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Automatic Diagnosis of Mild Cognitive Impairment Using Electroencephalogram Spectral Features

Masoud Kashefpoor[1,2], Hossein Rabbani[1,3], Majid Barekatain[4]

[1]Department of Biomedical Engineering, Faculty of Advanced Medical Technologies, Isfahan University of Medical Sciences, [2]Student Research Center, Isfahan University of Medical Sciences, [3]Medical Image and Signal Processing Research Center, Isfahan University of Medical Sciences, [4]Psychosomatic Research Center, Department of Psychiatry,, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Alzheimer's disease (AD) is one of the most expensive and fatal diseases in the elderly population. Up to now, no cure have been found for AD, so early stage diagnosis is the only way to control it. Mild cognitive impairment (MCI) usually is the early stage of AD which is defined as decreasing in mental abilities such a cognition, memory, and speech not too severe to interfere daily activities. MCI diagnosis is rather hard and usually assumed as normal consequences of aging. This study proposes an accurate, mobile, and nonexpensive diagnostic approach based on electroencephalogram (EEG) signal. EEG signals were recorded using 19 electrodes positioned according to the 10–20 International system at resting eyes closed state from 16 normal and 11 MCI participants. Nineteen Spectral features are computed for each channel and examined using a correlation based algorithm to select the best discriminative features. Selected features are classified using a combination of neurofuzzy system and k-nearest neighbor classifier. Final results reach 88.89%, 100%, and 83.33% for accuracy, sensitivity, and specificity, respectively, which shows the potential of proposed method to be used as an MCI diagnostic tool, especially for screening a large population.

Key words: *Early Alzheimer's disease, electroencephalogram spectral features, k-nearest neighbor, mild cognitive impairment, neurofuzzy*

INTRODUCTION

Every 4 s, someone in the world develops dementia. Dementia is a definition for decline in various mental abilities such as memory, speech, and cognition severe enough to interfere with daily life. It mainly affects people after the age of 60; however, there are some reports of cases that start before this age. In 2013, there were an estimated 44.4 million people with dementia worldwide. This number will increase to an estimated 75.6 million in 2030, and 135.5 million in 2050. Already 62% of people with dementia live in developing countries, but by 2050, this will rise to 71%.[1,2]

Alzheimer's disease (AD) is the most common form of dementia which accounts for 60–80 percent of dementia cases and is the third most expensive disease and sixth leading cause of death in the United States.[2] It affects more than 11% of people over age 65 and about 32% of people older than 85 worldwide,[3] and it is estimated that the number of the patient will triple within the next 50 years.[4] AD is a neurodegenerative nonreversible disorder. AD has no known cure now and related medications can only delay the symptoms and slow the progression of the disease, so the most important concern is to diagnose AD as soon as possible.

As mentioned before, having great medication impact directly depends on diagnosing of AD at its early stages. The first stage of AD is mild cognitive impairment (MCI). MCI causes cognitive changes that are serious enough to be noticed by the affected subjects or to their families, but it is not severe enough to interfere with daily life or

Address for correspondence:
Department of Advanced Medical Technologies, Medical Image and Signal Processing Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: h_rabbani@med.mui.ac.ir

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basic independent function. Because MCI does not severely affect daily life, affected subjects do not meet diagnostic guidelines for AD or dementia, so they have high risk of eventually developing AD or another type of dementia; about 15–20% of MCI patients convert to AD each year while the conversion rate for the general population is 1–2%.[5]

Since MCI is the first symptomatic stage of AD, accurate detecting of MCI is the most important tool to control this incurable disease. Medical diagnosis of MCI is hard, and symptoms are often dismissed as normal consequences of aging. Diagnosis is usually performed through a combination of extensive testing and eliminations of other possible causes. Psychological tests (e.g. Mini-Mental State Examinations [MMSE]), blood tests, spinal fluid, neurological examination, and magnetic resonance imaging (MRI)[6] are used to help diagnose the MCI.

Since electroencephalogram (EEG) recording systems are noninvasive, inexpensive, and (usually) mobile, it would be very efficient and effective screening tool to detect the AD and MCI patients. In the recent years, several research groups have applied different analyzing methods to find some relations between EEG signal and AD/MCI. Their foundation shows that the effects of AD/MCI on EEG can be divided to the following categories:[4] Slowing of EEG, reducing the complexity of EEG, perturbation in EEG synchrony, and increasing gamma activity. Table 1 is a briefly categorized review of previous studies and the methods they used to extract discriminative features. Unfortunately, most of those researches have not specifically focused on diagnosis of MCI, especially to the best of our knowledge, an accurate and reliable method for classification normal versus MCI has not been reported in the literature yet.

The rest of paper is arranged as follows; the second section, materials, and methods, will illustrate MCI/normal group selection criteria, EEG recording protocol, preprocessing and feature extraction, selection, and reduction. The third section will show obtained results in figure and table format, and the last section belongs to discussion and conclusions.

MATERIALS AND METHODS

Subjects

Twenty-seven subjects (11 MCI and 16 normal) were selected from participants of previous study,[31,32] which included subjects above 60 years with elementary or higher education and history of coronary angiography during

Table 1: Brief categorized summary of performed studies

Category	Researchers	Method	Year
Slowing of EEG signal	McBride *et al*.[7]	Fourier power	2014
	Baker *et al*.[8]	Fourier power	2008
	van der Hiele *et al*.[9]	Fourier power	2007
	Czigler *et al*.[10]	Fourier power	2008
	Gianotti *et al*.[11]	Fourier power	2007
	Dauwels *et al*.[12]	Fourier power	2011
	Latchoumane *et al*.[13]	Fourier power	2009
	Schreiter Gasser *et al*.[14]	Fourier power	2008
	Moretti[15]	Fourier power	2012
	Polikar *et al*.[16]	Time-frequency map	2007
	Vialatte and Maurice[17]	Bump models	2008
Reducing complexity of signal	McBride[18]	Transfer entropy	2015
	Hornero *et al*.[19]	Approximate/sample/multi scale entropy/lempel-ziv complexity/auto-mutual information	2009
	Abásolo[20]	Approximate entropy/auto-mutual information	2008
	Woon *et al*.[21]	Sample entropy	2007
	Zhao *et al*.[22]	Tsallis entropy/universal compression	2007
	Jeong *et al*.[23]	Auto-mutual information	2001
	Adeli *et al*.[24]	Correlation dimension/largest lyapunov exponent	2008
Perturbation in EEG synchrony	McBride[25]	Sugihara causality	2015
	Dauwels *et al*.[26]	Pearson correlation coefficient/magnitude and phase coherence/phase synchrony/state space synchrony/information theoretic measures	2009
	Babiloni *et al*.[27]	Granger causality	2009
	Czigler *et al*.[10]	Phase synchrony/State space synchrony	2008
	Jeong *et al*.[23]	Information theoretic measures	2001
	Dauwels *et al*.[12]	Stochastic event synchrony/granger causality	2011
	Stam *et al*.[28]	Graph-theoretic methods	2007
	Gallego-Jutgla *et al*.[29]	phase synchrony, granger causality	2012
Increasing gamma band activity	van Deursen *et al*.[30]	Fourier power	2009
	McBride *et al*.[7]	Fourier power	2014

EEG – Electroencephalogram

recent year. They were selected from patients who admitted to cardiac catheterization units of Sina and Nour Hospitals, Isfahan, Iran. The study design was ethically discussed and approved by the Deputy of Research and Technology, Isfahan University of Medical Sciences, Isfahan, Iran. Subjects with a history of major psychiatric disorders, substance misuse, head trauma, serious medical disease, and dementia were excluded. The study process was explained for all subjects, and written informed consent was obtained. Neuropsychiatric interview considering Peterson's criteria for MCI[33] has been done for all subjects. MMSE scores from 21 to 26 were utilized for validation of MCI diagnosis and scores more than 26, were considered normal controls.[4] Neuropsychiatry unit cognitive assessment tool (NUCOG) has been used to confirm the diagnosis of MCI and as a dependent variable.[9] The NUCOG scores more than 86.5, between 75 and 86.5, and lower than 75 were considered as normal cognitive state, MCI, and dementia, respectively, in Iranian population.[32] Subject's demographics and psychiatric test scores are summarized in Table 2.

Electroencephalogram Recording

All EEG signals were recorded in the morning times while subjects resting comfortably in a quiet room with closed eyes. The EEG activity was recorded continuously from 19 electrodes positioned according to the 10–20 International system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). Figure 1 shows electrode placement and scalp zoning used in this study. Data were recorded using 32 channel digital EEG device with 256 Hz sampling rate (Galileo NT, EBneuro, Italy). Electrodes-skin impedance was set below 5 kΩ. The recording duration was 30 min because longer recordings would reduce the variability of the data and suppress noise and artifacts, but also possibly increase the slowing of EEG oscillations due to reduced vigilance. Hence, during recording procedure, subjects were been checked out continuously to keep them conscious and avoid drowsiness. After recording procedure, a notch filter was used to remove 50 Hz frequency noise amplified by background electronic devices. Artifacts due to slipping of electrodes or subject's movement were manually removed by visual inspection to obtain clean pieces of signal.

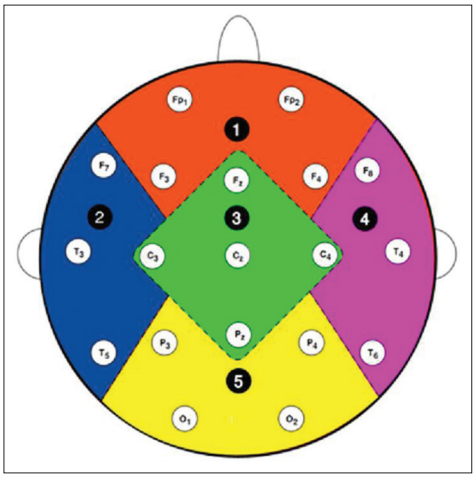

Figure 1: Electrode placement and scalp zones: 1 = frontal, 2 = left temporal, 3 = central, 4 = right temporal, 5 = occipital

Feature Extraction and Selection

For this step, cleaned EEG signals should be divided into small segments. We tried 0.5, 1, 1.5, and 2 s length with 0%, 25%, 75%, and 50% overlap, which the best results were obtained for 1 s length with 50% overlap. About 19 spectral features[4,7] were computed for each segment and then averaged along whole EEG signal length to obtain 19 overall features for each channel. Table 3 shows those features' name and their descriptions.

As mentioned before, 19 overall features were extracted from each channel and as there are 19 EEG channels in

Table 2: Subject's demographics and psychiatric test scores

Characteristic	MCI	Control	*P*
Age (years)	66.4±4.6	65.3±3.9	0.4
Education (years)	10.3±3.8	11.1±3	0.4
GHQ scores	20.5±9.4	17.9±6.6	0.3
BMI (kg/m^2)	25.7±2.2	26.6±3.6	0.3
Fasting glucose (mg/dl)	115.5±24.3	121.8±36.9	0.3
Total cholesterol (mg/dl)	170.6±61.4	169.1±42.6	0.9
Triglycerides (mg/dl)	157.3±100.9	160±80.7	0.9
Creatinine (mg/dl)	1.2±0.2	1.3±0.3	0.1
MMSE scores	27.6±0.9	29.0±0.8	<0.001
NUCOG scores	82.4±3.6	91.1±3	<0.001
Gensini scores	33.3±31.9	20.3±21.7	0.1

GHQ – General health questionnaire; BMI – Body mass index; MMSE – Mini-mental state examination; NUCOG – Neuropsychiatry unit cognitive assessment tool; MCI - Mild cognitive impairment

Table 3: Names and descriptions of extracted features

Number	Name	Description
1	delta	Power in the δ band (0.5-3.5 Hz)
2	r-delta	Relative power in the δ band
3	theta	Power in the θ band (3.5-7.5 Hz)
4	r-theta	Relative power in the θ band
5	alpha1n	Power in the α1 band (7.5-9.5 Hz)
6	r-alpha1	Relative power in the α1 band
7	alpha2n	Power in the α2 band (9.5-12.5 Hz)
8	r-alpha2	Relative power in the α2 band
9	betta1n	Power in the β1 band (12.5-17.5 Hz)
10	r-betta1	Relative power in the β1 band
11	betta2n	Power in the β2 band (17.5-25 Hz)
12	r-betta2	Relative power in the β2 band
13	gamma	Power in the γ band (25-40 Hz)
14	r-gamma	Relative power in the γ band
15	total	Total power of the EEG power spectrum (0.5-40 Hz)
16	R1	Power ratio: R1=θ/(α1+α2+β1)
17	R2	Power ratio: R2=(δ+θ)/(α1+α2+β1+β2)
18	R3	Power ratio: R3=θ/(α1+α2)
19	PAF	Peak α frequency

PAF – Peak alpha frequency; EEG – Electroencephalogram

our recordings, so a 19 × 19 feature matrix obtained for each participant. As there were no reliable evidence on which feature/features, channel/channels, or zone/zones are the best for our purpose, we started a correlation based pursuit for feature selection step. In our pursuit, we examined features and channels individually, zone-grouped and zone-group-averaged to find the best discriminative features. Tables 4 and 5 show correlations between calculated features and desired results for each channel and zone, respectively. These tables have been color filled (red for negative and blue for positive correlations) for better visualization, which color intensity is proportional to absolute value of correlation.

Somebody may ask why we did not use well-known, easy, and fast feature selection methods such as Principal Component Analysis (PCA) and Independent Component Analysis (ICA) to select the best features. The answer is that almost these methods combine initial features to produce new and more discriminative ones, and we did not want that because we wanted to preserve neurophysiological interpretation of selected features. However, such automated feature selection methods are very powerful and may be used in future studies, especially to build new features that can be used as MCI biomarkers.

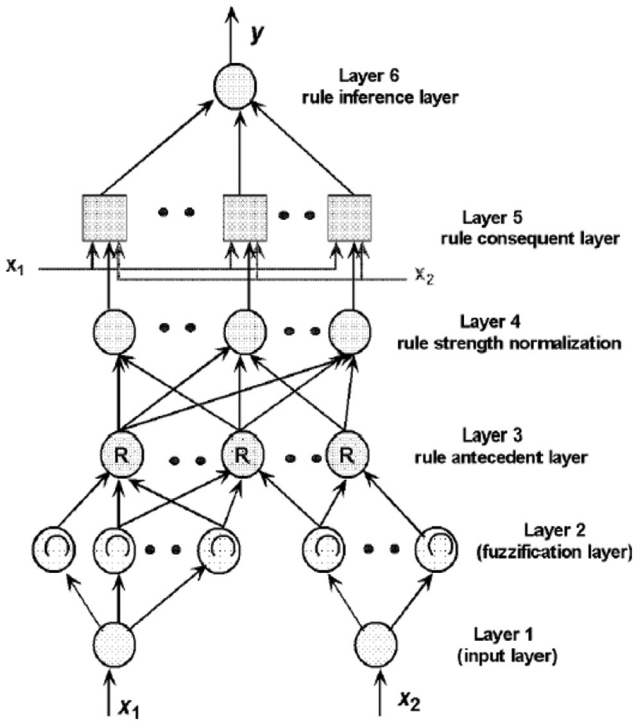

Figure 2: Typical structure for Takagi-Sugeno inference system

Classification

Selected feature, we call them features vector, is now ready for classification step. We used Takagi-Sugeno neurofuzzy (NF) inference system as the main part of our classification step. NF refers to combinations of artificial neural networks and fuzzy logic which results in a hybrid intelligent system that synergizes these two techniques by combining the human-like reasoning style of fuzzy systems with the learning structure of neural networks. The main strength of NF systems is that they are universal approximators with the ability of producing interpretable IF-THEN rules. The strength of NF systems involves two contradictory requirements in fuzzy modeling: Interpretability versus accuracy. In practice, one of the two properties surpasses. The neurofuzzy in fuzzy modeling research field is divided into two areas: Linguistic fuzzy modeling that is focused on interpretability, mainly the Mamdani model; and precise fuzzy modeling that is focused on accuracy, mainly the Takagi-Sugeno model. The structure of a typical Takagi-Sugeno system is shown in Figure 2.[33] First to train NF system, feature vectors of train data were shown to NF system as inputs and their respected values as outputs (MCI = 1, normal = 2). We used two-third of our data to train NF system and gathered final output for each case to construct a k-nearest neighbor (KNN) classifier.

This KNN classifier has two classes with centers specified from NF system outputs from training data and will be used as a complementary part in our classification step, so outputs of NF system will be finally labeled using that. We add this part because the outputs of NF system do not exactly match the labeled value and has, at least, two benefits; first, there is no need to use large number of iterations to force NF system's outputs come closer to exact values, and second, it plays the role of a decision making and labeling system without any time consuming or complicated rules. Block diagram of proposed method including classification step is shown in Figure 3.

RESULTS

As stated earlier, feature selection has been performed through a pursuit that described in section 2.3. Tables 4 and 5 show computed correlations between features and desired results that were used in our pursuit to find features vector for 1 s length segments with 50% overlap. They have been color formatted for faster and easier perception. We used 18 cases (9 MCI and 9 normal) for training NF system, but because our dataset was small, we used half-length of them for training and used other half for testing of total samples. Because of implementing KNN complementary classifier, there was no need for large number of iterations, so we set that to 5 and construct KNN based on final outputs of training step. After training phase, we cascaded KNN classifier to trained NF and began testing phase. Feature vectors of all samples are used in testing phase, but classification measure, i.e., accuracy, sensitivity, and specificity are calculated from samples that not proposed in training phase.

Table 4: Correlation between channel features and desired results

	delta	r-delta	theta	r-theta	alpha1	r-alpha1	alpha2	r-alpha2	betta1	r-betta1	betta2	r-betta2	gamma	r-gamma	total	R1	R2	R3	PAF
'Fp1'	-0.21	0.04	-0.21	0.21	-0.37	0.43	-0.31	0.38	-0.32	0.24	-0.49	-0.04	-0.52	-0.18	-0.12	-0.31	-0.13	-0.43	0.01
'Fp2'	-0.19	-0.23	-0.10	-0.14	-0.22	0.12	-0.22	0.16	-0.14	0.33	-0.04	0.32	-0.02	0.15	-0.05	-0.36	-0.34	-0.31	0.01
'F7'	0.13	0.02	0.12	-0.23	-0.02	0.18	-0.11	0.00	-0.21	-0.06	-0.41	-0.02	-0.36	-0.01	0.14	-0.28	-0.06	-0.32	0.16
'F3'	-0.09	-0.19	0.00	-0.05	-0.07	0.08	-0.04	0.24	0.07	0.25	0.01	0.16	0.04	0.15	0.12	-0.23	-0.23	-0.23	0.24
'Fz'	-0.02	-0.06	-0.09	-0.25	-0.32	-0.01	-0.24	0.17	-0.23	0.16	-0.29	0.07	-0.18	0.09	0.13	-0.27	-0.12	-0.27	0.24
'F4'	-0.32	-0.32	-0.29	-0.05	-0.38	0.33	-0.30	0.38	-0.32	0.32	-0.34	0.27	-0.35	0.19	-0.17	-0.44	-0.36	-0.45	0.30
'F8'	-0.21	-0.22	-0.18	-0.03	-0.35	0.18	-0.31	0.31	-0.26	0.33	-0.30	0.24	-0.38	0.11	-0.20	-0.36	-0.26	-0.37	0.21
'T3'	-0.11	-0.14	-0.08	-0.04	-0.24	0.07	-0.29	0.05	-0.35	0.24	-0.45	0.17	-0.30	0.07	0.05	-0.19	-0.15	-0.23	-0.17
'C3'	0.09	-0.12	-0.02	-0.22	-0.28	-0.07	-0.25	0.04	-0.25	0.16	-0.28	0.17	-0.03	0.21	0.12	-0.17	-0.10	-0.18	-0.27
'Cz'	0.04	-0.23	0.11	-0.06	-0.16	0.08	-0.12	0.17	-0.09	0.20	-0.12	0.24	0.10	0.29	0.16	-0.20	-0.18	-0.20	0.20
'C4'	-0.13	-0.28	-0.13	-0.12	-0.25	0.14	-0.18	0.24	-0.20	0.24	-0.21	0.32	-0.10	0.26	0.00	-0.29	-0.24	-0.28	0.19
'T4'	-0.30	-0.27	-0.21	-0.15	-0.33	0.18	-0.27	0.25	-0.19	0.29	-0.30	0.28	-0.08	0.12	-0.09	-0.28	-0.24	-0.29	-0.15
'T5'	-0.14	-0.27	0.12	0.04	-0.05	0.18	-0.07	0.11	0.14	0.32	0.04	0.25	0.07	0.16	0.15	-0.27	-0.26	-0.26	-0.06
'P3'	0.14	-0.10	0.13	-0.19	-0.28	0.01	-0.21	0.01	0.01	0.18	0.03	0.21	0.13	0.27	0.22	-0.19	-0.13	-0.17	-0.25
'Pz'	0.10	-0.14	0.17	-0.11	-0.13	0.07	-0.16	0.01	-0.05	0.15	0.07	0.19	0.16	0.26	0.20	-0.20	-0.16	-0.21	-0.22
'P4'	0.07	-0.23	0.11	-0.20	-0.15	0.14	0.01	0.19	0.09	0.26	0.04	0.24	0.09	0.22	0.16	-0.26	-0.16	-0.26	-0.32
'T6'	-0.14	-0.28	-0.02	-0.24	-0.10	0.22	-0.03	0.23	0.19	0.38		0.21	-0.06	0.02	0.12	-0.31	-0.24	-0.29	0.21
'O1'	-0.12	-0.23	0.06	-0.09	-0.20	0.14	-0.17	0.12	0.07	0.25	0.18	0.31	0.01	0.13	0.16	-0.25	-0.25	-0.23	-0.08
'O2'	0.00	-0.23	0.30	-0.13	0.17	0.18	0.34	0.14	0.39	0.21	0.26	0.20	0.08	0.11	0.28	-0.22	-0.21	-0.19	-0.15

Table 5: Correlation between zone-averaged features and desired results

	delta	r-delta	theta	r-theta	alpha1	r-alpha1	alpha2	r-alpha2	betta1	r-betta1	betta2	r-betta2	gamma	r-gamma	total	R1	R2	R3	PAF
'F-avg'	-0.23	-0.21	-0.16	0.01	-0.27	0.29	-0.23	0.36	-0.13	0.34	-0.22	0.18	-0.26	0.07	-0.01	0.36	-0.31	-0.39	0.24
'LT-avg'	-0.03	-0.18	0.06	-0.08	-0.13	0.15	-0.19	0.08	-0.16	0.26	-0.35	0.16	-0.25	0.08	0.12	-0.26	-0.17	-0.29	-0.05
'C-avg'	0.03	-0.20	0.03	-0.14	-0.23	0.07	-0.19	0.13	-0.17	0.20	-0.17	0.21	0.01	0.22	0.14	-0.24	-0.17	-0.24	-0.03
'RT-avg'	-0.26	-0.30	-0.16	-0.13	-0.31	0.21	-0.22	0.26	-0.15	0.36	-0.31	0.28	-0.25	0.10	-0.12	-0.35	-0.28	-0.34	0.04
'O-avg'	0.03	-0.22	0.18	-0.14	-0.17	0.14	0.00	0.13	0.18	0.25	0.14	0.25	0.08	0.20	0.22	-0.23	-0.20	-0.22	-0.23

Repeating whole procedure for different segmenting length and different overlap showed that 1 s length segments with 50% overlap have the best results so only these results have been shown and discussed.

As can be seen in Tables 4 and 5, some features have good correlations with desired results in one or more channels but not in all, so we should find a method to select features and channels simultaneously. There were two main problems here; first, some of the good features and good channels attenuate each other when applied together. Second and the most important was that channel based methods are not so suitable in real application because they are very sensitive to noises, artifacts, or disconnection on base channels. The best solution for the last problem was using zone-based approach instead of channel-based one. Best averaged features for each zone were calculated, which are shown in Table 6, and it can be seen that some of them are consistent with recent similar work.[7] Table 6 indicates selected features and their classification results for each zone using proposed classifier. Figure 4 shows classification results before and after cascading KNN. To have a comparison, classification also has been done using a single supervised KNN classifier which Table 7 shows its results.

CONCLUSION

In this study, we proposed a reliable and accurate method to discriminate MCI versus normal cases using simple spectral EEG features. The proposed feature selection and classification procedure shows very promising and interesting results using these features. Tables 6 and 7

Table 6: Accuracy, sensitivity, and specificity of proposed method, feature selected for each zone individually

Zones	Selected features	Accuracy %	Sensitivity %	Specificity %
Frontal	6,10, 11, 14, 16, 17	77.78	66.67	83.33
Left temporal	6,10, 11, 14, 16, 17, 18	88.89	66.67	100.00
Central	6, 11, 14, 16, 17	88.89	100.00	83.33
Right temporal	6,11, 14, 16, 17, 18	88.89	100.00	83.33
Occipital	6,11, 14, 16, 17, 18	88.89	100.00	83.33

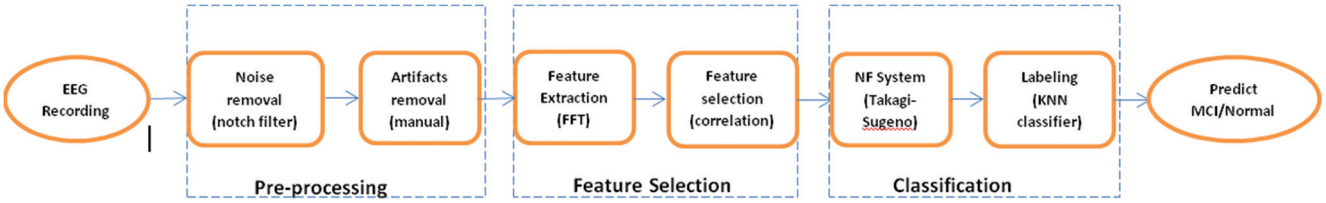

Figure 3: Block diagram of proposed method

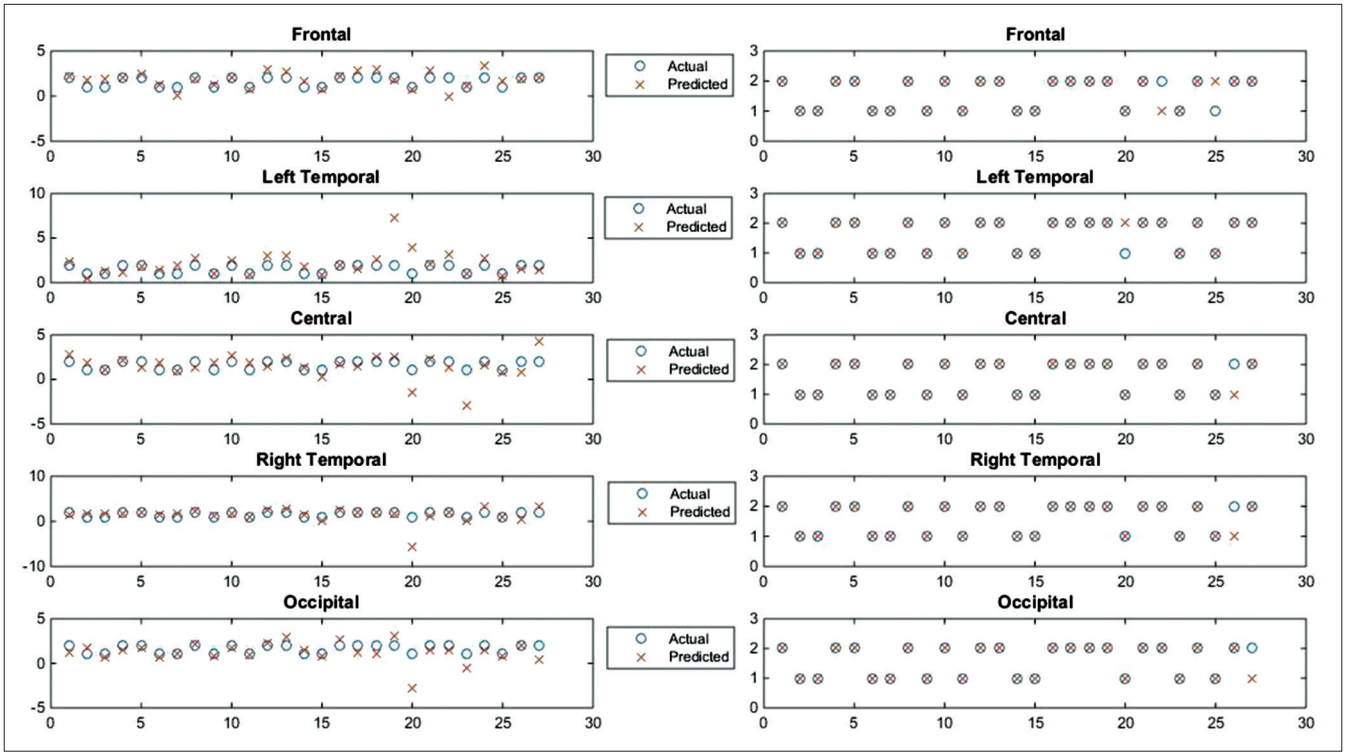

Figure 4: Classification results for zone individually selected features, before (left) and after cascading k-nearest neighbor (right)

Table 7: Accuracy, sensitivity, and specificity of k-nearest neighbors method, feature selected for all zone identically

Zones	Selected features	Accuracy %	Sensitivity %	Specificity %
Frontal	6,10, 11, 14, 16, 17	66.67	66.67	66.67
Left temporal	6,10, 11, 14, 16, 17, 18	55.56	33.33	83.33
Central	6, 11, 14, 16, 17	80.00	75.00	83.33
Right temporal	6,11, 14, 16, 17, 18	60.00	55.56	85.71
Occipital	6,11, 14, 16, 17, 18	66.67	75.00	60.00

show that using NF-KNN combination has noticeably better results compared to KNN. Having accuracy above 88% proves the hypothesis that EEG signals can be used in MCI diagnosing and reaching to 100% sensitivity make the proposed method as a suitable tool for large population screening. The highest obstacle in this way is generalization problem due to small sample size of this study, so one of the most important complementary works is to increase the number of cases in both normal and MCI group, and we have it on the run currently. We also are establishing an online biomedical signal and image database to share our data with other researchers.

Another interesting aspect this way is applying well-known feature selection techniques (e.g. PCA, ICA) or using time-frequency transforms such as wavelet[5,34] to produce new reliable and powerful discriminative features which can be used as diagnostic biomarkers or even as measuring quantities for the degree of MCI/AD. Sparse modeling of EEG signal in MCI and normal group using overcomplete dictionaries is a new, interesting, and almost intact approach that seems to be practical because spectral changes in EEG signal due to MCI/AD has been proved and evidenced in a wide variety of recent studies. In addition, combining data from EEG signals and brain images provided via one of the standard brain imaging techniques such as positron emission tomography, computed tomography scan, fMRI, and especially MRI provides a motivating and interesting area for future works in MCI diagnosis.

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Conflicts of Interest

There are no conflicts of interest.

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BIOGRAPHIES

Masoud Kashefpoor is a PhD student in Biomedical Engineering Department, Isfahan University of Medical Sciences, Isfahan, Iran. His main research interest includes brain signal/image processing and neuroscience.

E-mail: kashefpoor@gmail.com

Hossein Rabbani received the B.Sc. degree in Electrical Engineering (Communications) from Isfahan University of Technology, Isfahan, Iran, in 2000 with the highest honors, and the M.Sc. and Ph.D. degrees in Bioelectrical Engineering in 2002 and 2008, respectively, from Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran. In 2007 he was with the Department of Electrical and Computer Engineering, Queen's University, Kingston, ON, Canada, as a Visiting Researcher, in 2011 with the University of Iowa, IA, United States, as a Postdoctoral Research Scholar, and in 2013-2014 with Duke University Eye Center as a Postdoctoral Fellow. He is now an Associate Professor in Biomedical Engineering Department and Medical Image & Signal Processing Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Dr. Rabbani is a Senior Member of IEEE (Signal Processing Society, Engineering in Medicine and Biology Society, Circuits and Systems Society, Computer Society), and Editor in-Chief of Journal of Medical Signals and Sensors. His main research interests are medical image analysis and modeling, statistical (multidimensional) signal processing, sparse transforms, and image restoration, which more than 110 papers and book chapters have been published by him as an author or co-author in these areas.

E-mail: h_rabbani@med.mui.ac.ir

Majid Barekatain received the M.D. degree from Tehran University of Medical Sciences, Tehran, Iran, in 1994 and trained as a resident of psychiatry from 2000 to 2003 in Isfahan University of Medical Sciences, Isfahan, Iran. He has been working as academic staff of Isfahan University of Medical Sciences. He is full professor of psychiatry. He spent his fellowship in neuropsychiatry at Melbourne Neuropsychiatry Center, Melbourne, Australia, in 2007. His main area of research interest includes biomarkers of neurological diseases especially cognitive disorders and epilepsy.

E-mail: barekatain@yahoo.com