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Feature extraction of time series data on functional near-infrared spectroscopy and comparison of deep learning performance for classifying patients with Alzheimer's-related mild cognitive impairment: a post-hoc analysis of a diagnostic interventional trial

J. KIM[1], S.-C. KIM[2], D. KANG[2], S.-Y. KIM[3], R. KWON[4], D.K. YON[4], J.G. KIM[1]

[1]Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju, South Korea
[2]Institute for Artificial Intelligence, N.CER, Gwangju, South Korea
[3]Department of Family Medicine, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea
[4]Center for Digital Health, Medical Science Research Institute, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea

J. Kim and S.-C. Kim are first authors

Abstract. – OBJECTIVE: This study aimed to define a method of classifying patients with mild cognitive impairment caused by Alzheimer's disease by the retrieval of functional near-infrared spectroscopy (fNIRS) signal characteristics obtained during olfactory stimulation and the validation of deep learning findings.

PATIENTS AND METHODS: Participants were recruited for the study from March 02 and August 30, 2021. A total of 78 participants met the criteria for categorization. The Mini-Mental State Examination and the Seoul Neuropsychological Scale were used to distinguish between patients with mild Alzheimer's disease-related cognitive impairment and healthy controls. fNIRS data received during olfactory stimulation were used to create 1,680 time-series sample values. A total of 150 indices with a *p*-value ≤ 0.1 were used as deep learning features to construct the result values for 120 models accounting for all conceivable combinations of data ratios.

RESULTS: For this trial, 78 participants were recruited for the original intervention trial. The average accuracy of the 120 deep-learning models for classifying patients with Alzheimer's-related mild cognitive impairment ranged from 0.78 to 0.90. Sensitivity ranged from 0.88 to 0.96 for the 120 models, while specificity ranged from 0.86 to 0.94. The F1 scores ranged from 0.74 to 0.88. At 0.78 to 0.90, the precision and recall were equivalent.

CONCLUSIONS: This trial using a deep-learning model found that the representative value extracted from the time series data of each channel could distinguish between healthy people and patients with mild cognitive impairment caused by Alzheimer's disease.

Key Words:
fNIRS, Alzheimer's disease, Dementia, Deep learning.

Introduction

The most prevalent cause of dementia is Alzheimer's disease[1], the early stages of which are characterized by mild cognitive impairment as beta-amyloid and tau proteins are deposited[2]. Without appropriate interventional treatment, mild cognitive impairment (MCI) progresses to Alzheimer's disease[3]. As there is little effective management and treatment for Alzheimer's disease, it is crucial to detect it in the early stages of dementia or mild cognitive impairment and treat it in a palliative way[4]. It is difficult to distinguish patients with mild cognitive impairment caused by Alzheimer's disease from healthy individuals without a detailed examination[5]. Various studies[6,7] have been conducted to identify biomarkers suitable for discovering Alzheimer's disease at the mild cognitive impairment stage. Among them, studies[7,8] on the olfactory nerve have shown promising results. Additionally, the olfactory nerve function decreases in the early stages of Alzheimer's disease. Detection of this decrease in function is more sensitive than the functional decline of any other sensory organ[9]. Therefore, many studies[10,11] have attempted to detect Alzhei-

Corresponding Authors: Dong Keon Yon, MD; e-mail: yonkkang@gmail.com; Jae Gwan Kim, Ph.D; e-mail: jaekim@gist.ac.kr

mer's disease early by quantifying olfactory function using functional MRI and questionnaires.

In the past, we have identified the stages of Alzheimer's disease using the left-right oxygen consumption difference estimated from time series data on olfactory-stimulated functional near-infrared spectroscopy (fNIRS)[7,8]. Although we have investigated whether olfactory-stimulated oxygenation differences detected by fNIRS were related to cognitive impairment, previous trials[7,8] used only one feature from fNIRS through conventional statistical techniques. Thus, using deep learning and 1,680 representative features of time series data from fNIRS, including complexity, asymmetry, and new similarity of fNIRS signals obtained by two of six channels, we aimed to differentiate between patients with mild cognitive impairment caused by Alzheimer's disease and healthy individuals through comprehensive post-hoc analysis of a diagnostic interventional trial.

Patients and Methods

Participants

Between March 02 and August 30, 2021, 97 participants were recruited for the original trial from which our data were derived[7,8]. First, patients with Alzheimer's dementia, severe head injuries, systemic malignancies, cerebral hemorrhages, or strokes were excluded from the trial. Second, those with olfactory problems, such as olfactory nerve tumors and physical blockage of the nose, were excluded. Third, those with psychiatric illnesses, such as major depressive disorder and substance abuse, were also excluded. Finally, 19 patients were excluded who were unable to cooperate throughout the fNIRS exam and questionnaire. Of the total recruited participant group, a final sample size of 78 was included in the study (females, n = 41; males, n = 37).

The protocol for the patient study was approved by the Gwangju Institute of Science and Technology Clinical Review Board (20210115-HR-58-01-02). The clinical trial was registered with the Korea Clinical Research Information Service (CRIS number: KCT0006197). We adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from each subject or legal guardian at the time of recruitment.

Alzheimer's Disease Classification Criteria

The participants in this study underwent cognitive function tests using the Mini-Mental State Examination (MMSE) and the Seoul Neuropsychological Screening Battery (SNSB) to determine the Alzheimer's disease stage. Additionally, MRI (MPRAGE; *TR,* 2,300 ms; *TE,* 2.143 ms; *TI,* 900 ms; *FA,* 9°; *FoV,* 256 × 256; matrix, 320 × 320; slice thickness, 0.8 mm) using a 3.0 T magnetic resonance (MR) scanner (MAGNETOM Skyra; Siemens Healthineers, Erlangen, Germany) and amyloid PET-CT (Discovery STE PET-CT scanner; GE Medical Systems, Chicago, IL, USA) were used to verify the progression of Alzheimer's disease[7,8,12]. Based on test data and the 2011 recommendations of the National Institute on Aging Alzheimer's Association (NIA-AA)[13], patients with mild cognitive impairment caused due to Alzheimer's disease were discriminated against healthy individuals. Using the SNSB cognitive domain exam, criteria for mild cognitive impairment were established for patients who met the Jak/Bondi comprehensive criteria[14].

In this study, patients with Alzheimer's disease with mild cognitive impairment were defined as those with amyloid accumulation verified by an amyloid PET-CT and a standardized distribution index z-value of ≤ -1.0 in two or more cognitive domains[15].

Study Protocol

Participants who completed the cognitive function test and imaging examination were provided with a smell stick-scented pen to perform the olfactory test in the clinic. The olfactory test was performed with the fNIRS probe connected to the forehead. The order of inspection was as follows: (1) no fragrance, (2) three varieties of fragrances (Downy, mint, leather), and (3) no fragrance. In the olfactory test, the individual was given no additional instructions other than to sniff the pen[16,17].

Features for Deep Learning Models

Several signal processing stages were performed to select the features to be used in deep learning. The light from the LED passes through the cerebral cortex and uses a filter that removes noise caused by motion from the signal entering the light receiver. This passes through a band-pass filter (0.01-2.5 Hz) and uses the modified Beer-Lambert law formula to signal red blood cell oxygen concentration[18]. This was then changed to a Gaussian filter, a Task-related component analysis (TRCA) algorithm, and a corrected fNIRS signal with skin signals removed was obtained. TRCA is an algorithm that attempts to reduce the dimensionality of the hyperplane used

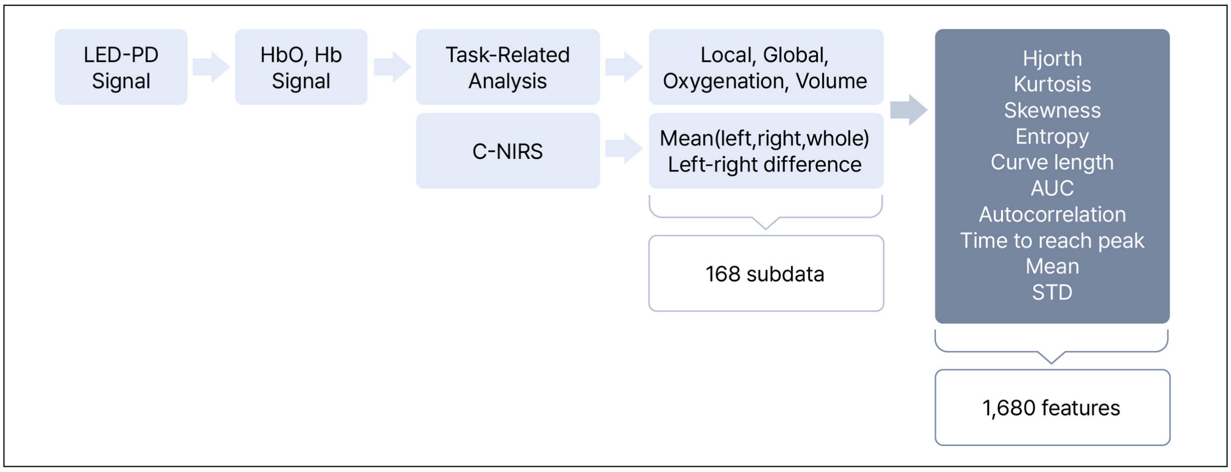

Figure 1. Schematic diagram of feature extraction algorithm for time series data. The difference between patients with normal group and those with mild cognitive impairment was determined for these 1,680 fetuses, and only 150 traits with a *p*-value ≤ 0.1 were chosen.

in the principal components by using the task time section[19]. Thus, the features used for deep learning were the left average, right average, total average left and right differences for each channel (1-6), corrected fNIRS, and oxy-hemoglobin and deoxy-hemoglobin. Finally, the TRCA can be obtained using four items: local, global, oxygenation, and volume. We used 168 sub-data and 1,680 features (10-time series data characteristics [Hjorth, kurtosis, skewness, entropy, curve length, area under the curve (AUC), autocorrelation, and time to peak]). There were 10 traits altogether, providing each person with 1,680 features. This was leveraged for deep learning (Figure 1). We selected features with $p \leq 0.1$ in the *t*-test[20-22].

Proposed Deep Learning Models

Figure 2 depicts the structure of the model for identifying patients with Alzheimer's-related mild cognitive impairment in the normal group. While retaining the normal-to-mild cognitive impairment patient ratio, 10 groups of 79 patients were selected randomly, and the number of all cases in which the training set and test set could be separated by 7:3 was applied. Thus, 120 training sets and 120 test sets were constructed. In this dataset, a six-layer multi-perceptron was used to develop a deep learning classification model, and hyperparameter tuning was performed using Optuna (version 3.0.5; Preferred Networks, Inc., Tokyo, Japan). All processing steps were executed on a machine with an Intel Core i7-12700F 4.9 GHz processor (Intel Inc., Santa Clara, CA, USA), 512 GB of RAM, and NVIDIA GEForce RTX 3080 Ti. (NVIDIA Inc, Santa Clara, CA, USA), Python (version 3.7.13; Python Software Foundation, Wilmington, DE, USA), with TensorFlow-gpu (version 2.6.0; Google, Mountain View, CA, USA), Keras (version 2.9.0; Google, Mountain View, CA, USA), NumPy (version 1.19.5), Pandas (version 1.3.5), Matplotlib (version 3.5.1), and sci-kit-learn models (version 1.0.2).

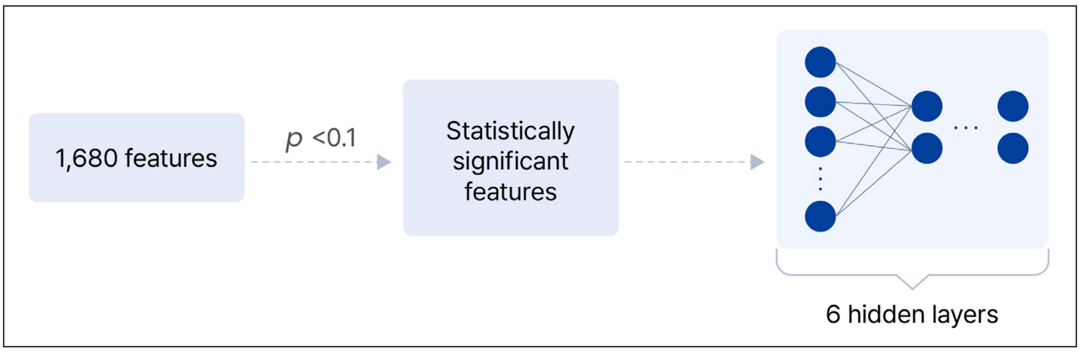

Figure 2. Summary of the structure of deep learning models and the characteristics to be included in model inputs.

Statistical Analysis

The epidemiological data of the patients were presented as mean and standard deviation (SD). All statistical analyses were performed using SPSS (version 25.0; IBM Corp, Armonk, NY, USA) and R software (version 3.1.1; R Foundation, Vienna, Austria). One-dimensional representative values of the time series data were compared between the normal and mild cognitive impairment groups using a *t*-test, and only representative values with a two-sided *p*-value lower than 0.1 were used for machine learning.

Results

A total of 78 senior citizens aged 60 years or older met the eligibility criteria for this study. The baseline characteristics of the remaining patients are summarized in Table I. Among 1,680 features in 52 healthy patients and 26 patients with mild cognitive impairment, 150 features showed $p \leq 0.1$ in the *t*-test of the patients with and without mild cognitive impairment. The accuracy of 120 deep-learning models using 150 features extracted from time series data was 0.78-0.90. The sensitivity and specificity of the 120 models were in the range of 0.88-0.96 and 0.86-0.94, respectively. The F1 score range was 0.74-0.88. Recall and precision were also in the range of 0.78-0.90. The AUC calculated from the receiver operating characteristic curve is shown in Figure 3.

Discussion

Through post-hoc analysis of the diagnostic intervention trial, we identified a novel deep learning model with high sensitivity (0.88-0.96), specificity (0.86-0.94), and accuracy (0.78-0.90) for classifying individuals with mild cognitive disorder caused by Alzheimer's disease using comprehensive features (n = 1,680) from fNIRS time series data. Specifically, the following fNIRS time series data were selected: Hjorth, kurtosis, skewness, entropy, curve length, AUC, autocorrelation, and time to peak.

Various approaches employing sensory nerves originating directly from the brain have been developed for the early detection of Alzheimer's disease-related mild cognitive impairment[23]. Numerous attempts have been made to categorize individuals with Alzheimer's-related mild cognitive impairment or dementia using machine learning or deep learning, in addition to simple statistical analysis of biosignals that excite sensory organs[23]. Among the senses, the sense of smell has been shown to be closely associated with Alzheimer's disease[24]. fNIRS was utilized to evaluate olfactory stimulation, and statistically associated indications were used to investigate the comparison between healthy individuals and those with mild cognitive impairment[25].

Using various methods, the proposed model method generated representative values for the characteristics displayed in each area of the time series data. This strategy can compensate for changes in data length resulting from differences in subject cooperation in other research utilizing time series data, as well as for instances in which the protocol was not followed at the precise time point.

This study has many limitations. First, compared to previous research, this was a comparatively large sample, yet the sample size was small. Underfitting was identified in 120 models and the performance of the model would likely improve as the sample size increased.

Table I. Factors independently associated with in-hospital mortality by means of multivariate analysis.

Variables	CN	MCI
Number (%)	52 (67)	26 (33)
Age, years, median (SD)	73.7 ± 6.2	73.4 ± 6.4
Sex, female (%)	28 (50.9)	13 (50.0)
Mini-Mental State Examination, median (range)	27.8 ± 1.3	25.8 ± 2.1
Cognitive measures (composite z score), mean (SD)		
SNSB attention	-0.07 (0.92)	-0.52 (0.79)
SNSB language and related function	0.51 (0.65)	0.02 (1.22)
SNSB visuospatial function	1.01 (0.68)	0.17 (1.69)
SNSB memory	0.73 (1.08)	-0.64 (1.46)
SNSB frontal/executive function	0.55 (0.80)	-0.47 (1.06)

CN, cognitively normal; MCI, mild cognitive impairment; SD, standard deviation; SNSB, Seoul Neuropsychological Screening Battery.

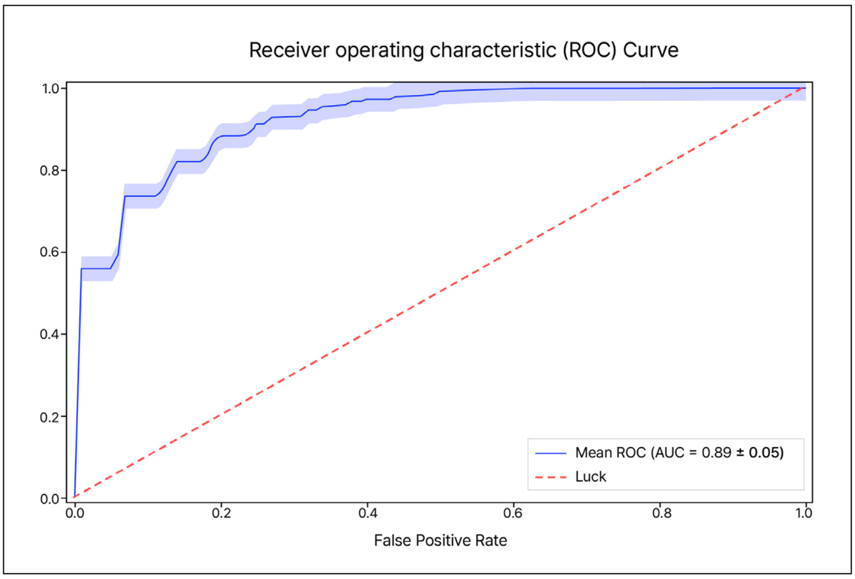

Figure 3. Model area under the curve (AUC) average across 120 dataset combinations.

Limitations

While our model was able to distinguish patients with mild cognitive impairment from healthy individuals it is not capable of forecasting if this is caused by vascular dementia or dementia with Lewy bodies.

This, however, presents a small problem as you may need to state specifically whether it can detect MCI caused by Alzheimer's disease only or if it can detect MCI caused by other forms of dementia[27]. Depending on the circumstances, this can be circumvented with a sufficient paperweight in advance[26]. Nevertheless, despite these limitations, our findings may assist general practitioners and non-neurologists in evaluating patients with mild cognitive impairment in a rapidly expanding older population[28-31].

Conclusions

Through post-hoc analysis of diagnostic intervention trials, we found a novel deep learning model with high sensitivity, specificity, and accuracy for classifying individuals with Alzheimer's disease-related mild cognitive impairment using comprehensive features from fNIRS time-series data. In particular, the following fNIRS time series data were selected: Hjorth, kurtosis, skewness, entropy, curve length, AUC, autocorrelation, and time to peak. This novel algorithm may assist in distinguishing between patients with or without mild cognitive impairment due to Alzheimer's disease and may improve the general public health system, medical cost-effectiveness, and understanding of the pathophysiology of Alzheimer's dementia.

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Ethics Approval

The protocol for the patient study was approved by the Gwangju Institute of Science and Technology Clinical Review Board (20210115-HR-58-01-02).

Trial Registration

CRIS number KCT0006197.

Informed Consent

We adhered to the tenets of the Declaration of Helsinki, and informed consent was obtained from each subject or legal guardian at the time of recruitment.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request (Dong Keon Yon; yonkkang@gmail.com).

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Jaewon Kim, Sungchul Kim, Donghuk Kang, Sunyoung Kim, Rosie Kwon, Dong Keon Yon, and Jae Gwan Kim contributed to the conception and design of the study. SK, JK, and DKY contributed to the acquisition and analysis of the data. JK and SK contributed to drafting the text or preparing the figures. All authors critically revised the manuscript. JGK and DKY proofread and approved the final manuscript. Dong Keon Yon, and Jae Gwan Kim were the study guarantors. The corresponding authors attest that all listed authors meet the authorship criteria and that no other individuals meeting the criteria have been omitted. Jaewon Kim and Sungchul Kim contributed equally as co-first authors.

ORCID ID

Jaewon Kim: 0000-0003-1365-3089
Sungchul Kim:0000-0001-6774-263x
Donghuk Kang:0009-0002-2386-2546
Sunyoung Kim: 0000-0003-4115-4455
Rosie Kwon: 0000-0001-5422-4446
Dong Keon Yon: 0000-0003-1628-9948
Jae Gwan Kim: 0000-0002-1010-7712

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