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

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Abstract

Brain degeneration and dementias are progressive disorders causing memory loss and cognitive impairment due to brain atrophy and pathological lesions associated with abnormal protein deposits and death of neurons. In recent decades, advances in non-invasive molecular imaging of the brain have provided effective visualization of brain atrophy and dysfunction in dementia. Researchers have developed numerous radiotracers that bind to both normal and abnormal biomarkers in the brain, creating distinct topographic patterns characteristic of different stages in diverse neurodegenerative disorders. In this review, we discuss the use of molecular imaging, specifically positron emission tomography (PET), for facilitating diagnosis and monitoring progression of brain degeneration. Differential diagnosis of degenerative brain disorders with PET brain imaging can be achieved with high accuracy. Continuing development of new radiotracers with increased sensitivity and specificity for different aspects of the pathophysiology of brain degeneration will enhance the use of PET brain imaging to elucidate the causal mechanisms of the dementias and to monitor the efficacy of pharmacologic interventions intended to slow the progression of the dementias.

Keywords

Molecular imaging, dementia, brain degeneration, brain imaging, PET-CT scans, PET-MR scans.

Contents

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Introduction

In 1906, Dr. Alois Alzheimer's description of a previously unknown brain disorder would change the course of psychiatry forever (Hippius and Neundörfer 2003). 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 to 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. Upon *post mortem* examination of her brain, Alzheimer discovered severe brain atrophy and unusual plaques. 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 has fallen apart, and only a tangled bundle of fibrils points to the place in which there once was a ganglion cell. (Alzheimer 1907)

Today, we know these neurofibrilary tangles to be accumulations of tau protein with beta-amyloid proteins building up around cells.

As reviewed by Taylor (2002), these and other proteins and proteinopathies play a role in degenerative brain diseases, such as Huntington's disease (HD), Parkinson's disease (PD), Pick's disease also known as fronto-temporal dementia (FTD), and Lewy body dementia (LBD). The progression of each condition begins with dysfunction in a specific region of the brain due to the presence of proteinopathy. However, the natural course with sequence of harmful effects of each proteinopathy has yet to be fully discovered. With the advent of new diagnostic technologies, we are now able to visualize internal organs and cell functions

prior to a patient's death, enabling us to diagnose more accurately and better help a patient who is experiencing symptoms typical of brain degeneration with a dementia of some kind. The need for such diagnostic tools is urgent because increasing lifespans around the world have lead to a growing burden of older-age related diseases with AD among the most common.

AD had an estimated total care cost close to $305 billion USD in the US in 2020 (W. Wong 2020), and $604 billion USD globally in 2010 (Winblad et al. 2016). This rising tide of dementia cases has been a cause for concern over several decades, with AD accounting for 50% to 70 % of dementia cases in western countries and 62% in Asia. AD has a global prevalence of dementia starting at 0.3 to 0.5 cases per 100 people aged 60 to 65 and rising exponentially with age up to 12 per 100 aged 80 to 84 in the Americas, Europe, and Asia according to pooled data collected over the course of the 1990s (Fratiglioni, Ronchi, et al. 1999). Epidemiological studies consistently identify AD as the most common cause of dementia, accounting for 60-80% of cases in a 2020 Alzheimer's Foundation report (Alzheimer's Association 2022). Based on data from the mid-to-late 2000s, the causes of dementia with highest prevalence per 1000 people over age 65 are AD (40-60), PD (10-20), and LBD (1-20) (Fratiglioni and Qiu 2009).

As the most common of the dementias, AD remains an overwhelming challenge and burden (C. J. Murray and US Burden of Disease Collaborators 2013; Adelman et al. 2014) for patients as well as their caregivers, families, and communities, including public health agencies, that must cope with the cost of dementia care, which continues to grow as the elderly come to constitute a larger proportion of the population (World Health Organization and Alzheimer's Disease International 2012). In addition to financial costs, caring for patients with dementia places psychological strain on their families and professional caregivers (Etters et al. 2008). According to the World Health Organization (WHO), the various forms of dementia together affected 55 million people globally, imposing a cost of 1.3 trillion USD for treatments and informal care in 2019 (World Health Organization and Alzheimer's Disease International 2012). They project that the number of people affected will surpass 78 million, and the cost may exceed $2.8 trillion USD by 2030 (World Health Organization 2021). By 2050, the number of AD patients alone may surpass 100 million (Qiu et al. 2022).

Despite more than a century of scientific and clinical research on AD (Goedert and Spillantini 2006) and the approval in the United States of several drugs for the treatment of AD (Roberson and Mucke 2006), no known therapy can prevent or reverse the effects of AD (Selkoe 2012). Furthermore, managing other chronic illnesses in the hopes of reducing the likelihood of the disease has not lessened the burden of care (Zissimopoulos et al. 2018). However, some evidence shows that early diagnosis and treatment can help improve quality of life for patients as well as their caregivers (Kawakita et al. 2020). This review aims to discuss how molecular imaging provides supporting evidence for the differential diagnosis of brain degeneration, the discovery of the mechanisms behind it, and the search for more effective treatments (Choi et al. 2014).

Brain Degeneration and Dementia

Brain degeneration, regardless of disease type, presents as some form of atrophy in the brain, resulting in a loss of function. Neurological changes known as dementia are associated with loss of cognitive function including thinking, memory, language, and reasoning, and also with loss of normal sensory and motor function with changes in behavior, emotion, and psychological well-being, depending on the atrophied region of the brain. In general, the term *dementia* has been used for irreversible causes of neurodegeneration with pathophysiologic causes and lesions identified before and/or after death (McCullagh et al. 2001), whereas the term *pseudo-dementia* has been used in those situations such as severe depression that may present with the appearance of a dementia but can be treated and reversed with return to normal function. For those irreversible dementias, as neurodegeneration progresses, a patient exhibiting symptoms more associated with motor impairment may later exhibit cognitive impairment as well, and vice versa, a patient with cognitive impairment may eventually exhibit motor impairment (Tolea et al. 2016). Studies have shown that, as each of these diseases progresses, connectivity between various regions of the brain begins to decay with neuron death (Bohanna et al. 2011; Helmich et al. 2009; Pievani et al. 2014).

Using the terminology above, when making the diagnosis of dementia, clinicians must be careful to distinguish between dementia and pseudo-dementia, in which severe depression causes symptoms that are similar to dementia but reversible (Pozzoli et al. 2018). However, it should also be noted that Saez-Fonseca et al. (2007) estimated the likelihood that pseudo-dementia would progress to dementia and found that 71% of 182 patients screened with pseudo-dementia developed dementia later in life, which indicates a need for continued monitoring of patients with pseudo-dementia. Some evidence suggests that imaging with facial recognition and analysis can be used to help distinguish between AD and depressive pseudo-dementia, but further investigation is needed (Sahin et al. 2017).

Pathogenic Proteins

Excluding from consideration the pseudo-dementias, those irreversible dementias resulting from degenerative brain diseases with identifiable pathophysiologic lesions all appear to have in common the abnormal accumulation of toxic, misfolded proteins of some kind (Taylor 2002; Soto and Pritzkow 2018). Each of these degenerative brain diseases share a common pathology in the aggregation and deposition of misfolded proteins typically at the site of focal onset for the dementia. The differences in the toxic accumulation of the pathogenic proteins characterize the onset and symptoms of each disease as well as the progression of degeneration.

AD can be identified pathologically by the formation of beta-amyloid plaques and tau neurofibrilary tangles usually first appearing in the medial temporal lobe then progressing outward (Thal et al. 2002; Neddens et al. 2018). These abnormal proteins accelerate progression of the disease, leading to overall cell death and loss of neuronal function. Clinically, these findings manifest as a severe and progressive decline in memory with worsening dementia (Winblad et al. 2016). 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 confounding with other diseases (Sahin et al. 2017).

The diagnostic criteria for PD have evolved over the years (Tolosa et al. 2006), with the most recent generally accepted criteria for diagnosis published in 2015 by the Movement Disorders Society (Postuma, Berg, Stern, et al. 2015; Postuma, Berg, Adler, et al. 2016). PD patients exhibit Lewy body pathology with accumulation of Lewy neurites (Tredici et al. 2010) associated with the toxic protein alpha-synuclein (Taylor 2002). These proteins appear not only in the brain but also in CSF, and could be used as biomarkers to help identify presence of the disease (Budelier and Bateman 2019; Murakami et al. 2019). PD presents clinically with

inital motor symptoms of unusual gait, masked facies, and bradykinesia with physical tremors and/or rigidity (Postuma, Berg, Stern, et al. 2015).

HD is a genetic degenerative brain disease characterized by the progressive loss of nerve cells in the brain, causing motor, cognitive, and psychiatric impairments (Wagner et al. 2008). While spiny projection neurons are most susceptible to HD, notable atrophy occurs throughout the brain, including the white matter in addition to the grey matter (Parsons and Raymond 2015). HD results from 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 (Shacham et al. 2019). The more glutamines that are present in the mutation, the earlier the onset of the disease (Fan et al. 2014). The polyglutamine lengths aggregate themselves or cause the huntingtin protein to aggregate into amyloid-like fibrils, with the rate of aggregation depending on the length of the polyglutamine protein. Expanded glutamine codons cause cellular toxicity, disrupting the homeostasis of protein turnover (Hatters 2008).

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 (Peters et al. 2015). Although some patients have a genetic etiology, all cases are associated with with the presence of ubiquitinated aggregation of protein especially TDP-43 or TAR DNA-binding Protein-43 (Blokhuis et al. 2013). These various proteins aggregate within motor neurons, then trigger a series of events which interfere with the cells ability to import nuclear proteins and export nuclear RNA (Chou et al. 2018). 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 (Benkler et al. 2018).

Originally coined by Prusiner (1982), the term *prion* derives from the phrase "proteinaceous infectious particle". In prion diseases such as Creutzfeldt-Jakob disease, a pathogenic prion infects a person, then induces the misfolding of the susceptible protein, causing it to undergo a conformational change and transforming it into a similar abnormal prion (Iwasaki 2016). 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 (Mackenzie and Will 2017). The most common of these prion diseases is Creutzfeldt-Jakob disease, commonly known as mad cow disease. Transmission of these prions to humans occurs most commonly when eating food from another infected organism such as cows, but can occur even in medical settings via seeding of prions in skin cells (Orrú et al. 2017).

Table 1 summarizes imaging biomarkers for some of these degenerative brain diseases and the corresponding radiotracers for use with brain molecular imaging. See further discussion by Gharibkandi and Hosseinimehr (2019) on radiotracers for PD, and by Bauckneht et al. (2019) on radiotracers for multiple sclerosis (MS).

Focal-Onset Dementia Variants

Although a prototypical presentation exists conceptually for AD, heterogenous variations in onset, progression, symptoms and biomarkers 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) (Kramer and Miller 2000; Kertesz et al. 2000; Armstrong et al. 2013; Hodges 2013). Differentiation of these focal variants of AD must also be studied within the context of pathophysiological differences between the three major cortical dementias and their presumed distinguishing anatomical loci: AD in parietotemporal cortex (Oboudiyat et al. 2013), Pick's disease or frontotemporal dementia (FTD) in frontotemporal cortex (Perry and Miller 2013), and Lewy body dementia (LBD) in occipitotemporal cortex (Molano 2013). When possibly involving the temporal lobe and associated language centers with the consequence of disrupting the ability to process language (Saffran 2000), any of these disorders may be confounded with the LODs now also known as primary progressive aphasia (Jung et al. 2013).

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 (Kertesz 2003; Harciarek and Kertesz 2011). The disorder *slowly progressive aphasia* was first named by M. M. Mesulam (1982) and then later renamed *primary progressive aphasia* by M. M. Mesulam and Weintraub (1992). 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. (2011). 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) (M. Mesulam, Wieneke, et al. 2009; Gliebus 2010; Leyton et al. 2011; Gefen et al. 2012; Harris et al. 2013; Jung et al. 2013; M. Mesulam and Weintraub 2014; Wicklund et al. 2014). The asymmetry and heterogeneity of AD and FTD in association with PPA have been reviewed by M. Mesulam, Weintraub, et al. (2014). 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 (Josephs et al. 2012; Jung et al. 2013; Ballard et al. 2014).

Pathophysiology Theories

Several theories about the etiology of these degenerative brain diseases have been proposed. Marien et al. (2004) discussed the loss of noradrenergic function in specific regions of the brain as a mechanism leading to cascading decay elsewhere due to the protective nature of these neurotransmitters. This particular theory can be related to the manner in which PD patients often respond positively to dopaminergic medication (Postuma, Berg, Stern, et al. 2015). Goedert (2015) discussed the possibility that proteinopathies in the brain cause the degenerative disease as a prion-like decay where the presence of proteins such as alpha-synuclein, beta-amyloid, and tau lead to further accumulation of these toxic proteins inducing further atrophy of brain tissue with neuronal cell death. More recently, Fanning et al. (2020) explained that an interaction may exist between these toxic proteins and lipids in cell membranes that results in neuronal cell death. Each of these theories may have some role in overall disease progression and none are mutually exclusive. However, each assumes a worsening rate of decline as the disease progresses.

Molecular Imaging and Monitoring

It is difficult, impractical, and unethical to probe invasively into a living patient's brain to determine their disease status for a neurodegenerative disorder — unless a rationale can be provided for medical

Table 1: Biomarkers for several degenerative brain diseases.
Sources: Gharibkandi and Hosseinimehr (2019) and Bauckneht et al. (2019)

Disease	Target	Radiotracer
Parkinson's disease (PD)	alpha-synuclein	in development
Alzheimer's disease (AD)	tau, beta amyloid	PiB, florbetaben, florbetapir, flutemetamol, flortaucipir
Multiple sclerosis (MS)	demyelination	amyloid tracers
	neurodegeneration	FDG, AchE binding tracers, flumazenil
	microglia activation and neuroinflammation	FDG, TSPO binding tracers, CB2 binding tracers, adenosine receptor tracers, S1PR1 binding tracers

benefits outweighing surgical risks and unless informed consent can be obtained from the patient. But waiting to probe a donor's brain post-mortem does not provide any evidence that can be used during the patient's lifetime to alleviate suffering. Fortunately, non-invasive molecular imaging provides a much safer alternative to invasive tests ante-mortem during the patient's course of the degenerative disease. As defined by Mankoff (2007), 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. Typically, molecular imaging requires the use of some type of 2 or 3 dimensional imaging technology that is measured and monitored over time.

Some common imaging technologies include magnetic resonance (MR) spectroscopy (Castillo et al. 1996), MR imaging (Reimer et al. 2010), ultrasound (US) (Wells 2006), computed tomography (CT) (Kircher and Willmann 2012), positron emission tomography (PET) and single photon emission computed tomography (SPECT) (Lu and Yuan 2015). These imaging modalities function by sending and receiving signals in the form of magnetic resonance pulses for MR, sound waves for US, X-rays for CT, or photons for PET and SPECT, which can move through the tissues of the body without the need for an invasive surgical procedure while producing data, commonly called scans, that enables visualization of the cells, tissues, and organs of the body. 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 evaluation, but are not considered a requirement for clinical diagnosis (Gómez-Río et al. 2016). However, the development of novel radiotracers and diverse methods of molecular imaging remain imperative for progress with early diagnosis of degenerative brain diseases and/or dementia and aid correct diagnosis when compared to clinical evaluation without molecular imaging. Moreover, molecular imaging has been observed to reduce misdiagnosis of dementia significantly with a false-negative rate of 3.1% compared to 8.2% without imaging and false-positive rate of 12.0% compared to 23.0% without imaging. 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 (D. H. S. Silverman et al. 2002; D. H. Silverman and Small 2002).

PET Scans

PET scans use radiotracers to track normal and abnormal biomolecular activity in the body. The tracer may accumulate in those areas that have higher levels of biochemical and metabolic activity compared to normal levels which can then pinpoint the location of disease lesions. If absence, instead of presence, of the tracer binding activity is associated with disease lesions, then levels of activity lower than normal help to identify the location of disease lesions. PET brain scans are often used together with CT or MR scans to obtain better visualization (Mayo Clinic 2021). Various radiotracers are indicated for use to investigate different disease states. For brain scans, the molecule must be biologically viable, safe, and able to pass through the blood-brain barrier to assess brain function (Pike 2009).

Radiotracers have been developed to track beta-amyloid proteins for monitoring brain degeneration in AD. Mathis, Bacskai, et al. (2002) were successful in creating the first beta-amyloid binding radiotracer ^{11}C-labeled Pittsburgh Compound B (^{11}C-PiB) enabling the visualization of amyloid in the brain for AD (Mathis, Wang, Holt, et al. 2003; Mathis, Wang, and Klunk 2004; Klunk, Engler, et al. 2004; Klunk, Mathis, et al. 2006; Klunk 2008; Klunk 2011; Mathis, Mason, et al. 2012). However, ^{11}C-PiB had increased uptake in regions where it was considered noise rather than signal. Moreover, ^{11}C-PiB required an on-site cyclotron, so the search continued (C. C. Rowe and Villemagne 2013b).

Radiotracers other than ^{11}C-PiB for amyloid imaging have since been developed (C. C. Rowe, Ng, et al. 2007; C. C. Rowe, Ackerman, et al. 2008; C. Rowe 2011; Villemagne, Mulligan, et al. 2012; Villemagne, Burnham, et al. 2013; C. C. Rowe and Villemagne 2013a; Villemagne, Furumoto, et al. 2014). In such clinical trials, the PET scanners detected a higher radioactivity bound to beta-amyloid in known AD cortical areas such as the FTC (frontal cortex) and PRC (precuneus). ^{18}F labeled tracers were selected as viable alternatives due to a longer half-life resulting in the radiopharmaceuticals florbetaben (C. C. Rowe, Ackerman, et al. 2008; Villemagne, Ong, et al. 2011; Barthel and Sabri 2011), flobetapir (D. F. Wong et al. 2010), and flutemetamol (Vandenberghe et al. 2010), which were all successful and approved for safe use in brain imaging. Recent reviews on PET brain imaging that discuss amyloid imaging include those by A. D. Murray (2012), I. Nasrallah and Dubroff (2013) and Ishii (2014).

Radiotracers have also been developed for tau imaging with the first tau tracer to be officially approved by the FDA for clinical use in 2020 (FDA 2020). ^{18}F-flortaucipir has been approved after 15 years with a large improvements in binding to tau protein over the years (Hall et al. 2017; Devous et al. 2017; Villemagne, Barkhof, et al. 2021)

The original radiotracer for investigating dementia is ^{18}F-fluorodeoxyglucose (FDG). 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, Kuhl, Phelps, et al. (1981); Benson, Kuhl, Hawkins, et al. (1983), Alavi, Reivich, et al. (1981); Alavi, Reivich, et al. (1982); Alavi, Dann, et al. (1986); Alavi and Hirsch (1991), Foster, Chase, Fedio, et al. (1983); Foster, Chase, Mansi, et al. (1984); Foster, Chase, Patronas, et al. (1986), and Friedland, Budinger, Ganz, et al. (1983); Friedland, Budinger, Brant-Zawadzki, et al. (1984); Friedland, Brun, et al. (1985). It has since been well established in the 1990's by the work of Herholz,

Perani, et al. (1993); Herholz (1995); Herholz, Salmon, et al. (2002); Herholz, Schopphoff, et al. (2002) and Minoshima, Foster, and Kuhl (1994); Minoshima, Frey, Koeppe, et al. (1995); Minoshima, Frey, Foster, et al. (1995); Minoshima, Frey, and Kuhl (1998); Minoshima, Foster, Sima, et al. (2001), and then further validated in the 2000's by D. H. Silverman and Phelps (2000); D. H. Silverman, Small, et al. (2001); D. H. S. Silverman (2004); D. H. Silverman, Mosconi, et al. (2008) and Mosconi, Pupi, et al. (2004); Mosconi, W.-H. Tsui, et al. (2005); Mosconi (2005); Mosconi, W. H. Tsui, Pupi, et al. (2007); Mosconi, W. H. Tsui, Herholz, et al. (2008); Mosconi, Mistur, et al. (2009).

More recent evidence has been published demonstrating an 84% accuracy of diagnosis when using ^{18}F-FDG brain imaging in comparison to 65% accuracy when using clinical symptom assessment alone (Taswell et al. 2015). Other studies have confirmed that when comparing the two different approaches of amyloid imaging and metabolic imaging, the diagnostic accuracy for differentiating AD and frontotemporal lobar degeneration (FTLD) were similar in patients with known histopathology (Rabinovici et al. 2011; Foster, Heidebrink, et al. 2007). Relevant to our current review reported here on PET brain imaging markers and metrics, there have been a number of studies published previously (Patwardhan et al. 2004; Foster, Heidebrink, et al. 2007; Morinaga et al. 2010; Herholz, Westwood, et al. 2011; Bohnen and Minoshima 2012; Caroli et al. 2012; Frisoni, Bocchetta, et al. 2013; Yamane et al. 2014) that evaluated the performance of various metrics derived from 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.

As of 2021, radiotracers for alpha-synuclein have proven to be more challenging to develop due to the difficulty of binding selectively to alpha-synuclein proteins. Many proposed ligands have not been able to differentiate between alpha-synuclein, beta-amyloid, and tau, hence showing unclear non-specific results. The difficulties have motivated the alpha-synuclein radiotracer prize posted by the Michael J. Fox Foundation (see $2 million USD prize). Research into alpha-synuclein PET tracers has considered tracers that utilize similar binding methods between alpha-synuclein and beta-amyloid, enabling scientists to derive radiopharmaceuticals from the existing ^{11}C-PiB and other beta-amyloid radiotracers (Xu et al. 2019). Some promising compounds have been studied within the past year, such as ^{11}C-labeled anle253b (Maurer et al. 2020)

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 since publication of the 2002 cost analysis by D. H. Silverman and Small (2002). That same year, Silverman also published a compelling individual case presentation (D. H. S. Silverman et al. 2002) 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, enabling visualization of metabolically active regions of the brain. The ^{18}F-FDG PET scan's estimation of cerebral metabolic rate can efficiently detect hypometabolism, which has been associated with dementia (Caroli et al. 2012; Mosconi, W. H. Tsui, Herholz, et al. 2008; I. M. Nasrallah and Wolk 2014).

Dementia diagnostic guidelines should follow those outlined by National Institute on Aging-Alzheimer's Association (G. McKhann et al. 1984) 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 (Jack, Albert, et al. 2011; G. M. McKhann et al. 2011; Albert et al. 2011; Sperling et al. 2011). 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 molecular imaging tests must be done to differentiate a PD and AD patients. Further tests would have to provide sufficient metabolic or anatomical information to confirm the patient's diagnosis amongst the various types of dementia. Since then, additional diagnostic criteria have been recommended, such as the use of various molecular imaging methods to assist in diagnosis of patients (Sperling et al. 2011; Budson and Solomon 2012; Dubois et al. 2014).

Appropriate use criteria for PET brain scans have been published by the Society of Nuclear Medicine for FDG-PET imaging (Waxman et al. 2009) and European Association of Nuclear Medicine (Varrone et al. 2009). Additional reports have been published to provide guidance on interpretation of FDG-PET scans in dementia patients (Torosyan and D. H. S. Silverman 2012; Herholz 2014). Johnson *et al.* (Johnson, Minoshima, Bohnen, Donohoe, Foster, Herscovitch, Karlawish, C. C. Rowe, Carrillo, et al. 2013; Johnson, Minoshima, Bohnen, Donohoe, Foster, Herscovitch, Karlawish, C. C. Rowe, Hedrick, et al. 2013) provide guidance on when it is appropriate to use amyloid PET imaging, and which criteria should be met to diagnose dementia and movement disorders (Wippold II et al. 2015; Centers for Medicare & Medicaid Services 2009). Data from PET brain scans may be analyzed by stereotactic surface projection software such as Neurostat 3D-SSP (Minoshima, Frey, Koeppe, et al. 1995). 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) (Minoshima, Koeppe, Mintun, et al. 1993; Minoshima, Koeppe, Frey, et al. 1994; Minoshima, Frey, Koeppe, et al. 1995; Burdette et al. 1996). Neurostat software has been validated independently in several different applied contexts since then (Ishii, Willoch, et al. 2001; Imabayashi et al. 2004; Hosaka et al. 2005; Ishii, Kono, et al. 2006; Uemura et al. 2011).

Multimodal Imaging

Magnetic resonance imaging was developed in the 1970's by Damadian (1971); Damadian et al. (1973)) and first used in the brain by Young et al. (1981) (see also Young (1994); Bydder (2020)). 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 alpha-synuclein, beta-amyloid, and tau, PET molecular imaging must be used. MR 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 (O'brien et al. 2001; Korf et al. 2004; Fazekas et al. 1989). The tissue loss and structural changes shown by MR often correlate with cognitive performance in studies such as Whitwell et al. (2005). Some studies suggest that MR structural markers serve as better identifiers of AD than the biomarker of beta-amyloid deposition (Frisoni, Fox, et al. 2010; Choo et al. 2010; Jack, Lowe, et al. 2009). Each imaging modality adopts different methods which have different use cases depending on what a physician or scientist is investigating.

The development of CT scanners entered the scene the same decade as MR scanners. CT scans were invented in 1972 by British engineer Godfrey Hounsfield and physicist Allan Cormack (Hsieh and Flohr 2021). A CT 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 (Mayo Clinic 2020). CT scans in the context of a dementia evaluation can be used for clinical diagnosis to identify structural abnormalities, space-occupying lesions, or intracranial neoplasms. Diagnostic evaluation may include a full neuropsychological exam, routine blood chemistries, and a noncontrast CT scan (Health Quality Ontario 2014). Erkinjuntti et al. (1987) describe the presence or absence of infarcts on CT scans as the distinguishing feature for differential diagnosis between Alzheimer's disease and vascular dementia.

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 improving the image quality for regions of interest, accurate registration of objects between the images, and speed of image processing will aid in practical advancements of imaging techniques with medical image fusion (James and Dasarathy 2014).

Conclusion

After more than a century of studying degenerative brain diseases, the fields of brain sciences and medicine, now enhanced by molecular imaging, are slowly but surely finding answers to questions about the causes of brain degeneration. As more specific radiotracers become available, we will see a clearer picture of the proteinopathies associated with neurodegeneration. However, molecular imaging is not the only avenue of research to pursue. To properly understand the pathophysiology of neurodegeneration, researchers must study not just the proteinopathy associated with each disease, but underlying and contributing factors such as genetic susceptibilities, the misfolding of proteins, the biochemical impacts of the misfolded proteins, and consequential brain atrophy. We must strive to reveal a full picture with understanding of not just PET scan imaging biomarkers, but the biological pipeline from genotypes to phenotypes and clinical behavior symptoms. Some investigators have begun to address these questions (Taylor 2002; Lourida et al. 2019). By pursuing multidisciplinary research across fields of medicine and science, we will be able to find answers to questions about not just the causes of degenerative brain disease, but also treatments for intervention.

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