Early Detection of Alzheimer's Disease Using Nonlinear Analysis of EEG via Tsallis Entropy

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***Abstract*— A preliminary study by Sneddon et al. (2005) using visual working memory tasks coupled with quantified EEG (qEEG) analysis distinguished mild dementia subjects from normal aging ones with a high degree of accuracy. The present study hypothesizes that a simpler task such as having a subject count backwards mentally by ones can be coupled with qEEG to yield a similar degree of accuracy for classifying early dementia. The study focuses on participants with mild cognitive impairment (MCI) and includes both a delayed visual match-to-sample (working memory) task and a counting backwards task (eyes closed) for comparison. The counting backwards protocol included 15 normal aging and 11 MCI participants, and the working memory task included 9 normal aging and 7 MCI individuals. The EEG data were quantified using Tsallis entropy, and the brain regions analyzed included the prefrontal cortex, occipital lobe, and the posterior parietal cortex. The counting backwards task had a sensitivity of 82%, a specificity of 73%, and an overall accuracy of 77% whereas the working memory task had a sensitivity of 100%, a specificity of 89%, and an overall accuracy of 94%. The results suggest that simple tasks such as having a subject count backwards may distinguish MCI ($p<0.05$) sufficiently to use as a rough screening tool, but psychophysical tasks such as working memory tests appear a potentially much more useful approach for diagnosing either MCI or very early Alzheimer's disease.**

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I. Introduction

NEURODEGENERATIVE diseases such as Alzheimer's have long been a focus of research in the scientific community. Alzheimer's disease (AD) is the most common form of dementia, and gradually destroys the host's brain cells. Recent findings estimate that 35 million people worldwide currently suffer from AD. The number is expected to reach 115 million by the year 2050. Mild cognitive impairment (MCI) is a transitional stage of impairment that is not as severe as AD. Persons with MCI show short term memory loss, yet their symptoms do not interfere with daily activities. This condition can develop into any of several forms of dementia or revert back to a normal state. Nevertheless, a patient with MCI has a greater risk of developing AD as opposed to a cognitively normal older adult. It is hoped that early detection of MCI will allow therapeutic interventions to slow or halt progression of the condition.

Neuroimaging is a well-accepted approach for definitive diagnosis of dementia. The neuroimaging methods include single-photon emission computerized tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI). SPECT, PET, and MRI have been successful at recognizing AD at an early stage but they all present problems that detract from their use as routine screening methods. Both PET and SPECT pose radiation risks and all are time-consuming, inconvenient, and expensive.

Electroencephalography (EEG) is another well-accepted technology that may potentially solve this problem. Nonlinear analysis of rapidly sampled EEG data has been shown to reveal unique features of various dynamical neurological diseases such as Parkinson's, epilepsy and AD [1], [2].

Linear and nonlinear analyses of EEG have shown promise for discriminating mild and severe dementia sufferers from normally aging persons [3]-[7]. Nonlinear analysis has given better results because brain dynamics embodied in EEG data show nonlinear characteristics. Applying linear methods to a nonlinear system often provides confounding results. Among other approaches, EEG has been used for studying dementias for several decades [8]. The promising results with nonlinear approaches have led to an increasing interest in their clinical applications for early dementia diagnosis.

To achieve a high level of accuracy in distinguishing very mildly impaired individuals from normal aging ones, a working memory task may need to be used with an appropriate method of analyzing the EEG. A previous study has shown that one qEEG measure for EEG analysis failed to discriminate normal from cognitively impaired participants when using a psychophysical task that did not tax the brain areas affected earliest by Alzheimer's changes in contrast to the use of working memory tasks [9].

II. Methodology

Data were gathered at the University of Kentucky Medical Center (UK) and analyzed through a collaboration between Oak Ridge National Laboratory (ORNL) and the University of Tennessee Knoxville (UT). Institutional Review Board approvals were obtained for ORNL, UK, and UT before any EEG data acquisition or analysis was conducted. Participants were identified by the UK Alzheimer's Disease Research Center and EEG data were recorded in the laboratory of Dr. Y. Jiang of the Behavioral Science Department in the College of Medicine. Participants were free of genetic risk factors for AD, co-existing brain conditions, or influence of psychoactive drugs.

Electroencephalograms (EEG) were recorded from 64 scalp electrodes on each subject with a sampling rate of 500 Hz using Neuroscan equipment. The electrode arrangement is the standard 10-20 system, consistent with the guideline from the American Clinical Neurophysiology Society. EEG was recorded during two tasks: (1) counting backwards with eyes closed (ORNL protocol), and (2)a delayed match-to-sample task (visual working memory task). Non-invasive EEG is prone to picking up many muscle artifacts such as eye blinks. Having the subjects close their eyes for the ORNL protocol helped minimize the EEG noise. Data from 26 participants were analyzed for the ORNL protocol, 15 normal aging and 11 MCI, and data from 16 participants were analyzed for the visual recall task, 9 normal aging and 7 MCI.

Tsallis entropy is a nonlinear measure for quantifying EEG data by analyzing the variance of the signal in both a slow and rapid manner [9]. Equations (1) and (2) show how the slow and rapid variances, respectively, were computed using MATLAB. The slow variance is simply the measure of variance throughout the entire signal (or epoch of signal being analyzed), and the rapid variance is the variance from each critical point to the next. Critical points correspond to local maxima and minima in the data. The Tsallis entropy value (qEEG) is then simply the ratio of all rapid variances divided by the slow variance and then subtracted from one as shown in equation (3). Tsallis entropy has been shown to be a good analysis method to use with working memory tasks [9], and this study used the same method for the ORNL protocol tasks.

$$\mathrm{var}_{Slow} \equiv \sum_{i=1}^{N} \left(x_i - \bar{x} \right)^2 \qquad \text{.....(1)}$$

$$\mathrm{var}_{Rapid} \equiv \sum_{x_i \in Interval_j} \left(x_i - \overline{x_j} \right)^2 \qquad \text{.....(2)}$$

$$qEEG = 1 - \frac{\sum_{Interval_j} \mathrm{var}_{Rapid}}{\mathrm{var}_{Slow}} \qquad \text{.....(3)}$$

For the ORNL protocol, 30 seconds of data were used from each participant, and all 64 channels were analyzed for qEEG values. Brain regions analyzed consisted of the prefrontal cortex (electrodes FP1, FPZ, and FP3) as well as the posterior parietal (electrodes PO3, POZ, and PO4) and occipital regions (electrodes CB1, O1, OZ, O2, and CB2). Dementia affects the brain early in the prefrontal, temporal, parietal, and occipital regions [10].

The delayed match-to-sample task was very similar to that used by Sneddon et al. [9]. This working memory task was a simplified version of that used by Guo et al [11], in which participants were shown a sample target object at the beginning of each memory trial. They were then asked to identify a sequence of common objects, including the target object and non-targets, via button press. Event-related potentials (ERP) responses were averaged EEG signals that were time locked with the presentation of each visual stimulus. After presentation of the picture, we identified ERP responses at 150 milliseconds (P150) and 300 milliseconds (P300). For the first 150 milliseconds after the stimulus was shown, ERPs were selected from the posterior parietal region (PO3, POZ, and PO4). For 151-300 milliseconds (P300) after the stimulus, ERPs were selected from the prefrontal cortex (FP1, FPZ, and FP3). These time intervals for corresponding brain regions are based on previous ERP and fMRI studies involving the working memory [11]-[14].

III. Results

A. ORNL Protocol

Two separate qEEG ratios were computed for the Oak Ridge protocol using unfiltered data: a ratio between the

prefrontal cortex and posterior parietal lobe, and one between the prefrontal cortex and occipital lobe. For the prefrontal cortex and posterior parietal lobe, the ratio was computed as the prefrontal qEEG value divided by the posterior parietal qEEG. These qEEG ratios had a range of 0.81 to 2.18. A qEEG ratio of 1.15 seemed to best distinguish between normal and MCI participants. Nine out of the 11 MCI patients (two false negatives) had qEEG ratios above 1.15 with a mean of 1.31. On the other hand, 11 out of 15 normal (four false positives) participants had a qEEG ratio below 1.15 with a mean of 1.17. The sensitivity was found to be 82%, the specificity was 73%, and the accuracy was 77%. A graphical representation of the range of qEEG values for this ratio is shown in Figure 1.

For the qEEG ratio obtained from prefrontal cortex and occipital lobe, the ratio was computed as the qEEG value from the prefrontal cortex divided by the qEEG value from the occipital lobe. The ratios ranged from 0.84 to 3.19 (graphical representation in Figure 2). For this specific ratio, a qEEG ratio of 1.2 seemed to discriminate best between the two groups. Once again, 9 out of the 11 MCI patients showed a qEEG ratio above 1.2 whereas 11 out of 15 normal participants showed a ratio below 1.2. The mean qEEG ratio was 1.65 for the MCI patients and 1.21 for the normal participants. The sensitivity and specificity were again 82% and 73% respectively, with overall accuracy of 77%.

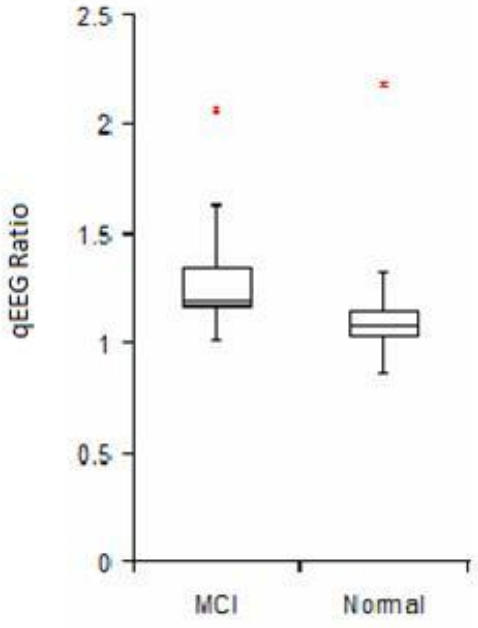

Fig. 1. Boxplot representing the differences of the qEEG ratio of the prefrontal cortex and posterior parietal lobe between the MCI and normal aging subjects (ORNL protocol). Boxplots give 0, 25th, median, 75th, and 100 percentile values; red dots represent outliers.

A two sample F-test to check for equal variance was carried out for both the posterior parietal and occipital qEEG ratios. The prefrontal vs. posterior parietal qEEG ratio had an F-value of 1.31 which was less than the F-critical value of 2.86 suggesting the variance between the qEEG ratios for all the participants were equal. On the other hand, the prefrontal vs. occipital lobe qEEG ratio showed an F-value larger than the F-critical value (3.07>2.60) indicating an unequal variance between the two groups.

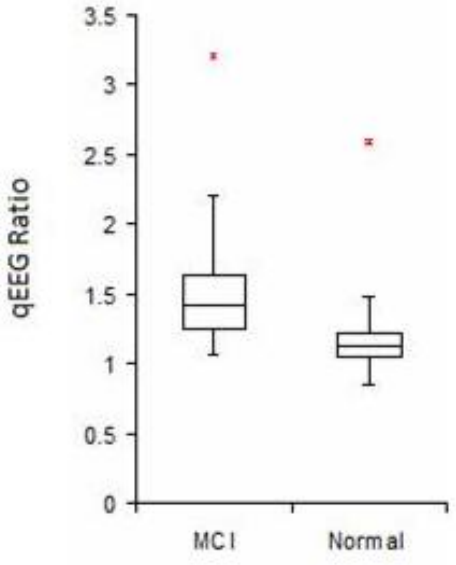

Fig. 2. Boxplot representing the differences of the qEEG ratio of the prefrontal cortex and occipital lobe between the MCI and normal aging subjects (ORNL protocol). Boxplots give 0, 25th, median, 75th, and 100 percentile values; red dots represent outliers.

After identifying the variances as equal or unequal, a one tailed t-test was performed for each dataset. The t-statistic obtained from the prefrontal vs. occipital qEEG ratio showed that there was a statistically significant difference in mean qEEG ratios between normal and MCI participants ($p<0.05$).

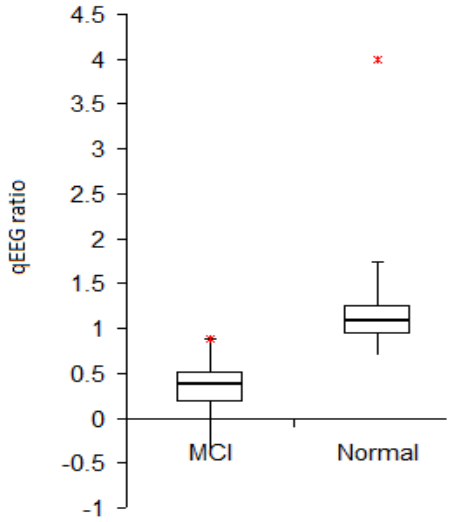

Fig. 3. Boxplot representing the differences of the qEEG ratio of the prefrontal cortex (P300) and posterior parietal cortex (P150) between the MCI and normal aging subjects (visual working memory task). Boxplots give 0, 25th, median, 75th, and 100 percentile values; red dots represent outliers (none for the MCI group).

However, the prefrontal vs. posterior parietal qEEG ratio failed to show any significant discrimination in mean qEEG ratios between normal and MCI participants ($p>0.15$).

B. Visual Working Memory Task

A qEEG ratio was calculated for the prefrontal cortex (P300) divided by the posterior parietal lobe (P150) for all the participants. The qEEG ratios ranged from -2.61 to 0.88 for MCI patients and from 0.7 to 4.0 for the normal participants. The mean qEEG ratios were 0.004 and 1.52 for the MCI and normal groups respectively (graphical representation in Figure 3). A ratio of 0.9 seemed to be the optimum cutoff point for both groups. Using this criterion, 7 out of 7 MCI patients had a qEEG ratio below 0.9, and 8 out of 9 normal participants had a ratio above 0.9. The sensitivity was 100% (7 out of 7 MCI patients) and the specificity was 89% (8 out of 9 normal participants). The overall accuracy was 93.75%.

The F-test performed on the working memory task to check for equal variance yielded an F-value of 0.84. Since the F-value was greater than the critical value of 0.28, we concluded that the variances in the MCI and normal groups were unequal. A two sample, one tailed t-test assuming unequal variance showed that pre-dementia had a significant effect on the mean qEEG ratio between normal and MCI participants in the prefrontal and posterior parietal electrodes ($p<0.02$).

IV. DISCUSSION

For the ORNL protocol, multiple regions were explored to find the best possible combinations of electrodes to successfully differentiate the subjects. Statistical analyses of the results indicated there was no significant difference in the qEEG ratios between normal and MCI patients using the prefrontal vs. posterior parietal regions ($p>0.14$). The occipital ratio achieved a significant p-value, so it appears that the occipital ratio is preferable for the ORNL protocol. However, the results indicate that this simple protocol might serve at best as a screening tool unless better discrimination can be achieved with further work. Additional brain regions such as the temporal lobe could be analyzed for this protocol as this region has been suggested as a target area for detecting early AD-related changes. Use of an artifact filter to remove eye blinks and other muscle movement for the ORNL protocol might also be explored since it uses longer periods of scalp data than the visual working memory task.

Analysis of the working memory task showed a large and statistically significant difference ($p<0.02$) in mean qEEG ratios between the groups This finding is supported by the Sneddon et al preliminary study [9], which found a sensitivity of 88% and specificity of 94% in unmatched participants using a very similar psychophysical task that involves brain areas affected early in the cognitive impairment process.

The sample sizes were quite small for both protocols. Future studies should expand these sample sizes.

In summary, coupling the use of a delayed visual working memory task with Tsallis entropy-based qEEG analysis has been shown to be a highly promising potential diagnostic tool for MCI and early dementia.

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