Alzheimer's Disease: Structural, Functional, and Molecular Imaging

Briana Polt

Clarkson College

Abstract

Ever since German physician Alois Alzheimer came across this perplexing disease in 1906, later named after the physician, Alzheimer's disease (AD) is still a mystery today (Alzheimer's Association, 2016). Over the past century, numerous scientists and inventors have been devoted to finding a cure for this disease (Alzheimer's Association, 2016). A promising area of research in radiologic neuroimaging procedures may have the potential to be the key to unlocking this mystery. These radiologic neuroimaging procedures can be further divided into structural, functional, and molecular imaging. In regards to structural imaging, computed tomography (CT) and magnetic resonance imaging (MRI) have been proven to be the top line research tools used in this ongoing research process. Functional MRI (fMRI) and fluoro-deoxy-d-glucose positron emission tomography (FDG PET) analyze cell activities in functional imaging. Lastly, molecular imaging utilizes PET and single photon emission computed tomography (SPECT) to follow the course of radioactive tracers to discover chemical changes of the brain in relation to AD. The ability to identify AD through radiographic neuroimaging procedures, monitor it through its progression, and understand the alterations of the brain's structures are some of the monumental research achievements. Each study performed adds more promising information on how to combat this disease.

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Introduction

Alzheimer's disease is a slow destroyer, progressively deteriorating the brain's structural and functional abilities (National Institute on Aging, 2015). AD attacks healthy neurons in the brain, which leads to an abnormal abundance of amyloid plaques, neurofibrillary tangles, and a loss of connection between neurons (National Institute on Aging, 2015). Amyloid plaques are present in a healthy aging brain, but are abnormally abundant in a brain with AD. Amyloid plaques can be found between nerve cells of the brain, and can consist of toxic protein peptide fragments called beta-amyloids (β-amyloid) (National Institute on Aging, 2015). Neurofibrillary tangles result from tau, a chief protein of the tangles, unbinding from microtubules and recombining to form other tau threads (National Institute on Aging, 2015). The loss of connection between neurons is a result of the damage incurred by the amyloid plaques and neurofibrillary tangles, with brain atrophy also being a consequence (National Institute on Aging, 2015). There is still uncertainty if the amyloid plaques and neurofibrillary tangles cause AD or are merely a result of this disease infiltrating the brain (National Institute on Aging, 2015).

Alzheimer's disease affects nearly 5.3 million people in the United States, with another person being diagnosed with this disease every 68 seconds. By 2050, this rate of affliction will increase to every 33 seconds (Reynolds, 2013). The priority of finding a cure for this devastating disease is at its highest urgency. The most promising beginning of research is with radiologic neuroimaging procedures.

Radiologic neuroimaging procedures are the top line research tools used for the evaluation of AD. Alzheimer's disease research has been revitalized with the help of

three radiologic neuroimaging procedures. Structural imaging is one of three research tools used to help diagnose AD. The second aspect allowing further research in AD is functional imaging. Molecular imaging is the third and final imaging research tool used to help monitor the progression of AD (Reynolds, 2013). According to the National Institute on Aging (2015), radiologic neuroimaging procedures have become "one of the most exciting areas of ongoing research" (para. 10) over the past decade. These neuroimaging procedures are merely research tools in helping to identify AD at the very first stage of this disease, and helping to monitor its progression (National Institute on Aging, 2015).

Structural Imaging

Structural imaging, one of three research tools, is used to assess the brain's structures and their atrophy rates in relation to diagnosing AD. With the help of CT and MRI, researchers are able to visualize the brain's shape and volume under these structural imaging modalities (Reynolds, 2013). CT and MRI focus on the atrophy of the medial temporal lobe of the brain because this is the place where neuropathologic changes first start to occur. The medial temporal lobe is made up of the hippocampus, entorhinal cortex, parahippocampal gyrus, and the amygdala (Reynolds, 2013).

CT is considered to be one of the most effective modalities in diagnosing AD (Reynolds, 2013). CT helps diagnose AD by assessing the brain's atrophy rates and brain size over a certain amount of progressed time, in association with cognitive loss. In individuals with AD, the growth of the third and lateral ventricles and the expansion of the sulci and perihippocampal fissure can be observed with the help of CT (Reynolds, 2013). The dilation of the perihippocampal fissure is a foretell sign of AD, with a

diagnosing accuracy rate of 91% (Reynolds, 2013). These findings were confirmed when a study of 34 AD patients were matched with 20 age appropriate (65-80 years old) control patients without AD. Both groups of patients were imaged under CT, using 5mm slices of the temporal lobe and oriented 20° caudal to the canthomeatal plane (Reynolds, 2013). Resulting from this study was the conclusion that most patients with AD had a mild to severe overall atrophy of the temporal lobe as compared to the group of patients without AD (Reynolds, 2013).

Pineal gland calcification can also be evaluated using CT (Reynolds, 2013). The main function of the pineal gland is the secretion of melatonin, a regulatory hormone of the reproductive system. In patients with AD, the pineal gland is said to calcify, which in turn makes the pineal gland not secrete as much melatonin (Reynolds, 2013). The calcification of the pineal gland can be a biomarker for melatonin deficiency, and possibly AD (Reynolds, 2013). A 2008 study of 279 patients from a memory clinic, with some having AD, and 37 control patients without AD was performed (Reynolds, 2013). The conclusion from this study was patients with AD had a higher degree of pineal calcification than the patients without AD (Reynolds, 2013). Two conclusions about melatonin, due to either a small uncalcified pineal gland or a calcified pineal gland, were also associated with this study: a decrease in melatonin secretion reduces its neuroprotective properties and a decrease in melatonin affects its circadian properties (Reynolds, 2013).

Perfusion CT is used to evaluate cerebral perfusion in individuals with symptoms of dementia (Reynolds, 2013). Although perfusion CT is primarily used to rapidly evaluate patients with stroke symptoms, there is a promising area with perfusion CT

evaluating patients with dementia related diseases. Contrast material is used to highlight cerebral arteries in order to evaluate cerebral blood flow, cerebral blood volume, and the time it takes for the blood to flow through the brain (Reynolds, 2013).

A 2008 perfusion CT study was conducted with 55 dementia individuals (Reynolds, 2013). All participants were evaluated under unenhanced, contrast-enhanced, and perfusion CT's of the head. With perfusion CT, researchers found that the dementia individuals showed reduced cerebral blood flow in the frontal lobe, occipital regions, and basal ganglia, while also concluding a reduction of blood volume in the occipital and temporal regions of the brain and an increased transit time in the basal ganglia (Reynolds, 2013). In conclusion, as the degree of dementia increases, cerebral perfusion decreases (Reynolds, 2013). In the future, these studies could help researchers learn more information on specific regions of the brain to determine the different types and severities of dementia and its related diseases (Reynolds, 2013).

In a 2010 study, a positive interconnection between cerebral blood volume and blood flow in the basal ganglia and the lateral and third ventricles was concluded (Reynolds, 2013). Both perfusion CT and CT volumetry were used with the 48 AD participants (Reynolds, 2013). The outcome of the study resulted in this conclusion: brain atrophy is not directly related to a decrease in cerebral perfusion in the basal ganglia region of the brain, indicating that the structural and functional changes related to AD are not associated (Reynolds, 2013).

Along with CT, structural MRI is also utilized to assess the atrophy and volume of an individual's brain with AD (Johnson, Fox, Sperling, & Klunk, 2012). With structural MRI, researchers are able to identify and measure brain atrophy. One benefit

arising from using structural MRI on patients with AD is its availability and utility. On the flip side, limitations of structural MRI have surfaced (Johnson et al, 2012).

Structural MRI shows the establishment of atrophy in a brain with AD. As with CT, structural MRI shows brain atrophy starting in the medial temporal lobe, more specifically the entorhinal cortex, and then working its way to the hippocampus, amygdala, and parahippocampus (Johnson et al, 2012). Structural MRI has achieved positive atrophic assessments of the medial temporal lobe by distinguishing individuals who will be diagnosed with AD compared to those who will not, with an affirmative prediction rate of nearly 50-70% (Johnson et al, 2012). Differentiating AD from mild cognitive impairment (MCI), dementia with Lewy bodies (DLB), or vascular dementia (VaD) can also be determined by assessing the overall imaging patterns and atrophy rates in other parts of the brain in association to one of the other diseases. The use of MRI for differentiation of MCI, DLB, and VaD is used in clinical practices, but MRI has yet to be used clinically to distinguish AD from other dementias (Johnson et al, 2012).

A benefit associated with structural MRI is its availability and utility in relation to assessing AD. In fact, European and U.S. guidelines suggest that individuals with diminishingly cognitive impairments undergo a structural imaging procedure, either MRI or CT, because of structural imaging's high diagnostic criteria for AD and other dementias (Johnson et al, 2012). MRI is proving to be an essential procedure in diagnosing AD. Although MRI is not as fast as CT, it does not use ionization radiation. MRI uses strong magnets to detect relaxation rates of certain anatomy after being bombarded by radiofrequencies. MRI also has higher resolution volumetric sequence abilities in order to better visualize soft tissue characteristics (Johnson et al., 2012).

Limitations have also come about with the use of structural MRI in assessing AD. Structural MRI does not have the ability to detect molecular pathology, which includes amyloid plaques and neurofibrillary tangles (Johnson et al, 2012). Molecular imaging is used to visualize the molecular pathologies structural MRI cannot. As mentioned before, MRI does not image the body as rapidly as CT, which could be a problem for claustrophobic patients lying in MRI machines for a longer period of time. Lastly, structural imaging cannot assess the functional aspects of the brain; that is where functional imaging takes precedence. Structural imaging cannot be solely used alone to assess and diagnose AD because of the overlap of atrophy patterns that may mimic other dementias (Johnson et al., 2012).

Functional Imaging

Functional imaging is another research tool that is specifically used to analyze certain cell activities within a brain with AD. FDG PET and fMRI are two neuroimaging procedures used to evaluate and measure functional aspects of the brain, such as brain metabolism and synaptic activity (Reynolds, 2013). Resting-state functional magnetic resonance imaging (rs-fMRI) is also utilized in measuring blood oxygen level-dependent (BOLD) MRI signals (Vemuri, Jones, & Jack, 2012).

The utilization of fMRI allows for the evaluation of structures within the lobes of the brain. fMRI can be utilized two ways: during cognitive based tasks or during a resting state (Johnson et al., 2012). The number of fMRI research studies has been relatively small. However, fMRI has found decreased hippocampal activity in individuals with AD due to hippocampal atrophy, but has also found an increase in prefrontal cortical activity (Johnson et al., 2012). This increased activity is said to be a counterbalance mechanism

to the decreased ability of the hippocampus (Johnson et al., 2012). Contrary to previous statements, fMRI studies have also discovered hyperactivity in the medial temporal lobe when at-risk AD individuals performed successful memory trials. This hyperactivity is said to be present only in the early stages of AD, whereas when the disease progresses, the activity does become decreased (Johnson et al., 2012). Researchers are saying this influx in medial temporal lobe activity is a precursor for neuronal failure. Interestingly, regions of the brain with neuronal disconnections overlap the regions of the brain that have high levels of amyloid plaques (Johnson et al., 2012).

As with most technology today, functional imaging as a research tool has some limitations. For those patients who are severely cognitively impaired, fMRI may be troublesome because it is very sensitive to head motion. In this case, rs-fMRI may be more beneficial for severely impaired individuals (Johnson et al., 2012). With rs-fMRI, it measures the variations in blood oxygen level-dependent (BOLD) MRI signals when the brain is in a "resting state," although the brain is never truly resting. rs-fMRI is a fairly new research tool for neuroimaging procedures, but is becoming increasingly popular (Vemuri et al., 2012).

Molecular Imaging

The third research tool used to assist in the diagnosis of AD is molecular imaging. Molecular imaging has provided another noninvasive method for diagnosing AD, along with the help of structural and functional imaging as well. PET and SPECT both use radioactive tracers to measure their uptake and record their routes to demonstrate changes of an AD brain on a cellular and molecular level (Arora & Bhagat, 2016). According to

Arora & Bhagat (2016) the radiotracers that are used in PET and SPECT have to adhere to the following:

> A radiotracer used for neurological diagnostics must have optimal uptake, specific binding, and efficient clearance of the radiotracer. The radiotracer being designed for diagnostics purposes must be of nontoxic and lipophilic nature. It should have a low molecular weight so that it may easily transverse the blood brain barrier in order to enter the brain. The radiotracer should be designed to reduce the incidences of nonspecific binding, should not get metabolized, and should be rapidly cleared from the blood. The binding to its target must be specific and reversible in nature. (para. 29)

Positron emission tomography (PET) uses radiopharmaceuticals, also known as radiotracers, to measure the rate of uptake and decay and to record their routes throughout the brain. Once a radiotracer has passed through the blood brain barrier (BBB), it accrues in a specific area of the brain in accordance to the physiological condition being monitored (Arora & Bhagat, 2016). Positrons are consequentially emitted once the radiotracer starts to decay. The end result is annihilation, which is the production of two gamma rays being emitted from the positron interacting with neuronal electrons. The PET scanner picks up these gamma rays, or positrons, to produce 3-D views of the radiotracer's route through the patient's body (Arora & Bhagat, 2016).

Amyloid PET imaging is used to visualize a normal brain's amyloid plaques and demonstrate how these plaques accumulate in relation to a brain with AD (Johnson et al., 2012). According to a hypothesis, a series of neurodegenerative events occur after the onset of beta-amyloid accumulation in a brain with AD (Kadir et al., 2011). In

accordance to 15 research groups that have performed amyloid PET imaging on AD individuals, 96% of the AD individuals were said to be amyloid positive (Johnson et al., 2012). Suggestions based on why the other 4% were amyloid negative were the AD individuals may have been clinically diagnosed incorrectly with AD, or the AD individuals have not acquired enough amyloid plaques for the sensitive amyloid PET scan to pick up (Johnson et al., 2012). It is in the asymptomatic stage of the cognitively normal elderly that is of utmost importance in discovering treatments for AD. Cerebral β-amyloid accumulation was found in 24% of cognitively normal individuals in another study series from 13 different sites (Johnson et al., 2012).

In 2002, a 53-year-old woman became the first to undergo a PET procedure that used an amyloid tracer, the Pittsburgh Compound B (PiB) (Kadir et al., 2011). Before the PiB amyloid tracer was used, the only way to diagnose AD was by post-mortem analysis of the tissue changes of the brain caused by the disease. The use of the PiB amyloid tracer has opened new doors for the early detection of brain diseases by being able to detect deposits of β-amyloid on PET scans. The Karolinska University Hospital Huddinge in Stockholm, Sweden, started what would become a renowned series of studies from 1999 to 2007 on a 53-year-old woman after she was having trouble with her memory (Kadir et al., 2011). Among the tests taken were CT and SPECT and the first PET scan using a PiB amyloid tracer. Although her CT results came back normal, her SPECT scan found cerebral perfusion in the parietal cortex to be below normal levels (Kadir et al., 2011). After being diagnosed with AD, she underwent clinical assessments every six months, including PET scans using radiotracers 18F-FDG and 11C-PIB at Uppsala Academic Hospital in Sweden. At 56 years of age in February 2002 marked the first time she

underwent the first ever PET scan using the amyloid tracer 11C-PIB in the world. At ages 53, 56, and 58 years old, the patient underwent three 18F-FDG PET scans. The series of three 18F-FDG scans visualized a gradual decrease in cerebral glucose metabolism and an increase in the 18F-FDG tracer uptake, while also depicting a deterioration in cognitive performance as her AD progressed (See Figure 1) (Kadir et al., 2011).

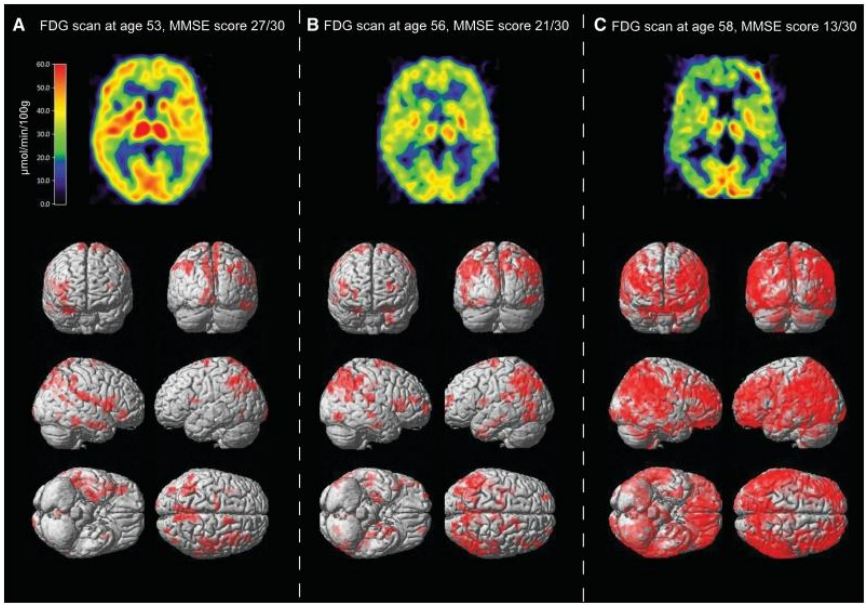

Figure 1. 18F-FDG scans of the brain. Colors represent the rate of radiotracer uptake at 53-years-old (a), 56-years-old (b), and 58-years-old (c). Reprinted from "Positron Emission Tomography Imaging and Clinical Progression in Relation to Molecular Pathology in the First Pittsburgh Compound B Positron Emission Tomography Patient with Alzheimer's Disease," by A. Kadir et al. 2011, *Brain*, *134*(1), para 34. Copyright 2010 by the Oxford University Press.

Single photon emission computed tomography (SPECT), along with PET, assists in the diagnosis of AD by experimenting on both molecular and cellular levels (Arora & Bhagat, 2016). The radioactive tracers used in SPECT are similar to those used in PET, and are visualized through the use of a gamma camera. In PET, gamma rays are indirectly emitted; however, in SPECT, the gamma rays are directly emitted. At the time of decay, one gamma ray is emitted and detected by the gamma camera's rotating configuration (Arora & Bhagat, 2016).

Along with being able to image β-amyloid depositions, SPECT also has the ability to image tau neurofibrillary tangles (Reynolds, 2013). However, because both PET and SPECT radiotracers bind to β-amyloid and tau neurofibrillary tangles, the evaluation of tau-specific aspects of AD are limited. The identification of numerous quinolone by-products has solved this limited ability. These derivatives, such as radioiodinated rhodanin and thiohydantoin (TH2), are able to bind specifically to tau neurofibrillary tangles (Reynolds, 2013).

Conclusion

Structural, functional, and molecular radiologic neuroimaging procedures are becoming the leading areas of research for Alzheimer's disease. While these radiologic neuroimaging procedures are still primarily research tools, the introduction of these procedures into the clinical setting may one day bring about another way for doctors to diagnose and treat Alzheimer's disease. Alzheimer's disease affects millions of people each year. With the help of radiologic neuroimaging procedures, this disease can be researched and evaluated, with the goal of finding a cure.

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