

Quantitative Evidence of EEG Amplitude Modulation Changes in Alzheimer's Disease: Implications for Early Detection and Treatment Outcome Measurement

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PURPOSE: Recent *experimental* evidence has suggested that patients with Alzheimer's disease (AD) have atypical electrophysiological brain activity modulation which can be regulated via deep brain stimulation [1]. In the present study, we provide *quantitative* evidence of such neuromodulatory changes in AD; implications for early disease detection and treatment monitoring are also discussed.

METHODS: An innovative measure was developed to objectively quantify the temporal dynamics of resting-awake EEG amplitude modulations (AM). To compute the proposed parameter, full-band EEG signals were decomposed into delta, theta, alpha, beta, and gamma sub-bands. The Hilbert temporal envelope of each sub-band signal was then computed and the rate-of-change of each envelope quantified via Fourier analysis. Multi-channel EEG data collected from 22 patients with probable AD as per NINCDS-ADRDA and DSMIII-R criteria and 12 age- and education-matched healthy control participants were used to explore significant differences in AM information between the two groups and to develop a linear classifier for AD diagnostics.

FINDINGS: One-way ANOVA showed significant differences ($p < 0.001$) in AM information between the two groups, particularly in the temporal, parietal, and frontal regions. For the AD group, higher AMs were found in the delta and theta frequency bands and lower modulations in the beta and gamma bands; no differences were observed in the alpha band. For AD diagnostics, accuracy, sensitivity, and specificity levels of 88.4%, 90.9%, and 83.3% were achieved, respectively. When combined with conventional EEG power parameters, performance increased to 94.1%, 95.5%, and 91.7%, respectively.

DISCUSSION: AM analysis uncovered significant differences between healthy and AD patients and provided an innovative modality for automated disease detection. The analysis also uncovered an interesting finding: the beta frequency band was mostly modulated at a rate that coincides with theta band frequency. Such behaviour was more pronounced in the control group, suggesting a decrease in theta-beta interaction with AD. Decreased theta-beta interaction has been attributed to poorer working memory performance [2] and to lower reward-gain motivation [3]. Hence, the observed neuromodulatory deficit may be linked to a brainstem regulation issue [4] where neurofibrillary plaques have been found [5]. A second hypothesis is that the deficit is linked to impaired cerebral blood flow caused by such plaques [6]. Ultimately, the developed measure may serve as a quantitative metric to monitor e.g., behavioural or cholinesterase inhibitor drug treatment outcomes.

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