USE OF MULTI-MODAL STRUCTURAL MRI AND PATTERN RECOGNITION TECHNIQUES TO PREDICT AMYLOID DEPOSITION

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INTRODUCTION
In the United States alone, there are more than 5 million cases of Alzheimer’s Disease (AD) [1]. AD is a neurodegenerative disease that causes severe dementia. This dementia causes severe problems with learning, memory, thinking, and even behavior. It is accompanied by a physical shrinking of the human brain.

There is no simple cause of AD, but something that correlates with AD is Amyloid Beta Protein (amyloid). This is because amyloid accumulation is consistent with structural and functional brain changes that are consistent with AD [2]. Amyloid’s detrimental effect is thought to occur when it builds up into plaques and blocks neural junctions or synapses [1]. Currently, amyloid can be seen through Positron Emission Tomography (PET). PET uses gamma rays and tracers for imaging, and there is one particular tracer called Pittsburgh Compound B (PiB) that can allow scientists to detect amyloid in the brain.

Currently, there is an unmet need for early AD detection. It is estimated that early detection of AD could nearly halve the number of people with clinical AD [2]. This is because currently, AD is not a disease that can be eliminated or cured. With current drugs, its progression can only be slowed down. Unfortunately, once clinical signs of AD are noticed, the patient is already physiologically in the dementia phase. An alternative approach to detecting AD is by measuring amyloid levels. This approach is used because amyloid spikes to abnormal levels while the patient is still in the preclinical phase of AD. Figure 1. below shows the difference between detecting abnormal amyloid levels and abnormal clinical signs in relation to the progression of AD.

Figure 1. shows how measuring amyloid levels frequently can be a good way of detecting AD early. Unfortunately, frequent screening for amyloid using PET cannot be performed. This is because PET scans are expensive and radioactive. A much better imaging alternative would be to use Magnetic Resonance Imaging (MRI). MRI is cheaper and it relies on magnetism to obtain its images, so it is not radioactive. Unfortunately, there is nothing like PiB, the radioactive tracer in PET that images amyloid, in MRI.

OBJECTIVE
The primary objective of this study is to write an algorithm that uses MRI images as an input and outputs the same result as the PiB PET scan. The PiB PET scan is not usable as a frequent scanning method for amyloid, but it can still operate as the ground truth for amyloid imaging.

HYPOTHESIS/SUCCESS CRITERIA
Our hypothesis is that an algorithm using MRI images as an input can effectively replace PiB PET scans by predicting the outcome of the PiB PET scan. This has not been done before because there is nothing linking MRI to amyloid deposition. We are attempting to not “see” amyloid with MRI. We are attempting to use MRI to predict the PiB PET scan image of amyloid, which would allow MRI to “see” amyloid through the algorithm. Using different MRI modalities, in other words, being able to take multiple, different scans of the same brain each having different data, we are able to take advantage of a massive amount of data to implement machine learning algorithms to “match” the MRI images to the ground truth PiB PET scan.

Assessing the accuracy of the algorithm is not the main success criteria. This is a methods study, so the success of the algorithm will be determined in a future study. We are successful if we develop the algorithm and assess that it has the potential to predict the results of the PiB PET scans. This assessment will be performed using correlational coefficients.

METHODS
All of the work done using the MRI images, PiB PET scan, and algorithm was performed in Matlab. All images used are from the Klunk database in the Geriatric Psychiatry.
Neuroimaging Laboratory (GPN). Six different MRI modalities were used as inputs to the algorithm: Hires, Flair, MD (diffusion), PD, SWI, and T2. The PET scan was PiB.

First, the images were processed, then features were extracted, then within subject analysis was performed, and lastly between subjects analysis was conducted. For image processing, MRI modalities needed to be compared to the PET scan voxel to voxel. First, the PiB images were flipped to the proper orientation. Next, the MRI images were coregistered to the PiB image using the Statistical Parametric Mapping (SPM) add on in Matlab. Coregistering the images manipulates the MRI images so that they are in the same physical space as the PiB image so that they are able to be compared voxel to voxel. Then, the MRI images are segmented and skull stripped using SPM, because we are only interested in using the grey matter for this study (PiB only has meaningful information in grey matter). Lastly, the images are normalized so that the brightness values of the voxels are comparable between images.

Now that the images can be compared, features need to be extracted from the images. Features are the physical, quantifiable properties of images. Some examples of features are image intensity, which is the brightness of the voxels, and various Gabor filters, which quantify edge detection.

The link between the MRI images and PiB PET scan is found using a form a linear regression, \( y = mx \), where “\( y \)” is the PiB image’s amyloid values, “\( x \)” is the set of feature values from each of the MRI modalities, and “\( m \)” is the set of values that links the MRI modalities’ feature values with the PiB amyloid values. Simple linear regression does not work due to the size of the data set. Since there are 6 MRI image modalities, each of which with 22 features, as well as roughly 100,000 voxels per subject (depending on the size of their head), the “\( x \)” matrix is a 100,000 x 132 matrix, so there are potentially 13.2 million data points.

The method to find the “\( m \)” values is a form of the Least Absolute Shrinkage and Selection Operator (LASSO) algorithm called Elastic Net. This algorithm eliminates features that are too highly correlated with other features. This happens frequently, since the same features are being applied to different MRI modalities, which have some of the same properties. The Elastic Net algorithm has parameters that were optimized using code written in Matlab. The output of this code is the algorithm specific to one subject. This code was extrapolated to other subjects using a method called Canonical Correlation Analysis (CCA), which is outside the scope of this paper.

RESULTS

The effectiveness of the within subject algorithm to predict amyloid deposition was evaluated using the Concordance Correlation Coefficient (CCC), and the Pearson Correlation Coefficient (R). CCC measures the agreement between two variables, and R measures the linear dependence of two variables. The two variables being compared are the predicted PiB values from the algorithm, and the actual PiB values from the PET scan. Results from a group of subjects are shown in figure 2.

Figure 2. The CCC and R values comparing PiB predicted and PiB actual for a group of subjects.

DISCUSSION

The mean values of CCC and R from the results indicate that there is a moderately strong correlation between the PiB predicted by the algorithm, and the actual PiB value. After being extrapolated between subjects, the algorithm still functions with promising results (outside the scope of this paper). The effectiveness of the algorithm developed in this study will be tested in a future study. If the algorithm is successful in predicting the results of PiB PET scans, then the algorithm can theoretically be used clinically. An aging patient who is at risk for AD could get MRI scans, and the algorithm could be applied to predict the amyloid deposition in the patient. If the amyloid levels are abnormal, then the patient will be told they are potentially in the preclinical phase of AD, and they will be frequently screened and perhaps get started on an AD prevention program.

An important thing to note is that this is a methods paper, and therefore the methods can be applied outside the scope of the intended clinical use. For example, the methods described in this study are currently being applied in another GPN study. The study requires coronal T2 images, but the GPN only has axial T2 images, so the algorithm is being used to predict the coronal T2 images using the axial T2 images (and other information). In general, this study presents a machine learning, image analysis approach to identifying AD for early treatment, and can be applied to many other facets of imaging based research.

REFERENCES