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Exploring Diagnoses of Alzheimer's Using fMRI and Machine Learning

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Abstract

Machine learning is rapidly becoming useful in many contexts, particularly in the medical field. This paper explores the usage of functional magnetic resonance imaging (fMRI) and machine learning in the diagnoses of Alzheimer's over the past six years. The most common machine learning methods used in the diagnoses of Alzheimer's are feature selection and classification, specifically support vector machines. More recent studies have used lesser known or more up-and-coming methods such as Gaussian processes and deep learning.

1 Introduction

Alzheimer's is a devastating disease that affects more than 5 million Americans that begins as mild memory loss and progresses to inability to have a conversation and respond to surroundings. More than five million Americans suffer from this form of dementia, with a new diagnosis approximately once a minute. There is currently no cure, but research is ongoing[2, 1]. Some recent efforts involve analyzing functional magnetic resonance imaging (fMRI) with machine learning techniques such as feature selection and classification.

2 Background

2.1 fMRI

fMRI is a non-invasive neuroimaging technique used to show the behavior of the brain during various activities. Unlike structural MRI, which only shows anatomical features, fMRI uses "imaging of the endogenous bold-oxygen-level dependent (BOLD) contrast." Neuron activation is accompanied by an increase in blood flow to the respective area of the brain[7]. fMRIs are usually taken either while the person is doing a task or while they are resting, creating what is referred to as a resting-state fMRI, or rs-fMRI. fMRI is also taken over a period of time, allowing doctors to see the change in activated brain areas over the course of a task. The resulting data is represented in **voxels**, which are the three-dimensional analogs to pixels, each representing approximately one million brain cells[20]. fMRI studies generate an enormous amount of data despite the small number of participants, thus making them ideal candidates for computerized processing[5].

2.2 Using fMRI to Study Alzheimer's

There are a number of pros and cons to using fMRI to study Alzheimer's. fMRI is "non-invasive, radiation-free and and offers a combination of good spatial and reasonable temporal resolution"[7]. In addition, many fMRIs can be taken over the course of a longitudinal study, and because studies involving fMRI are focused on the events taking place while the images are being created, it's possible to study the "hemodynamic correlates of specific behavioral events", which are critical to understanding Alzheimer's[4].

Researchers have also proposed that studying the brain as a network could lead to new insights on Alzheimer's[6, 8]. The features of fMRI, particularly spatial resolution and BOLD contrast, make it well-suited for testing these hypotheses.

One of the keys to studying any disease is finding **biomarkers**. Biomarkers are "objective, quantifiable characteristics of biological processes"[16]. Biomarkers are key to diagnosis. Some have suggested that fMRI itself could potentially be a biomarker[15, 10] Recently, researchers have started to use supervised machine learning methods, specifically feature selection and classification, to find biomarkers for Alzheimer's[12, 19].

Feature selection is invaluable for processing the huge amount of data produced by fMRI and incredibly useful for identifying biomarkers. It is also essential to classification by reducing the dimensionality of the data to a manageable amount for the classifier, thus improving performance[19].

In Alzheimer's fMRI studies, classification is commonly used to separate participants into either the three categories of healthy controls, those with mild cognitive impairment (an intermediate stage of mental dysfunction that causes a higher risk of developing Alzheimer's[6]), and those with Alzheimer's; or two categories of healthy controls and those with Alzheimer's[11, 6, 19]. Like many other types of data, classifying fMRI data comes with its own set of challenges. Unlike typical classification problems with many more samples than features, fMRI data has many more features than samples because of the small number of participants per study. In addition, due to the thousands of voxels needed to represent a brain, fMRI data is very high dimensional. fMRI data is also known for producing noisy signals. Finally, fMRI data suffers from high subject variability. In addition to the standard differences in brain sizes and shapes, Alzheimer's fMRI data has higher subject variability because of the effects of the disease, which in its later stages causes those with it to lose motor control. fMRI is extremely sensitive to head motion, which can reduce its already relatively low spatial resolution. In addition, "differences in task performance between patient and control groups complicate data interpretation, as the ability to perform the task may greatly influence the pattern and degree of observed fMRI activity." Resting state fMRI can counteract some of these effects and can be used to study those with more advanced stages of the disease [7].

3 Search Process

3.1 Research Questions

The questions motivating my analysis were inspired by Wen et. al. 2012[18]. I wanted to summarize the recent research on diagnosing Alzheimer's disease from fMRI data using machine learning. Thus, my questions were as follows:

1. What machine learning techniques have been used for diagnosis of Alzheimer's using fMRI data?
2. In general, how effective/accurate are machine learning models at diagnosing Alzheimer's from fMRI data?
3. Of the machine learning models currently in use, which (if any) perform better than others?
4. Why do some methods perform better than others?

3.2 Selected Studies

Studies were included in my analysis if they used machine learning methods in either preprocessing, feature selection, or final classification. They had to include a clear description of the methods used and why they were chosen and a thorough analysis of the results. Only studies that restricted their data to fMRI were chosen, and of the classes to separate data into, Alzheimer's had to be one of them. The studies chosen were either empirical or proposals for automated diagnoses of Alzheimer's with fMRI data.

4 Results and Discussion

For this literature review, I reviewed seven studies using fMRI and machine learning to diagnose Alzheimer's ranging from 2009 to 2016. Two of the studies and the article were overviews or detailed descriptions of suggested methods for studying and diagnosing Alzheimer's using machine learning and fMRI. The other six studies either implemented these frameworks or an adaptation of them or used their own methods. I will explore these studies categorically based on my research questions.

4.1 Question 1: What Machine Learning Techniques are being Used?

The studies chosen display a wide array of machine learning methods from naïve Bayes to neural networks. All of the machine learning methods fell into one of two categories: feature selection or classification. I found eighteen different methods of feature selection, listed below:

- Random selection
- ReliefF
- Voxel activation sum
- Voxel activation per class
- Kendall tau correlation
- Gaussian process covariance function
- Fisher score
- Forward sequential feature selection
- Convolutional neural networks

- Threshold split region
- Principal components analysis
- Independent components analysis
- Most discriminative voxels
- Most active voxels
- $16 \times 16 \times 16mm^3$ cubes
- Searchlight
- Recursive elimination
- Symmetric uncertainty

Fourteen different types of classifiers were found, listed below:

Table 1: Frequencies of Classifiers

Classifier	Frequency
SVM	6
Naive Bayes	3
Random Forests	2
Random Subspace	1
Random Linear Oracle	1
Logistic Regression	2
KNN	2
Linear Discriminant	3
Quadratic Classifier	1
Decision Tree	1
LeNet-5	1
Decision Stump	2

There was no overlap between studies for feature selection methods; however, there was much more overlap for classifiers. Six different forms of support vector machines appeared in these studies. The second most popular classifier were forms of linear discriminants, naïve Bayes, and random forests each appearing 3 times. Figure 1 shows this graphically.

Figure 1: Distribution of the Classifiers used in the Studies

4.2 Question 2: How Effective/Accurate are Machine Learning Models at Diagnosing Alzheimer's?

While not perfect, machine learning models actually perform remarkably well at predicting Alzheimer's diagnoses. Many of the models achieved over 80% accuracy across multiple studies. Figure 2 compares the accuracy of the four most popular classifiers from their best performances. SVMs, the most common classifier, were regularly accurate more than 90% of the time.

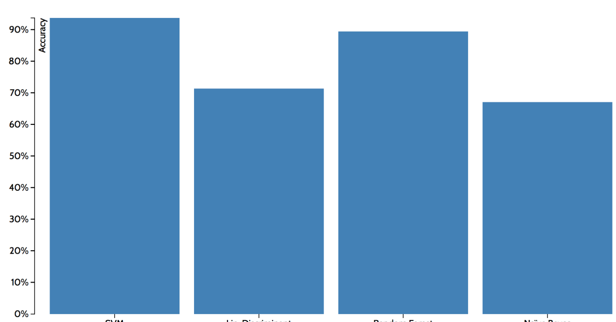

Figure 2: Mean Accuracy of the four most popular classifiers

4.3 Question 3: Of currently used models, which ones perform the best?

Of the studies reviewed, the most accurate ones for distinguishing Alzheimer's patients from healthy patients were random forests with improvements from [17], the support vector machine with sequential minimal optimization using 25 features from [3] and convolutional neural networks from [14], which achieved 98%, $97.14 \pm 2.33\%$, and 96.85% accuracy respectively.

4.4 Question 4: Why do some methods perform better than others?

Out of the four most common classifiers, naïve Bayes had the worst performance consistently. The highest accuracy was in Khazaee et. al. [6] using all features with feature selection at 80%. However, the other two studies using naïve Bayes had accuracies much closer to Khazaee et. al.'s results without feature selection: the mean across studies was 54%, not much better than random selection. As explained in Armañanzas, "This is numerical proof of a biologically expected phenomenon: the dependence between neighboring voxel signals. Spatially close voxels will behave in accordance with fashions as large neuronal circuits activate the whole region." Since the efficacy of naïve Bayes is directly dependent on the conditional independence of the predictive variables, it makes sense that naïve Bayes performs poorly in this case[3].

Linear discriminant analysis (LDA) performed similarly poorly to naïve Bayes. Like naïve Bayes, LDA assumes that the predictive variables are independent and additionally assumes that they are normally distributed. The most predictive voxels for Alzheimer's are neither independent nor normally distributed, so LDA's poor performance is understandable. Liong and Foo [9] suggest that logistic regression may have better performance when these assumptions are not met "because the results of [logistic regression] are not affected by the degree of normality of the independent variables." Although this was not supported in the data from [5], Challis et. al.'s Gaussian process logistic regression performed much more favorably, accurately separating 75% of healthy controls from amnesic-MCI patients and 90% of amnesic-MCI patients from Alzheimer's patients. Furthermore, according to Pereira et. al., "LDA needs to be used either in conjunction with extreme feature selection or with dimensionality reduction, as otherwise there are typically not enough examples to estimate its covariance matrix reliably"[13], so it is possible that LDA could have performed better if better features were chosen or if used in conjunction a support vector machine for dimensionality reduction.

Random forests performed second best, despite having the highest individual performance in Tripoliti et. al.'s study [17] because of improvements such as weighted voting and multiple estimators. The strength of random forests is in its ensemble based nature. "[S]ubstantially different trees can be constructed from identical training data" [3]. This leads to many different perspectives on the most important features, limited only by the number of trees determined to be in the forest.

Support vector machines consistently performed well across all the studies that used them. According to [3], support vector machines have been very popular in fMRI data analysis previously, so it is unsurprising that it was also very popular in this subset. "The ability of SVM to project data to higher dimensions in the search of linear separability makes them especially suitable for large sized feature spaces", like voxels from fMRI data. Support vector machines do not depend on the assumptions that linear discriminant analysis and naïve Bayes depend on, so they are much more flexible and applicable to many more classification problems.

5 Conclusion

6 Honor Code

This represents my own work in accordance with university policies.

References

[1] Alzheimer's Association, "2016 Alzheimer's Disease Facts and Figures." [Online]. Available: http://www.alz.org/facts/overview.asp

[2] ——, "What is Alzheimer's?" 2016. [Online]. Available: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp

[3] R. Armananzas, M. Iglesias, D. A. Morales, and L. Alonso-Nanclares, "Voxel-based diagnosis of Alzheimer's disease using classifier ensembles," *IEEE J Biomed Health Inform*, vol. XX, no. X, pp. 1–7, 2015.

[4] B. C. Dickerson and R. A. Sperling, "Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies," *Neuropsychologia*, vol. 46, no. 6, pp. 1624–1635, 2008.

[5] J. Honorio, D. Tomasi, R. Z. Goldstein, H.-C. Leung, and D. Samaras, "Can a Single Brain Region Predict a Disorder?" *IEEE Transactions on Medical Imaging*, vol. 31, no. 11, pp. 2062–2072, 2012.

[6] A. Khazaee, A. Ebrahimzadeh, and A. Babajani-Feremi, "Application of advanced machine learning methods on resting-state fMRI network for identification of mild cognitive impairment and Alzheimer's disease," *Brain Imaging and Behavior*, 2015.

[7] J. Kivisitö, H. Soininen, and M. Pihlajamäki, "Functional MRI in Alzheimer's Disease," in *Advanced Brain Neuroimaging Topics in Health and Disease - Methods and Applications*, ch. 19, pp. 509–531.

[8] Y. Li, Y. Qin, X. Chen, and W. Li, "Exploring the functional brain network of Alzheimer's disease: based on the computational experiment." *PloS one*, vol. 8, no. 9, p. e73186, 2013. [Online]. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3760893{&}tool=pmcentrez{&}rendertype=abstract

[9] C.-Y. Liong and S.-F. Foo, "Comparison of linear discriminant analysis and logistic regression for data classification." *AIP Conference Proceedings*, vol. 1522, no. 1, pp. 1159–1165, 2013. [Online]. Available: 10.1063/1.4801262$\delimiter"026E30F$nhttp://lumen.cgsccarl.com/login?url=http://search.ebscohost.com/login.aspx?direct=true{&}db=a9h{&}AN=87085892{&}site=ehost-live

[10] E. Moradi, A. Pepe, C. Gaser, H. Huttunen, and J. Tohka, "Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects," *NeuroImage*, vol. 104, pp. 398–412, 2015. [Online]. Available: http://linkinghub.elsevier.com/retrieve/pii/S1053811914008131$\delimiter"026E30F$nhttp://www.ncbi.nlm.nih.gov/pubmed/25312773

[11] J. H. Morra, Z. Tu, L. G. Apostolova, A. E. Green, A. W. Toga, and P. M. Thompson, "Comparison of AdaBoost and Support Vector Machines for Detecting Alzheimer's Disease through Automated Hippocampal Segmentation," *IEEE Transactions on Medical Imaging*, vol. 29, no. 1, pp. 30–43, 2010.

[12] G. Orrù, W. Pettersson-Yeo, A. F. Marquand, G. Sartori, and A. Mechelli, "Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: A critical review," *Neuroscience and Biobehavioral Reviews*, vol. 36, no. 4, pp. 1140–1152, 2012. [Online]. Available: http://dx.doi.org/10.1016/j.neubiorev.2012.01.004

[13] F. Pereira, T. Mitchell, and M. Botvinick, "Machine learning classifiers and fMRI: a tutorial overview." 2009.

[14] S. Sarraf and G. Tofighi, "Classification of Alzheimer's Disease using fMRI Data and Deep Learning Convolutional Neural Networks," pp. 8–12, 2016. [Online]. Available: http://arxiv.org/abs/1603.08631

[15] R. Sperling, "The potential of functional MRI as a biomarker in early Alzheimer's disease," *Neurobiology of Aging*, vol. December 2, no. 32, pp. S37–S43, 2011.

[16] K. Strimbu and J. A. Tavel, "What are biomarkers?" *Current Opinion HIV AIDS*, pp. 463–466, November 2010.

[17] E. E. Tripoliti, D. I. Fotiadis, M. Argyropoulou, and G. Manis, "A six stage approach for the diagnosis of the Alzheimer's disease based on fMRI data," *Journal of Biomedical Informatics*, vol. 43, no. 2, pp. 307–320, 2010. [Online]. Available: http://dx.doi.org/10.1016/j.jbi.2009.10.004

[18] J. Wen, S. Li, Z. Lin, Y. Hu, and C. Huang, "Systematic literature review of machine learning based software development effort estimation models," *Information and Software Technology*, vol. 54, no. 1, pp. 41–59, 2012. [Online]. Available: http://dx.doi.org/10.1016/j.infsof.2011.09.002

[19] J. Ye, T. Wu, J. Li, and K. Chen, "Machine Learning Approaches for the Neuroimaging Study of Alzheimer's Disease," *IEEE Computer*, vol. 44, no. 4, pp. 99–101, 2011.

[20] D. Yuhas, "What's a Voxel and What Can It Tell Us? A Primer on fMRI," 2012. [Online]. Available: http://blogs.scientificamerican.com/observations/whats-a-voxel-and-what-can-it-tell-us-a-primer-on-fmri/