Early detection of Alzheimer's Disease in the military population

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that is currently affecting more than five million Americans. The aging military veterans are one of the populations most affected with Alzheimer's disease. Evidence suggest that this aging military population has potentially been subjected to additional risk factors compared to the general population. Consequently, it is believed that this population represents an elevated risk for AD and other dementias. Therefore, the goal of our study was to use existing statistical classification methods to be able to detect AD at an early stage and determine important biomarkers for the military population.

Subject Keywords: Alzheimer's disease (AD), AUC, biomarkers, veterans, traumatic brain injury (TBI), post-traumatic stress disorder (PTSD)

Introduction

Alzheimer's disease (AD) is the most common form of dementia. It is an irreversible and neurodegenerative disease. There are more than five million Americans living with Alzheimer's disease and by 2050 it is estimated that this number will rise to 16 million (Alzheimer's disease facts and figures.2017). According to the Alzheimer's Association, by the end of 2017, AD and other dementias will cost Americans 259 million dollars; it is estimated that these costs could rise as high as 1.1 trillion dollars by 2050. This makes it the most expensive disease in America and it cost more than heart disease and cancer (Alzheimer's disease facts and figures.2017).

From this rapidly increasing number of people being affected with AD, the aging military veterans are one of the populations most affected by it (Sibener et al., 2014). This is an important public health challenge and has become a priority for the military because of this the rapidly growing number of veterans be affected with AD and other dementias. The aging military population have been subjected to the same risk factors as the general population for AD and other dementias; but, evidence suggest that this population has potentially been subjected to additional risk factors compared to the general population. Therefore, it is believed that this population represents an elevated risk for AD and other dementias. Evidence suggest that some of the potential military risk factors include exposure to: a traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), chemicals, such as pesticides, and lifestyle, such as depression that all eventually trigger the development of neurodegenerative diseases such as AD. Therefore, understanding this potential association has become a priority for the military since evidence show that these are common military risk factors for AD and other neurogenerative diseases (Khachaturian & Khachaturian, 2014).

The goal of our study was to use existing statistical classifications methods to be able to detect AD at an early stage for the military population. For this, we needed to identify the most important biomarkers for the military population. The statistical methods used for this study were Su and Liu's (1993) combination methods based on AUC (area under the curve) and the stepwise method proposed by Kang et al (Kang, Liu, & Tian, 2016). The overall goal was to improve the classification rate of these biomarkers.

Biomarkers

The biomarkers considered for this study were the following: Mini-Mental State Exam (MMSE), the volume of hippocampus, the apolipoprotein gene (APOE ε4), TBI, and PTSD. Evidence indicate that these biomarkers are strong indicators of early stages of AD. The MMSE consist of a 30-point questionnaire and it is recommended for primary care physicians to use when evaluating older patients for cognitive impairments. It is used to estimate the progression of a cognitive impairment but it can have a low sensitivity when distinguishing between normal and mild cognitive impairment (MCI) (Trzepacz, Hochstetler, Wang, Walker, & Saykin, 2015). Additionally, loss of tissue throughout the brain and decreasing hippocampal volumes are characteristics associated with AD. Studies have shown that short-term memory loss results from the shrinkage of the hippocampus (Mu & Gage, 2011). Correspondingly, APOE ε4 is known to be a risk-factor gene since evidence show that it increases a person's risk of developing AD (Alzheimer's disease facts and figures.2017; Petersen et al., 2010). Furthermore, an association of TBI with dementia has be found in studies involving the veteran and nonveteran populations. TBI consist of any injuring to the head from any external force. Also, the National Patient Care Database found that those individuals diagnosed with PTSD are twice more likely to develop dementia. Unlike TBI, PTSD is a psychological condition developed from the failure to recover from a distressing event (Weiner et al., 2013).

DOD ADNI Data

For this study, data were obtained from the Department of Defense (DOD) Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI was launched in 2003 and it is a longitudinal study that evaluates a range of biomarkers that could be used to measure the progression of AD (Jedynak et al., 2012). Some of these biomarkers include brain metrics derived from magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, and blood, cerebrospinal fluid, and other biological markers (Braskie & Thompson, 2014). The ADNI study consists of three phases: ADNI1, ADNI GO and ADNI2. New participants were added with each phase, but some were carried on from the previous phase to the new phase.

For our classification analysis, this study consisted of four biomarker profiles and each profile included the following three biomarkers: MMSE based on a scale of 24-30; APOE ε4 based on the number of genes; hippocampal volumes measured with MRI. The

second profile consisted of the three biomarkers in combination with TBI which was based on the number of TBI's encountered during service. The third profile included the three biomarkers in combination with PTSD which was based on the Current Clinician Administered PTSD scale score. The final profile consisted of all five biomarkers combined. When the biomarkers were combined, some of the data were lost. Table 1 consists of a more detailed statistical description of the data at baseline (i.e. at the time that participants entered the ADNI study).

Table 1. Statistical Description of Biomarkers at Baseline

Biomarkers	Sample size	Mean	Standard Deviation	Missing Data Rates
MMSE (scale 24-30)	441	28.84	1.38	7.03%
Hippocampal Volumes (mm^3, MRI scans)	411	7251.08	987.29	0.24%
APOE ε4 (number of genes)	440	0.35	0.55	6.79%
TBI (numbers encountered during service)	69	1.64	1.64	83.25%
PTSD (scale)	32	47.34	36.98	92.22%

Statistical Analysis

In classification studies, the area under the ROC curve (AUC) is the classification analysis typically used for biomarker selection and evaluation. A greater AUC indicates a stronger classifier, so the AUC for a strong classifier is closer to the value one than to zero. The AUC is the most prevalent diagnostic accuracy index used by many researchers when combing multiple biomarkers into a single score (Yin & Tian, 2014). In our study, the AUC was calculated for all five biomarkers (MMSE, hippocampus, APOE ε4, TBI, and PTSD) using two different methods. The combination of these biomarkers was performed to obtain sufficient information for more accurate disease diagnosis. The biomarkers MMSE, APOE ε4, and the hippocampal volumes were the three biomarkers used for every profile. The methods were performed by using real data from the DOD ADNI for all those individuals that were classified as normal at baseline. Then these individuals were either classified as healthy (N_h) or diseased (N_d) if during any follow-ups

they were diagnosed with AD. The following were the two methods used to calculate the AUC for each profile:

- Method 1: Su and Liu's combination based on AUC (Su & Liu, 1993)
  - This approach consists of a linear combination under the multivariate normality assumption. Under the assumption of normality, a large sample size is required for optimal results.
- Method 2: Stepwise method proposed by Kang et al (Kang et al., 2016)
  - This is a nonparametric approach that maximizes the AUC by linearly combining markers by using a 'distribution-free' stepwise approach.

These two existing methods have been reported in the literature for their good performances in classification and hence we adopted these methods directly in our study. We considered four biomarker profiles for the classification analyses. All the analyses were performed using R packages.

Results

The results were given in Table 2. All biomarker profiles consisted of a high AUC using both methods. Comparing both methods (Su and Liu's combination methods based on AUC and the stepwise method), the AUC were similar for all four biomarker profiles. The three biomarkers (MMSE, APOE ε4, and hippocampal volumes), TBI, and PTSD combined consisted of the highest AUC results compared to all the other profiles, though the valid sample size was relatively small. The profile with the three biomarkers combined with the PTSD biomarker had the lowest AUC compared to all the other biomarkers. The three biomarkers combined with TBI had similar results compared to the profile with the three biomarkers alone.

Table 2. The AUC of Various Biomarker Profiles using Two Classification Methods

Sample size (N)	**3 Biomarkers**	**3 Biomarkers + TBI**	**3 Biomarkers + PTSD**	**3 Biomarkers + TBI + PTSD**
Healthy (N_h)	375	57	26	12
Diseased (N_d)	37	6	5	2

	AUC			
Su and Liu's method	0.889	0.857	0.800	0.958
Stepwise method	0.851	0.857	0.800	>0.999

Discussion

The results reveal that TBI might be a stronger biomarker compared to PTSD. When PTSD was included in combination with MMSE, APOE ε4, and hippocampal volumes, the AUC values decreased compared to when PTSD was not included. When TBI was included with the other three biomarkers, the AUC was higher compared to the one of PTSD and other three biomarkers using both methods. This is an indicator that TBI is a stronger biomarker compared to PTSD for early detection. The three biomarkers, TBI and PTSD, combined with MMSE, APOE ε4 and the hippocampal volumes had an exceptionally high AUC. This indicates that the combination of all biomarkers could be strong indicators of AD at an early stage. In this combination, the AUC reached up to almost 1 using the Stepwise method. However, the sample size in this study was a crucial limitation encountered, since a large portion of the data was missing, specifically data for TBI and PTSD. This could have potential affected the AUC since one of the methods (i.e. Su and Liu's method) used is approached under the assumptions of normality.

Furthermore, the three biomarkers (MMSE, APOE ε4, and hippocampal volumes) alone were also strong biomarkers for AD. This shows consistency with numerous literature reviews since these three biomarkers are frequently being used for the detection of AD in the general population (Alzheimer's disease genetics fact sheet.2017; Mu & Gage, 2011; Trzepacz et al., 2015). In addition to these biomarkers, covariates such as age and history of TBI could have enhanced the performance of these statistical methods. In conclusion, having had a larger sample may improve the performance of these statistical methods. A possible way to overcome this limitation is by adapting existing imputations methods which can be used to input the missing values in our data based on other covariates or demographic information. In a future study, this may allow us to re-evaluate the biomarkers of TBI and PTSD for early detection of AD.

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