Concept Paper

Not peer-reviewed version

Multiple Sclerosis Treatment Strategy Optimization by PREdicting DIsease Progression through Linear and Non-linear Dynamics of Eeg Time-Series: The “MuST Predict” Conceptual Framework

Vasilis-Spyridon Tseriotis *

Posted Date: 6 December 2023

doi: 10.20944/preprints202312.0374.v1

Keywords: Multiple sclerosis; progression; treatment optimization; EEG; non-linear dynamics; criticality

Concept Paper

Multiple Sclerosis Treatment Strategy Optimization by PREdicting DIsease Progression through Linear and Non-Linear Dynamics of EEG Time-Series: The "MuST PREDICT" Conceptual Framework

Vasilis-Spyridon Tseriotis [1,2]

[1] Department of Neurology, "Agios Pavlos" General Hospital of Thessaloniki, Thessaloniki, Greece; vasilistseriotis@hotmail.com

[2] Laboratory of Clinical Pharmacology, Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract: Gradual disability worsening in Multiple Sclerosis (MS) is indicative of confirmed progression that mostly involves progression independent of relapse activity (PIRA) and is associated with neurodegeneration. Insights from pathology reveal grey matter involvement (neocortex, hippocampus, spinal cord, and deep grey matter structures) and microglia activation in early stages of MS. Cortical lesions result in thinning and atrophy and are considered accurate predictors of disability progression and cognitive decline. Neuroimaging biomarkers, such as high-resolution 7T MR images and TSPO-PET, have been examined for the detection of cortical pathology linked to cognitive deficits and thus progression, but are limited in clinical practice due to availability, time constraints, and cost. Electroencephalography (EEG) emerges as a non-invasive, cost-effective tool that reflects cortical activity in MS. Its potential in monitoring cognitive impairment is explored by focusing on nonlinear EEG analysis. The MuST PREDICT™ project aims to extract linear and nonlinear EEG features, investigating their role in predicting disease progression and optimizing treatment. The study employs retrospective, cross-sectional, and prospective designs, utilizing EEGs from various MS forms, cognitive assessments, serum/cerebrospinal fluid biomarkers and neuroimaging. The methodology involves time-based and spectral feature extraction, employing artificial intelligence classifiers and brain criticality-based approaches. The conceptual framework of an innovative modality is herein presented, that would EEG for early MS progression detection. Standardization of the methodology could lead to the creation of a digital tool for better prognostication and treatment strategy optimization.

Keywords: multiple sclerosis; progression; treatment optimization; EEG; non-linear dynamics; criticality

Introduction

Gradual disability worsening in Multiple Sclerosis (MS) is the hallmark of "confirmed progression". Both relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA) have been thought to contribute to confirmed disability accumulation. However, PIRA is linked to the neurodegenerative aspect and disability progression that would eventually lead to a progressive disease form (1).

Insights from pathology and immunocytochemical studies have indicated grey matter involvement (neocortex, hippocampus, spinal cord and deep grey matter structures) with non-inflammatory lesion, as well as microglia activation from the early stages of the disease (2). Cortical lesions result to thinning and atrophy, that are considered the strongest predictors of disability progression and cognitive function (3–5).

Since cognitive decline presents significantly different prevalence among the various MS forms, reaching up to 79.4% and 91.3% in populations with secondary progressive MS (SPMS) and primary progressive MS (PPMS), respectively (6,7), numerous studies have examined the use of possible neuroimaging biomarkers for the detection of cortical pathology as a sign of disease progression. High-resolution 7T MR images with cortical segmentation, iron-sensitive techniques and TSPO-PET have thus been used (8) to identify cortical pathology, and the lesions are further categorized into

 doi:10.20944/preprints202312.0374.v1

subpial, intracortical and leukocortical (9). However, the afore-mentioned techniques remain widely unavailable, since they have mainly been investigated in research protocols. Furthermore, they are time-consuming and their accuracy in vivo remains questionable. Their application in the everyday clinical practice seems to be also be limited by the time-sensitive nature of segmentation techniques, the need for evaluators with high expertise and their cost.

Electroencephalography (EEG) on the other hand is a non-invasive, low-cost, widely available and easy to perform technique that can directly reflect cortical activity. Its utility in the detection of cortical involvement in MS has been studied both in a resting state and during tasks, suggesting its use as a tool for the monitoring of cognitive impairment (10–13). However, in the recent years interest has been shifting to non-linear analysis of EEG recordings. Since EEG signals are deterministic and present a chaotic behavior (14) with signal fluctuation randomness in respect to time (15), the theories of non-linear dynamical systems and the theory of chaos, along with their respective signal-processing algorithms, have been introduced in the study of complex pathologies that affect the human brain as a whole, in an attempt to uncover information that may appear random and cannot be otherwise analysed (16,17). A recent systematic review by Hernandez et al. presented seventeen studies that had used either resting-state or task-based EEG, focusing mainly on the diagnosis of MS and differentiation of patients from controls based on EEG (18). Fractal dimension, recurrence quantification analysis, mutual information, and coherence function and wavelet analysis were the most frequently encountered nonlinear dynamics analyses.

MuST PREDICT Conceptual Framework

Focusing on cortical pathology, the conceptual framework of the present paper regards the use of EEG analysis through various signal-processing algorithms, exploring its clinical utility as a biomarker for the detection of underlying disease progression and thus early treatment optimization in patients with MS (pwMS). Moreover, apart from the investigation of cortical pathology in EEG features, the hypothesis also supports a possible role of this methodology in early detection of disruption of functional connectivity in pwMS. MuST PREDICT™ (Multiple Sclerosis Treatment strategy optimization by PREdicting DIsease progression through linear and non-linear dynamics of EEG Time-series) comprises an umbrella-project, in which linear and non-linear EEG features will be extracted in different groups of pwMS. Herein, an initial scheme of the experimental design is provided. Analysis of EEG characteristics will thus first be conducted in a pilot study with a retrospective design, in which EEGs from pwMS (obtained for other reasons in the past at any point of the disease course and stored in clinics' biobanks) will be used. The results will then be interpreted after categorization of different disease forms and association with available patients' characteristics like sex, age, measures of disability (e.g., EDSS, T25-FW), disease duration, clinical relapses, treatment regimen, as well as MRI characteristics. As a next step, cross-sectional studies will be conducted in which EEGs will be obtained from patients with progressive forms of MS that also present cognitive deficits; thus, EEG features of cognitively affected patients will be compared to patients that present with a first demyelinating episode, clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), and/or relapsing-remitting MS (RRMS), in conjunction to cognitive assessment and neuropsychological tests. MRI characteristics and serum/cerebrospinal fluid biomarkers of disease progression (e.g., neurofilament light chains, GFAP) will also be studied, when available, and their association to EEG results will be investigated with the appropriate statistical model. Subjects with PMS and RRMS will be further grouped according to the efficacy of their treatment regimen and treatment duration. Patients will be matched in terms of basic characteristics and a statistical analysis of will explore differences in EEG features between groups of different disease-modifying treatment. Plus, a within-groups analysis will examine EEG differences in conjunction to treatment duration, linking EEGs to the achieved clinical outcomes and investigating early treatment initiation. Finally, a prospective study will be designed, in which the subjects will have regular follow-ups and a new EEG in a period of 1-2 years. RRMS subjects with high risk for conversion to SPMS (19,20) will be investigated and EEG features will be analyzed in association to the patients' DMT efficacy, measures of disability, MRI and serum/cerebrospinal fluid biomarkers. Of special interest will be the study of

patients that were diagnosed with SPMS and in which the appropriate treatment was initiated. In all steps, the use of EEGs from healthy controls will also be used, if reasonable.

Regarding the methodology of EEG analysis, both time-based and spectral features will be extracted. The extracted features will then be used as input for artificial intelligence classifiers, in order to train the model and evaluate both whole-brain dynamics as well as changes in specific topographies. Multivariate multi-scale methodologies will also be employed, if indicated. Additionally, a criticality-based approach will also be investigated using the method of critical fluctuations and Haar-wavelet analysis (21).

Disccussion

Even though a number of tools and algorithms have been proposed for early detection of disease progression, recognition of the transition phase from has been challenging (22). Our approach will attempt to investigate the role of EEG, an easy-to-perform neurophysiologic modality, in the prediction of the clinical course of the disease and response to treatment regimens, by extracting and analyzing measures from different MS forms. The generation and validation of an automated methodology that would analyze EEG datasets from pwMS or early forms of the disease and compare them with standardized values according (also taking into account specific patient's characteristics) could comprise a digital tool for better prognostication and treatment strategy optimization.

References

1. Kappos L, Wolinsky JS, Giovannoni G, Arnold DL, Wang Q, Bernasconi C, et al. Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. JAMA Neurol [Internet]. 2020 Sep 1 [cited 2023 Dec 5];77(9):1132–40. Available from: https://pubmed.ncbi.nlm.nih.gov/32511687/
2. Klaver R, De Vries HE, Schenk GJ, Geurts JJG. Grey matter damage in multiple sclerosis: a pathology perspective. Prion [Internet]. 2013 Jan [cited 2023 Dec 5];7(1):66–75. Available from: https://pubmed.ncbi.nlm.nih.gov/23324595/
3. Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis – insights from pathology. Curr Opin Neurol [Internet]. 2014 [cited 2023 Dec 5];27(3):271. Available from: /pmc/articles/PMC4132635/
4. Calabrese M, Poretto V, Favaretto A, Alessio S, Bernardi V, Romualdi C, et al. Cortical lesion load associates with progression of disability in multiple sclerosis. Brain [Internet]. 2012 [cited 2023 Dec 5];135(Pt 10):2952–61. Available from: https://pubmed.ncbi.nlm.nih.gov/23065788/
5. Beck ES, Maranzano J, Luciano NJ, Parvathaneni P, Filippini S, Morrison M, et al. Cortical lesion hotspots and association of subpial lesions with disability in multiple sclerosis. Mult Scler [Internet]. 2022 Aug 1 [cited 2023 Dec 5];28(9):1351–63. Available from: https://pubmed.ncbi.nlm.nih.gov/35142571/
6. Ruano L, Portaccio E, Goretti B, Niccolai C, Severo M, Patti F, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult Scler [Internet]. 2017 Aug 1 [cited 2023 Dec 5];23(9):1258–67. Available from: https://pubmed.ncbi.nlm.nih.gov/27738090/
7. Brochet B, Ruet A. Cognitive Impairment in Multiple Sclerosis With Regards to Disease Duration and Clinical Phenotypes. Front Neurol [Internet]. 2019 Mar 20 [cited 2023 Dec 5];10. Available from: https://pubmed.ncbi.nlm.nih.gov/30949122/
8. Kolb H, Al-Louzi O, Beck ES, Sati P, Absinta M, Reich DS. From pathology to MRI and back: Clinically relevant biomarkers of multiple sclerosis lesions. Neuroimage Clin [Internet]. 2022 Jan 1 [cited 2023 Dec 5];36:103194. Available from: /pmc/articles/PMC9668624/
9. La Rosa F, Wynen M, Al-Louzi O, Beck ES, Huelnhagen T, Maggi P, et al. Cortical lesions, central vein sign, and paramagnetic rim lesions in multiple sclerosis: Emerging machine learning techniques and future avenues. Neuroimage Clin [Internet]. 2022 Jan 1 [cited 2023 Dec 5];36:103205. Available from: /pmc/articles/PMC9668629/
10. Jamoussi H, Ali N Ben, Missaoui Y, Cherif A, Oudia N, Anane N, et al. Cognitive impairment in multiple sclerosis: Utility of electroencephalography. Mult Scler Relat Disord [Internet]. 2023 Feb 1 [cited 2023 Dec 5];70. Available from: https://pubmed.ncbi.nlm.nih.gov/36657327/
11. Keune PM, Hansen S, Weber E, Zapf F, Habich J, Muenssinger J, et al. Exploring resting-state EEG brain oscillatory activity in relation to cognitive functioning in multiple sclerosis. Clin Neurophysiol [Internet]. 2017 Sep 1 [cited 2023 Dec 5];128(9):1746–54. Available from: https://pubmed.ncbi.nlm.nih.gov/28772244/

12. Leocani L, Gonzalez-Rosa JJ, Comi G. Neurophysiological correlates of cognitive disturbances in multiple sclerosis. Neurol Sci [Internet]. 2010 Nov [cited 2023 Dec 5];31(Suppl 2). Available from: https://pubmed.ncbi.nlm.nih.gov/20842399/
13. Vazquez-Marrufo M, Sarrias-Arrabal E, Martin-Clemente R, Galvao-Carmona A, Navarro G, Izquierdo G. Altered phase and nonphase EEG activity expose impaired maintenance of a spatial-object attentional focus in multiple sclerosis patients. Sci Rep [Internet]. 2020 Dec 1 [cited 2023 Dec 5];10(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33244155/
14. Rodríguez-Bermúdez G, García-Laencina PJ. Analysis of EEG signals using nonlinear dynamics and chaos: A review. Applied Mathematics and Information Sciences. 2015;9(5):2309–21.
15. PRITCHARD WS, DUKE DW, KRIEBLE KK. Dimensional analysis of resting human EEG. II: Surrogate-data testing indicates nonlinearity but not low-dimensional chaos. Psychophysiology [Internet]. 1995 [cited 2023 Dec 5];32(5):486–91. Available from: https://pubmed.ncbi.nlm.nih.gov/7568643/
16. Kargarnovin S, Hernandez C, Farahani F V., Karwowski W. Evidence of Chaos in Electroencephalogram Signatures of Human Performance: A Systematic Review. Brain Sci [Internet]. 2023 May 1 [cited 2023 Dec 5];13(5). Available from: https://pubmed.ncbi.nlm.nih.gov/37239285/
17. Di Ieva A, Esteban FJ, Grizzi F, Klonowski W, Martín-Landrove M. Fractals in the neurosciences, Part II: clinical applications and future perspectives. Neuroscientist [Internet]. 2015 Feb 17 [cited 2023 Dec 5];21(1):30–43. Available from: https://pubmed.ncbi.nlm.nih.gov/24362814/
18. Hernandez CI, Kargarnovin S, Hejazi S, Karwowski W. Examining electroencephalogram signatures of people with multiple sclerosis using a nonlinear dynamics approach: a systematic review and bibliographic analysis. Front Comput Neurosci. 2023 Jun 29;17:1207067.
19. Fambiatos A, Jokubaitis V, Horakova D, Kubala Havrdova E, Trojano M, Prat A, et al. Risk of secondary progressive multiple sclerosis: A longitudinal study. Mult Scler [Internet]. 2020 Jan 1 [cited 2023 Dec 5];26(1):79–90. Available from: https://pubmed.ncbi.nlm.nih.gov/31397221/
20. Krajnc N, Bsteh G, Berger T. Clinical and Paraclinical Biomarkers and the Hitches to Assess Conversion to Secondary Progressive Multiple Sclerosis: A Systematic Review. Front Neurol [Internet]. 2021 Aug 26 [cited 2023 Dec 5];12. Available from: https://pubmed.ncbi.nlm.nih.gov/34512500/
21. Contoyiannis Y, Papadopoulos P, Potirakis SM, Kampitakis M, Matiadou NL, Kosmidis E. Analysis of Electroencephalography (EEG) Signals Based on the Haar Wavelet Transformation. Springer Optimization and Its Applications [Internet]. 2022 [cited 2023 Dec 5];180:157–66. Available from: https://link.springer.com/chapter/10.1007/978-3-030-84122-5_10
22. Ziemssen T, Bhan V, Chataway J, Chitnis T, Anthony B, Cree C, et al. Secondary Progressive Multiple Sclerosis. Neurology - Neuroimmunology Neuroinflammation [Internet]. 2023 Jan 1 [cited 2023 Dec 5];10(1):381–4. Available from: http://nn.neurology.org/content/10/1/e200064