Regional metabolic activity and cognitive ability in AD patients

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Abstract

Alzheimer's Disease is a disease that causes memory loss, cognitive impairment and problems with behavior. It affects approximately 5 million people in the US. There is no identified cure, nor an identified cause of this disease. The purpose of the study was to identify potential causes of the disease, and to examine the changes that occur in the brain of an AD patient. To examine such elements, this study required the use of PET scans, which conveyed the region of hypometabolism, indicating the extremity of AD based on how many impaired lobes there were. 40 patients were also assessed with cognitive assessments to see if a specific grouping of people with AD regional hypometabolism would score better or worse. Also, education level was considered as a variable when looking into the extremity of the disease. Findings showed that the group of patients with damage only to the parietal region scored the highest on a specific cognitive assessment, known as a literal fluency test. However, for other tests, such as the MMSE and the SAC, the scores did not prove the hypothesis that the group of patients with least number of damage lobes scored the highest. In respect to education level, the group of patients with the highest level of education was composed of those with the least amount of cognitive impairment, indicating that education level may play a dominant role in the occurrence and extent of AD. This study shows what occurs in various regions of the brain of an AD patient and it shows that higher education level may reduce the extent of this disease.

Review of Literature

Alzheimer's Disease has become a major issue in every region of the United States of America as it affects more than 4.5 million Americans and continues to cause more and more people to suffer (Bellenir, 2008). One major reason that this disease is so widespread is because the greatest risk factor is aging—at the age of 60 people become even more susceptible to developing AD (Bellenir, 2008). However, the reason that this disease is so detrimental to one's health is because it affects the parts of the brain that control memory, social behavior, language, reasoning and often a person's abilities to perform everyday ordinary functions (CDC).

Approximately ten years ago, the American Academy of Neurology recommended that brain imaging be implemented when dealing with potential dementia, or Alzheimer's Disease (AD) patients (Roman, 2012). Another issue that came with the discovery of AD was what technology should be used (Khachaturian, 1985). However, it was soon evident that MRI, CT scans, PET scans, and SPECT scans were some of the most promising ways of assessing the presence of Alzheimer's disease (Chapman, 2010). Another predicament included the best way to assess Alzheimer's disease out of these brain-imaging systems as opposed to simply distributing a hand-written neuropsychological test to assess cognitive abilities (Chapman, 2010). CT and MRI scans are used to identify white matter and tissue softness in the brain. PET scans measure overall regional glucose metabolism, while SPECT scans measures the regional cerebral perfusion (Roman, 2012). One relevant issue that is studied with such brain-imaging devices is the

decline in metabolism in the brain, as that is linked with cognitive dysfunction (Silverman, 2001).

Although scientists have not yet found a cause for this disease, it has been noted that those individuals with a higher education level, and who choose to stimulate their brains with crossword puzzles, or other sorts of brain-stimulating activities have a reduced risk (Bellenir, 2008). These activities are useful as they act as cognitive trainers and can actually increase brain metabolism (Belleville, 2012). Also, those who participate in even physical and social activities often have a reduced risk of developing AD; however, even by doing so it is still impossible to distinguish why one particular person develops AD over another person who has nearly the same lifestyle (Bellenir, 2008). Hopefully, with research it will be possible to detect key differences between people who do not develop AD and those who do, and also the changes that occur in the brain that cause one to develop a more extreme case of AD—or perform worse on the neuropsychological tests that assess Alzheimer's Disease.

There is a multitude of ways to assess the prevalence of AD. However, often the only way to actually know is to examine the brain after the patient has died. Certain physical neurological signs of AD include high PET amyloid binding in the brain, decreased brain volume, more tracer retention on the PET scans, more tau protein, hypometabolism, and thinning of the cerebrum (Sperling 2011). Specifically, this disease is characterized by the death of neurons in the brain, which also accounts for the symptom of decreased brain volume. The tau protein that is symptomatic for this disease is actually present in everyone's brain but is of a much greater amount

in an Alzheimer's patient's brain (Gavett et al 2011). Tau is normally regulated by phosphorylation; however in AD patients the tau protein becomes hyperphosphorylated and turns into neurofibrillary tangles (Riemenschneider 2012). Amyloid plaque buildup is another symptom that occurs when there is abnormal folding of the plaques (Swerdlow 2011). Finally, a prime method of detecting AD involves the use of PET scans. Specifically, hypometabolism in AD-like patterns were looked for on PET scans (Sperling 2011). Essentially, the PET scan works by utilizing the biomarker, 18F-FDG to detect AD by using FDG, which mimics glucose in the body, as cells use the FDG for fuel and thus researchers may examine the different patterns of the uptake of these cells to identify an abnormality (Bohnen, 2011). Scientists are now aware that using PET scans is actually a very effective method in indicating AD as it remains crucial to examine regional brain metabolism (Silverman, 2001).

Another part of studying AD is assessing the extents of the disease. Specifically cognitive assessments can be used to test the cognitive abilities of the suspected Alzheimer's Disease patient (Jordan, 2012). In a study with 216 patients, each AD patient was given a neuropsychological test and then scores were further categorized into the appropriate stage of Alzheimer's each patient was in (Chapman 2010).

This research looks at whether the specific area of hypometabolism (as evidenced by a PET scan) has an effect on the cognitive and functional activities in a memory-impaired population? The second research question asseses whether

education level has an effect on the extent of AD (extent will be measured by number of lobes with hypometabolism)?

The hypotheses were that patients with metabolic decline in more lobes will perform worse on the MMSE, SAC, and literal fluency tests. The second hypothesis is that patients with damage to just the parietal region will score higher on these tests. The final hypothesis is people with higher education levels will score better on the tests indicating that they have a less extreme case of AD, as they have fewer damaged lobes.

Methods:

Subjects

Subjects consisted of 30 patients who were diagnosed with Alzheimer's Disease and 10 controls who were tested for Alzheimer's Disease but had negative PET scans, meaning that they did not have AD but were sent to the hospital because they had AD-like symptoms, such as memory loss. Gender was equally divided, as there were a total of 20 female patients and 20 male patients. Regarding the conditions that may have affected the patients' scores on the cognitive ability assessments 7 had sustained a serious head trauma, 27 claimed they suffered from depression, along with 12 who also stated they suffered from anxiety. All 40 patients were sent to the hospital for an AD evaluation because of their symptoms. The other 10 subjects were diagnosed with cognitive impairment, and AD-like symptoms, among other health conditions. These patients were ordered to be evaluated because of the diagnosis they had received—the majority was simply

diagnosed with AD, while others were diagnosed with as having cognitive impairment, symptoms of dementia/posttraumatic dementia, among other health conditions.

PET scans

PET scans were performed by using a PET biomarker known as 18F-FDG which includes a radionuclide combined with fluorodeoxyglucose, or FDG, which imitates glucose in the brain. The radionuclide is attached to a glucose molecule to achieve this effect on the brain. The amount of uptake of FDG is a strong indicator as to the extent of the disease. Figure 1 conveys an example of the PET scan of an AD patient; the arrows specify the areas of hypometabolism.

Procedures

PET scans had been performed on approximately 40 patients. The patients were also asked to complete a cognitive assessment. Then, medical records were extracted from patient files. This information was input onto Excel and scrutinized for correlations.

Data Analysis

Data on the regional hypometabolism in the brain of the AD patients was input into an Excel file by first and last name, age at time of PET scan, whether or not the PET scan was positive, specific area of metabolic decline in the brain, and scores on cognitive and functional ability assessments. Then, information dealing with area of regional metabolic decline was binarized; 0 represented no metabolic decline in that area, while 1 represented that there was indeed metabolic decline in that area. Finally, after binarizing these areas, it was necessary to separate the

patients that only had damage in one area, or those that had it in two areas, and so on. Essentially, this process was just making different categories based on the quantity of lobes damaged and which lobes were damaged. After doing so bar graphs were implemented, which consisted of the "1"s in each of the separate categories and seeing if there was a correlation with the people who had damage in that area and the scores on certain assessments.

Results

Figure 1 shows a PET scan demonstrating bilateral medial temporal lobe and bilateral parietal lobe hypometabolism consistent with Alzheimer's Disease.

Figure 1: PET scan of a subject with Alzheimer's Disease
(Arrows portray area of hypometabolism)

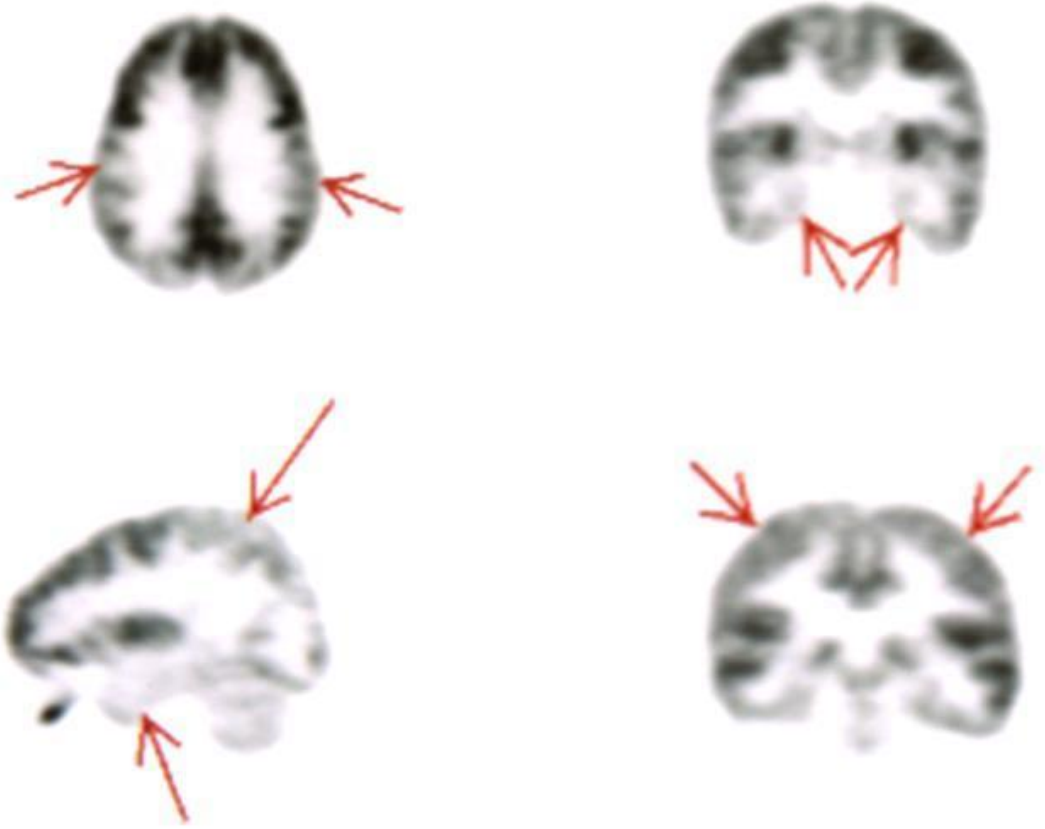
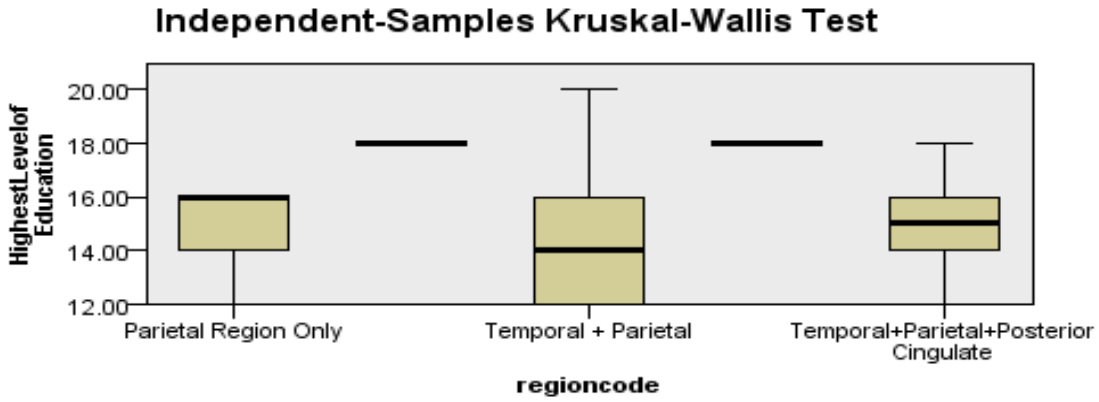


Figure 2: Level of Education and region of hypometabolism
(Please note that the region code indicates the regions of hypometabolism.)



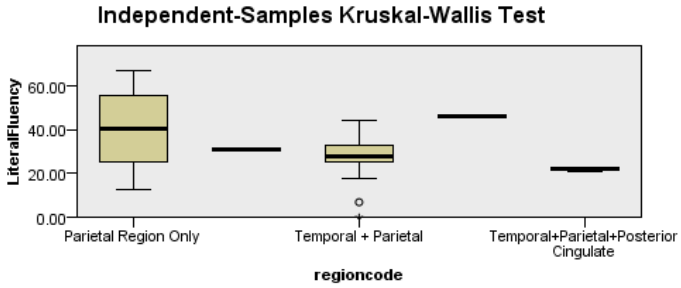
Total N	28
Test Statistic	4.237
Degrees of Freedom	4
Asymptotic Sig. (2-sided test)	.375

Figure 2 shows level of education was another variable was tested. This time it was assessed by average years of education for each group of people with regional hypometabolism in the brain. The dark lines on this graph represent the average "rank" for each category. The test takes all the values and orders them (ranks them), and then it pulls out the average for each category. Therefore, the chart

shows that the patients with the highest level of education displayed hypometabolism in the fewest regions of the brain. The people with the highest level of education had the least amount of hypometabolism decline in the brain, meaning they had the least extreme cases of this disease. This is to be expected as people with damage only in the parietal region seemingly had the least regional hypometabolism because it was only in two lobes. Meanwhile, people with damage to both temporal and parietal lobes seemed to be composed of patients with the lowest level of education; the group with all of the brain lobes was actually composed of people with a slightly higher level of education than those in the group of damaged temporal and parietal lobes. However, this graph ultimately proves that education level is not an accurate indicator of later cognitive impairments, being that the group with hypometabolism in all lobes of the brain performed significantly worse on most cognitive and functional tests, despite the average level of education. Also, the p value is .375 and therefore it is not significant.

As evident in Fig. 3, for the most part the group that had damage bilaterally in the temporal, parietal and the additional posterior cingulate performed significantly worse on the cognitive tests. The dark lines on this graph represent the average "rank" for each category. The test takes all the values and orders them (ranks them), and then it pulls out the average for each category. Therefore, this graph shows that people with damage in the four main lobes but not the posterior cingulate performed slightly better, and those with just damage to the parietal region performed the best. This literal fluency test essentially assesed a different set of abilities in the brain—mainly consisting of being able to list names of fruits for an example, or being able to list the words in a specific group.

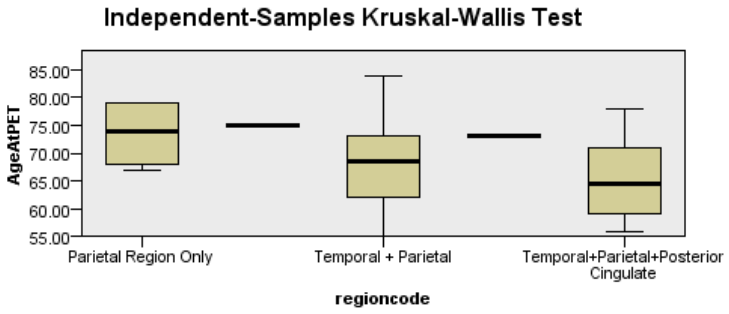
Fig. 3: Literal fluency test scores and region of hypometabolism



Total N	24
Test Statistic	6.469
Degrees of Freedom	4
Asymptotic Sig. (2-sided test)	.167

1. The test statistic is adjusted for ties.
2. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

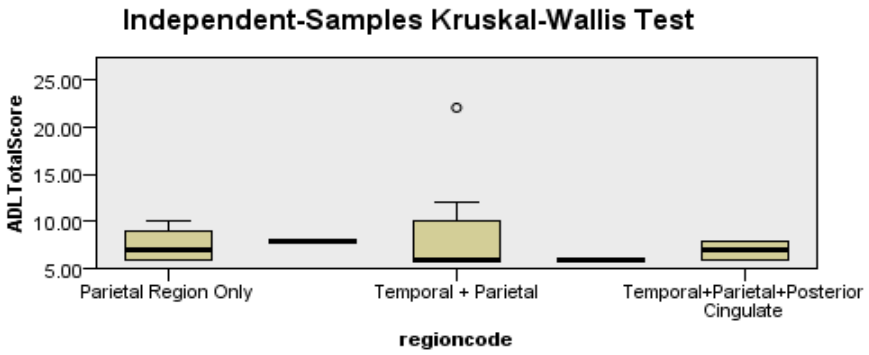
Fig. 4: Age (at time PET scan was taken)
and region of hypometabolism



Total N	30
Test Statistic	4.421
Degrees of Freedom	4
Asymptotic Sig. (2-sided test)	.352

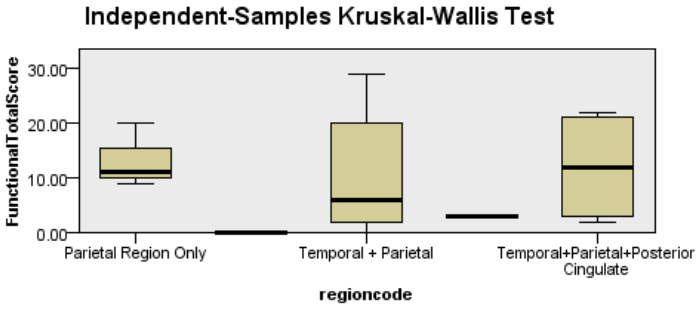
Another contributing factor and what is perhaps also defined as an inevitable contributor to Alzheimer's Disease is age. For this project, the age at the time of PET scan was looked at and the region of hypometabolism to see if age had an influence on the amount of lobes in which there was hypometabolism. Figure 4 displays that the people with the fewest damaged lobes were composed of the oldest people. Meanwhile, the group with the temporal lobe included and the group with the posterior cingulate added as well were composed of even younger patients. This indicates that age did not affect the overall outcome of this study.

Fig. 5: ADL total score and region of hypometabolism



Total N	29
Test Statistic	1.747
Degrees of Freedom	4
Asymptotic Sig. (2-sided test)	.782

Fig. 6: Functional total score and region of hypometabolism



Total N	28
Test Statistic	3.274
Degrees of Freedom	4
Asymptotic Sig. (2-sided test)	.513

In Fig. 5 and Fig. 6, it is not evident that hypometabolism in the temporal region along with the parietal region did not have as much of an effect on ADL scores or functional ability scores. Also, in Figure 5 and Figure 6, the data was insignificant as the p value was .782. For both tests it is best for the patients to score lower as that indicates less reliance on others for help and more capability of accomplishing activities by oneself. This is very relevant because it shows that the subjects with damage in the temporal and parietal regions were more independent compared to those with damage in other areas.

Discussion

As seen in a study reported by the Society of Nuclear Medicine, a similar study was conducted in which AD patients had received a PET scan and the radionuclide uptake was recorded (2012). Major differences between these studies are that much greater sample size that was used and the type of radionuclide

utilized. As this study used FDG to mimic the effect of glucose, the Society of Nuclear Medicine study had used C-11, which allows for the ability to see amyloid-binding. This study does not confirm the findings in the Society of Nuclear Medicine study probably because of the small sample size.

In the Small et al. 2000 study, very similar things were done—both this study and the Small et al 2000 study used PET scans to examine the metabolism in the brain. However, the 2000 study consisted of a larger sample size, which therefore led to more accurate results; the sample size used in that study was composed of both those who had AD and normal subjects with no cognitive impairment. Meanwhile, in this study, there was no group of "normal" subjects, as each group had cognitive impairment to the extent that they needed to be evaluated for AD. The results in the 2000 study were fairly similar to the results of this study, as both studies proved that metabolism in the brain plays a dominant role on the onset of AD; additionally, in the 2000 study which examined Alzheimer's disease more in-depth, the study also proved that genetic factors plays a large role as well.

Conclusion

Future research should consist of more subjects, that way the groups of patients with damage in the different lobes will each be composed of more people, which may result in more significant results and stronger/more accurate correlations. Future research should also examine the amount of white matter in the brain, which could be detected by sensor imaging. Also, more specific research on the different areas of the brain, not only the lobes, would add to this topic.

Major limitations for this project were the small sample size and the limited data. Additionally, the PET scans generally did not convey too much information. The main thing that was obtained from these scans was the region of metabolic decline. If, however, there was more information about the condition of the brain, and other factors, such as genes, and diet habits, perhaps finding out why and how to prevent Alzheimer's Disease would be more promising.

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("Alzheimer's Association")

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