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Molecular Imaging for Investigation of the Pathophysiology of Brain Degeneration and Dementia*

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Abstract

Brain degeneration and dementia are progressive brain disorders, causing memory loss and cognitive impairment due to brain atrophy and pathological lesions caused by abnormal protein deposits. In recent decades, advances in brain molecular imaging, a non-invasive method for imaging the brain, have provided an effective visual representation of brain atrophy in dementia. In this review, we discuss the use of molecular imaging of the brain, specifically positron emission tomography (PET) brain imaging, for facilitating diagnosis and monitoring progression of brain degeneration. To support clinical diagnosis, molecular imaging reveals biomarker features in distinct topographic patterns associated with the binding activity of specific radiopharmaceuticals for visualization of the diverse degenerative disorders. Differential diagnosis of degenerative brain disorders with PET brain imaging can be achieved with high accuracy. The development of a variety of new radiotracers with increased sensitivity and specificity will enhance the use of PET brain imaging to monitor the efficacy of pharmacologic interventions intended to slow the progression of dementia .

Keywords

Molecular imaging, brain degeneration, dementia, PET brain imaging, imaging biomarker.

Contents

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Introduction

In 1906, Dr. Alois Alzheimer described a disorder which would change the course of psychiatry forever [1]. Originally explained as some form of psychological disorder, Alzheimer's disease (AD) presented in a 51-year-old woman who had severe memory impairment, paranoia, confusion, auditory hallucinations and frequent vocal outbursts. She was admitted into the Frankfurt insane asylum after her husband noticed she could no longer remember conversations held moments before or understand where she was in her own house. Her condition continued to decline for the next 4.5 years with no clear indication as to the cause until her death. After she passed away, Alzheimer discovered severe brain atrophy and unusual pathology which could explain the loss in function. In his original report, Alzheimer reported the strange changes that the brain matter seemed to undergo:

> Preparations stained with Bielschowsky's silver method reveal peculiar changes of the neurofibrils. Inside an otherwise apparently still normal cell, first one or more fibrils stand out prominently because of their unusual thickness and unusual ability to take up stain. Later on, there are many such fibrils lying next to each other, all changed in some way. These are eventually seen as clustering together in thick bundles which gradually emerge at the surface of the cell. Finally the nucleus and the cell have fallen apart and only a tangled bundle of fibrils points to the place in which there once was a ganglion cell. [2]

Today, this discovery is understood to be tau proteins accumulating to form neurofibrilary tangles with β-amyloid proteins building up around cells. Furthermore, it has been discovered that these proteins, combined with others, play a role in other degenerative brain diseases such as Parkinson's disease, Pick's disease, Lewy body dementia, Huntington's disease, and more [3]. In each of these diseases, a specific region of the brain begins to atrophy due to the presence of these proteins, however, the exact nature and action of each protein has yet

to be fully discovered. With the advent of new diagnostic technologies, we are able to view internal organs and cell function prior to a patient's death, letting us more accurately diagnose and help a patient who is experiencing symptoms typical of dementia and/or brain degeneration.

In the US alone, AD has an estimated total care cost close to $305 billion USD [4] and an international burden with data from Europe [5] and Asia [6]. Studies have shown that this is not new, as dementia had a relatively high prevalence more than two decades ago [7] and there was no lessened burden of care when managing other chronic illnesses in the hopes of reducing likelihood of the disease [8]. Although the exact numbers are a little unclear, the two most common degenerative brain diseases are Alzheimer's disease and Parkinson's disease with estimated numbers of 40-80 per 1000 people and 10-20 per 1000 people in persons aged 65 and older, respectively [9]–[11]. Outside of financial burden and patient health, caregivers and family members experience psychological difficulty when trying to care for patients [12], but some evidence shows that with early diagnosis and treatment we can help improve quality of life for patients as well as their caregivers [13].

Despite more than a century of scientific and clinical research on Alzheimer's disease (AD) [14] and the approval in the United States of several drugs for the treatment of AD [15], therapies with a major impact on the disease relieving its individual and societal burden have not yet been found [16]. The recent development of a human neural cell culture model of AD [17] has raised hopes for accelerating a path to discovering a cure. However, as the most common of the dementias, AD remains an overwhelming challenge and burden [18], [19] for the persons affected, their caregivers and families, and the communities and public health agencies that must cope with the cost of dementia care (estimated at $604 billion as of 2010 worldwide) which continues to grow due to an increasingly aging population [20]. When including all other forms of dementia, the WHO estimates 55 million people to be affected globally, with a cost of $1.3 trillion USD in 2019 for treatments and informal care. The number of people affected is projected to surpass 78 million patients and $2.8 trillion USD by 2030 [21].

This review aims to discuss some of the possible causes of brain degeneration and how we can use new technologies to understand these diseases better and get to an eventual goal of treating them more effectively.

Brain Degeneration and Dementia

Brain degeneration, regardless of disease type, presents itself as some form of atrophy in the brain, impacting function. Impacts to neurological function can appear as loss in cognitive function, also known as dementia, or loss in motor function depending on the atrophied region of the brain. The term dementia simply refers to the loss of cognitive function and is a symptom caused by an underlying condition. This can be disease or injury, though the most common cause is brain degeneration [22]. Additionally, as the degeneration progresses, a patient exhibiting symptoms more associated with motor impairment may end up exhibiting cognitive impairment as well, and vice versa, a patient with cognitive impairment may eventually exhibit motor impairment [23]. As each of these diseases progress, studies have shown that connectivity between various regions of the brain begin to decay with neuron death [24]–[26].

When diagnosing dementia, clinicians must be careful to distinguish between dementia and pseudodementia, where severe depression causes symptoms identical to dementia, but are reversible [27]. In a 2007 study, Sáez-Fonseca et al looked at the likelihood that pseudodementia progressed to dementia and found that 71.4% of 182 patients screened with pseudodementia ended up having dementia later in life, indicating a need for monitoring of patients with pseudodementia as an indicator for possible dementia later on [28]. Some evidence indicates that imaging and facial recognition can be used together to help distinguish between AD and depressive pseudodementia, but further investigation is needed [29]. All degenerative brain diseases have one thing in common, the abnormal accumulation of toxic, misfolded proteins [3], [30].

Pathogenic Proteins

Each degenerative brain disease share a common pathology in the aggregation or placement of misfolded proteins at the site of focal onset for degeneration. The variation of misfolded proteins characterizes the onset and symptoms of each disease as well as the progression of degeneration.

Alzheimer's disease (AD) can be identified pathologically by the formation of β-amyloid plaques and tau neurofibrilary tangles first appearing in the medial temporal lobe progressing outward [31], [32]. These proteins seem to function to accelerate progression of the disease, leading to overall cell death and loss in neuronal function. Clinically, these findings manifest as a severe and progressive decline in memory with worsening dementia [5]. Another potential marker for the disease is volume loss in the hippocampus, but should not be used as the sole diagnostic criteria due to potential confusion with pseudodementia and other diseases [29].

The diagnostic criteria of Parkinson's disease (PD) has evolved over the years [33], with the most recent generally accepted criteria for diagnosis published in 2015 by the Movement Disorders Society [34], [35]. PD patients exhibit Lewy body pathology with the build up of Lewy neurites [36] of the toxic protein α-synuclein [3]. These proteins appear not only in the brain, but also in CSF, and might be able to be used as biomarkers which could help identify presence of the disease [37], [38] Parkinson's presents clinically as unusual gait, masked facies, and bradykinesia with physical tremors, rigidity, or both [34].

Huntington's Disease (HD) is a genetic degenerative brain disorder characterized by the progressive loss of nerve cells in the brain, causing motor, cognitive, and psychiatric impairments [39]. While spiny projection neurons are most susceptible to HD, it causes notable atrophy through the brain, including white matter [40]. HD is a result of an autosomal dominant mutation in the gene for the huntingtin protein, which is pathogenic when it contains more than 35 glutamines while normal alleles contain between 7 to 35 glutamines [41]. The more glutamines that are present in the mutation, the earlier the onset of the disease [42]. The polyglutamine lengths aggregate themselves or cause the huntingtin protein to aggregate into amyloid-like fibrils, the rate of aggregation depending on the length of the polyglutamine protein. Expanded glutamine codons cause cellular toxicity, disrupting the homeostasis of protein turnover [43].

Amyotropic lateral sclerosis (ALS), also commonly known as Lou Gehrig's disease, causes progressive loss of motor neurons in the brain, brain stem, and spinal cord eventually leading to paralysis and death [44]. Although some patients have a clear genetic cause of their dis-

ease, all cases link to ubiquitinated protein aggregation, especially that of TAR DNA-binding Protein-43 (TDP-43) [45]. These various proteins aggregate within motor neurons, then trigger a series of events which interfere with the cells ability to import of nuclear proteins and export of RNA [46]. TDP-43 and other similar disease protein aggregates, like superoxide dismutase, associated with ALS spread from neuron to neuron in a prion-like fashion, taken up by cells via a process similar to endocytosis [47].

Originally coined by Prusiner in 1982, the term "prion" derives from the phrase "proteinaceous infectious particle" [48]. In prion diseases such as Creutzfeldt-Jakob disease, a pathogenic prion infects a subject induce the misfolding of the protein, causing it to undergo a conformational change and turning it into a similar abnormal prion. Once abnormal prions start forming and aggregating, the accumulation of abnormal prion proteins result in neuronal degeneration, astrocytic gliosis, and spongiform change, all contributing to a fatal neurological disorder [49]. The most common of these prion diseases is Creutzfeldt-Jakob disease or more commonly known as mad cow disease. Transmission of these prions occurs most commonly when eating another infected organism, but can occur even in medical settings via seeding of prion in skin cells [50].

Table 1 demonstrates the imaging protein biomarker for each discussed degenerative brain disease and its corresponding radiotracer for use with molecular brain imaging.

Table 1: Proteins for each degenerative brain disease

Disease	Target Molecule	Radiotracer
Alzheimer's Disease	tau, beta amyloid	[C-11] PiB, florbetaben, florbetapir, flutemetamol, 18F-flortaucipir
Parkinson's Disease	α-synuclein	In development

Focal Onset Variants of Various Dementias

Although a prototypical presentation exists conceptually for AD, heterogenous variations in onset, progression, symptoms and markers have been studied and associated with anatomically focal variants. These variants may present with features of frontotemporal lobar degeneration (FTLD), corticobasal degeneration (CBD), posterior cortical atrophy (PCA), and the language onset dementias (LOD) [51]–[54]. Differentiation of these focal variants of AD must also be studied within the context of any pathophysiological differences between the three major cortical dementias and their presumed distinguishing anatomical loci: AD in parietotemporal cortex [55], Pick's disease or frontotemporal dementia (FTD) in frontotemporal cortex [56], and Lewy body dementia (LBD) in occipitotemporal cortex [57]. When possibly involving the temporal lobe and associated language centers with the consequence of impacting the ability to process language [58], any of these disorders may be confounded with the LODs now known as primary progressive aphasia (PPA) [59].

Progressive language disorders associated with frontal and temporal regions of the brain were first described in the early 1890's by Arnold Pick and Paul Serieux (see reviews by Kertesz [60] and Harciarek [61]. The disorder *slowly progressive aphasia* was first named by Mesulam [62] and then later renamed *primary progressive aphasia* by him [63]. The latter name, primary progressive aphasia (PPA), has become widely adopted and its variants have been classified with formal criteria by Gorno-Tempini *et al.* [64]. These forms of PPA and their acronyms include: nonfluent agrammatic variant (PPA-G, naPPA, agPPA, nfvPPA), logopenic variant (PPA-L, lvPPA), and semantic variant (PPA-S, svPPA) [59], [65]–[71]. The asymmetry and heterogeneity of AD and FTD in association with PPA have been reviewed recently by Mesulam *et al.* [72]. When considering speech and language pathology, the terms *dysarthria*, *apraxia* and *aphasia* should be distinguished. As pathologic phenomena, they may co-occur and thus can be difficult to differentiate when present in association with a degenerative brain disorder such as AD, FTD or CBD rather than with an acute vascular event such as left hemisphere stroke [59], [73], [74].

Pathophysiology Theories

Several theories as to the cause of these degenerative brain diseases have been made. Marien et al proposed that the loss of noradrenergic function in specific regions of the brain may be causing cascading decay elsewhere due to the protective nature of these neurotransmitters [75]. This particular theory could make sense, especially since Parkinson's disease patients often respond positively to dopaminergic medication [34].

In 2015, Goedert discussed the possibility that these proteinopathies cause the disease as a prion-like decay where the presence of proteins such as tau, α-synuclein, and β-amyloid cause further creation of these toxic proteins inducing further atrophy [76]. More recently, Fanning et al explained that there may be an interaction between these toxic proteins and lipids in cell membranes, resulting in cell death [77].

Each of these theories may have some role in overall disease progression and none are mutually exclusive, however, each indicate an increasingly steep curve of decline as the disease progresses.

Molecular Imaging and Monitoring

Since it is difficult and highly invasive to probe into a living patient's brain to determine their disease status and we cannot wait until after a patient passes away to asses their neurological status, molecular imaging provides a safer alternative to invasive tests. As defined by Mankoff, molecular imaging refers to the use of technology to visualize and understand the structure and function of biological processes at a molecular and cellular level [78]. Typically, molecular imaging requires the use of some type of 2 or 3 dimensional imaging technique that is measured over time. Some common techniques which fall into this category include magnetic resonance (MR) Spectroscopy [79], MR imaging [80], and ultrasound [81]. These imaging modalities function by sending or receiving a signal in the form of magnetic resonance, radiation, or sound frequencies which can penetrate the body harmlessly without the need for an invasive procedure.

Established clinical criteria is used for the differential diagnosis between various types of neurodegenerative disorders Imaging modalities, such as PET, MR, and CT scans, play a role in informing the patient's physician and allowing for high specificity in clinical assessment

but it is not a requirement for diagnosis [82]. Thus, the advancement of radiotracers and various methods of imaging are imperative to progress early diagnosis of degenerative brain diseases and/or dementia to aid diagnostic validity.

The molecular imaging has also observed to significantly reduce misdiagnosis of dementia with a false-negative rate of 3.1% compared to the conventional 8.2% and false-positive rate of 12.0% compared to a conventional 23.0%. With the reduced rate of misdiagnosis also comes financial benefits to the patients and their families, with an estimated net saving of $1,138 per correct diagnosis [83], [84].

PET Scans

Positron Emission Tomography (PET) scans use radiotracers to track normal and abnormal metabolic activity in the body. The tracer collects in the areas that have higher levels of metabolic and biochemical activity and can pinpoint the location of the disease. PET brain imaging is often used in conjunction with CT or MRI scans to obtain greater visualization [85].

Various radiotracers are indicated for use to investigate different disease states, but for the brain, the molecule must be biologically viable, safe, and able to pass the blood-brain barrier to accurately assess brain function [86]. Various radiotracers have been developed to track beta-amyloid proteins in various forms of brain degeneration. In 2002, Mathis et al and Klunk et al were successful in creating the first β-amyloid binding radiotracer ^{11}C-labeled Pittsburgh Compound B (^{11}C-PiB) allowing for the visualization of amyloid in the brain for Alzheimer's disease [87]–[94], however, ^{11}C-PiB had increased uptake in regions which were not desired to be imaged and required an on-site cyclotron, so the search continued [95]. Radiotracers for amyloid imaging other than ^{11}C-PiBhave also been developed [96]–[102]. In such clinical trials, the PET scanners detected a higher radioactivity in β-amyloid in known AD cortical areas such as the FTC (frontal cortex) and PRC (precuneus). ^{18}F labeled tracers were selected as a viable alternative due to a longer half-life resulting in the radiopharmaceuticals florbetaben [97], [103], [104], flobetapir [105], and flutemetamol [106], which were all successful in and indicated for safe use in brain imaging. Recent reviews on PET brain imaging that also discuss amyloid imaging include those by Murray [107], Nasrallah [108] and Ishii [109].

Numerous radiotracers were created for tau imaging with the first tau tracer to be officially approved by the FDA for clinical use in 2020[110]. ^{18}F-flortaucipir has been approved after 15 years with a large improvements in binding to tau protein over the years[111]–[113]

Another radiotracer for researching dementia includes Fluorodeoxyglucose (FDG), which functions very similar to glucose. The FDG mimics glucose, a natural energy source for the brain, and can safely pass through the blood brain barrier to be monitored by the PET scan. PET brain metabolic imaging with F18-FDG for AD was originally developed in the early 1980's by Benson *et al.* [114], [115], Alavi *et al.* [116]–[118], Foster *et al.* [119]–[121], and Friedland *et al.* [122]–[124]. It has since been well established in the 1990's by the work of Herholz *et al.* [125]–[128] and Minoshima *et al.* [129]–[133], and then further validated in the 2000's by Silverman *et al.* [134]–[137] and Mosconi *et al.* [138]–[143].

Though serving a similar purpose to ^{11}C-PiB)amyloid imaging, a drastically different metabolic PET imaging method has also been used to diagnose dementia in patients using metabolic monitoring with ^{18}F-deoxyglucose (^{18}F-FDG). The process has been developed and practiced since the 1980s [114], [144]. More recent evidence showing an 84% accuracy of diagnosis when using ^{18}F-FDG in comparison to 65% accuracy when using clinical symptom assessment alone [145]. Numerous studies outline that these two different approaches of ^{11}C-PiB amyloid imaging and ^{18}F-FDG metabolic imaging, the diagnostic accuracy of differentiating AD and frontotemporal lobar degeneration (FTLD) were similar in patients with known histopathology [146], [147].

Relevant to our current study reported here on PET brain imaging markers and metrics, there have been a number of studies and reviews published previously [147]–[154] that evaluated the performance of various metrics derived from F18-FDG PET metabolic imaging as a marker for the detection of AD. This past work has demonstrated that when compared with clinical evaluations, PET brain imaging yields higher sensitivity, specificity and accuracy for AD and increases the treating physician's level of confidence in diagnosing AD and in differentiating AD from other dementias.

Radiotracers for α-synuclein have proven to be much harder to create due to the difficulty selectively binding to α-synuclein proteins. Many proposed ligands have struggled to differentiate between α-synuclein , β-amyloid , and tau, hence showing unclear results. The difficulties have resulted in the long standing α-synuclein radiotracer prize posted by the Michael J. Fox Foundation (see here) for $2 million USD prize. Research into α-synuclein PET tracers has looked into tracers that utilize the similar binding methods between α-synuclein and β-amyloid, enabling scientists to base radiopharmaceuticals off of the existing ^{11}C-PiB and other β-amyloid tracers, however this is still very new [155]. Some promising compounds have been studied within the past year, such as ^{11}C-labeled anle253b [156]

From the risk-benefit perspective, ^{18}F-FDG PET metabolic imaging has been considered appropriate for the evaluation of AD by many clinicians and investigators for at least a decade since publication of the 2002 cost analysis by Silverman *et al.* [84]. That same year, Silverman also published a compelling individual case presentation [83] demonstrating the important benefit obtained with PET metabolic imaging as shown by its ability to detect AD in an unfortunate patient who had been given multiple prior incorrect diagnoses of other neuropsychiatric disorders over the course of several years. This radiotracer functions by being metabolized similar to glucose in tissue, allowing us to which regions of the brain are active. The ^{18}F-FDG PET scanner's estimation of cerebral metabolic rate of glucose has efficiently detected hypometabolism, which has often been associated with dementia [142], [152], [157].

The dementia diagnostic guidelines should follow that of as outlined by National Institute on Aging-Alzheimer's Association [158] and elaborated by Jack *et al.* McKhann *et al.* Albert *et al.* and Sperling *et al.* on the diagnosis of mild cognitive impaiment due to AD and defining AD's preclinical stages [159]–[162]. In such discussions, the diagnosis of AD has been divided into three portions: the dementia phase; symptomatic, pre-dementia phase; and the asymptomatic, preclinical phase. For example, basic neuropsychological tests can be conducted to diagnose a certain patient with dementia, but other histopathological or molecular imaging tests must be done to differentiate a Parkinson's Disease patient with an Alzheimer's disease patient. Further tests would have to provide sufficient metabolic or anatomical information to confirm the patient's diagnosis of the various types of dementia. Since then, more diagnostic criterias have been proposed to be added, such as the use of various molecular imaging methods like FDG-PET

to aid in diagnosis of patients [162]–[164].

The appropriate use criteria of the different scanners were outlined in numerous papers, with the Society of Nuclear medicine releasing guidelines for FDG-PET imaging in 2009 [165] and European Association of Nuclear Medicine in 2009 [166]. Addition studies have also been published to guide how to read FDG-PET scans in confirmed dementia patients [167], [168]. Johnson *et al.*[169], [170] outlines when it is appropriate to use amyloid PET imaging, and what sorts of criteria must be met to diagnose dementia and movement disorders [171], [172]. The scanning process is often aided by stereotaxic surface project software such as Neurostate 3D-SSP. Such programs map the intercommissural (AC-PC) line to differentiate four landmarks frontal pole point (FP), anterior corpus callosum (CC), subthalamus (TH), and occipital pole point (OP) [130], [173]–[175]. Neurostat software has been validated independently in several different applied contexts since then [176]–[180].

Although PET technology has improved in every aspect from radiotracers to image processing software, continued research has slowed during the COVID-19 pandemic.

Multimodal Imaging

Magnetic resonance imaging was developed in the 1970's by Dalmadian *et al.*[181], [182] and first used in the brain by Young *et al.*[183]–[185]. Variants of MR are fantastic for extremely high spatial resolution imaging of internal anatomical structures which could be used in determining the volume and changes in volume of a patients brain; however, to determine the presence of toxic proteins such as β-amyloid, α-synuclein, and tau, different techniques must be utilized. MRI has also been used to identify dementia and brain atrophy especially in combination with other imaging methods such as CT scans to help assess the diagnostic criteria [186]–[188]. The tissue loss and structural changes shown by the MRI often correlates to cognitive performance in numerous studies such as [189]. Some studies even state that MRI structural markers being a better identifier of AD than the markers of Aβ deposition [190]–[192]. Each imaging technique utilizes different methods which have different use cases depending on what a physician or scientist is trying to investigate.

After MRI machines were introduced, the development of CT scans entered the scene within the same decade. CT scans were invented in 1972 by British engineer Godfrey Hounsfield and physicist Allan Cormack [193]. A CT scan, or a computerized tomography scan combines a series of X-ray images taken from different angles and creates cross-sectional slices of the bones, blood vessels, and tissues within the body [194]. CT images for dementia can be used for clinical diagnosis to identify structural abnormalities, space-occupying lesions, or intracranial neoplasms. Diagnoses processes include a full neuropsychological exam, routine blood chemistries, and a noncontrast CT scan [195]. Erkinjuntti *et al.* [196] describes the presence or absence of infarcts on CT scans as the differentiated diagnosis between Alzheimer's disease and vascular dementia. The presence of infarcts on CT differentiated AD from multi-infarct dementia (MID) and probable vascular dementia with one patient with clinical diagnosis of AD having a small area scored as an infarct. The use of CT demonstrated identification of a diagnosis marker between AD and dementia with the presence of infarcts in providing more information to the clinician for diagnosis.

Medical image fusion is often used to provide a more reliable and acccurate assessment for clinical analysis of brain disorders using two imaging modalities. Image fusion has been used for segmentation of brain tissue, classification of abnormal brain tissue, and and the 2D-3D registration of brain images. Identifying new methods for improve imaging quality of regions of interest, accurate registration of objects between the images, and speed of image processing will aid in practical advancements of imaging techniques and medical image fusion [197].

Conclusion

After over 100 years of studying degenerative brain diseases, the field of neuroscience and imaging is slowly but surely approaching an answer as to the causes of brain degeneration. As more, higher quality radiotracers become available, it is likely that we will see a clearer picture as to the exact function of these proteins leading to a greater understanding of the disease and earlier diagnosis; however, radiopharmaceutical imaging is not the only avenue of research to pursue. To properly understand the entire process of the disease, researchers must study not just the proteins associated with each disease, but the underlying factors such as genetics which cause the misfolding of these proteins, the chemical action of these proteins, and how these proteins are associated with brain atrophy. In other words, we must strive to find a full picture understanding, not just imaging proteins with PET scans, but of the whole biological pipeline - genotype to phenotype and disease symptoms, something not covered by this paper. Some studies have begun to research this[3], [198], and by performing comprehensive multidisciplinary research across fields of medicine and science, we will hopefully be able to find that final answer to not just the cause of degenerative brain disease, but also successful treatment.

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