ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/336110596

# A Novel Detection Tool for Mild Cognitive Impairment Patients Based on Eye Movement and Electroencephalogram

**Article** *in* Journal of Alzheimer's disease: JAD · September 2019

DOI: 10.3233/JAD-190628

CITATIONS
24

READS
562

**8 authors**, including:

Juanjuan Jiang
Shanghai University
**16** PUBLICATIONS **157** CITATIONS
SEE PROFILE

Can Sheng
The first hospital of Tsinghua University, Beijing, China
**54** PUBLICATIONS **678** CITATIONS
SEE PROFILE

Wang Min
Shanghai University
**45** PUBLICATIONS **331** CITATIONS
SEE PROFILE

Ying Han
Xuanwu hospital
**453** PUBLICATIONS **11,784** CITATIONS
SEE PROFILE

All content following this page was uploaded by Wang Min on 08 January 2020.

The user has requested enhancement of the downloaded file.

Journal of Alzheimer's Disease 72 (2019) 389–399
DOI 10.3233/JAD-190628
IOS Press



# A Novel Detection Tool for Mild Cognitive Impairment Patients Based on Eye Movement and Electroencephalogram

Juanjuan Jiang[a,b,1], Zhuangzhi Yan[b], Can Sheng[d,1], Min Wang[a,b], Qinglan Guan[c], Zhihua Yu[c,*], Ying Han[d,e,f,g,*] and Jiehui Jiang[a,b,*]

[a]*Shanghai Institute for Advanced Communication and Data Science, Shanghai University, Shanghai, China*
[b]*Institute of Biomedical Engineering, School of Communication and Information Engineering, Shanghai University, Shanghai, China*
[c]*Shanghai Geriatric Institute of Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China*
[d]*Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing, China*
[e]*Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, China*
[f]*Beijing Institute of Geriatrics, Beijing, China*
[g]*National Clinical Research Center for Geriatric Disorders, Beijing, China*

Accepted 27 August 2019

**Abstract**.
**Background:** Detecting subtle changes in visual attention from electroencephalography (EEG) and the perspective of eye movement in mild cognitive impairment (MCI) patients can be of great significance in screening early Alzheimer's disease (AD) in a large population at primary care.
**Objective:** We proposed an automatic, non-invasive, and quick MCI detection approach based on multimodal physiological signals for clinical decision-marking.
**Methods:** The proposed model recruited 152 patients with MCI and 184 healthy elderly controls (HC) who underwent EEG and eye movement signal recording under a visual stimuli task, as well as other neuropsychological assessments. Forty features were extracted from EEG and eye movement signals by linear and nonlinear analysis. The features related to MCI were selected by logistic regression analysis. To evaluate the efficacy of this MCI detection approach, we applied the same procedures to achieve the Clinical model, EEG model, Eye movement model, EEG+ Clinical model, Eye movement+ Clinical model, and Combined model, and compared the classification accuracy between the MCI and HC groups with the above six models.
**Results:** After the penalization of logistic regression analysis, five features from EEG and eye movement features exhibited significant differences ($p < 0.05$). In the classification experiment, the combined model resulted in the best accuracy. The average accuracy for the Clinical/EEG/Eye movement/EEG+ Clinical/Eye movement+ Clinical/Combined model was 68.69%, 61.79%, 73.13%, 69.46%, 75.61%, and 81.51%, respectively.

[1]These authors have contributed equally to this work.

*Correspondence to: Jiehui Jiang, PhD, Institute of Biomedical Engineering, School of Communication and Information Engineering, Shanghai University, 99 Shangda Road, Shanghai 200444, China. E-mail: jiangjiehui@shu.edu.cn and Ying Han, MD, PhD, Department of Neurology, Xuanwu Hospital of Capital Medical University, Beijing 100053, China. Tel.: +86 18515692701; Fax: +86 10 83167306; E-mail: hanying@xwh.ccmu.edu.cn and ZhihuaYu, MD, Shanghai Geriatric Institute of Chinese Medicine, Shanghai University of Traditional Chinese Medicine, 265 South Xiangyang Road, Shanghai, 200031, China. E-mail: yzh119@hotmail.com.

ISSN 1387-2877/19/$35.00 © 2019 – IOS Press and the authors. All rights reserved

**Conclusion:** These results suggest that the proposed MCI detection tool has the potential to screen MCI patients from HCs and may be a powerful tool for personalized precision MCI screening in the large-scale population under primary care condition.

Keywords: Attention, electroencephalography, eye movement, mild cognitive impairment, multimodal detection

Trial registration: Clinical Trials.gov Identifier: 2017LCSY345.

## INTRODUCTION

Alzheimer's disease (AD), characterized by the irreversible deterioration of cognitive functions, such as memory loss, executive dysfunction, and attention defect has been considered as the most common cause of dementia. Mild cognitive impairment (MCI), a transitional stage between normal aging and probable AD, is likely to be of great value in screening early AD in a large population [1, 2]. To facilitate relatively earlier and accurate clinical diagnosis for MCI, the development of new sensitive, non-invasive, and *in vivo* biomarkers may be of great significance [3].

Recently, research has confirmed the significant abnormality in some aspects of attentional function and attention-related reaction time (RT) for AD and MCI patients [4, 5]. Impaired visual attention processing is a potential feature present at the MCI stage and might represent a distinct biomarker of upcoming AD independently from memory deficits. Pasgreta et al. have found that declined attention among patients with MCI led to profound daily function disturbance, suggesting an early indicator of conversion to dementia [6]. Additionally, the dysfunction of attentional control has also been identified in development from MCI to AD [2]. The current approaches for attention assessment included choosing or designing proper neuropsychological tasks, then comparing and incorporating findings from comprehensive neuropsychological tests, neuroimaging, or eye movement analysis. However, due to the complexity of neuropsychological tasks and relatively high reliance on verbal communication capabilities, the above-mentioned attentional assessments have not been widely applied in routine clinical work. Thus, effective and convenient tools for estimating attentional functions are useful for fast diagnosis of MCI [7].

Previous studies have shown that abnormal resting delta and alpha electroencephalography (EEG) rhythms were observed in MCI patients. The resting EEG of alpha relative power in the frontal area was decreased and the power in the theta band was increased for AD diagnosis [8]. Furthermore, these EEG rhythms were correlated with the neuropsychological measures, including attention-based immediate memory in the continuum of MCI and AD [9]. For instance, Babiloni et al. reported that there was a positive correlation between synchronization likelihood and Mini-Mental State Examination score at delta for right Fronto-parietal electrode pair, at alpha 1 for midline electrode pair, and right Fronto-parietal electrode pair [10]. Therefore, the abnormalities of resting state EEG in the frontal region might have a likelihood to be a non-invasive and relatively cost-effective tool for early MCI detection in the attention dysfunction. However, the use of multi-electrode EEG recording systems in traditional EEG was limited to hospitals rather than in primary care or similar settings. Mobile EEG devices might have the potential to serve as a more convenient tool for early identification of MCI. Additionally, researchers have also shown that the abnormality in eye movements might reflect mild or even latent cognitive dysfunction via various eye tracking measurements [11–13]. However, few existing studies concentrated on building an effective screening approach for MCI patients combing mobile EEG and eye tracking measurements. Therefore, we aim to combine visual attention and EEG analysis to generate a non-invasive, fast, and inexpensive detection to screen MCI patients in primary care. In this study, we set out to 1) design a visual tracking task to measure sustained attention; 2) determine the features extracted from EEG and Eye movement data, during which visual tracking task was related to sustained attention deficits; and 3) use machine learning techniques to develop an automatic, non-invasive and reliable detection tool to identify MCI from healthy elderly controls.

## MATERIALS AND METHODS

Figure 1 presents the proposed MCI detection procedure including the following steps: 1) eligible

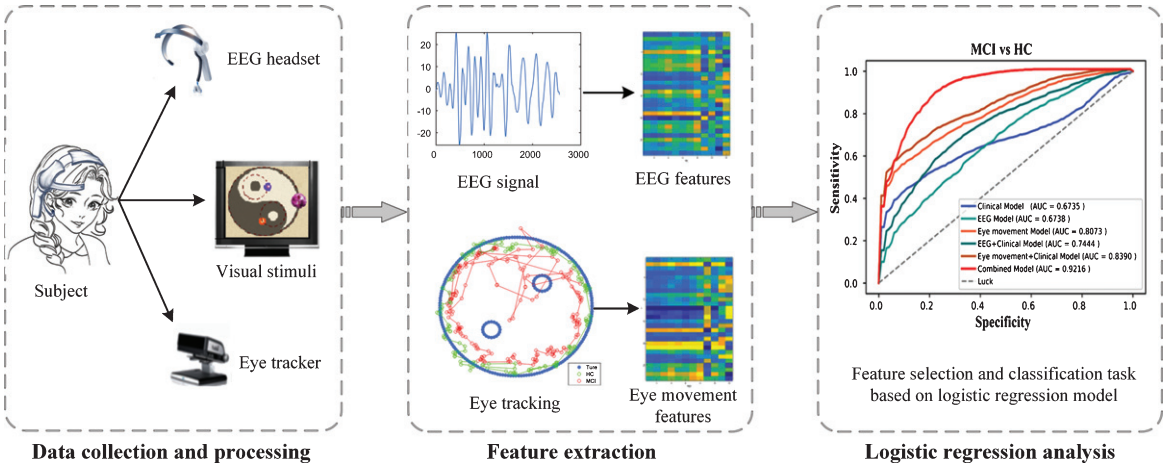


Fig. 1. The flowchart of the proposed model, which was composed of three steps: data collection and preprocessing, feature extraction, feature selection and classification tasks based on Logistic Regression model.

participants underwent the EEG recording in both resting state and Eye movement recording in a visual stimulation task; 2) the linear and nonlinear features were extracted from the obtained data of EEG and Eye; 3) the Logistic Regression (LR) analysis was implemented to select the discriminating features and performed the classification of different models for diagnosing MCI and healthy controls (HCs).

*Subjects*

We recruited 336 subjects from four communities in Shanghai, including 152 patients with MCI and 184 HCs in the present study. All subjects completed a standardized diagnostic assessment comprising of past history, medical, neurological, and psychiatric examination, and neuropsychological tests. MCI patients were diagnosed according to the previous criteria [14–16], which included memory loss or other cognitive field dysfunctions confirmed by an informant, objective cognitive impairment in single or multiple domains, adjusted for age and education, preserved general cognitive function, and failure to meet the criteria for dementia. The eligibility criteria for HCs included neither any complaint of memory loss nor any severe visual or auditory impairment. All the subjects were right-handed and had either normal or corrected-to-normal vision without any suffering from color blindness. After collecting the physiological signals of 810 subjects (540 HCs and 270 MCIs), 474 subjects (356 HCs and 118 MCI subjects) with invalid EEG or Eye movement data were excluded by signal abnormalities. The detailed eligibility criteria for the subjects are shown in Fig. 2.

Research activities involved in the present study was conducted in accordance with the ethical standards of the Helsinki Declaration and approved by the Medical Research Ethics Committee and Institutional Review Board of Long Hua Hospital in Shanghai University of Traditional Chinese Medicine (Clinical Trials.gov Identifier: 2017LCSY345). All subjects were voluntarily participated in the study and provided written informed consents. The demographic and clinical characteristics of subjects are summarized in Table 1.

*Visual tracking task and visual stimuli*

Figure 3 presents the visual tracking paradigm referred to the previous study and a schematic illustration of an experimental trial. Normally, visual tracking paradigm permutes specific task rules from attention domains (i.e., sustained attention) to generate a novel and unique task to assess the condition of attention function. In the present study, a visual tracking task was dynamic, stimuli were involved with a moving object (purple ball) and two interference objects (two small balls). Therefore, these three balls rotated in a counterclockwise direction and moved around a specific track for 45 s. For our visual tracking task, subjects were asked to follow the auditory instruction, maintaining the head fixation, gazing the moving purple ball, pursuing its moving direction, and localizing the final position during each trial. A mini-block design was used in which 4 consecutive trials were presented for a given task and each trial lasted for 45 s without inter-trial interval. The paradigm was presented using E-Prime software

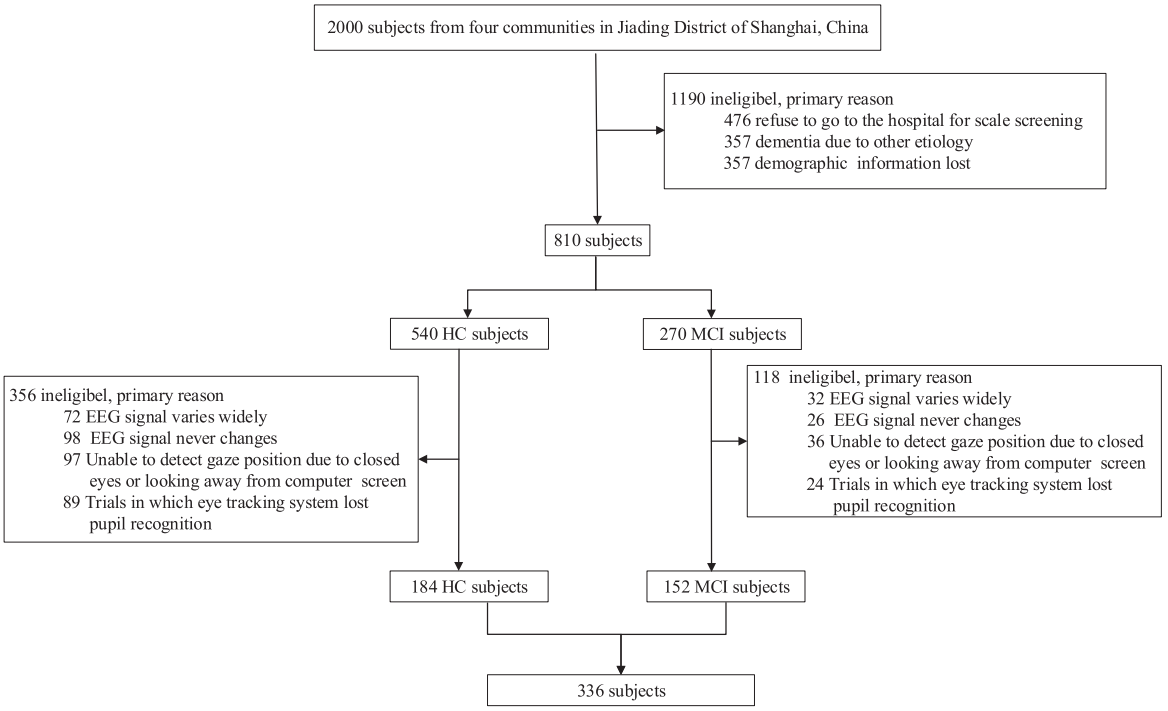


Fig. 2. Trial profile of subject selection.

Table 1
Demographic and clinical characteristics of all subjects.

| Characteristic | HC ($n = 184$) | MCI ($n = 152$) | $p$ |
|---|---|---|---|
| Age (y) | $71.7 \pm 4.66$ | $71.6 \pm 4.15$ | $0.875^a$ |
| Gender (M/F) | 101/83 | 78/74 | $0.541^b$ |
| Education (y) | $9.36 \pm 3.47$ | $8.16 \pm 3.74$ | $0.071^c$ |
| MoCA-B | $28.3 \pm 0.95$ | $23.2 \pm 3.40$ | $<0.001^a$ |

Data are presented as mean ± standard deviation. MCI, mild cognitive impairment; HC, healthy control; MoCA-B: The Montreal Cognitive Assessment-Basic. $p^a$, the two-sample $t$-test; $p^b$, the chi-square test; $p^c$, the Wilcoxon rank-sum test.

version 2.0.10.35363 (http://pstnet.com/products/e-prime/).

*Data acquisition*

All subjects were arranged to sit on a comfortable chair in a room with diffuse light and noise-isolated wearable EEG device. EEG device mentioned above was single-channel MindWave MW001, produced by Neuro sky Inc., San Jose, CA. Two dry sensors were used to detect and filter the EEG signals of subjects. The sensor tip basically detected the electrical signals from the forehead of the brain (corresponding to Fp1 in the 10–20 system). The second sensor was the ear clip, which was grounded and acted as the reference (corresponding to A1 in the 10–20 system), allowing the Think Gear chip to filter out the electrical noise.

Subjects watched visual stimuli with a distance of approximately 65 cm from a 23" monitor ($1920 \times 1080$ pixel resolutions) and recorded visual scanning parameters by an eye-tracker which was assembled at the bottom of the monitor. Eye-tracker Tobii TX-300 recorded the line of sight of subjects and eye movement data, such as a saccadic, the size of the pupil and the blink of an eye. It also allowed the tracking of both the eyes simultaneously which offered better robustness for head motion tracking. Hence, tracking continued even if one eye was hidden from the field of view of the eye-tracker. The data was collected in every 8 ms (120 Hz). Figure 3B describes the experimental arrangement of visual tracking task.

Figure 3C presents the flowchart of the procedures of a visual tracking task. After the initiation of the EEG device, a 9-point eye-tracking calibration step was started in which the subjects followed a moving target on the display screen. Following the calibration (approximately about 120 s), subjects were measured by EEG device and recorded their eye movements by eye tracker during the test phase. This non-contact point of gaze estimation method was shown to effectively tolerate the head movement and to calculate

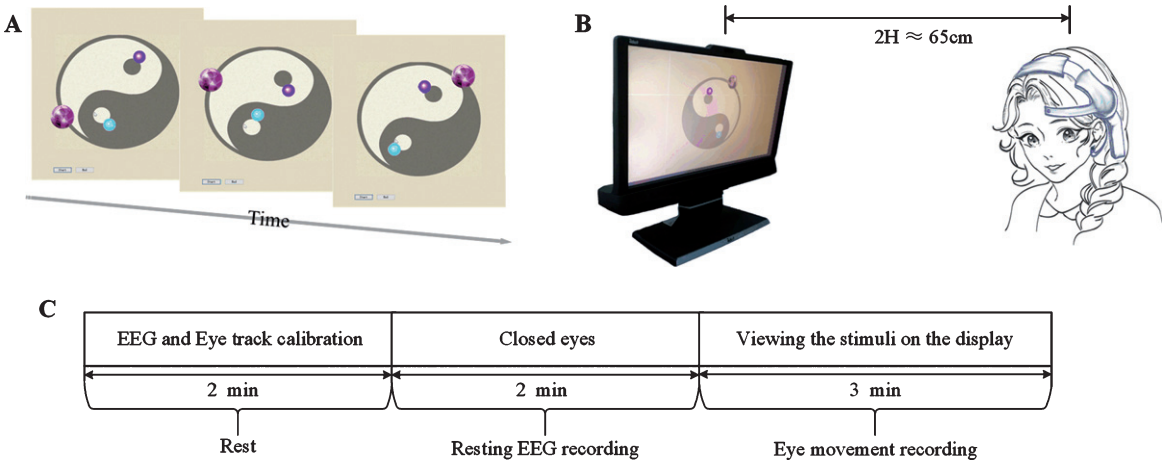


Fig. 3. The paradigm of visual tracking task in the present study: A) Visual stimulus, the stimulus consisting of three moving balls was presented on the screen. B) Experimental agreement in the visual tracking task, in which the viewing distance was approximately 65 cm from the monitor. C) The flowchart of the visual tracking task, the resting state EEG of 2 minutes before the task and the Eye movement data during the task execution were measured.

accurately the gaze-positions. Each data point had an associated timestamp and the series of data points were associated with the phase (rest or test) of visual tracking task. The resting state EEG of 2 min was given before measuring the visual tracking task.

*Data preprocessing*

In the experiment, EEG data was recorded at 500 Hz for each subject of about 7 min in the experiment and then a simple 2nd order Butterworth filtering was performed offline with a passband frequency range of 0.5–30 Hz. A pre-processed data of EEG was segmented by applying a moving window of 5 s with 60% overlapping of EEG data, which provided 15 overlapping segments for each subject. The EEG signal was preprocessing using EEGLAB toolbox implemented in MATLAB 2016b [17]. To filter the eye movement data, the criterion for excluding a trial was a loss of subject recognition that resulted in less than 1 s of total gaze time for the entire trial. In addition, all subjects tested had at least 4 usable trials, providing sufficient data for analysis.

*Feature extraction*

We selected the linear and nonlinear measures for feature extraction in this study, including EEG and Eye movement measures. We filtered the EEG dataset of subjects into four EEG frequency bands of frontal lobe region (delta 0.5–4 Hz, theta 4–8 Hz, alpha 8–13 Hz, and beta 13–30 Hz), computed the power spectrum of each frequency band and specific spectral power ratios like alpha/theta power [18, 19]. The alpha/theta power ratio can be considered as a typical feature of cognitive decline, which discriminates MCI from normal aging significantly [20, 21]. At some level, the neuronal systems have shown to exhibit various nonlinear behaviors and by applying non-linear time series analysis to EEGs indicated new information about the complex dynamics of underlying neuronal networks [22–26]. The approximate entropy and Multiscale entropy of EEG signal provided information about the fluctuation of EEG signal with time as compared with the time series with a delayed version of itself [27, 28]. Lempel–Ziv Complexity and Lattice complexity methods of EEG are used to analyze the brain function which can also be applied as an objective of EEG nonlinear detection method of cognitive function [18, 29, 30]. These linear and nonlinear analyses were used for extracting relevant features from the EEG signal.

The features extracted from Eye movement data were applied by using linear approaches [31]. The process of Eye gaze data included the segmentation of gaze-position to saccades and fixations. We put more attention to the association of fixations and saccades with moving ball on the specific regions of visual stimuli, and calculate the visual scanning parameters, such as blink frequency, blink time, fixation time and sustained attention duration [31–33]. To measure the Eye movement signal complexity, both Lempel-Ziv and Lattice Complexity were applied to extract the non-linear features of eye movement [30, 34, 35]. A

total of 40 physiological features were extracted from each subject, including 28 EEG based features and 12 Eye dynamics features. The detailed characterization of EEG and Eye dynamics features are listed in Supplementary Table 1.

*Feature selection and classification*

Logistic regression (LR) is a type of probabilistic statistical classification model which estimates the probabilities $p$ between the dependent variable $Y$ and the multiple independent variables $X_1$, $X_2$ ... by using a logistic function:

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots \beta_m X_m \tag{1}$$

where $p$ denoted as:

$$p = P(Y = 1|X_1, X_2, \ldots X_m) \tag{2}$$

Where $p$ indicates the probability of positive results under the action of m independent variables, $\beta_0$ is constant term, and $\beta_1, \beta_2, \ldots \beta_m$ are the regression coefficient.

LR can be applied in feature selection of which the extracted features pointed out high relevance with MCI and HC. The features extracted from EEG and Eye movement measurement by subjects were used as the candidate input features $X_1, X_2, \ldots X_m$. The stepwise selection and Wald test were used to select the independent variables with significant regression effect into LR model and excluding the independent variables with insignificant effect. The maximum likelihood (ML) method was used to estimate the parameters of logistic regression model. Thus, selecting the candidate features as independent variables was the primary goal and then standardized them by Z-transformation.

The classification algorithm based on Logistic regression was performed in the present study. Features selected by LR model from EEG/Eye movement and clinical demographic characteristics of subjects were used as the input of LR classifier. Based on the variability of samples which came from the group of training dataset and test dataset, the randomized cross validation method was used to randomly partition into 80% training dataset and 20% test dataset with multiple times (100 times). For each multiple cross validation, the evaluation indicators (Accuracy, Sensitivity, Specificity, AUC) of training dataset and test dataset were calculated to verify the performance and effectiveness of the model.

*Comparison experiments*

To evaluate the effectiveness of the proposed method, we examined six different models: 1) Clinical (gender, age, education, and The Montreal Cognitive Assessment-Basic (MoCA-B)); 2) EEG; 3) Eye movement; 4) EEG +Clinical; 5) Eye movement + Clinical; and 6) Combined (clinical variables combined with features of EEG and Eye movement) models. The above models underwent the same classification strategy and experimental data.

*Statistical analysis*

Demographic and clinical characteristics (age, gender, education, MoCA-B) were assessed using a two-sample $t$-test, the chi-square test or Wilcoxon rank-sum test. In the classification model training stage, LR based stepwise selection was applied to select a feature subset associated with MCI disease. An assessed was done to verify the selecting features with sufficient discriminative ability by using the two-sample $t$-test. All statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL) and MATLAB 2016b (Math Works Inc., Sherborn, MA) run on a Windows platform. Values were considered as significant for $p < 0.05$, 2-tailed.

## RESULTS

*Clinical characteristics*

The detailed demographic and clinical characteristics of subjects are reported in Table 1. The results showed that the MoCA-B scores in MCI patients were significantly lower than HC scores ($p < 0.001$, two-sample $t$-test). There were no significant differences in age ($p = 0.875$; two-sample $t$-test), gender ($p = 0.541$; chi-square test), or years of education ($p = 0.071$; Wilcoxon rank-sum test).

*Fixation distribution in the Eye tracking task*

The EEG and Eye features across subjects were obtained by using linear and nonlinear approach. In the case of Eye tracking task, MCI patients demonstrated a significant difference in the fixations distribution. Figure 4 depicts that the fixations distribution of MCI is far away from the trajectory of the moving purple ball, which is obviously affected by the interference from two small balls. The Fixations distribution also reflects the concentration state

of the subjects during the task execution, showing the significance in the difference of sustained attention.

*Classification analysis*

The stepwise logistic regression method to penalize the extracted total of 40 physiological features, including 28 EEG based features and 12 Eye dynamics features was used for the present analysis. For avoiding the variability of samples of training and test datasets and obtaining more stable features associated with MCI diagnosis, 100 iterations of random partition and selection feature were implemented. After the above strategies, only five top quantitative features from EEG and Eye modalities were ultimately selected, including alpha/theta ratio (linear feature of EEG), Lempel-Ziv complexity of delta (nonlinear feature of EEG), Multiscale Entropy of delta (nonlinear feature of EEG), Multiscale Entropy of eye movement (nonlinear feature of Eye movement) and maximum time for Sustain attention (linear feature of Eye movement). The selected features had significant differences and summarized in one random iteration result, as shown in Table 2. The result indicated that the alpha/theta ratio had greatest statistical significance (odds ratio (OR): 6.41, 95% CI: 1.75∼23.4; $p = 0.005$; Bonferroni correction).

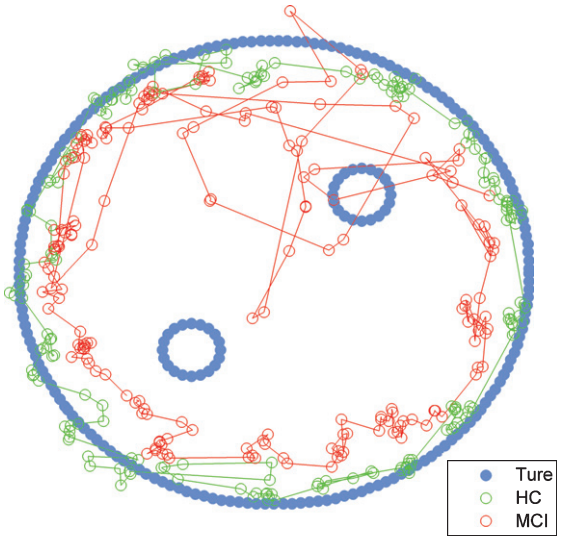


Fig. 4. The Eye tracking task and fixation distribution in this study. The blue dots represent the true trace of task ball. The green dot trajectory was of the healthy controls and the red one belonged to MCI patients.

The effects of the corresponding LR classification model based on the selected top features were assessed on the training and test datasets. The following six models were used to evaluate our proposed approach: 1) Clinical model; 2) EEG model with 3 selected features; 3) Eye movement model with 2 selected features; 4) EEG +Clinical model; 5) Eye movement + Clinical model; and 6) Combined model (all prognostic variables, including clinical, 3 EEG and 2 Eye movement variables). The average evaluation indicators of each model were compared in the 100 randomized iterations. Table 3 presents the classification results of the different models. The areas under the receiver operating curve (AUC) of different models are presented in Fig. 5. The above

Table 2
The LR model results of one random selected feature

| Measure | *b* | $S_b$ | *Wald*$\chi^2$ | *p* | *OR (95% CI)* |
|---|---|---|---|---|---|
| Alpha/theta ratio | 0.186 | 0.662 | 7.88 | 0.005 | 6.41 (1.75∼23.4) |
| Lempel-Ziv complexity of delta | 0.121 | 0.005 | 4.95 | 0.019 | 1.35 (1.05∼1.74) |
| Multiscale Entropy of delta | 0.974 | 0.343 | 8.08 | 0.011 | 0.44 (0.23∼0.83) |
| Multiscale Entropy of eye movement | 2.047 | 0.605 | 11.4 | <0.001 | 0.81 (0.75∼0.88) |
| Maximum time for Sustain attention | –1.223 | 0.518 | 5.56 | <0.001 | 0.94 (0.91∼0.97) |

b, standard regression coefficient; $S_b$: standard deviation of variables; Wald$\chi^2$, Wald Test and Pearson $\chi^2$; p, *p* value; OR, odds ratio.

Table 3
The classification performance of different MCI detection models in the test dataset

| Classification Model | Accuracy (%) | Sensitivity (%) | Specificity (%) | AUC (95% CI) |
|---|---|---|---|---|
| Clinical Model | 68.69 ± 4.36 | 45.87 ± 9.00 | 87.08 ± 7.54 | 0.6735 (0.5627∼0.8009) |
| EEG Model | 61.79 ± 5.29 | 43.82 ± 8.80 | 76.35 ± 7.66 | 0.6738 (0.5271∼0.7729) |
| Eye movement Model | 73.13 ± 5.52 | 64.40 ± 8.19 | 80.36 ± 7.20 | 0.8073 (0.7086∼0.8956) |
| EEG + Clinical Model | 69.46 ± 5.04 | 59.37 ± 9.08 | 76.02 ± 7.91 | 0.7444 (0.6218∼0.8527) |
| Eye movement + Clinical Model | 75.61 ± 5.09 | 66.96 ± 9.08 | 82.69 ± 6.35 | 0.8390 (0.7409∼ 0.9244) |
| Combined Model | 81.51 ± 4.26 | 78.67 ± 7.67 | 84.10 ± 6.00 | 0.9216 (0.8550∼0.9702) |

All data are given as mean ± standard.

results showed that the performance of the combined model in the test dataset was better than the other models (Accuracy: 81.51%; Sensitivity: 78.67%; Specificity: 84.10%; AUC: 0.9216). The comparison of all six models showed that the combined model had an excellent identification ability and performed as the best model for MCI diagnosis (Accuracy: Clinical: 68.69%; EEG: 61.79%; Eye movement: 73.13%; EEG+ Clinical: 69.46%; Eye movement+ Clinical:75.61%; Combined model: 81.51%). The detailed features of above six models are listed in Supplementary Table 2.

## DISCUSSION

In the present study, we proposed an automatic, non-invasive, and cost-effective detection tool for large-scale screening of MCI patients in the primary care. Based on the published report, we claim that this is the first study that combines EEG and Eye movement methods to investigate abnormal attention. EEG and Eye movement methods were applied to identify the abnormalities of MCI-related features. Then, logistic regression analysis was performed to generate the ultimate MCI screening model through feature selection and classification. Our findings indicated that the combination of EEG, Eye movement, and clinical assessment could be used to build a powerful MCI screening approach in primary care.

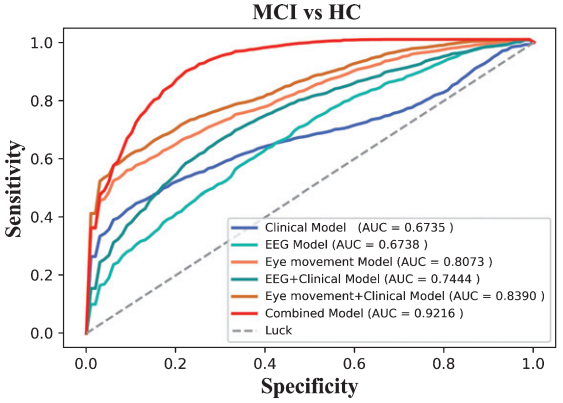


Fig. 5. The receiver operating curves of different MCI detection models.

There have been numerous investigations into MCI diagnosis, with many demonstrating an excellent ability to screen MCI patients and healthy people. Table 4 lists detailed information about these previous studies. Although the results obtained from these efforts displayed powerful discrimination for MCI diagnosis reaching results of about 97.8%, they used expensive and time consuming physiological signal collection devices, which are seldom used in primary care [21]. The previous satisfactory results were performed in the laboratory, which was not suitable for large-scale clinical MCI screening work. In contrast, the present approach targeted the frontal brain region with emerging EEG and Eye movement analysis techniques and provided a sufficient screening model for clinical decision-making. It is worth noting that our approach takes only 5 minutes to complete the MCI diagnosis task excluding the eye movement calibration, while other methods took at least 10 minutes or more [13, 18, 21, 36]. In addition, these studies were used with the help of more sensitive and

Table 4
The classification performance of different MCI detection models in the test dataset

| Detection Tools | Reference | Modality | Subject | Time (min) | Method | Result |
|---|---|---|---|---|---|---|
| EEG based Detection | Houmani et al., 2018 [36] | EEG (30 electrodes) | 169 | 20 | EEG features (Epoch-based entropy, bump model) and support vector machine (SVM) | 91.6%[a] |
| EEG based Detection | Buscema et al., 2015 [21] | EEG (19 electrodes) | 272 | >10 | MS-ROM Features and k-Nearest Neighbor, Naïve Bayes | 97.8%[a] |
| EEG-based Biomarkers | McBride et al., 2014 [18] | EEG (32 electrodes) | 48 | 30 | Scalp EEG spectral, Complexity features and SVM | 96.8%[a] |
| The King-Devick Test | Galetta et al., 2017 [13] | Neuropsychological test | 206 | 1-2 | The King-Devick Test (with saccadic and other movements) was applied to subjects | 0.71[b] |
| Eye movement Detection | Lagun et al., 2011 [31] | Eye movement | 60 | >10 | Eye Dynamics' features and SVM classifier | 87%[a] |
| EEG and Eye movement Detection | Proposed Method | EEG (1 electrode) & Eye movement | 336 | 5 | EEG and Eye features (linear and nonlinear methods) and logistic regression | 81.51%[a] |

[a]Accuracy; [b]Area Under Curve (AUC).

expensive multi-electrode EEG collection and Eye movement equipment [31]. In contrast, the present approach only used a single electrode EEG acquisition and Eye movement equipment, which turned out to perform surprisingly well (accuracy: 81.51%). It is to be noted that the present approach suits primary care, which allows non-invasive, portable, economical, and fast devices in most cases. In addition, this approach demonstrates powerful adaptability and MCI discriminating ability even for the analogous limited environment.

Recently, both linear and nonlinear feature analysis has been successfully used to identify the powerful biomarkers for neurophysiological diseases, such as AD [37–39]. In the present study, we applied the linear and nonlinear methods to extract 40 EEG and Eye movement features. After stepwise logistic regression analysis penalized the 40 features, only five top features were selected, which included alpha/theta ratio (linear feature of EEG), Lempel-Ziv complexity of delta (nonlinear feature of EEG), Multiscale Entropy of delta (nonlinear feature of EEG), Multiscale Entropy of eye movement (nonlinear feature of Eye movement), and maximum time for Sustain attention (linear feature of Eye movement). Detailed selected feature information is shown in Fig. 6. The results indicate that the characteristics of EEG and Eye movement signals had a significant difference among the MCI patients and HC. The alpha/theta ratio increases in MCI patients ($p = 0.026$), representing the abnormal activity of alpha frequency happened in the frontal gyrus. The Lempel-Ziv complexity of delta decreases in MCI patients ($p = 0.0092$) and the Multiscale Entropy of delta also increases for MCI patients ($p = 0.011$). Significant differences in the above EEG features indicated that the brain neuronal information communication impairments in MCI might cause a complicated and altered EEG activity of alpha and delta frequency in the frontal gyrus region. These findings are consistent with other analogous studies [18, 29, 36, 40, 41]. For the Eye movement features, the Multiscale Entropy of eye movement increases ($p = 0.0042$), while the maximum time for sustain attention decreases ($p = 0.01$), representing that the eye movement tracking methodology could capture subtle differences associated with cognitive decline in MCI disease [42]. The abnormalities of Eye movement features indicate that sustained attention differs from healthy individuals under high task demands. Hence, the above striking difference between EEG and Eye movement features can be considered as physiological biomarkers for MCI diagnosis. Furthermore, the combination of EEG, Eye movement, and clinical assessments will provide a potential clinical MCI screening tool for the translational application.

In this research, we proposed an unprecedented automatic screening approach for large-scale MCI diagnosis in primary care. There are some limitations in the present approach, which are as follows: 1)

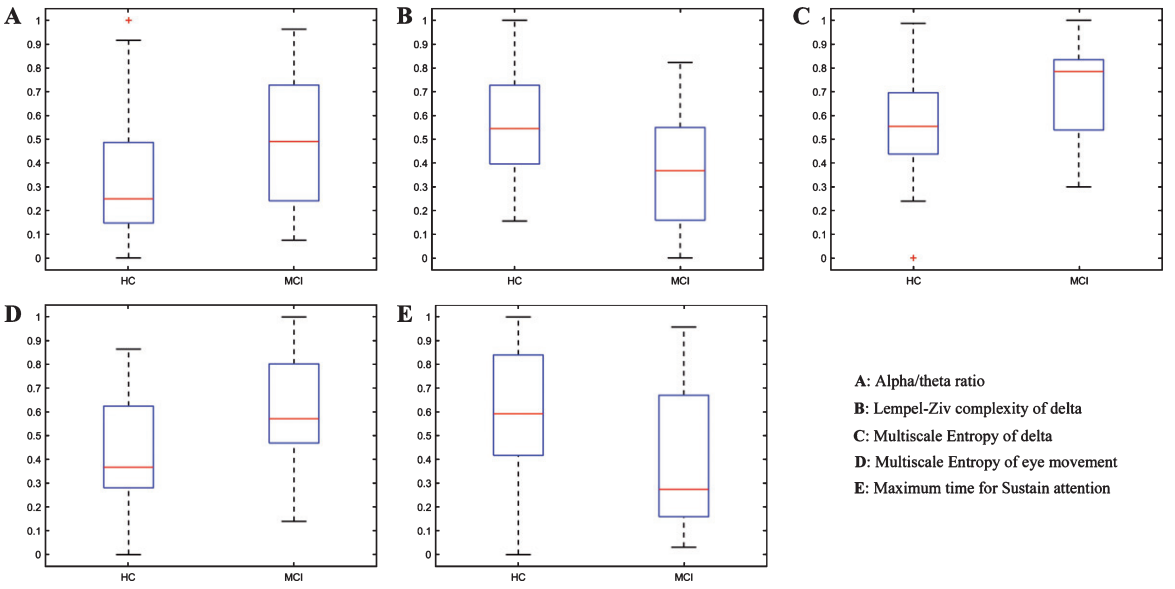


Fig. 6. The difference between the selected top features associated with MCI diagnosis between MCI patients and healthy controls.

The number of experimental subjects including MCI patients and HC was limited. We will recruit more subjects to verify the extensibility and generalizability of our proposed model in the near future; 2) We only considered the MCI patients and did not subdivide various MCI subtypes, such as amnestic MCI and Non-memory MCI. We will put more attention to investigate the characteristics of different types of MCI in the future; 3) We only used the monoelectrode EEG equipment to detect the MCI diagnosis in this work. To further improve the detection accuracy of our tool, we intend to use a mobile multi-electrodes EEG tool in the future.

In conclusion, we proposed an automatic, fast, and cost-effective MCI screening tool for primary care. The findings of the combination of EEG, Eye movement techniques, and clinical assessments indicated that this approach had the potential for MCI detection and an ultimate criterion for a more comprehensive evaluation to facilitate early intervention in primary care.

## ACKNOWLEDGMENTS

This article was supported by the National Natural Science Foundation of China No.61603236; Shanghai Technology and Science Key Project in Healthcare No. 17441902100; Scientific and Technological Innovation Project of Traditional Chinese Medicine in Shanghai No. ZYKC201602002 and Natural Science Foundation of Shanghai No. 17ZR1427700.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0628r1).

## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-190628.

## REFERENCES

[1] Tschanz JT, Welsh-Bohmer KA, Lyketsos CG, Corcoran C, Green RC, Hayden K, Norton MC, Zandi PP, Toone L, West NA, Breitner JC, Cache County Investigators (2006) Conversion to dementia from mild cognitive disorder: The Cache County Study. *Neurology* **67**, 229-234.

[2] Belleville S, Chertkow H, Gauthier S (2007) Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology* **21**, 458-469.

[3] Woo CW, Chang LJ, Lindquist MA, Wager TD (2017) Building better biomarkers: Brain models in translational neuroimaging. *Nat Neurosci* **20**, 365-377.

[4] Bublak P, Redel P, Sorg C, Kurz A, Forstl H, Muller HJ, Schneider WX, Finke K (2011) Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **32**, 1219-1230.

[5] Haworth J, Phillips M, Newson M, Rogers PJ, Torrens-Burton A, Tales A (2016) Measuring information processing speed in mild cognitive impairment: Clinical versus research dichotomy. *J Alzheimers Dis* **51**, 263-275.

[6] Pasgreta K, Nowińska E, Feit J, Płaszczyca N, Walecki P, Gorzelańczyk E (2012) P-1028 – The parameters of saccadic eye movements in individuals with alzheimer's disease compared with those of healthy subjects. *Eur Psychiatr* **27** (Suppl 1), 1.

[7] Chau SA, Herrmann N, Sherman C, Chung J, Eizenman M, Kiss A, Lanctot KL (2017) Visual selective attention toward novel stimuli predicts cognitive decline in Alzheimer's disease patients. *J Alzheimers Dis* **55**, 1339-1349.

[8] Garbutt S, Matlin A, Hellmuth J, Schenk AK, Johnson JK, Rosen H, Dean D, Kramer J, Neuhaus J, Miller BL, Lisberger SG, Boxer AL (2008) Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. *Brain* **131**, 1268-1281.

[9] Babiloni C, Ferri R, Binetti G, Cassarino A, Dal Forno G, Ercolani M, Ferreri F, Frisoni GB, Lanuzza B, Miniussi C, Nobili F, Rodriguez G, Rundo F, Stam CJ, Musha T, Vecchio F, Rossini PM (2006) Fronto-parietal coupling of brain rhythms in mild cognitive impairment: A multicentric EEG study. *Brain Res Bull* **69**, 63-73.

[10] Babiloni C, Carducci F, Lizio R, Vecchio F, Baglieri A, Bernardini S, Cavedo E, Bozzao A, Buttinelli C, Esposito F, Giubilei F, Guizzaro A, Marino S, Montella P, Quattrocchi CC, Redolfi A, Soricelli A, Tedeschi G, Ferri R, Rossi-Fedele G, Ursini F, Scrascia F, Vernieri F, Pedersen TJ, Hardemark HG, Rossini PM, Frisoni GB (2013) Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease. *Hum Brain Mapp* **34**, 1427-1446.

[11] MacAskill MR, Anderson TJ (2016) Eye movements in neurodegenerative diseases. *Curr Opin Neurol* **29**, 61-68.

[12] Anderson TJ, MacAskill MR (2013) Eye movements in patients with neurodegenerative disorders. *Nat Rev Neurol* **9**, 74-85.

[13] Galetta KM, Chapman KR, Essis MD, Alosco ML, Gillard D, Steinberg E, Dixon D, Martin B, Chaisson CE, Kowall NW, Tripodis Y, Balcer LJ, Stern RA (2017) Screening utility of the King-Devick Test in mild cognitive impairment and Alzheimer disease dementia. *Alzheimer Dis Assoc Disord* **31**, 152-158.

[14] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. *Arch Neurol* **58**, 1985-1992.

[15] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.

[16] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[17] Delorme A, Makeig S (2004) EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* **134**, 9-21.

[18] McBride JC, Zhao X, Munro NB, Smith CD, Jicha GA, Hively L, Broster LS, Schmitt FA, Kryscio RJ, Jiang Y (2014) Spectral and complexity analysis of scalp EEG characteristics for mild cognitive impairment and early Alzheimer's disease. *Comput Methods Programs Biomed* **114**, 153-163.

[19] Schmidt MT, Kanda PAM, Basile LFH, da Silva Lopes HF, Baratho R, Demario JLC, Jorge MS, Nardi AE, Machado S, Ianof JN, Nitrini R, Anghinah R (2013) Index of alpha/theta ratio of the electroencephalogram: A new marker for Alzheimer's disease. *Front Aging Neurosci* **5**, 60.

[20] Chai R, Ling SH, San PP, Naik GR, Nguyen TN, Tran Y, Craig A, Nguyen HT (2017) Improving EEG-based driver fatigue classification using sparse-deep belief networks. *Front Neurosci* **11**, 103.

[21] Buscema M, Vernieri F, Massini G, Scrascia F, Breda M, Rossini PM, Grossi E (2015) An improved I-FAST system for the diagnosis of Alzheimer's disease from unprocessed electroencephalograms by using robust invariant features. *Artif Intell Med* **64**, 59-74.

[22] Mazzon G, De Dea F, Cattaruzza T, Manganotti P, Monti F, Accardo A (2018) Memorization test and resting state EEG components in mild and subjective cognitive impairment. *Curr Alzheimer Res* **15**, 809-819.

[23] Persson PO (2013) A sparse and high-order accurate line-based discontinuous Galerkin method for unstructured meshes. *J Comput Phys* **233**, 414-429.

[24] Gao J, Hu J, Liu F, Cao Y (2015) Multiscale entropy analysis of biological signals: A fundamental bi-scaling law. *Front Comput Neurosci* **9**, 64.

[25] Costa M, Goldberger AL, C-K PJPRESN, Physics SM (2005) Multiscale entropy analysis of biological signals. *Phys Rev E Stat Nonlin Soft Matter Phys* **71**(2 Pt 1), 021906.

[26] Mizuno T, Takahashi T, Cho RY, Kikuchi M, Murata T, Takahashi K, Wada Y (2010) Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy. *Clin Neurophysiol* **121**, 1438-1446.

[27] Abasolo D, Hornero R, Espino P, Poza J, Sanchez CI, de la Rosa R (2005) Analysis of regularity in the EEG background activity of Alzheimer's disease patients with approximate entropy. *Clin Neurophysiol* **116**, 1826-1834.

[28] Pincus SM (2006) Approximate entropy as a measure of irregularity for psychiatric serial metrics. *Bipolar Disord* **8**, 430-440.

[29] Dauwels J, Srinivasan K, Ramasubba Reddy M, Musha T, Vialatte FB, Latchoumane C, Jeong J, Cichocki A (2011) Slowing and loss of complexity in Alzheimer's EEG: Two sides of the same coin? *Int J Alzheimers Dis* **2011**, 539621.

[30] Ke DG, Tong QY (2008) Easily adaptable complexity measure for finite time series. *Phys Rev E Stat Nonlin Soft Matter Phys* **77**, 066215.

[31] Lagun D, Manzanares C, Zola SM, Buffalo EA, Agichtein E (2011) Detecting cognitive impairment by eye movement analysis using automatic classification algorithms. *J Neurosci Methods* **201**, 196-203.

[32] Yang Q, Wang T, Su N, Xiao S, Kapoula Z (2013) Specific saccade deficits in patients with Alzheimer's disease at mild to moderate stage and in patients with amnestic mild cognitive impairment. *Age (Dordr)* **35**, 1287-1298.

[33] Crutcher MD, Calhoun-Haney R, Manzanares CM, Lah JJ, Levey AI, Zola SM (2009) Eye tracking during a visual paired comparison task as a predictor of early dementia. *Am J Alzheimers Dis Other Demen* **24**, 258-266.

[34] Abasolo D, Hornero R, Gomez C, Garcia M, Lopez M (2006) Analysis of EEG background activity in Alzheimer's disease patients with Lempel-Ziv complexity and central tendency measure. *Med Eng Phys* **28**, 315-322.

[35] Pincus SM (1991) Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A* **88**, 2297-2301.

[36] Houmani N, Vialatte F, Gallego-Jutgla E, Dreyfus G, Nguyen-Michel VH, Mariani J, Kinugawa K (2018) Diagnosis of Alzheimer's disease with electroencephalography in a differential framework. *PLoS One* **13**, e0193607.

[37] Al-Jumeily D, Iram S, Vialatte FB, Fergus P, Hussain A (2015) A novel method of early diagnosis of Alzheimer's disease based on EEG signals. *ScientificWorldJournal* **2015**, 931387.

[38] Amjad I, Toor H, Niazi IK, Pervaiz S, Jochumsen M, Shafique M, Haavik H, Ahmed T (2019) Xbox 360 Kinect cognitive games improve slowness, complexity of EEG, and cognitive functions in subjects with mild cognitive impairment: A randomized control trial. *Games Health J* **8**, 144-152.

[39] Babiloni C, Vecchio F, Lizio R, Ferri R, Rodriguez G, Marzano N, Frisoni GB, Rossini PM (2011) Resting state cortical rhythms in mild cognitive impairment and Alzheimer's disease: Electroencephalographic evidence. *J Alzheimers Dis* **26**(Suppl 3), 201-214.

[40] Houmani N, Dreyfus G, Vialatte FB (2015) Epoch-based entropy for early screening of Alzheimer's disease. *Int J Neural Syst* **25**, 1550032.

[41] Alberdi A, Aztiria A, Basarab A (2016) On the early diagnosis of Alzheimer's disease from multimodal signals: A survey. *Artif Intell Med* **71**, 1-29.

[42] Seligman SC, Giovannetti T (2015) The potential utility of eye movements in the detection and characterization of everyday functional difficulties in mild cognitive impairment. *Neuropsychol Rev* **25**, 199-215.

View publication stats