TMS-EEG Signatures of Neurophysiological Motor Network Dysfunction in Multiple Sclerosis: Clinical and Prognostic Correlates

Stefano Pellegrini[1], G. Leodori[1,2], M. Mancuso[1], D. Maccarrone[1], M. Tartaglia[1], M. I. De Bartolo[1,2], A. Collura[1], L. Malimpensa[1], D. Belvisi[1,2], G. Ferrazzano[1], U. Ziemann[3,4], A. Conte[1,2]

[1]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy; [2]IRCCS Neuromed, Pozzilli, IS, Italy; [3]Department of Neurology & Stroke, University Hospital Tübingen, Tübingen, Germany; [4]Hertie-Institute for Clinical Brain Research, University Hospital Tübingen, Tübingen, Germany

Introduction: Multiple sclerosis (MS) shows early synaptic and network dysfunction that escapes clinical/MRI metrics and drives smouldering progression. Motor disability is a major determinant of long-term impairment; the primary motor cortex (M1) is a key hub. TMS–EEG provides millisecond-resolution readouts of cortical reactivity and network interactions via TMS-evoked potentials (TEPs). Time–frequency analysis of TEPs quantifies TMS-related spectral perturbations (TRSPs), indexing behaviorally relevant oscillations central to sensorimotor function. TMS-EEG measures may sensitively capture motor-network integrity in MS and support prognostic/therapeutic stratification.

Objectives / Aims:

- Determine whether TMS-EEG measures differentiate patients with MS from healthy volunteers (HVs).
- Test associations of TEP/TRSP metrics with disease duration, EDSS, and neuro performance (9HPT, T25FW, SDMT).
- Assess prognostic value of TMS-EEG measures to predict 2-year NEDA-3 status.

Methods:

- Participants: 43 stable RRMS and 26 HC; right-handed; no CNS-active meds. MS patients followed for 2 years (T1) → NEDA-3 vs EDA classification.
- TMS: 120 single pulses over left M1 at 90% RMT (ISI 1.1–1.4 s); figure-of-eight coil; neuronavigation. EEG: 32-ch, noise-masking + foam.
- Preprocessing: EEGLAB/TESA pipeline; two-stage ICA; average re-ref.
- TEPs: Identified **P15**, **P30**, **N45**, **P60**, **N100** from grand-average; data-driven ROIs/TOIs; extracted peak **amplitude** & **latency**.
- TRSPs: Morlet 1–45 Hz; baseline −600…−100 ms; data-driven Beta TMS-related synchronization (TRS) (17–21 Hz, 63–171 ms), Gamma TRS (33–44 Hz, 15–55 ms), and Gamma TRD (33–41 Hz, 210–399 ms); **mean power** over ROI electrodes.
- Statistics: Mann–Whitney (HC vs MS; NEDA vs EDA) with FDR; Spearman correlations (duration, EDSS, 9HPT). Logistic regression for 2-y NEDA-3 (univariate $p<0.015$ entered multivariate).

Results:

- Cohort: 31 NEDA, 12 EDA; disease duration 7 y [1–26] (EDA vs NEDA ns). EDSS T0 higher in NEDA 1.5 vs EDA 1.0 ($p=0.04$); EDSS T1 ns; DMTs: NAT 30, CLA 9, DIM 2, OZA 1, TER 1. Groups matched for age/sex/TMS intensity.
- TEPs (MS vs HC): Canonical M1 profile. P60 amplitude ↓ in MS ($p=0.0098$; FDR=0.049). Other amplitudes/latencies ns; (NEDA vs EDA): P15 ns ↑ in NEDA ($p=0.0178$; FDR=0.089).
- TRSPs (MS vs HC): Similar topographies. Gamma TRD ns ↓ in MS ($p=0.025$; FDR=0.075); Beta TRS, Gamma TRS ns. (NEDA vs EDA): No TRSP differences.
- Correlations: Gamma TRD ↘ 9HPT time (better dexterity) ($rs=-0.504$, $p=0.001$). P60, P15: no correlations with duration/EDSS/9HPT.
- Prognosis: P15 amplitude predicts 2-y NEDA-3 (OR=2.32, $p=0.023$); classification accuracy 74.4% (sens 93.5%, spec 25%).

Fig.1

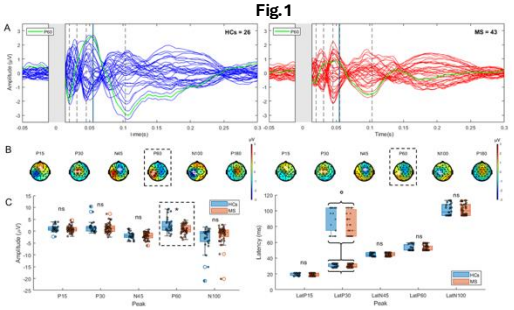


Fig.2

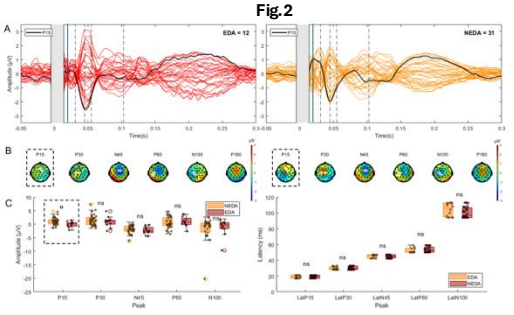


Fig.3

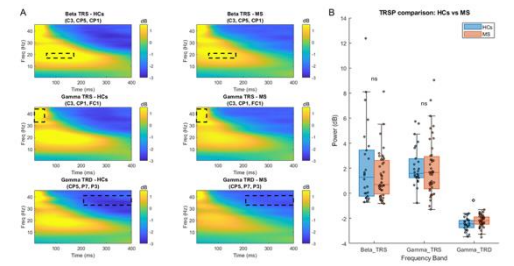
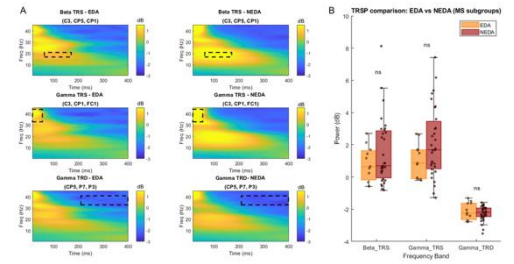


Fig.4



Conclusions: M1 TMS–EEG revealed a reduction in P60 amplitude in MS compared to HC, indicating impaired excitability and effective connectivity (cortico-cortical and subcortico-cortical dynamics); latencies were unchanged, suggesting changes in synaptic activity rather than conduction slowing. Gamma-band TRD tended to be lower in MS and negatively correlated with 9HPT time, consistent with compensatory "fine-tuning" of inhibition. Prognostically, higher baseline P15 — previously linked with interhemispheric transmission — was associated with—and alone predicted—2-year NEDA-3, albeit with limited specificity. Finally, P60 and P15 did not correlate with disease duration, EDSS, or 9HPT, suggesting subclinical network dysfunction detectable by TMS–EEG. TMS–EEG is a feasible, non-invasive probe of cortical network reactivity in MS. It may bridge structural pathology and clinical expression. Larger, longitudinal multimodal studies (reliability, MRI integration) are needed to validate prognostic utility.

Disdosure: Ulf Ziemann: Received consultation honoraria from Cortec and Neurocrine Biosciences. Antonella Conte received speaking honoraria from Roche, Biogen, Novartis, BMS, Allmiral, Merck, Lundbeck and research support from Biogen. The other authors have nothing to disclose.