NEUROPHYSIOLOGICAL PREDICTORS OF COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

Silvia Antonella Selvaggi 1, Francesco Motolese1,2, Davide Norata1, Gianmarco Iaccarino1, Elisabetta Sapio1, Fioravante Capone1,2, Fabio Pilato1,2, Francesca Ursini,2, Vincenzo Di Lazzaro1,2

1. Department of Medicine and Surgery, Unit of Neurology, Neurophysiology, Neurobiology and Psichiatry, Università Campus Bio-Medico di Roma, Via Alvaro del Portillo, 21 - 00128 Roma, Italy
2. Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo, 200 - 00128 Roma, Italy

AIM OF THE STUDY

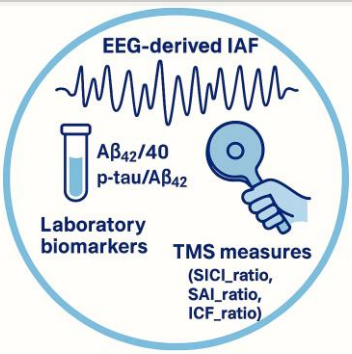
Alzheimer's disease (AD) is a neurodegenerative disorder characterized by beta-amyloid and tau tangles accumulation, leading to progressive cognitive decline. Apart from biological mechanisms, a critical role of brain networks dysfunction in AD pathogenesis has emerged. Neurophysiological tools such as EEG or TMS might detect functional dysfunction reflecting AD pathology. This study aims to integrate neurophysiological and biological biomarkers for defining prognosis, and to investigate if this approach leads to a more complete understanding of disease progression.

MATERIALS

This observational study involved twenty-four patients (with nine females) with a biological diagnosis of AD according to biological criteria, whose mean age at baseline was 70.7 (± 7.6) years. The mean Mini-Mental State Evaluation (MMSE) score at baseline was 23.7 (± 3.9) and of 20.6 (± 4.5) at T1. The mean MMSE score rate change per month was 0.3 points/month.

METHODS

At baseline (T0), each participant underwent lumbar puncture, high-density EEG, and transcranial magnetic stimulation (TMS) alongside a neuropsychological evaluation. The EEG measured individual alpha frequency (IAF), an index of global cognitive function, while TMS assessed intracortical connectivity through three paired-pulse protocols: SICI (GABAergic transmission), ICF (glutamatergic transmission), and SAI (cholinergic transmission). To monitor disease progression, MMSE was repeated after one year (T1), with a subset of patients undergoing a second round of EEG and TMS recordings.



RESULTS

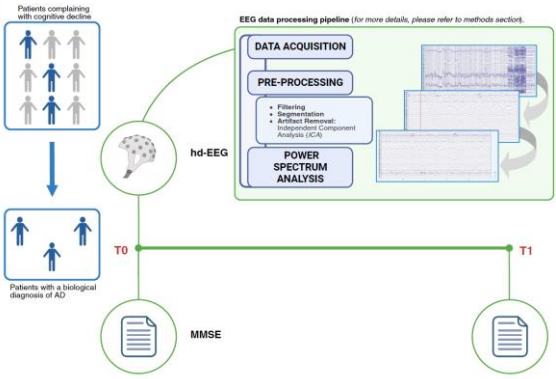
A multiple linear regression was performed, revealing that a combination of six predictors – EEG-derived IAF, TMS measures (SICI ratio, SAI ratio, ICF ratio), laboratoty biomarkers (Abeta42/40, p-tau/Abeta42) – accounted for 94.8% of the variation of MMSE score change ($F(6,3)$; $R^2=0.948$; $p=0.049$).

DISCUSSION

Our findings highlight the crucial role of network dysfunction in Alzheimer's disease (AD) progression, reinforcing the need for a holistic and multimodal assessment that integrates neurophysiological, clinical, and molecular biomarkers. Traditional diagnostic approaches primarily focus on tau and amyloid accumulation, overlooking the functional disruption of neural connectivity, which, from a neuropathological perspective, precedes the neurodegeneration driven by protein aggregation. In fact, network dysfunction emerges before any detectable structural changes, serving as a critical predictor of AD trajectory.

CONCLUSIONS

In conclusion, our study demonstrates that the combination of neurophysiological markers with laboratory parameters (Abeta42/40, p-tau/Abeta42) enhances prognostic accuracy, offering a more comprehensive framework for monitoring disease progression. This multimodal approach has the potential to improve early detection and personalized therapeutic strategies, ultimately tailoring patient care and addressing the complexities of neurodegeneration more effectively.



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