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Spectral and complexity analysis of scalp EEG characteristics for mild cognitive impairment and early Alzheimer's disease

Joseph C. McBride[a,*], Xiaopeng Zhao[a,b], Nancy B. Munro[c], Charles D. Smith[d,e], Gregory A. Jicha[d,e], Lee Hively[c], Lucas S. Broster[g,e], Frederick A. Schmitt[d,e], Richard J. Kryscio[e,f], Yang Jiang[e,g]

[a] Department of Mechanical, Aerospace, and Biomedical Engineering, University of Tennessee, Knoxville, Knoxville, TN 37996, United States
[b] National Institute for Mathematical and Biological Synthesis, University of Tennessee, Knoxville, Knoxville, TN 37996, United States
[c] Oak Ridge National Laboratory, Oak Ridge, TN 37831-6418, United States
[d] Department of Neurology, University of Kentucky, Lexington, KY 40356, United States
[e] Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40356, United States
[f] Department of Statistics, University of Kentucky, Lexington, KY 40356, United States
[g] Department of Behavioral Science, University of Kentucky, Lexington, KY 40356, United States

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ABSTRACT

Amnestic mild cognitive impairment (aMCI) often is an early stage of Alzheimer's disease (AD). MCI is characterized by cognitive decline departing from normal cognitive aging but that does not significantly interfere with daily activities. This study explores the potential of scalp EEG for early detection of alterations from cognitively normal status of older adults signifying MCI and AD. Resting 32-channel EEG records from 48 age-matched participants (mean age 75.7 years)—15 normal controls (NC), 16 early MCI, and 17 early stage AD—are examined. Regional spectral and complexity features are computed and used in a support vector machine model to discriminate between groups. Analyses based on three-way classifications demonstrate overall discrimination accuracies of 83.3%, 85.4%, and 79.2% for resting eyes open, counting eyes closed, and resting eyes closed protocols, respectively. These results demonstrate the great promise for scalp EEG spectral and complexity features as noninvasive biomarkers for detection of MCI and early AD.

1. Introduction

Mild cognitive impairment (MCI), especially the amnestic type, is a degenerative neurological disorder characterized by cognitive decline which is greater than expected for an individual's age, but does not necessarily interfere with daily activities [1]. Early stages of Alzheimer's disease (AD) are characterized by progressive memory loss, diminished vocabulary, and lowered ability to execute precise motor movements,

* *Corresponding author at*: 313 Perkins Hall, University of Tennessee, Knoxville, Knoxville, TN 37996-2010, United States. Tel.: +1 865 974 7682.
E-mail address: xzhao9@utk.edu (X. Zhao).
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together with impaired activities of daily living. Previous research has shown that MCI patients progress to AD at a rate of approximately 10–15% of patients per year [2,3]. The prevalence of MCI and AD increases with age, making MCI/AD research of significant interest in geriatric medicine. Current interest in the field is focused on detection of MCI at the earliest possible time for purposes of instituting medication and lifestyle changes to slow or halt progression of further cognitive decline. However, there is no biomarker-based test or screening tool of utility in the primary care setting.

Several causes of MCI and AD have been hypothesized based on pathologic features observed in the brains of AD patients. The current leading hypothesis for the cause of AD is abnormal deposition of amyloid beta protein in the brain together with a second abnormal protein, microtubule-associated tau [4,5]. No single root cause can be attributed to MCI. However, given the high number of MCI patients who progress to AD, the fundamental cause of both MCI and AD is likely to be the same in many cases [6]. In the current study, the MCI participants were all diagnosed as amnestic MCI.

The earliest stage of MCI and AD diagnosis is often based on neuropsychological tests and patient history evaluations [7]. Once it is determined that the subject is experiencing abnormal cognitive decline, physicians in advanced memory disorders clinics employ more quantitative diagnostic tools. One such tool is the analysis of cerebrospinal fluid (CSF) biomarkers. The most common CSF biomarkers used for AD diagnosis are amyloid beta and tau. These biomarkers provide a reliable means to distinguish AD from other forms of dementia and appear in characteristically abnormal levels at the earliest onset of the disease [8,9]. Published findings suggest that CSF examination can identify abnormal proteins in patients who went on to develop AD later [10].

Imaging in AD has been studied intensively in recent years [11]. Positron emission tomography (PET) detects fibrillar amyloid protein in living subjects using amyloid-binding tracer, Pittsburgh Compound B (PiB)[14]. The regional variations in PiB binding in vivo are strikingly similar to the deposits of amyloid beta and tau neurofibrillary tangle distributions post-mortem [12]. PET scans have been able to measure the PiB uptake in the neocortex and identify the regional distribution of amyloid beta plaque burden with high specificity in AD. Additionally, structural magnetic resonance imaging (sMRI) studies have shown reductions in volume of the hippocampus, one of the key areas of the brain affected by amyloid beta and tau deposition early in the disease [13]. Diffusion tensor MRI can measure white matter integrity in the brain and may be more useful as an earlier biomarker of AD than sMRI [14]. Structural MRI and amyloid-PET scans may be used in combination in AD, but they are complex, expensive, require radiation exposure in the case of PET, and are not yet standardized tools for AD detection and diagnosis.

EEG is a noninvasive method indirectly measuring brain neural electric activity from the scalp of the head. Even though it has been around for decades, using EEG as cognitive biomarker to detect and predict MCI and AD in individuals is a relatively new effort [15]. Scalp EEG has the potential to play a significant role as one of the earliest biomarkers for MCI and early stage AD, before clinical diagnosis. EEG operates through the recording of oscillations of brain electric potentials from electrodes attached to the scalp. EEG data from MCI and AD patients have been shown to have lower mean levels of channel-to-channel synchronization than those of healthy controls [16,17]. The effects of cortical neurons' deaths, axonal pathology, cholinergic deficits, and other neural network disconnections as concomitants of the disease are manifested by multiple changes in EEG characteristics [18–21]. Cognitive impairment as a result of AD is correlated with a reduction in dominant posterior rhythm while dementia in general correlates well with a rise in theta activity [19]. Decreased synchronization in local and global networks is also observed with AD [17,22,23]. Other potential differences in spectral features of EEG for MCI/AD have also been noted [24–28]. Experimental results using EEG to correctly distinguish AD patients from healthy controls have proven promising; however, researchers have encountered difficulty in distinguishing between different stages of dementia (e.g., MCI vs. AD) [29,30]. In many cases, group differences can be demonstrated, but group means are not sufficiently different to allow for diagnostic identification of an individual with a specific group [31–37]. If EEG technology can be developed to discriminate MCI from normal EEG for individuals and to show changes over relatively short time periods in and individual, it will be transformative in the early detection of MCI, AD, and other dementias, as it is more sensitive than behavioral testing, inexpensive, noninvasive, and can be made practical for primary care settings. In this study we focus on the spectral and complexity features of EEG as distinctions between normal older, MCI, and AD subjects.

2. Materials and methods

2.1. *Participants*

The EEG data used in this study were recorded in the Aging Brain and Cognition laboratory in the Behavioral Science Department and Sanders-Brown Center on Aging at the University of Kentucky (UK) College of Medicine. Participants between the ages of 60 and 90 years were recruited from a study cohort of cognitively normal older adults identified by the Alzheimer's Disease Center (ADC) of the UK College of Medicine. The normal older participants are screened annually and were followed into likely MCI or AD stage till autopsy. MCI and AD participants were diagnosed and recruited by cognitive neurologists Drs. C. Smith and G. Jicha at the UK ADC Clinical Core and from its Research Memory Disorders Clinic. All MCI participants belonged to the amnestic MCI subtype. A list of neurological assessments used to make MCI/AD diagnoses is provided in Table 1 [26]. Means and standard deviations for MMSE scores for the three groups are presented in Table 2. The MCI and early AD participants' EEG data were recorded as soon as possible after diagnoses were made.

All participants were screened to exclude active or unstable medical conditions, depression, and other psychiatric disorders, or history of neurologic or neurosurgical conditions. No participants were to have the ApoE4 allele for Alzheimer's risk or to be on any psychoactive medication other than antidepressants. For cognitively normal individuals, we excluded those with the ApoE4 genes risk factor in order to have low-risk