPs) are a quantitative measurement of signal propagation in different functional pathways of the central nervous system. EPs were previously included in the diagnostic criteria for MS and as such had a supportive and complementary role in the diagnosis of MS (McDonald et al., 2001; Thompson et al., 2000). The diagnostic utility of somatosensory EP (SEP), visual EP (VEP), and brainstem auditory EP (BAEP) in MS was first presented in the 1970s and was later followed by motor EP (MEP), and vestibular evoked myogenic potentials (Baker et al., 1968; Eleftheriadou et al., 2009; Halliday et al., 1973; Hess et al., 1986; Robinson and Rudge, 1977). The important role of MRI in the 2010 revised McDonald criteria, has largely overshadowed the diagnostic value of EPs.

Notwithstanding, EPs remain vital in unveiling the

pathophysiological consequences of MS, namely demyelination and axonal loss. These pathological hallmarks manifest as alterations in EPs, such as delayed latency, morphological transformations, wave cancellation, and an increased refractory period. Although not required for the diagnosis of MS, EPs provide significant value in disability outcome prediction, correlating well with shifts in the expanded disability status scale (EDSS), the primary metric for disease-related disability (Hardmeier and Fuhr, 2021; Invernizzi et al., 2011; Jung et al., 2008; Kallmann et al., 2006; London et al., 2017; Vucic, 2012). Moreover, EPs were useful in showing stable disease and even signs of remyelination following disease-modifying treatments (DMTs) (Iodice et al., 2016; Meuth et al., 2011; Wang et al., 2021).

Autologous hematopoietic stem cell transplantation (AHSCT) is an immune reconstitution therapy for MS, which resets the immune system and halts the inflammatory process that drives disease progression

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(Cencioni et al., 2021). AHSCT is a safe and highly effective treatment for relapsing-remitting MS (RRMS) particularly highly aggressive RRMS (Atkins et al., 2016). The efficacy of AHSCT has been demonstrated in several studies: disease remission has been sustained for up to 5 years in 80 % of treated patients, improvement in disability by 1.5 in EDSS scores has been demonstrated and the absence of new MRI lesions after 3 years was seen in 93 % of treated patients (Burt et al., 2019; Muraro et al., 2017; Zhukovsky et al., 2021). The treatment has become increasingly common in recent years, and the European Blood and Marrow Transplantation registry has now registered more than 1800 patients treated with AHSCT for MS. Less is known about how treatment with AHSCT affects signal transmission in the central nervous system. This study aimed to demonstrate changes in EPs as an objective measure of signal transmission in the CNS reflecting the observed clinical improvements.

## 2. Methods

This was an observational intervention study. The intervention was autologous hematopoietic stem cell transplantation, and the outcome was motor, sensory, and visual EPs and a compound EP score.

### 2.1. Ethical approval

The study was approved by the Regional Ethical Board of Uppsala (Dnr 2012/080/1). All patients provided informed and written consent following the Declaration of Helsinki.

### 2.2. Subjects

Twelve patients were included in the study. One patient withdrew consent after recording the first set of EPs, leaving eleven for further analysis. The median age at AHSCT was 30 (22–47) years and the median disease duration was 1.0 (0.2–11) years. Patients had a median of 2 (1–4) previous relapses and three patients underwent the baseline EP investigation within 1 month of clinical relapse. Four patients were previously untreated with disease-modifying treatments (DMTs), three were treated with natalizumab, three were treated with rituximab, and one was treated with teriflunomide. The demographics and clinical characteristics of the study patients are summarized in Table 1.

### 2.3. Procedures

Autologous hematopoietic stem cells were mobilized with a single dose of 2 g/m<sup>2</sup> cyclophosphamide followed by filgrastim 5–10 µg/kg/day for 6–7 days and then harvested approximately ten days after the start of the mobilization regimen. No ex-vivo graft manipulation was performed. Patients were conditioned with a combination of cyclophosphamide and rabbit anti-thymocyte globulin (cyclophosphamide 200 mg/kg; rATG 6 mg/kg). Prophylaxis for fungal, viral, and bacterial infection was administered during neutropenia. Prophylaxis for herpes viruses and *Pneumocystis jiroveci* continued for a minimum of three months.

**Table 1**  
Demographic and clinical characteristics of the sample (n = 11).

Characteristics	
Number of patients	11
Female, N (%)	9 (75)
Age (years), median (range)	30 (22–47)
Disease duration (years), median (range)	1 (0.2–11)
Baseline EDSS, median (range)	2.5 (2–6)
Relapses preceding AHSCT, median (range)	2 (1–4)

## 2.4. Electrodiagnostics

EPs were recorded at baseline and two follow-up visits, three and twelve months after the intervention. SEP and VEP examinations were conducted according to our clinical protocol, and the results were compared to normative data collected at the Department of Clinical Neurophysiology of Uppsala University Hospital. The 10–20 EEG system was used to describe the SEP scalp electrode positions and the “Queen Square system” was used for VEP electrode positions (Blumhardt et al., 1977). For SEP, electrodes were placed at the frontal midline (Fz), at the central midline (Cz), and left and right centroparietal positions (CP3 and CP4, respectively). VEPs were recorded from the midline parietal (MP), midline occipital (MO), left occipital (LO), and right occipital (RO) electrodes. The technique used for transcranial magnetic stimulation (TMS), MEP recording, and comparison with published normative data, were based on previous studies (Groppa et al., 2012; Barker et al., 1987). Surface electrodes were used for all recordings.

### 2.4.1. Motor evoked potentials

The patient was comfortably seated in a reclining chair during TMS. MEPs were elicited from the upper and lower extremities; abductor digiti minimi (ADM), tibialis anterior (TA), and abductor hallucis (AH) muscles. The recording electrodes were placed in a muscle belly-tendon manner in a similar way as for motor nerve conduction studies. The circular coil (C-100, Magventure, GA, USA) used for stimulation was centered on the vertex (Cz) with the handle pointing in a posterior direction. The coil was slightly tilted towards the stimulated hemisphere for upper extremity MEPs, while for lower extremity MEPs, the coil was kept in a horizontal plane. Predominantly left- or right-sided stimulation was achieved by alternating the current flow direction in the coil by alternating which side of the flat coil surface was facing the scalp. A software application was used to determine the resting motor threshold for ADM and TA (TMS MTAT 2.0) (Borckardt et al., 2006). MEPs were produced by applying suprathreshold stimulus intensities (140 % of the resting motor threshold up to a maximum of 100 % stimulator output) in subsequent sessions for each extremity. Only MEP latencies from relaxed muscle recordings were analyzed.

### 2.4.2. Sensory evoked potentials

The patients were positioned in a relaxed supine position. Repetitive transcutaneous electrical stimuli (2 Hz, duration 0.1 ms, typically at 10–30 mA intensity) were used to stimulate the tibial nerve at the medial malleolus of the foot (tibial SEP) and the median nerve approximately 3 cm proximal to the wrist (median SEP). Median N20 scalp SEP latencies were recorded from a CP3-Fz/CP4-Fz scalp montage. Tibial P40 scalp SEP latencies were recorded from two different montages, i.e., midline (Cz-Fz) and transverse (CP3-CP4/CP4-CP3) montages. The ground electrode was placed on the stimulated extremity. SEP signals were averaged from at least 200 stimuli to reduce background noise.

### 2.4.3. Visual evoked potentials

The patient was seated in a relaxed position in a dark room, 1 m in front of a computer screen while focusing on a red marker at the center of the screen. Each eye was stimulated with monocular full visual field stimulation while the other eye was covered. The visual stimulus consisted of alternating black or white squares in a checkboard pattern i.e., pattern reversal VEP, with 12×16 squares presented on the screen, and each square 25 mm × 25 mm in size. The final VEP signal was an average of 100–200 stimuli, and the examination was repeated 2–3 times for each eye to ensure reproducibility. Four different recording montages were used (MO-Fz, MP-Fz, LO-Fz, and RO-Fz).

### 2.4.4. Evoked potential scoring

MEP, SEP, and VEP results were scored based on response latencies and possible signal loss (range 0–2; 0 - normal latency; 1 - prolonged latency, 2 - absent signal). The MEP score was based on MEP responses

from one hand and one foot muscle (ADM and AH, respectively) on both sides (range 0–8). The upper normal limit for ADM and AH MEP onset latencies were 25.2 ms and 49.3 ms, respectively. The SEP score was based on SEP responses from median and tibial nerve stimulation on both sides (range 0–8). Since the tibial SEP was recorded from two montages, an average score was calculated for this examination. The upper normal limit for the median SEP N20 latency was 21.7 ms. The upper normal limit for the tibial SEP P40 latency was length dependent ( $11.76 \text{ ms} + 17.8 \text{ ms} * \text{height (m)}$ ). The VEP score was an average of scores from the two midline (MO-Fz and MP-Fz) recordings (range 0–4). For each patient, a compound score was calculated by adding separate EP scores for each modality (range 0–20). The upper normal limit for the VEP P100 latency was 122 ms.

### 2.5. Statistics

Statistical analyses were performed in GraphPad Prism 9.2 (GraphPad Software, La Jolla, CA, USA). Medians with range were used to summarize data. Correlations were described with Spearman's  $r$ . For comparisons between two measurement time points, the Wilcoxon signed-rank test was used. Friedman's test was applied for comparisons between three measurement time points. A two-tailed  $p < 0.05$  was considered statistically significant.

## 3. Results

### 3.1. EDSS and MSIS-29

EDSS and MSIS-29 physical scores for eleven patients were collected at two study time points, at baseline and 12 months post-AHST. Both EDSS and MSIS-29 physical scores improved post-AHST. The median EDSS score decreased from 2.5 (range 2–6) at baseline to 2 (range 0–2.5) 12 months post-AHST ( $p = 0.008$ ). The mean physical MSIS-29 score of 37 (range 5–74) at baseline dropped to 11 (range 1–45) 12 months post-AHST ( $p = 0.004$ ).

An EP score was generated for each patient to quantify the neurophysiological differences at baseline and at 12 months after the treatment (see Methods). In 7 of the 9 patients, the EP score improved at 12 months after AHST compared to baseline. The pre-AHST median EP score of 5 (range 0–10) decreased to 2.5 (range 0–9) at 12 months after AHST ( $p = 0.008$ ).

The changes in the EP scores were not correlated with the EDSS score changes (Spearman  $r = 0.16$ ,  $p = 0.53$ ), however, there was a possible correlation with the changes in the relevant functional system scores (pyramidal, sensory, and visual functional system scores) (Spearman  $r = 0.5$ ,  $p = 0.086$ ). EDSS pyramidal function scores range from 0 (normal function) to 6 (tetraplegia).

EDSS sensory and visual function scores range from 0 (normal functions) to 5 (sensory deficit  $\geq 3$  limbs and visual acuity  $< 0.1 / \leq 0.3$ ).

### 3.2. Evoked potentials

The median values of the latencies in milliseconds (ms) were calculated at the three different time points of the study (Table 2).

**Table 2**

Median values of the evoked potential latencies in milliseconds (ms) at baseline, 3 months, and 12 months post-AHST.

	Baseline	3 months	12 months	P
MEP	34.5	34.2	29.6	0.026
mSEP	19.4	19.3	19.0	0.11
tSEP	42.7	42.2	41.5	$< 0.001$
VEP	114	120	113	$< 0.001$

P-values for Friedman's test. The result of the post-hoc analyses are displayed in Fig. 4.

A correlation between MEP, SEP, VEP scores, and functional system scores was observed in most of the patients (Figs. 1–3). The MEP and tSEP latencies improved 12 months after AHST (Fig. 4), which explains the decrease in the EP scores.

### 3.3. MEP

In total, nine patients underwent MEP examination. The results at 12 months post-AHST showed improved MEP scores in four patients, unchanged scores in four patients, and worsened MEP scores in one patient compared to baseline. The differences in MEP scores and pyramidal function system scores at the two-time points are illustrated in Fig. 1. Fig. 5 illustrates improved transmission after AHST in an actual MEP recording. The median value of the MEP latencies when summing up the responses of all muscles was similar at baseline (34.5 ms) and 3 months (34.2 ms), but lower at 12 months (29.6 ms,  $p = 0.026$ ) after AHST (Table 2). MEP latencies for each muscle group separately were calculated for each timepoint (Table 3). Between the measurements at 3 months and 12 months, a statistically significant decrease in the combined MEP latencies was noted (Fig. 4). However, there was no statistically significant difference between the three examination time points for MEP latencies when measuring each muscle separately.

### 3.4. SEP

In total, eleven patients underwent an examination with SEP. The SEP score improved in four patients at 12 months post-AHST and remained unchanged in seven patients. The differences in SEP scores and the sensory functions system scores are presented in Fig. 2. Fig. 6 shows improved SEP latencies after AHST in an actual recording. The median mSEP latencies at baseline (19.4 ms), 3 months (19.3 ms), and 12 months (19.0 ms) were similar, without statistically significant difference between the groups. The median tSEP latency was lower at 12 months (41.5 ms) than at baseline (42.7 ms) and at 3 months (42.5 ms) with statistically significant differences between baseline and 12 months, as well as between 3 and 12 months post-AHST (Fig. 4).

### 3.5. VEP

In total, eleven patients underwent an examination with VEP. Improvements in the VEP scores were seen in three patients and remained unchanged in 8 patients. The differences in VEP scores and the visual functions system scores are illustrated in Fig. 3. As shown in Table 2, the median VEP latencies were significantly longer at 3 months (120 ms) than at baseline (114 ms) and at 12 months (113 ms). The significance of median VEP latencies changes is due to the deterioration at 3 months. Fig. 4 shows the worsening of VEP latencies at 3 months, and their recovery at 12 months. Fig. 7 demonstrates restoration of VEP after AHST in an actual recording.

## 4. Discussion

To our knowledge, this is the first study reporting on EPs following AHST for MS patients. Overall, EPs showed some considerable improvements post-AHST, and the EP scores were reduced to half at 12 months post-AHST. The effect was most pronounced on tSEP latencies, and a similar trend was observed for MEP latencies.

Although the exact anti-inflammatory mechanism of AHST is not fully understood, biomarkers of demyelination and axonal damage have been observed to decrease post-AHST (Zjukovskaja et al., 2022), suggesting potential pathophysiological mechanisms such as the stabilization of tissue injury. This might explain the improvements of EPs following AHST in our study, which also suggests possible remyelination. Prior research indicates that around half of the patients treated with AHST exhibit an improvement in disability, usually within the first year after the treatment (Burt et al., 2019; Zhukovsky et al., 2021;

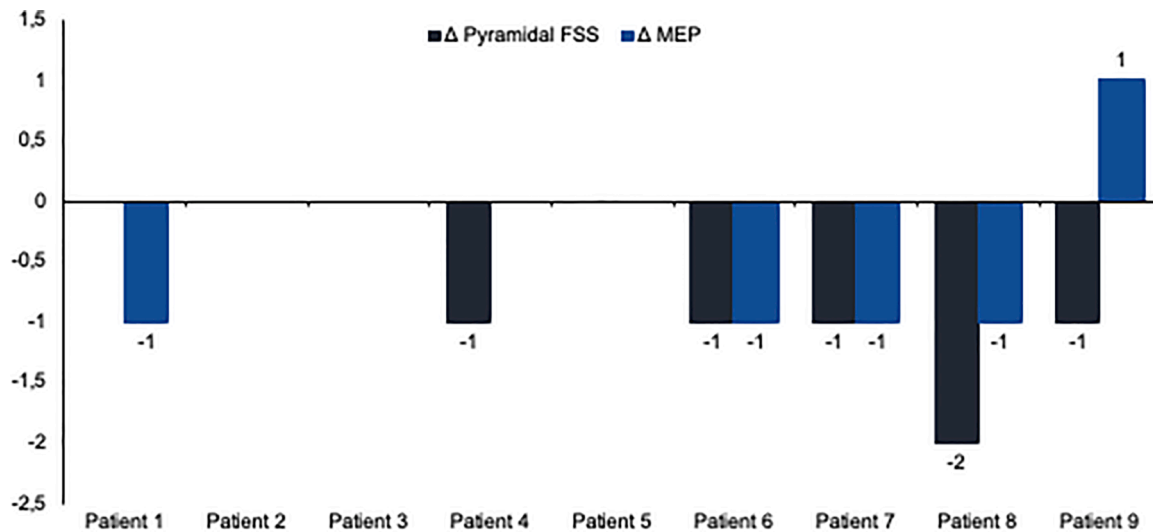


Fig. 1. Differences in MEP scores and pyramidal function system scores for each of the 9 patients between baseline and 12 months post-AHSCT (Score at 12 months – score at baseline). Negative values indicate improvement.

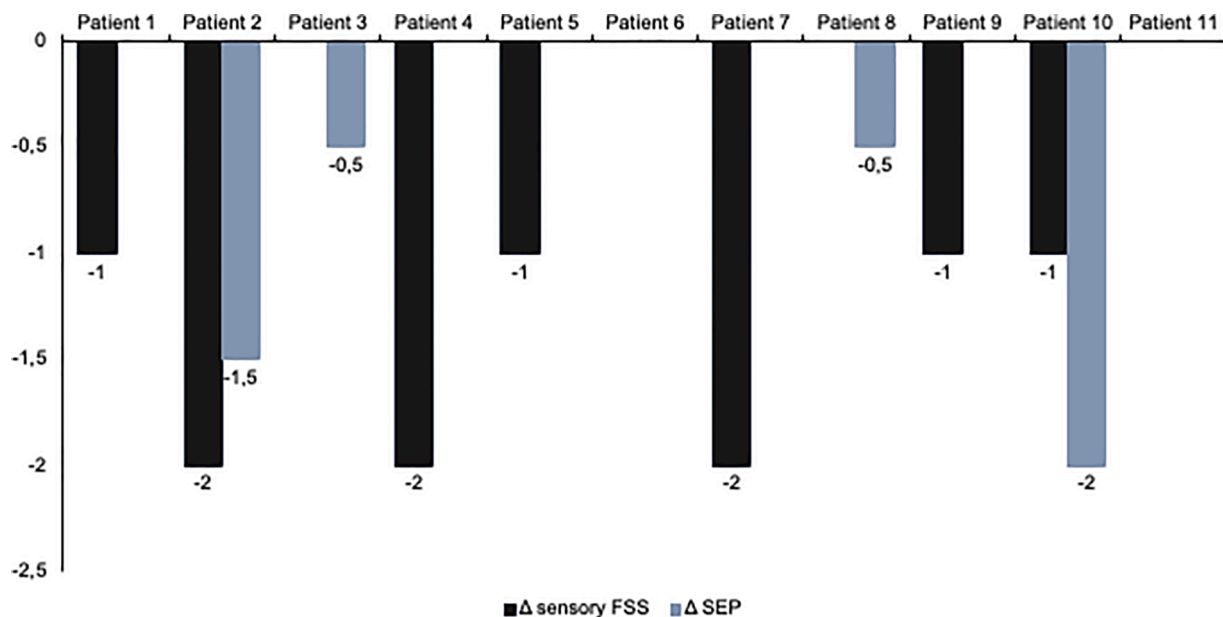


Fig. 2. Differences in SEP scores and sensory function system scores for each of the 11 patients between baseline and 12 months post-AHSCT (Score at 12 months – score at baseline). Negative values indicate improvement.

Burman et al., 2014). The selected study time points (baseline, 3 months, 12 months) were deliberately chosen to highlight when this improvement occurs. The findings in this study support a gradual improvement in disability throughout the initial year post-AHSCT.

Although MRI and EDSS scores are established markers of disease activity and progression, there are limitations in their usefulness for disease surveillance that may overlook crucial factors contributing to disease progression and disability. The inherent limitations of the EDSS scale can produce a misleading impression of stability, especially at higher EDSS scores. Cortical and spinal cord lesions have been associated with disability and disease progression (Beck et al., 2022; Bussas et al., 2022). However, cortical lesions are not readily detected with 1.5T MRI scans, and spinal cord lesions are missed when performing MRI restricted to the brain and cervical spine. Brain atrophy has known limitations as a monitoring tool as it is susceptible to intra-scanner variation and is only detected when it is already present (Sinnecker et al., 2022).

Multimodal EPs were shown to predict a significant proportion of EDSS score changes over years, and thus contribute to risk stratification of clinical worsening (Schlaeger et al., 2016). In a recent study of patients with primary progressive multiple sclerosis (PPMS), EP scores at baseline predicted 32 % of EDSS score changes over 3 years. MEP and tibial SEP latencies were found to have the greatest prognostic values, while the correlation between VEP and EDSS score changes was insignificant (Hardmeier et al., 2022).

In another study, multimodal EPs were recorded within 6 months of the diagnosis. These EP scores were predictive of higher EDSS scores and disability burden at 10 years, implying a possible role for risk classification early in the disease course (Schlaeger et al., 2012). Although changes in the EDSS score did not correlate well with changes in the EP score in our material, there was a clear association between changes in MEP and SEP scores and the corresponding functional system scores.

A significant finding of this study is that tSEP latencies decreased from baseline to 12 months post-AHSCT, while median somatosensory

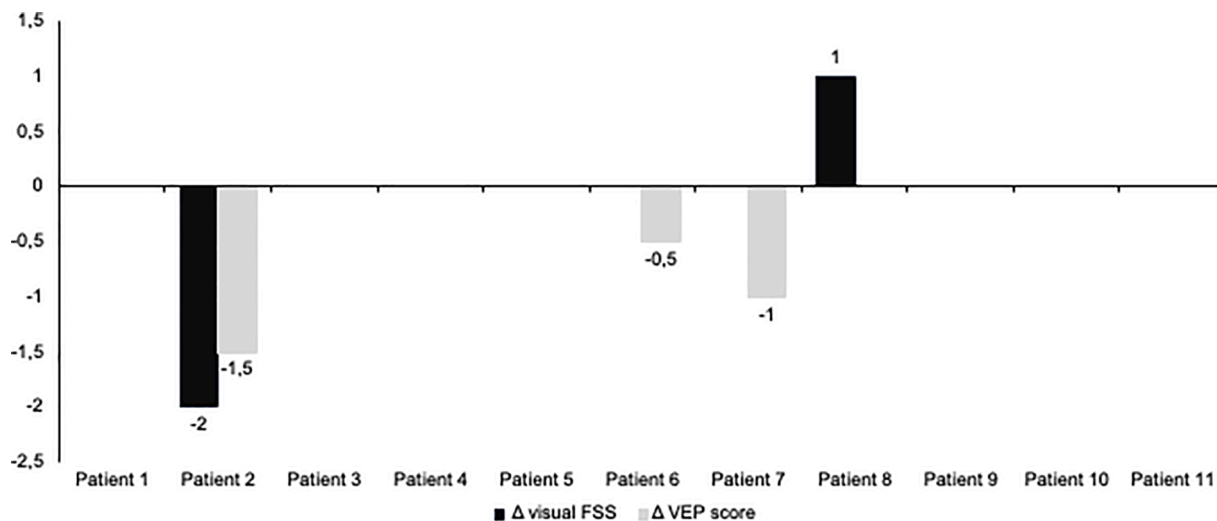


Fig. 3. Differences in VEP scores and visual function system scores for each of the 11 patients between baseline and 12 months post-AHSCT (Score at 12 months – score at baseline). Negative values indicate improvement.

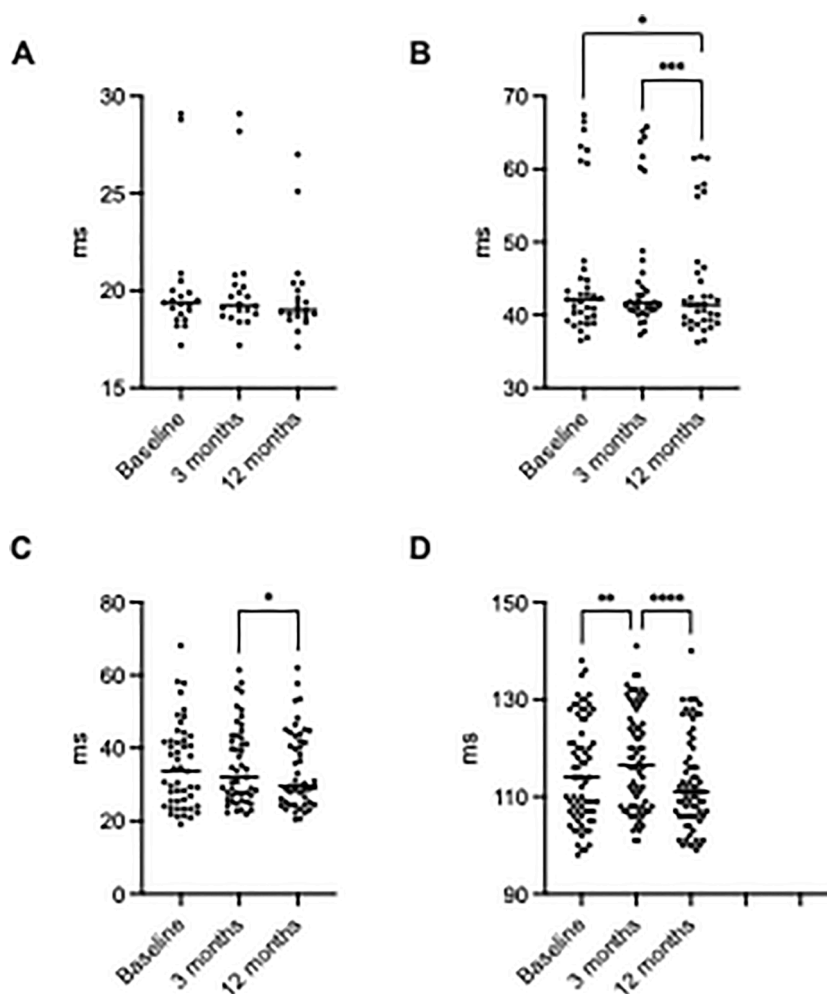
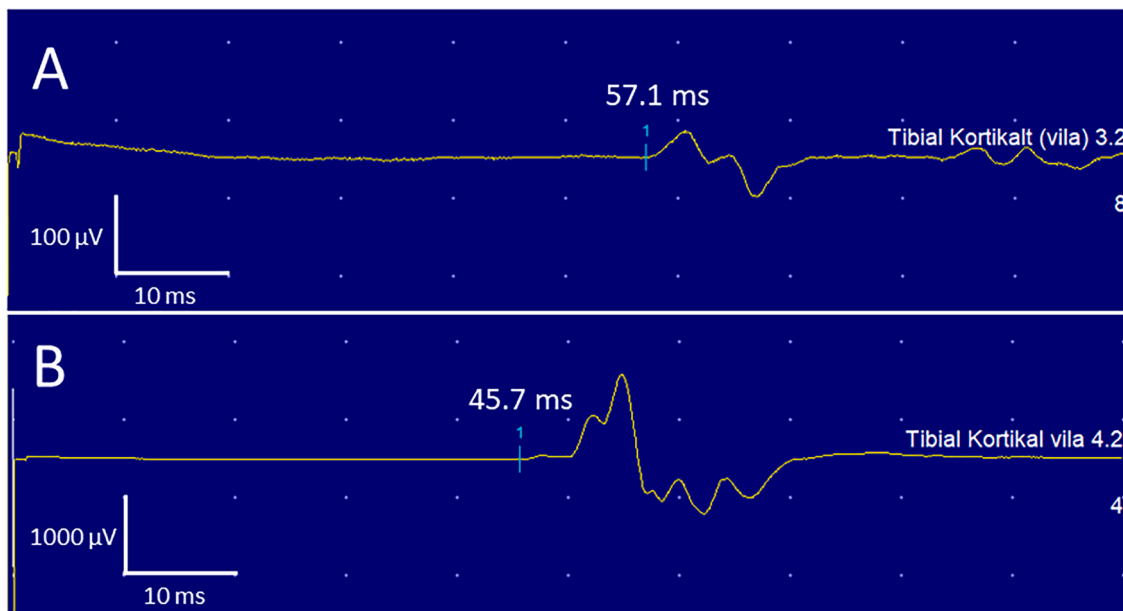


Fig. 4. Evoked potentials before and after AHSCT. Evoked potential latencies were recorded at three-time points: before AHSCT and 3 and 12 months after AHSCT. (A) median nerve SEP, (B) tibial nerve SEP, (C) MEP, and (D) VEP.

evoked potentials (mSEP) latencies showed no significant improvement. This could be attributed to the fact that a larger section of the sensory tract in the spinal cord contributes to tSEP compared to mSEP latencies.

Furthermore, MEP acted as a neurophysiological marker of pyramidal tract function in our study, with MEP latencies reducing from 3 to 12 months post-AHSCT. VEP latencies were paradoxically worsened at 3



**Fig. 5.** MEP responses from right m. abductor hallucis before (A) and 12 months post (B) AHST. After treatment, there is a reduction in MEP latency and a more than tenfold increase in amplitude, indicating improved transmission in the central motor pathways. In this case (patient 1 in Fig. 1), the improvement was not corroborated by clinical scoring. Note the different display gain in panel B.

**Table 3**

Mean MEP latencies in milliseconds (ms) from abductor digiti minimi (ADM), tibialis anterior (TA), and abductor hallucis (AH) muscles at baseline, 3 months and 12 months post- AHST. Standard deviation (SD).

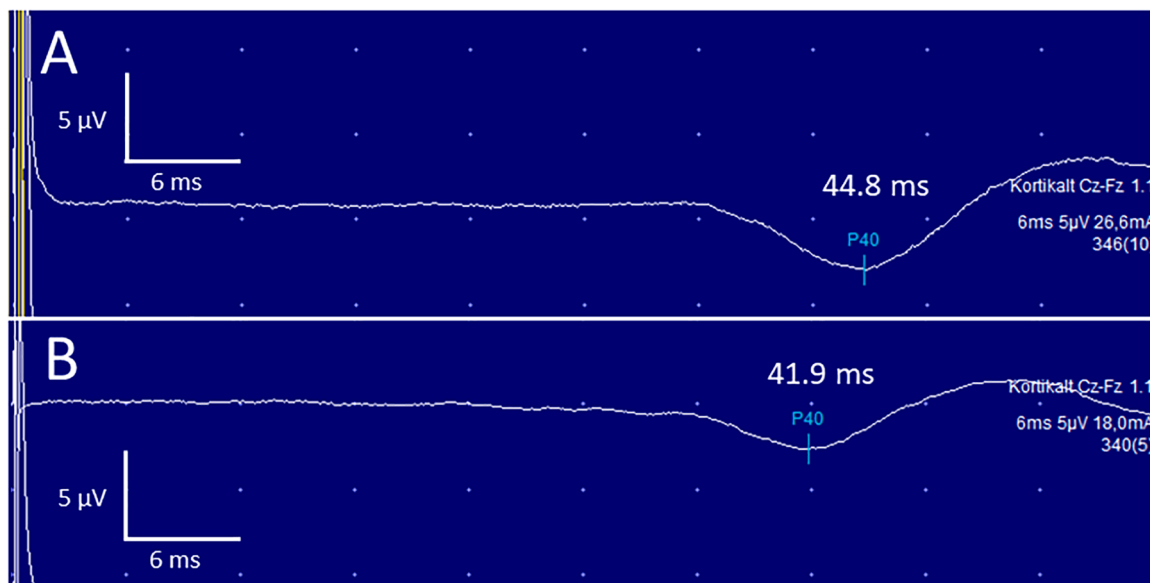
Mean MEP latencies	Baseline	SD	3 months	SD	12 months	SD
ADM	25.2	4.5	25.7	3.2	24.8	3.1
AH	49.1	10.2	48.8	6.7	46.3	6.9
TA	35.5	11	35.6	9.3	31.9	5.8

months post-AHST but were restored at 12 months. This was not accompanied by any clinically observable change in visual function and the relevance of this finding is unclear.

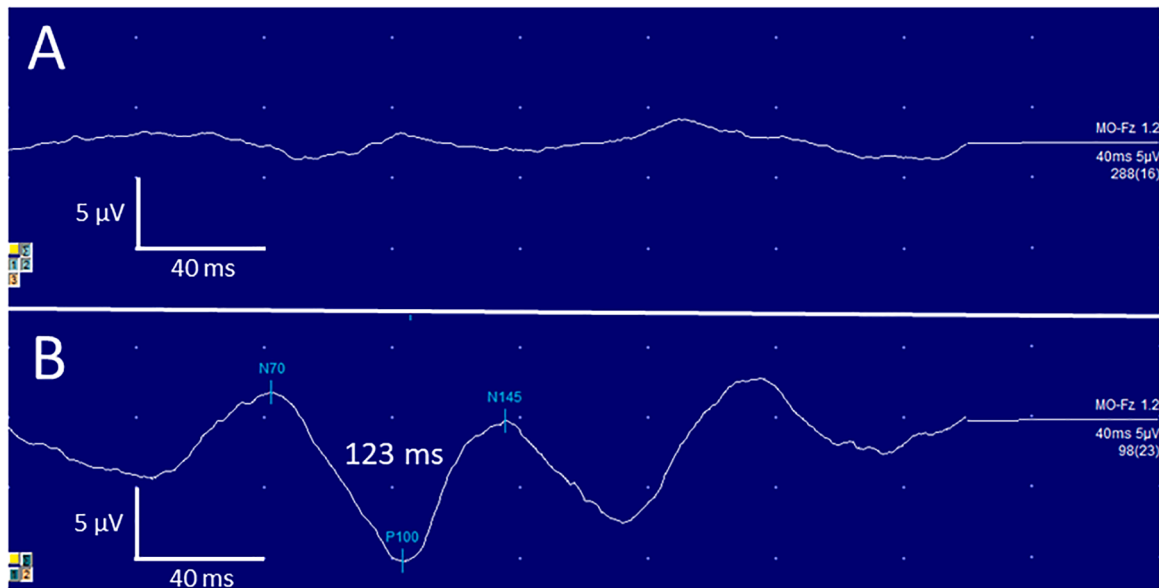
There is limited data on the influence of approved MS treatments on

EPs. In a recent study, treatment with alemtuzumab improved VEP latencies, with a mean shortening of the VEP latency by 1.21 ms, 24 months after treatment initiation (Wang et al., 2021). Two separate studies registered multimodal evoked potentials before treatment initiation and 12 months after with fingolimod and natalizumab (Iodice et al., 2016; Meuth et al., 2011). A significant improvement in VEP and SEP scores was demonstrated one year after each treatment. Neither fingolimod nor natalizumab showed a significant effect on the MEP scores.

The most important limitation of our study is the small number of participants. One patient withdrew consent before all tests were completed. MEPs could not be recorded in two patients due to relative contraindications. The statistical challenge of the missing MEP measurements could be partly circumvented by comparing compound EP



**Fig. 6.** Tibial SEP responses from stimulation of the right tibial nerve before (A) and 12 months post (B) AHST. After treatment, there is a reduction in SEP latency. There was also improvement in clinical scoring (patient 2 in Fig. 2).



**Fig. 7.** VEP recording from the MO-Fz montage after stimulation of the right eye before (A) and 12 months post (B) AHCST. There is no clear VEP response before treatment (A). The VEP is restored 12 months after treatment (B) with a close to normal latency. There was also improvement in clinical scoring (patient 2 in Fig. 3).

scores.

In summary, our study suggests that AHSCT improves nervous system conduction aligning with the growing body of research advocating the use of EPs as a tool for assessing clinical response to MS treatments.

#### CRediT authorship contribution statement

**Evangelos Katsarogiannis:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Hans Axelsson:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Shala Berntsson:** Conceptualization, Methodology, Writing – review & editing. **Holger Rothkegel:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Joachim Burman:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing.

#### Declaration of competing interest

The authors declare that there is no conflict of interest.

#### Funding

The author(s) disclosed receipt of the following financial support for this article's research, authorship, and/or publication: HA and HR were supported by grants from the Ivon Vikströms Memorial Fund.

#### Acknowledgments

Technician Nadine Musonera Jönsson is acknowledged for conducting the majority of the neurophysiological examinations and documentation.

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