Published in final edited form as:
Proceedings (IEEE Int Conf Bioinformatics Biomed). 2019 November ; 2019: 799–806. doi:10.1109/bibm47256.2019.8982955.

Deep Learning Prediction of Mild Cognitive Impairment using Electronic Health Records

Sajjad Fouladvand,
Department of Computer Science, Institute for Biomedical Informatics, University of Kentucky, Lexington, KY, USA

Michelle M. Mielke,
Division of Epidemiology, Department of Neurology, Mayo Clinic, Rochester, MN USA

Maria Vassilaki,
Division of Epidemiology, Mayo Clinic, Rochester, MN USA

Jennifer St. Sauver,
Division of Epidemiology, Mayo Clinic, Rochester, MN USA

Ronald C. Petersen,
Department of Neurology, Mayo Clinic, Rochester, MN USA

Sunghwan Sohn
Division of Digital Health Sciences, Mayo Clinic, Rochester, MN USA

Abstract

About 44.4 million people have been diagnosed with dementia worldwide, and it is estimated that this number will be almost tripled by 2050. Predicting mild cognitive impairment (MCI), an intermediate state between normal cognition and dementia and an important risk factor for the development of dementia is crucial in aging populations. MCI is formally determined by health professionals through a comprehensive cognitive evaluation, together with a clinical examination, medical history and often the input of an informant (an individual that know the patient very well). However, this is not routinely performed in primary care visits, and could result in a significant delay in diagnosis. In this study, we used deep learning and machine learning techniques to predict the progression from cognitively unimpaired to MCI and also to analyze the potential for patient clustering using routinely-collected electronic health records (EHRs). Our analysis of EHRs indicates that temporal characteristics of patient data incorporated in a deep learning model provides increased power in predicting MCI.

Keywords

mild cognitive impairment; dementia; Alzheimer’s disease; deep learning; machine learning; recurrent neural networks

Corresponding Author: sajjad.fouladvand@uky.edu.

I. Introduction

Dementia is one of the most prevalent health problems in the aging population. It is estimated that by 2030, 75.6 million people will suffer from various types of dementia worldwide, and that this number will increase to 135.5 million people in 2050 [1]. Such an increase will place a tremendous burden on patients, their families, society, and health care systems. Given that people with mild cognitive impairment (MCI) are at an increased risk for dementia, predicting MCI risk and understanding the progression from cognitively unimpaired (CU) to MCI and dementia is a crucial task to help the aging population with their health needs.

In general, MCI is formally determined by health professionals through a comprehensive cognitive evaluation, together with clinical examination, medical history and often the input of an informant (an individual that know the patient very well) to understand changes in cognition and daily function. However, this is not routinely performed in many primary care visits which results in a delay of timely diagnosis, misses opportunities for appropriate care plans, and leads to adverse clinical outcomes. Electronic health records (EHRs), especially clinical free text, contain valuable information that is routinely recorded as part of clinical care. This rich information may be used to identify patterns predicting the development of MCI and dementia. Previous studies have shown that some signals of cognitive decline exist in EHRs, years before the clinician diagnoses of cognitive impairment [2, 3].

Recently, deep learning models have demonstrated their capabilities in analyzing EHR data [4–8]. EHR data are a growing source of information that can be harnessed to provide an earlier diagnosis and to identify those at greatest risk for developing MCI. However, little is known about systematically analyzing patient data related to MCI in routinely-collected EHRs and how their temporal patterns are associated with the development of MCI. Although predicting MCI and understanding the progression from CU to MCI utilizing EHRs is a challenging and largely unexplored task, we believe deep learning models can be used to capture temporal characteristics of patient data in EHRs to predict early stages of MCI. In this study, we systematically investigated the application of EHR data analysis and deep learning models for predicting and clustering MCI patients.

II. Related works

Multiple studies to understand the progression from CU to MCI has been conducted. In [9], demographic, clinical, and neuropsychological measures implemented in Cox proportional hazard models were applied to predict progression from CU to MCI. The authors showed that MCI risk factors presented in their previous studies [10–13] can be used to predict MCI using multivariate models. They used the Mayo Clinic Study of Aging (MCSA) cohort [14, 15] and developed an augmented model capable of predicting progression from CU to MCI with AUC of 0.70. In [16], 224 CU participant were analyzed and followed up to detect measures or combination of measures that can be used to predict MCI. These researchers analyzed various MCI risk factors from different domains including cognitive, cerebrospinal fluid, magnetic resonance imaging (MRI), and genetic domain. They utilized timedependent receiver operating characteristic and showed the feasibility of MCI prediction (best AUC using all variables > 0.83).

Another line of research is the prediction of dementia and understanding progression from MCI to dementia. Biomarkers, genetics, brain imaging as well as demographic and various variables related to individual's lifestyle have been used in the literature to predict progression from MCI to dementia with AUC ranging from 0.48 to 0.91 [17]. In [18], [19] and [20] clinical variables were analyzed using logistic regression to predict progression of MCI to Alzheimer's disease (AD) dementia. Researchers also utilized primary care data to predict dementia [21]. In [22], they used general practice data to create risk prediction models for dementia with sensitivity of 0.58 and specificity of 0.98 in the year before diagnosis.

With the availability of public databases related to AD dementia, such as the North American Alzheimer's Disease Neuroimaging Initiative (ADNI) [23] and the European's AddNeuroMed Study [24], big data has been utilized in AD research the past couple of years. Most of this research focused on diagnosing AD dementia, identify those at greatest risk of MCI, and predicting progression from MCI to AD dementia. Much of this work has utilized the non-community-based ADNI dataset and traditional machine learning models including support vector machines (SVMs), logistic regression and random forest [25]. SVM and linear models have been used in [26] to discriminate patients with AD from MCI and CU patients in ADNI dataset. Moreover, SVMs have been utilized in separating patients with AD dementia or MCI from CU patients using MRIs [27, 28], and predicting progression from MCI to AD dementia using AddNeuroMed dataset [29]. MRI images from ADNI has also been used in [30]. These results show that convolutional neural network based deep learning models can detect AD progression. In [31], neuroimaging, machine learning and deep learning has been used to predict conversion from MCI to AD in ADNI. XGBoost [32] showed the best performance in predicting MCI to AD progression in [31]. A comprehensive review of applying big data prospective and machine learning models to advance AD research is provided in [25].

Multiple studies examined the progression from CU or MCI to dementia. However, only a few studies considered progression from CU to MCI or MCI prediction using patients EHR data. Often, MCI is not well recorded in EHR data because it is not a clinical diagnosis per se, and thus there are not enough datasets suitable to train MCI predictive models. In addition, discriminating CU patients from patients with MCI is a very challenging task as MCI is the stage between the expected cognitive decline of normal aging and the more serious decline of dementia [33]. In this study, we addressed the above-mentioned challenges and demonstrated a potential of a deep learning model, coupled with natural language processing, to extract MCI risk factors and signals from unstructured EHRs and to predict onset of MCI. In addition, we utilized machine learning and deep learning techniques to visualize and cluster patients using EHR data and described a mechanism for EHR-based clustering.

III. Materials and Methods

In this section, we first describe the dataset to train and test our models. Then, we describe the deep learning methods used in this study. This study includes two main components: MCI prediction and patient clustering. In MCI prediction, we used a deep learning technique, long short term memory (LSTM) [34] architecture described in section III.C to predict onset of MCI. In patient clustering, we used the denoising autoencoder described in section III.D to better represent the patient data. The outputs of this denoising autoencoder were visualized and clustered using t-Stochastic Neighbor Embedding (t-SNE) [35] and K-means algorithms [36].

A. Data

We used data obtain from the Mayo Clinic Study on Aging (n=5,923; 1,376 MCI) [15]. The MCSA is a prospective population-based cohort study with comprehensive periodic cognitive assessment (at baseline and repeated every 15 months), initiated in 2004 to investigate the epidemiology of MCI and dementia. Eligible subjects from the Olmsted County, Minn., population, were randomly selected and evaluated comprehensively in person using the clinical dementia rating scale, a neurological evaluation and neuropsychological testing. A consensus committee used previously published criteria to diagnose the participants with normal cognition, MCI or dementia.

MCSA participants have follow-up visits every 15 months and have accumulated more than 23,000 visits to date. In the current analyses, we only included MCI patients who progressed from CU to MCI; i.e., we excluded the patients who were diagnosed with MCI in their first visit to make sure we are predicting initial MCI diagnosis. The MCSA cohort mainly encounters Mayo Clinic, Olmsted County Medical Center, and Mayo Clinic Health System for the regular healthcare. This study used clinical notes to automatically extract MCI risk factors and signals. To simplify the study, we used patients who have any notes at Mayo Clinic—i.e., excluded patients who do not have any clinical notes at Mayo Clinic during each visit interval. This reduced the size of cohort (n=3,265; 558 MCI). The patient data after being diagnosed with MCI in MCSA were disregarded as we are aiming to predict MCI.

Different types of data were used to predict MCI: demographic information, diseases/disorders, and neuropsychiatric symptoms, and activity of daily living (ADL). Table I contains a complete list of variables and their EHR sources we used to train our models.

Total 783,090 clinical notes were used to extract diseases/disorders, neuropsychiatric symptoms, and other types of data (Table I). To extract variables from clinical notes, we used the MedTaggerIE module in MedTagger [37], which is the open-source clinical natural language pipeline developed by Mayo Clinic for pattern-based information extraction with a capability of assertion detection (i.e., negated, possible, hypothetical, associated with a patient). We only included non-negated variables associated with patients.

B. Patient Representation

We represented patients both in a temporal and static mode and used them to train a temporal model (LSTM recurrent neural network) and a static model (random forest) for MCI prediction. To incorporate temporality, we converted the data into a visit-time format X(V, T), where V is patients' visits and T is the visit dates, each visit v_i includes all variables for a given visit listed in Table I, and each date t_i is the relevant visit date. All of the patients' visits for a period of 5 years before their first diagnosis dates for MCI patients and the latest visit for CU patients were used. We used a 15-month sliding window for the past 5 years of history of visits to make the temporal pattern asynchronous. Within each window an element-wise operation was used to combine the visits within the window.

We also represented patients in a static mode to train the static model. Instead of sliding a 15-month wide window, we used a 5-years window to cover the entire visit history of patients. As a result, the longitudinal data was converted to a matrix Y(P, L), where P is the complete list of patients, each p_i is a vector including variables described in Table I and l_i is clinical diagnosis of MCI or CU of the patient p_i.

C. Long-Short Term Memory (LSTM) Models

The LSTM model is one of the most powerful recurrent neural networks (RNNs) in processing longitudinal data efficiently incorporating time-varying variables. Fig. 1 shows a full and unrolled structure of RNN in which circles represent the network layers and the solid lines represent the weighted connections [34]. In a LSTM model, nodes are replaced with a unit called memory cell as shown in Fig. 2 [38]. A memory cell includes the input gate, output gate, and forget gate. The input gate decides how to update the cell state using the new input and the output gate determines how to filter the output. The forget gate decides which information the LSTM is going to forget; it considers both i_t and h_t and then, utilizing a sigmoid function to generate a matrix with elements between 0 and 1. The previous cell state will be element-wisely multiplied by the numbers generated by the forget gate to determine how much information the LSTM unit wants to keep.

In this study, we utilized a dynamic LSTM to make the final predictions. We unroll the LSTM based on the number of time steps. The outputs of the last cell are then fed to a fully connected layer defined in (1).

$$F = softmax(W o_t + b) \tag{1}$$

Where, W is a n by m weight matrix in which n is the number of hidden neurons and m is the number of classes (two classes in this project), o_t is the last output in the unrolled network, and b is a bias matrix. A threshold is used to make the final predictions based on the values of F. We optimized this threshold using a validation set during training.

D. Denoising Autuencoders

Denoising autoencoders [40] showed strong performance in efficiently representing participants data [41]. A four-layer denoising autoencoder was used in this study: an input layer, two hidden layers (encoder and decoder layers) and an output layer. Fig. 3 shows the architecture of the network used in this study. The first hidden layer encodes the input x using (2) and then the decoder decodes the encoded vector using (3).

$$y = \sigma(Wx + b) \tag{2}$$

$$z = \sigma(W'y + b') \tag{3}$$

We corrupted 20 percent of the patient's information and plugged the corrupted information as x in (2). The loss function is a mean squared error of the output layer and the patient's information before the corruption.

Adam optimizer [42] at a learning rate of 0.01 was performed for 300 epochs to optimize the loss function. After training the autoencoder, all the samples were fed to the network without corruption and the outputs of the first hidden layer (y) were considered as a new representation for patient data. The new representation of data has lower dimension (we used 60 nodes for both of the hidden layers) and is less sparse. The dimensionality of trained autoencoder's hidden nodes was further reduced using tSNE for visualization and clustering purpose. We used K-means clustering with k=5 as a default value because there are 5 potential clinical subtypes: 1) CU patients, 2) MCI positive- amnestic, single domain, 3) MCI positive- amnestic, multiple domain, 4) MCI positive- non amnestic, single domain, 5) MCI positive- non amnestic, multiple domain.

IV. Experimental results

A. Prediction of MCI

The LSTM models were built under the Tensorflow platform [43] and were trained using two Tesla K80 GPUs. For systematic training and testing, we used a randomized cross validation method to find optimal parameters. We first randomly split the data into training (70 percent of data), validation (10 percent) and testing sets (20 percent). We used a stratified approach to split the data into train, validation and test sets; the patients were split based on their age at the study entry to make sure that different age groups are equally represented across training, validation and testing datasets.

Each time we randomly selected a set of parameters in a predefined data pool; train a LSTM model on the training set and determine model parameters on the validation set. We repeated this process 100 times and selected the best parameter set on the validation set. Then, we used the best model (based on their performance on the validation set) to evaluate prediction performance on the unseen test data.

Learning rates were randomly selected from [10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 5^{-2}, 8^{--2}, 10^{-1}]. The number of hidden neurons were selected from a wide range of integers which includes [10, 20, 40, 60, 80, 100, 140, 180, 200, 300, 600]. The batch size was set to be 2^n where n is an integer number in [5, 9]. The dropout probability was a random one decimal float number (%.1f) ranging from 0.3 to 0.7 and the number of iterations were selected from [10^4, 10^5, 10^6, 2×10^6, 5×10^6, 10×10^6, 15×10^6].

Random forests [44] serve as a baseline. Parameters of the random forests model were tuned using 5-fold cross validation. To search the hypothesis space, we used a random selection of parameters in a predefined pool of possible parameters. Number of estimators was a random integer number $n \times 100$ where n is an even number in [2, 20]. We used the same unseen test data as used in LSTM model to evaluate the performance. It should be noted that random forest models are trained on the static data and LSTM models are trained on the longitudinal temporal data (refer to section III.B).

Performance of the LSTM and the random forest models are in Table II. All the results reported are on the test set. In Table II, RF and LSTM respectively indicate a random forest model and a LSTM model trained and tested on the original data. RF over-sampled and LSTM over-sampled are the same models but trained using an over-sampled training data and tested on the original test data; we increased the population of MCI patients using a sampling with replacement approach (i.e., we randomly selected MCI cases and added them to the training set to balance between MCI and CU cases).

In Table II, the LSTM over-sampled produced both the highest F1-Score (0.46) and ROC AUC (0.75). Both LSTM and LSTM over-sampled performed better than the baselines in terms of F1 score. Both RF models produced higher accuracy than LSTM models but their recall were much lower than LSTM models, showing that random forest was biased due to the imbalanced class distribution (i.e., higher numbers of CU than MCI). These results indicate that LSTM models with temporal patterns of the data might have increased capability in predicting MCI compared to a traditional machine learning models using the static data.

In this study, we excluded the patients who were determined as MCI in their first visit to the MCSA. When including those MCI patients at the first visit (MCI=1,075), LSTM over-sampled produced higher performance than using the original data; i.e., precision, recall, F1-score and AUC were 0.53, 0.73, 0.61 and 0.74, respectively. This increased performance might be because there are more signals of patients who already had MCI before the first visit and/or the more data help create the more efficient deep learning models.

We also tested the random forests to investigate important risk factors for MCI. Random forests have a capability to identify the important variables based on impurity using information gain; i.e., how much each variable contributes to decreasing the impurity [44]. Table III shows the top 5 variables based on their effect in decreasing impurity.

As can be seen from Table III, age is the most important feature in discriminating between MCI and CU patients. Age, hypertension, education, depression and anxiety have also been reported as important risk factors in developing MCI in other literature [21, 45–47].

B. Clustering and Visualizing MCI Patients

We utilized a denoising autoencoder (section III.D) with four layers to efficiently represent the patient data addressing data sparsity and high dimensionality. Reduced dimensionality enables the patient data to map a more meaningful space for better clustering. The outputs of the first hidden layer were mapped to a 2D space for visualization and clustering using tSNE and K-means. Fig. 4 visualizes the patient data. CU patients are indicated by blue dots and MCI patients are represented by red dots.

Fig. 5 shows the distribution of MCI versus CU patients. Notably, ratio of MCI patients is much larger than the ratio of CU patients in cluster 2 but it is opposite in cluster 4. This may indicate the potential of a deep learning model for clustering distinct patient groups.

Fig. 6 (a) shows the distribution of males versus females and (b) further zoomed into males versus females for both CU and MCI patients. As can be seen, cluster 0 mostly includes males; almost 50 percent of males are clustered in this group. On the other hand, cluster 1 mostly includes females; half of the female population is clustered within this group.

V. Discussion

Despite the urgent need for early detection of MCI and dementia, there is a lack of automated tool available to healthcare providers using routine EHR data. Given that MCI is a precursor of dementia and could be a critical step in the prevention and control of AD and other dementias, it is crucial to find a more efficient way to determine MCI in its very early stages. This study addresses this issue by using routinely-collected EHR data as part of patient care for predicting onset of MCI.

The LSTM RNN demonstrated its potential for MCI prediction incorporating temporal patterns of patient data that were automatically extracted from EHRs. Although this study used limited set of MCI risk factors compared with the previous study that used manually annotated variables [9], our models still produced comparable (even slightly higher) performance. The LSTM RNN using longitudinal temporal data seems to be more efficient in predicting MCI compared to using the traditional machine learning models with static data. Machine learning techniques such as denoising autoencoders, K-means, and tSNE to visualize and cluster the patients EHR data also showed a good potential to identify certain patient groups. The predictive model and patient clustering could (have the potential to) assist in the clinic to support early identification of MCI patients as well as better characterization, determining more granular subgroups of MCI patients. This can enable tailored care plan and open up new clinical practice opportunities using routine EHR data.

The limitation of this study includes the use of only Mayo clinical notes even though participants enrolled in the MCSA visit other healthcare institutions, and thus the patients might not be ideally represented by their comprehensive longitudinal data. Use of EHR data from other institutions requires significant effort and this is aligned with our future work. We plan to use the medical record linkage system, the Rochester Epidemiology Project [48–50] to access other EHR data to compile comprehensive EHR data.

VI. CONCLUSION

A deep learning based model, LSTM RNN demonstrated a good potential incorporating temporal EHR patterns to predict the conversion from CU to MCI. When we combine this model with natural language processing to automatically extract MCI risk factors from EHR data, it could facilitate early detection of MCI addressing a current significant delay and thus improve treatment plans and health outcomes for patients.

The current model relies on a relatively small set of MCI patients and limited set of variables. In the future, we will use extended available and/or the entirety of patient EHR data instead of using known risk factors. We also plan to use publicly available data such as ADNI [23] for transfer learning or for testing the generalizability of the trained models. In addition, we will investigate multiple inputs multiple outputs models to enhance a prediction capability of MCI and dementia where the inputs are patient EHR data at different time steps and the outputs are MCI or dementia prediction at each time step.

Acknowledgment

This study was partially supported by NIAID R21AI 142702. The MCSA study was supported by NIH Grants U01 AG006786, P50 AG016574, the GHR Foundation, the Mayo Foundation for Medical Education and Research and was made possible by the Rochester Epidemiology Project (R01 AG034676).

CONFLICT OF INTERESTS

Maria Vassilaki receives research funding from NIH, Roche, and Biogen. Ronald C. Petersen consults for Roche, Inc, Merck, Inc, Biogen, Inc, Eisai, Inc; serves on the data and safety monitoring board for Genentech; and has given talks at national meetings for GE Healthcare.

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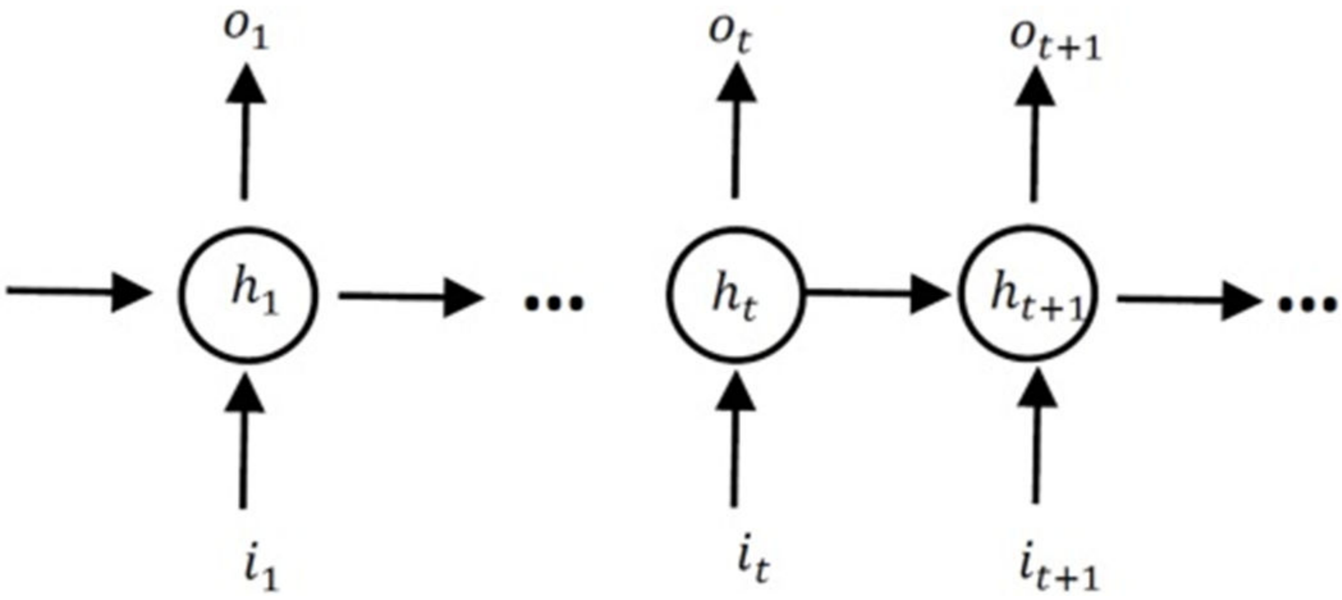


Fig 1.

Unrolled structure of RNNs. The circles present hidden layers, i_t, o_t and h_t are respectively input, output and hidden state at time step t.

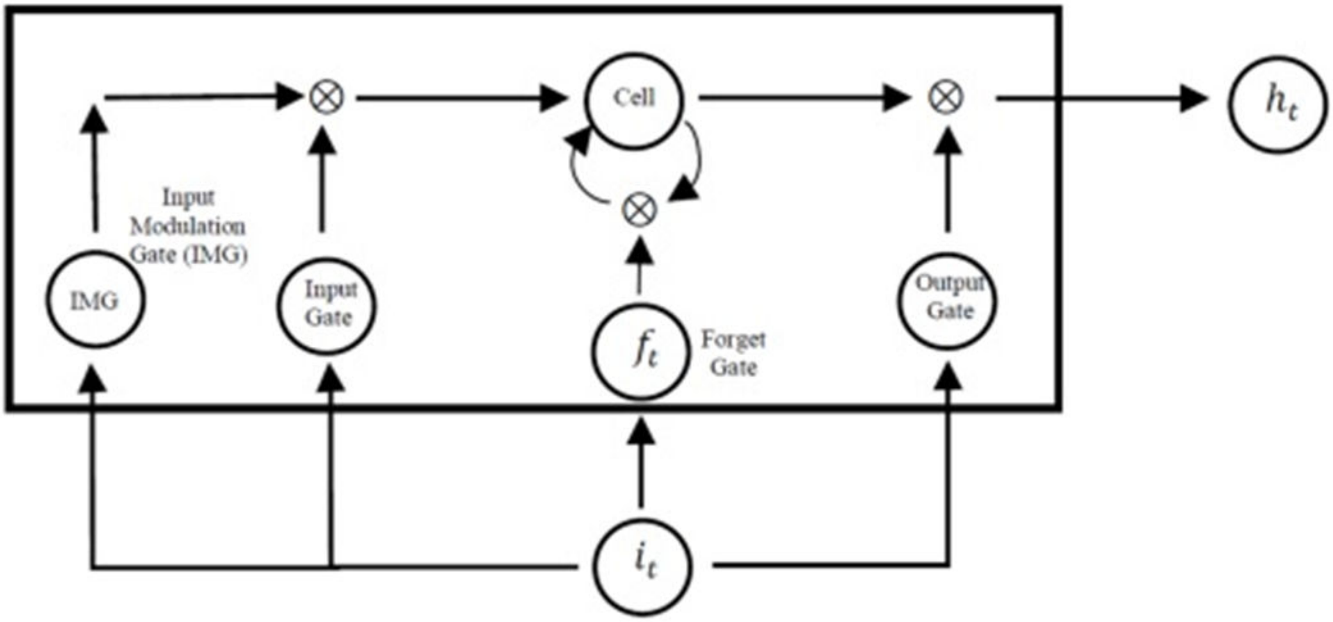


Fig 2.

A LSTM memory cell. Each LSTM unit includes the input gate, the output gate and the forget gate[39].

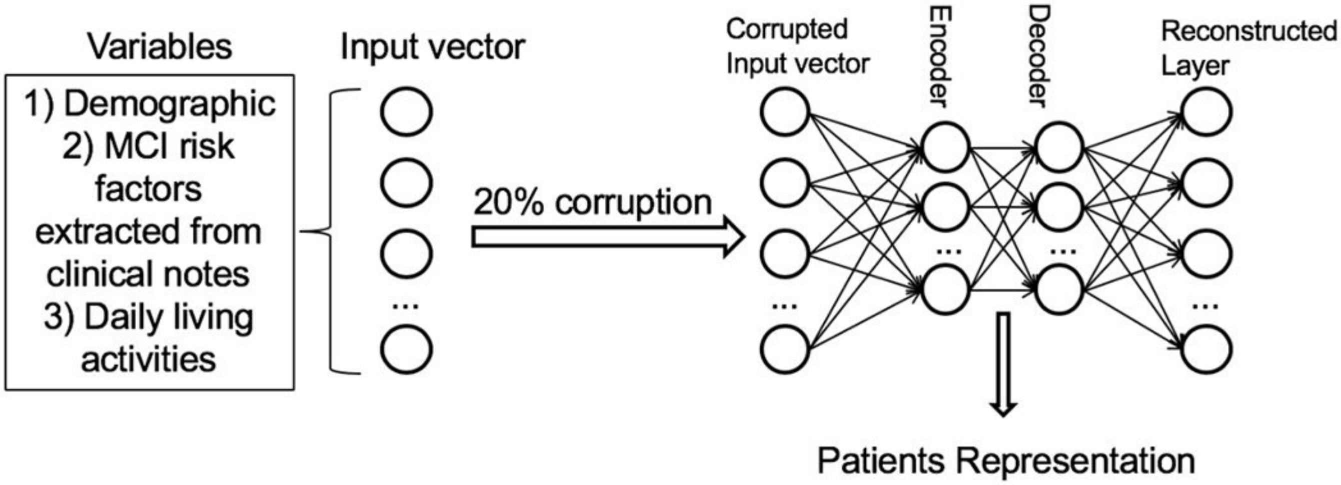


Fig 3.

Artitecture of the denoising autoencoder to represent patients using HER

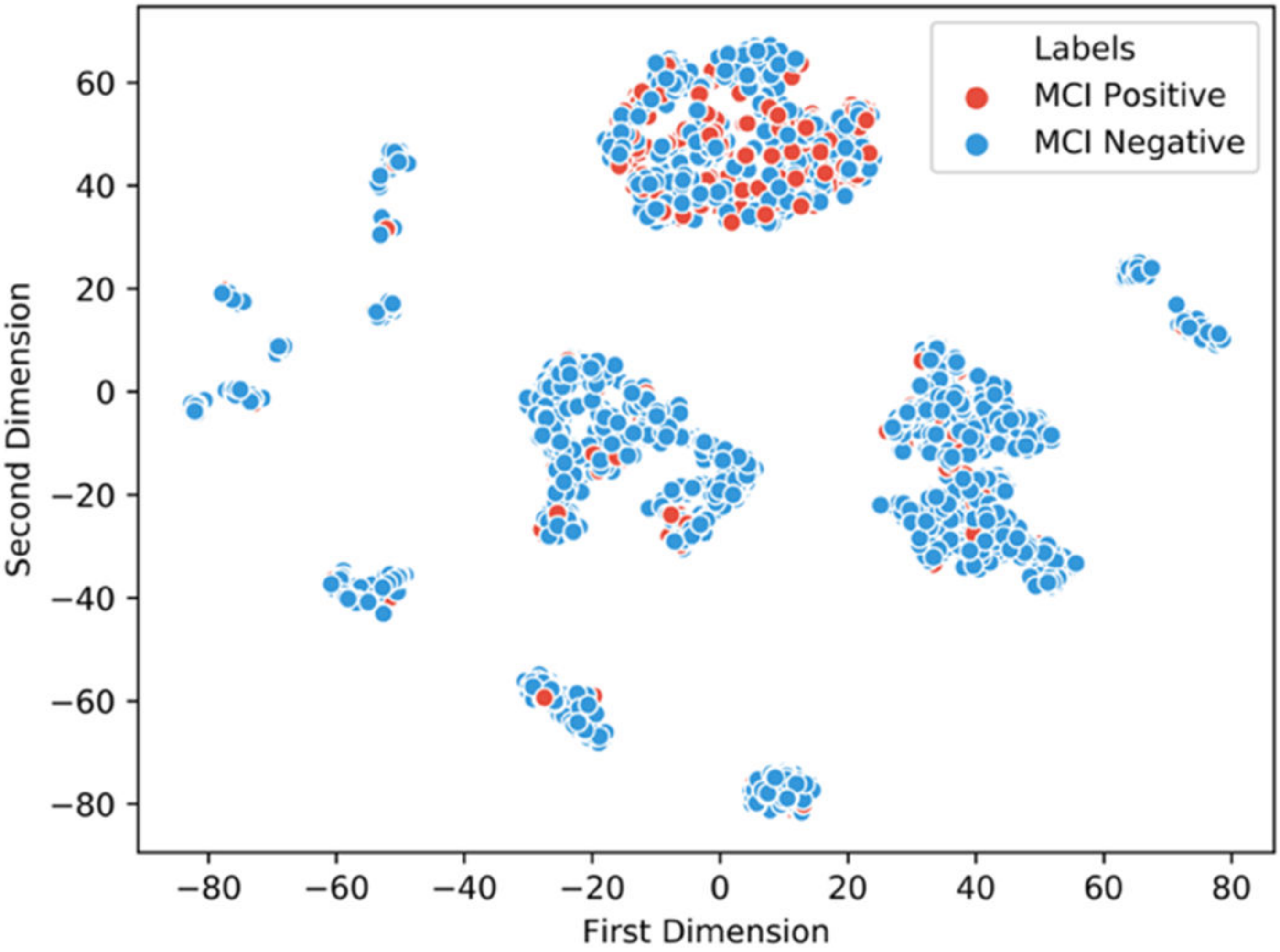


Fig 4.

Visualization of CU patients (blue dots) and patients with MCI (red dots).

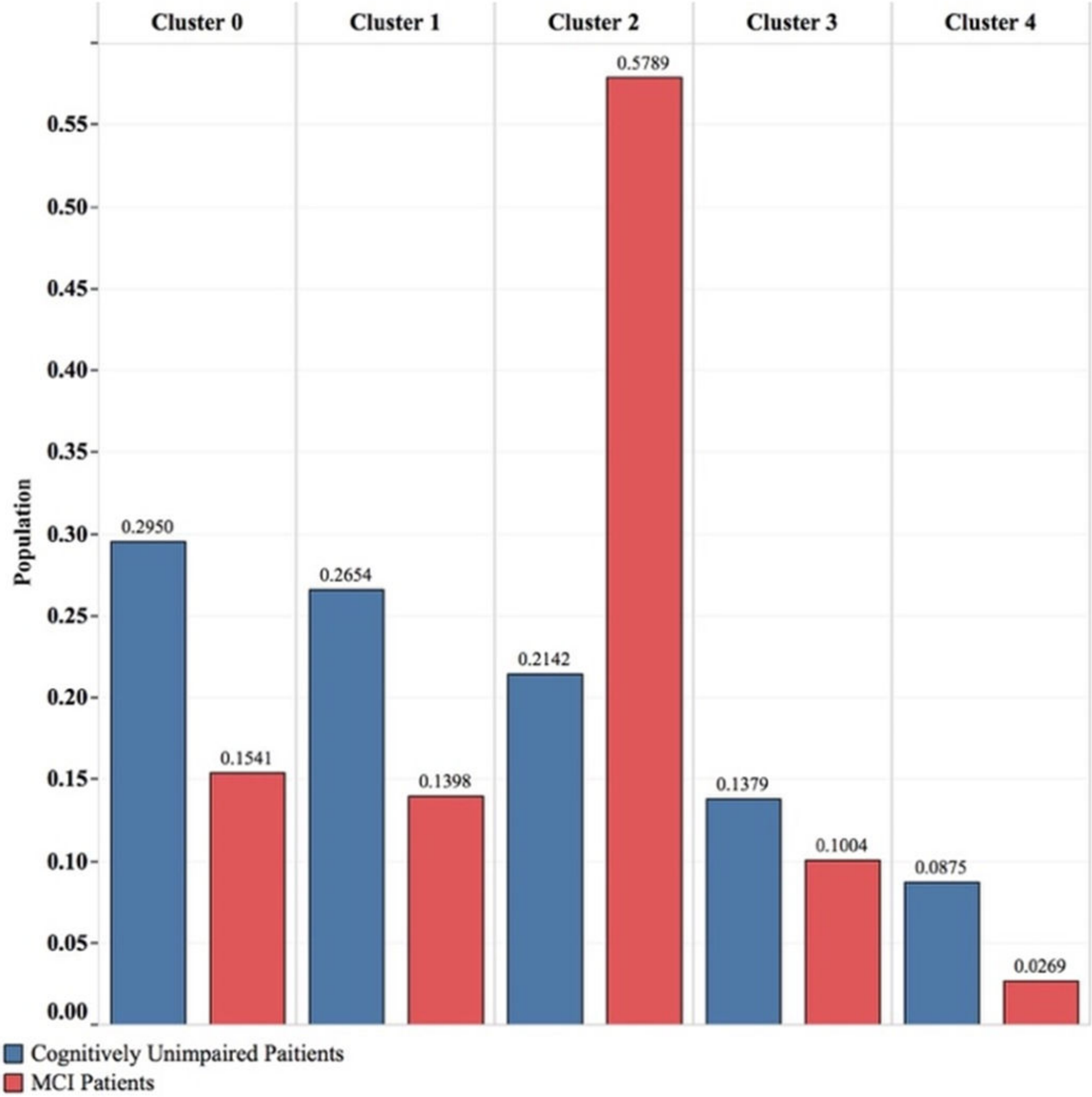
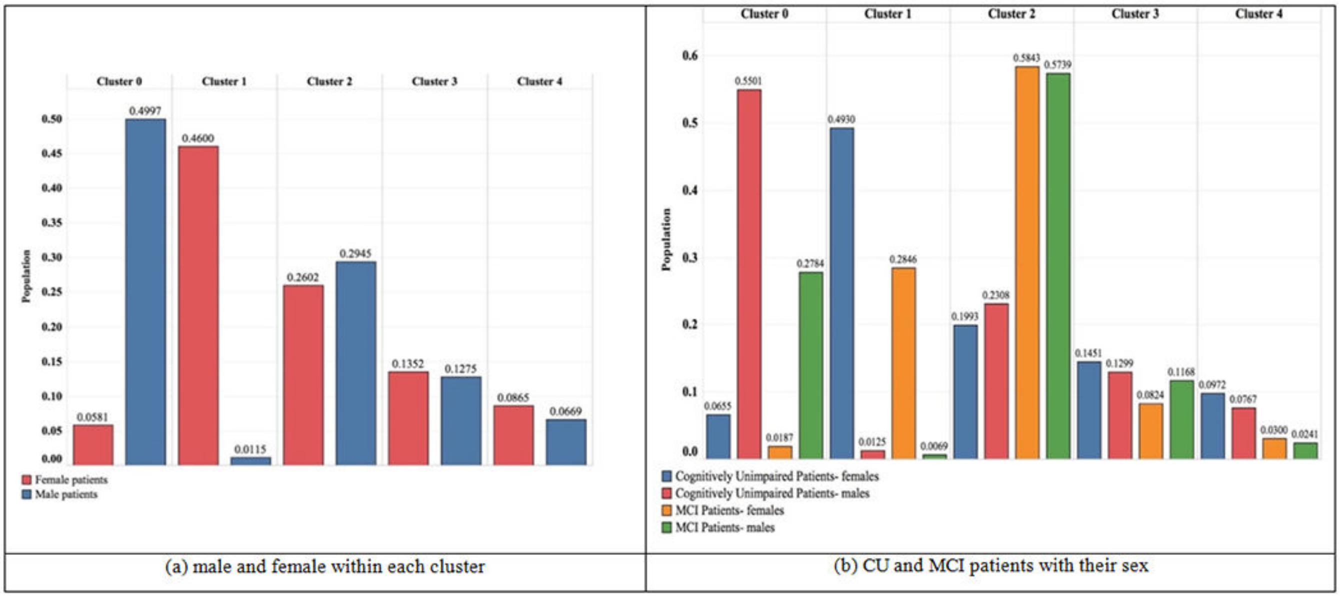


Fig 5.

Distribution of MCI versus CU patients within each cluster. Y-axis shows the ratio of CU or MCI population within the relevant cluster.



(a) male and female within each cluster

(b) CU and MCI patients with their sex

Fig 6.

Distribution of male and female patients within each cluster.

TABLE I.

LIST OF VARIABLES AND THEIR SOURCES.

Variable Category	Variable	Source
Demographics	Age, Sex, Education	MCSA
Diseases / disorders	Hypertension, Atrial fibrillation, Angina, Congestive heart failure, Coronary artery disease, Myocardial infarction, Coronary artery bypass graft, Diabetes	Clinical notes
Neuropsychiatric symptoms	Delusion, Hallucinations, Agitation, Depression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability/lability, Motor behavior, Appetite/eating change	Clinical notes
ADL	Bathing, Dressing, Feeding, Housekeeping, Responsible for own medication, Transportation, Toileting, Transferring, preparing food	Patient provided information
Others	Slow gait, cognitive complaint, impaired judgment/orientation, memory concern, difficulty for concentrating, difficulty for finance	Clinical notes

TABLE II.

Performance of MCI prediction

Model	Accuracy	Precision	Recall	F1 Score	AUC
RF	0.82	0.44	0.13	0.21	0.73
RF Over-sampled	0.79	0.33	0.25	0.28	0.69
LSTM	0.73	0.33	0.59	0.43	0.71
LSTM Over-sampled	0.71	0.33	0.76	0.46	0.75

TABLE III.

TOP 5 MCI RISK FACTORS DETERMINED BY RANDOM FORESTS

Risk Factor	**Score**
Age	0.16
Hypertension	0.08
Education	0.07
Depression	0.06
Anxiety	0.05