The Detection of Alzheimer’s Disease: A Literature Review and Case Study

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Abstract

Alzheimer’s disease is a neurological disease that affects memory and the livelihood of the people that are diagnosed with it. Many different imaging modalities have been used to help diagnose the disease. A few of them include: magnetic resonance imaging, positron emission tomography, computed tomography, magnetic resonance spectroscopy, and functional magnetic resonance imaging. Each of these modalities offers something different towards the detection and possible treatments for Alzheimer’s disease.
Introduction

“Alzheimer’s disease is a neurodegenerative disease that affects one out of every 10
individuals over the age of 65” (Diamond et al., 2007, p. 1331), and it “affects about 50-70 per
cent of people who suffer from dementia” (Pah-Lavan, 2006, p.4). Alzheimer’s disease (AD)
was named after the German psychiatrist and pathologist Alois Alzheimer after he examined a
female patient (post mortem) in 1906 that had died at age 51 after having severe memory
problems, confusion, and difficulty understanding questions. Alzheimer reported two common
abnormalities in the brain of this patient, “1. Dense layers of protein deposited outside and
between the nerve cells. 2. Areas of damaged nerve fibers, inside the nerve cells, which instead
of being straight had become tangled” (Pah-Lavan, 2006, p. 8). Moreover, these plaques and
tangles have been used to help diagnose AD.

“Amyloid plaques are sticky patches formed by insoluble proteins (Beta Amyloid)
surrounded by the debris of dying nerve cells” (Pah-Lavan, 2006, p. 6). Amyloid plaques can be
present with the normal aging process. “Neurofibrillary tangles result from alteration of a protein
called tau, which helps support nerve cell structure” (Pah-Lavan, 2006, p. 6). In AD, patients
have a lot of plaques and tangles that are found. When there are high levels of beta amyloid there
are generally reduced levels of acetylcholine. Acetylcholine is a neurotransmitter that a normal,
healthy brain relies upon very heavily. When Acetylcholine levels fall too low in AD patients
then memory and other brain functions become impaired. Even though we know more about the
brain now then when Alois Alzheimer existed, we still don’t know the cause of dementia.

According to the Alzheimer’s Association there are 3 phases of AD: preclinical, mild
cognitive impairment due to AD, and dementia due to AD. Preclinical AD includes
“Measureable changes in biomarkers (such as brain imaging and spinal fluid chemistry) that indicate the very earliest signs of disease, before outward symptoms are visible” (Pies, 2012, p. 24). Mild cognitive impairment (MCI) due to AD also includes “mild changes in memory and thinking abilities that are evident-enough to be noticed and measured- but are not accompanied by impairment that compromises everyday activities and functioning” (Pies, 2012, p. 24).

Dementia due to AD involves “cognitive and behavioral symptoms that are present and are of sufficient severity to impair the patient’s ability to function in daily life” (Pies, 2012, p. 24). The symptoms of AD vary between patients, and it often depends on the phase of the disease that they are in. However there are some common symptoms in all AD patients such as, depression, delusions, hallucinations, and behavioral disturbances. These symptoms tend to progress as the disease progresses. The patient’s anxiety and frustrations build upon each other as they become more frustrated with themselves at not being able to remember normal everyday things. As the disease continues to progress the patient becomes more secluded from others because of their increasing uncertainty. After a while the patient becomes severely dependant on others. They will eventually die because their body becomes unable to fight infections or regulate normal functions.

Even with all the symptoms and signs of AD, it can only be 100% diagnosed after the patient dies by examining the brain. According to Pah-Lavan (2006)

…. a person who has dementia whose illness has started slowly and has progressed gradually, has no sign of or risk factor for stroke, on blood tests shows no evidence of thyroid deficiency or vitamin deficiency or no other abnormalities and whose CT scan does not reveal any intracranial bleeding or brain tumor can be assumed with over 90 per cent confidence to be suffering from AD (p. 8).
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Even with a ninety percent confidence rate there are still tests that can be used to improve that rate over time.

**Literature Review**

**Evolution of Early Detection of Alzheimer’s Disease**

Some of the earlier tests that were established for AD are Computed Tomography (CT) scans, structural Magnetic Resonance Imaging (MRI), and neuropsychological tests. CT scans were used to look for atrophy of the brain, and increased ventricle size. It was believed at first that cerebral atrophy was significantly greater in patients with AD than those without. However it was discovered later that healthy people also have cerebral atrophy. Patients with dementia may not have cerebral atrophy at least in the early stages of the disease. From these findings it was determined that it can be difficult to distinguish between a healthy elderly patient and a patient with dementia. Therefore, CT scans have been deemed as clinically useless in the primary diagnosis of AD.

After CT was discredited, questions were raised about using structural MRI. Fleisher et al. (2008) performed a study to evaluate “predictive models of progression from amnestic MCI (mild cognitive impairment) to AD to assess the added benefit of structural MRI data compared to clinical measures alone” (p.192). Structural MRI measures the “medial temporal lobe structures, whole brain volumes, and ventricular volumes” (Fleisher et al., 2008, p. 192). This turned out similar to the CT scans that were done. It became hard to distinguish between AD patient’s brain atrophy and healthy patient’s brain atrophy. “Though we didn’t find MRI structural measures, compared to cognitive measures, to be necessary for predicting AD in subjects with moderate degrees of MCI, this doesn’t necessarily repudiate the utility of anatomic
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MRI as a potential biomarker for AD” (Fleisher et al., 2008, p. 196). Therefore MRI can be helpful in differentiating between MCI and AD.

**Neuropsychological Tests**

Neuropsychological tests are used to determine the specific type and level of cognitive impairment that the patient has. Schmand (2011) conducted a study using various types of neuropsychological tests. A few of them that were used include, “Rey Auditory Verbal Learning Test, category fluency, Trial Making Test parts A and B, Digit Symbol Substitution Test, Digit Span forward and backward, and the Clock Drawing task” (Schmand, Eikelenboom, & van Gool, 2011, p. 1706). These tests are summarized as follows:

**The Rey Auditory Verbal Learning and Category Fluency Tests**

The Rey Auditory Verbal Learning Test uses lists to see how patients recall words. Patients are given a list of 15 unrelated words that are repeated over 5 different trials. Then another list of 15 unrelated words was given to them. The patient then has to repeat the original list of 15 words and then again after 30 minutes. The test takes about 10 to 15 minutes with 30 minute intervals. The category fluency test is a psychological test where patients have to say as many words as possible in a certain category within about 60 seconds. The categories can be animals, fruits, vegetables, or words that begin with a particular letter of the alphabet.

**The Trail Making Test**

The Trail Making Test is used to measure the function of the brain in general. The test has two parts: Part A uses a series of numbers that the patient has to connect in sequential order (similar to a dot-to-dot). Part B uses a series of numbers and letters that the patient has to alternately connect letters and numbers in sequential order. Part A and Part B are scored
separately and measure the amount of time, in seconds, that it takes to finish the trails. The longer the completion time is the more it suggests there is a neurological deficit.

**The Digit Symbol Substitution Test and Clock Drawing Task**

The Digit Symbol Substitution Test has a list of numbers that correspond to different symbols. The patient is asked to match symbols to their corresponding numbers. The test has only a short amount of time so this makes the test incredibly difficult for the patient. The Clock Drawing task has patients draw a face of a clock with all the numbers and then they have to draw the clock hands for a particular time. This task is used for patients that have a hard time perceiving objects correctly along with how the objects correspond with other objects.

**Summary of Tests**

All of these tests help to show the memory recall of a patient and the possible areas where the patient may be deficient. Using these tests can be helpful to determine the types of treatment plans that can be used, however neuropsychological tests alone are not helpful in detecting early AD. Trials were then conducted combining neuropsychological tests with Positron Emission Tomography (PET) scans.

**Positron Emission Tomography (PET) Scans**

In addition, PET uses biochemical means of acquiring images rather than structural information. “PET technology involves the detection of photons by a camera-like device that records the levels of radioactivity originating from given points in space and time. Positron-emitting radioisotopes are used to generate the radioactivity” (Gill, Rochon, Guttman, & Laupacis, 2003, p. 258). PET scan measures different compounds in the brain, in the case of AD, PET is used to measure fluorodeoxyglucose (FDG). FDG can compete with glucose for absorption and metabolism in neurons. With dementia the neurons intake of glucose and FDG
becomes impaired. “By highlighting regions of decreased FDG uptake, PET can theoretically aid in the diagnosis of dementia, even in the absence of the gross structural damage detected by other imaging techniques such as CT or magnetic resonance imaging” (Gill et al., 2003, p. 258).

Some studies have been conducted to examine patients that are deemed amyloid positive or amyloid negative. Amyloid positive patients are said to be dominant carriers of AD, while amyloid negative patients are not. Jack et al. (2010) performed this kind of study and they found, “amyloid positive subjects with mild cognitive impairment were much more likely to progress to a clinical diagnosis of Alzheimer’s disease than amyloid negative subjects with mild cognitive impairment” (p. 3340). PET has been used extensively to study AD, and it is evolving into an effective tool for early diagnosis. PET has been used to detect people at risk for AD even before the symptoms start. PET is a very expensive scan to perform although it has been the most useful as far as providing visual images in the detection of AD. There are some new advances in technology that can not only detect AD, but possibly explain the symptoms and how the disease works.

Case Report

Case #1

According to, Ashford et al. (2011) conducted an experiment to determine whether adding magnetic resonance spectroscopy (MRS) to traditional MRI would help improve the detection of early AD. MRI measures the hippocampus and entorhinal cortex volume changes; however because of the complexity of AD MRI may not be sufficient enough on its own during the early stages of the disease. MRS works more at the chemical level and there are no images that are produced.
“Thirty patients with Alzheimer’s disease and 36 healthy volunteers were included in this study who had both MRI and hippocampal MRS” (Ashford et al., 2011, p. 308). The hippocampal region was chosen because it is one of the earliest sites that show change with AD. The data was broken up into three models, MRS, MRI, and MRS and MRI combined. Some of the measureable metabolites for MRS include N-acetylaspartate (a marker for neuronal density and/or function), the lactate and lipid groups (lactic acid and lipids that are released with cell destruction or synthesized in necrosis), and choline (as seen with tumors).

The results of the study showed that MRI had a positive likelihood ratio (LR+) of 5, MRS had a LR+ of 6, and MRI and MRS combined had a LR+ of 17. Likelihood ratio is the probability of a disease and the positive means that the disease is present. “Combining the automated MRS measures with MRI measures more than doubled the positive likelihood ratio from 6 to 17 which highlights the importance of MRS measures as a valuable complement to MRI in the diagnosis of Alzheimer’s disease” (Ashford et al., 2011, p. 316). One reason why adding MRS to MRI added more value is because they measure different things, such as brain atrophy and metabolic changes. Adding visual images to metabolic data can improve diagnosing AD at an earlier stage in the disease.

Case #2

Furthermore, Diamond et al. (2007) conducted a study to see if functional MRI (fMRI) can be used to help treat AD patients. They had 29 participants that had been diagnosed with probable AD. All of the subjects had a previous CT scan or MRI scan to make sure they did not have any lesions or anything else that does not correspond with AD. They also used neuropsychological tests at the baseline visit to see where each participant was at in the disease.
The fMRI test used pictures of unfamiliar faces to the participants and gave them fictional names that were common from 1910 to the present. The pictures were digital and in color and were placed on a black background with the names printed in white below the picture. Before the tests began all of the subjects were informed on exactly what they would have to do and how each test was going to work. There were three different ways they performed this test, by showing the pictures and names only once, showing two face-name pairs that are repeated in alternate order, and showing a white cross on a black background to look at the baseline of focused visual attention. “During each fMRI scan subjects were shown two Novel blocks (seven face-name pairs per block, each shown for 5 seconds) and two Repeated blocks of identical length, separated by a 25-second period of fixation” (Diamond et al., 2007, p. 1333). The entire scan included six runs and each lasted a little over four minutes. Over all of the six runs, “subjects saw 84 Novel face-name pairs and viewed each of the two Repeated face-name pairs 42 times” (Diamond et al., 2007, p. 1333). There are certain areas of the brain that the technologist is looking at with fMRI.

Several left sided regions of the brain are activated with fMRI that are correlated with verbal memory performance. The regions included the left inferior prefrontal cortex, left superior temporal gyrus, left fusiform gyrus, and the left hippocampus region. In a broader sense the study found that “fMRI activation during face-name encoding bears a significant relationship to performance on memory outcome measures supports the potential utility of fMRI to investigate regional mechanisms of treatment response in clinical trials of novel therapies for AD” (Diamond et al., 2007, p. 1337). This shows that fMRI can be useful in determining treatments for AD.

Discussion
Both of these new imaging modalities provide more information toward diagnosing and finding treatments for AD. MRS is becoming more frequently used and can be equipped to MRI machines. MRS uses Hunter’s angle to read the graphs that are produced. As stated earlier MRS measures levels of N-acetyl aspartate (the good), Choline (the bad), and Lactate and lipids (the ugly). These three compounds make up the points on Hunter’s angle. (See Figure 1) The N-acetyl aspartate is the one that deals with AD. When this peak is not the highest peak on Hunter’s angle, it indicates there is some neural damage that could correlate to AD. Choline is associated with tumors which generally show an increase in this compound. The lactate and lipid group has a double peak on the Hunter’s angle, and are associated with necrotic tumors, strokes, and abscess. Hunter’s angle measures these three metabolites at their peaks and when they form a 45 degree angle then the reading is normal. MRS has been a great noninvasive way to look at AD metabolically before visual symptoms and abnormalities are shown.

Moreover, functional MRI has become used more because it shows what is happening in the brain when the patient is doing something such as, looking at a picture and trying to remember who that person is or moving their fingers in a certain pattern that they are asked to remember. Functional MRI studies have included blood oxygenation level–dependent (BOLD) imaging, which uses the changes in the level of oxygenated blood in capillary beds to show the regions of brain activation. In AD, fMRI activation in the hippocampal and prefrontal regions is decreased. (See Figure 2)

Even with all of these advances in technology, AD is still not 100% detectable and there still has not been a cure found. With these advances physicians can detect signs of AD earlier and be able to help treat some of the symptoms. AD is a very complex disease and it is
devastating to those that are affected by it. However, by catching it early on with the use of fMRI, MRS, and PET then hopefully a cure is in sight.
Figures

**Figure 1.** MRI images coupled with MRS graphs that show the difference between a healthy brain and one affected by AD. Healthy brain is on the right and the AD brain is on the left.


![MRI images with MRS graphs](image1)

**Figure 2.** fMRI scan of a normal brain and a brain with AD.


![fMRI scan of normal and AD brain](image2)
References


