Brain PET in the Evaluation of Cognitive Function and Dysfunction

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Abstract:

During the past four decades, three dimensional neuroimaging tools have played a prominent role in both the study of normal cognitive processes and the evaluation of disorders affecting cognitive function. Positron Emission Tomography (PET) is capable of detecting biochemical changes in the human brain at early stages of disease, often years prior to detectable structural changes or clinical expression of symptoms. [^{18}F] fluorodeoxyglucose (FDG) is the most commonly imaged radiopharmaceutical in clinical PET studies. Several others are available, especially for use in patients with known or suspected neurodegenerative disease. Recently, the "Default Mode Network" has attracted substantial attention from investigators interested in normal and abnormal neuropsychology, and has been especially amenable to study through analysis of regional covariations of activities measurable with functional Magnetic Resonance (MR) or PET imaging. PET is particularly useful in illuminating neurodegenerative processes occurring in Alzheimer's Disease, Frontotemporal Dementia, Primary Progressive Aphasia, Parkinson's Disease, and other causes of cognitive and/or central motor decline. It can also be helpful in evaluation of patients with rarer conditions such as paraneoplastic neurologic syndromes, limbic encephalitis, chronic traumatic encephalopathy, and prion-based diseases.

Key Words: dementia; diagnosis; fluorodeoxyglucose; PET; prognosis; cognitive impairment; memory loss

Section 1 "Introduction"

Positron Emission Tomography (PET) is a medical imaging procedure that is capable of mapping spatiotemporal distribution of biochemical processes throughout the body. In the context of cognition-related assessments, this resulting biochemical information provided by the scan can be used to elucidate neurobiological substrates for normal abilities, as well as to detect many pathological processes in the brain prior to the occurrence of structural changes, or even the first expression of symptoms. This latter ability can be of particular clinical relevance, because by the time a disease has led to sufficient damage to brain tissue to be detected by structural imaging methods with computed tomography (CT) or magnetic resonance imaging MRI, or caused noticeable symptoms, the underlying pathological process may already be firmly entrenched or irreversible.

Preceding scanning, a small amount of radioactive substance is administered, typically intravenously. The PET scanner detects pairs of gamma rays created when electrons in tissue encounter positrons emitted from the injected radiotracers. Computer programs use these data to reconstruct multi-dimensional images that convey the distribution of these injected radiotracers, which can be done minute by minute or averaged over time. The amount of radionuclide taken up at each point in the tissue correlates with how intensely the tissue is visualized on the resulting PET image.

PET neuroimaging has been especially notable in aiding the diagnosis of neurodegenerative diseases (e.g. Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, and Huntington's disease) (Ref. Fig. 1), diseases associated with significant changes in brain metabolism. [1]

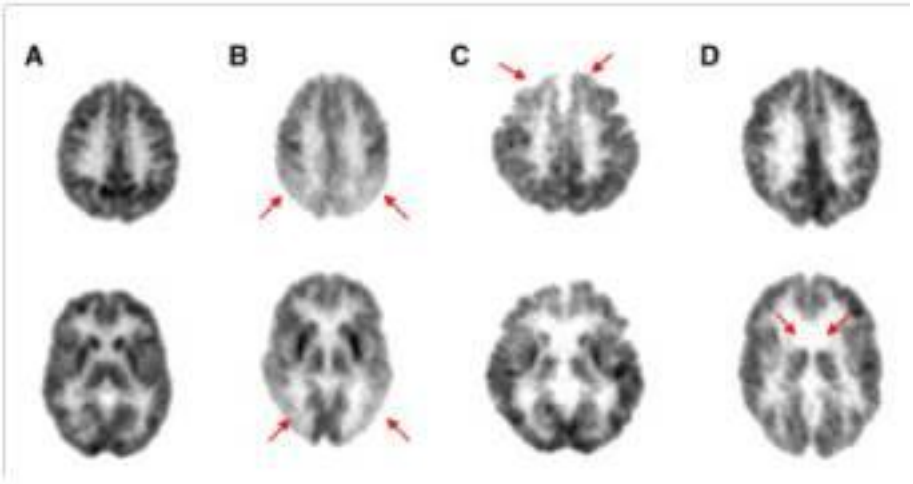

Fig. 1. FDG distribution patterns of normal and abnormal brains. PET images are presented in inverse gray scale. There is a linear relationship between pixel darkness level and radioactive counts per second. Image planes include high- (*top row*) and mid- (*bottom row*) transaxial levels. The FDG distribution shows (*A*) normal metabolic pattern, (*B*) posterior (parietal, temporal, posterior cingulate) hypometabolism characteristic of early AD, (*C*) anterior hypometabolism characteristic of early frontal lobe dementia, and (*D*) striatal hypometabolism characteristic of Huntington's disease**.** [1]

The most commonly used tracer in clinical PET imaging is a glucose analog, [^{18}F] fluorodeoxyglucose (FDG). After cellular uptake has occurred, hexokinase phosphorylates FDG, which then becomes trapped within cells, with the regional rate of uptake and trapping serving as an index of brain metabolism. The development of other radiotracers, such as dopaminergic and amyloid imaging agents is an area of expanding investigation. [2]

During the past one- and one-and one-half decades, PET has most often been used in conjunction with CT, acquired near-simultaneously with hybrid imaging instruments. More recently, the use of PET/MRI hybrid instruments is increasingly emerging, especially in research settings. [3]

Section 2 "Normal FDG-PET"

PET neuroimages can be interpreted both quantitatively and qualitatively. Typically, for clinical use, PET images are examined visually. On the other hand, quantitative and statistical mapping analyses are commonly used to analyze PET scans for research purposes. [4]

To successfully read and interpret PET images, the ability to recognize normal PET scans of healthy individuals of all ages is key. Measures of cerebral glucose metabolic rates in healthy brains have been determined to range from 3.6 to 5.2 mg glucose/min/100 g in tissue white matter structures, while gray matter structures have been found to range from 5.8 to 10.3 mg glucose/min/100 g. While regional differences in metabolism are present, glucose use is normally fairly symmetric between cerebral hemispheres. [2;5]

Normal and predictable metabolic changes occur as a healthy individual ages. Therefore, it is essential to keep the patient's age in mind when interpreting an FDG-PET scan to assess whether a scan falls beyond the normal limits of what is expected at a given age. For example, newborns exhibit highest levels of glucose metabolism in the primary sensorimotor cortex, cingulate cortex, hippocampal region, thalamus, cerebellar vermis, and midbrain. Throughout the first three months of life, glucose metabolism increases are largely seen in the cerebellar cortex, basal ganglia, and parietal, temporal, and primary visual cortical areas. By the first or second year, the frontal cortex displays increased glucose metabolism, and, at this point, the brain, as seen on FDG-PET, appears similar to that of an adult brain. The absolute rates of glucose metabolism are about 2 to 3 times greater than that of an adult brain by age 10. During adolescence, this level of metabolism decreases until it reaches normal adult levels. In healthy adults, the pattern and level of metabolism remains relatively constant. However, age-related declines in the medial frontal cortex, including the anterior cingulate cortex to the supplementary motor cortical area, and in the medial orbito-frontal cortex are typically seen. [1;2;5;6]

Section 3 "Default Mode Network"

The Default Mode Network (DMN), and the brain structures it includes have been implicated in a wide range of neurologic function and disorders. The DMN is characterized by its engagement during cognitive rest, and deactivation during performance of cognitive tasks.

Networks, or interacting brain regions with highly correlated activity distinct from other networks, may provide insight on the inner workings of the brain. In addition to purely structural abnormalities, disruptions in brain network activity can have devastating implications functionally. Numerous recent studies have employed PET imaging and other imaging modalities with hopes of gaining a more comprehensive

understanding of the DMN. In their study using FDG-PET, proton magnetic resonance spectroscopy, and resting-state functional MRI, Passow et al[7] aimed to determine whether local glucose consumption and local glutamatergic neurotransmission share a relationship with DMN functional connectivity during rest. They found that local glucose consumption, but not glutamatergic neurotransmission, was positively associated with functional connectivity within the DMN. The finding that there is a close association between metabolic activity and functional connectivity further validates the value of FDG PET images in understanding brain function.

Significant changes in the DMN are observed in certain disease states as well as in normal aging. The posterior cingulate cortex, dorsal and ventral medial prefrontal, lateral parietal cortices, and medial temporal lobes are brain structures involved in the DMN. Mevel et al.[8] determined that with normal aging comes significant reductions in activity in brain areas involved in the DMN at rest through the use of FDG-PET, H_2O-PET, and fMRI. While, currently, not entirely substantiated, Mevel et al. propose that changes in the DMN due to normal aging can be explained by a "posterior anterior shift in aging." This model postulates that, due to the posterior DMN decrease in resting-state activity, the frontal DMN areas compensate by increasing their activity. [8]

While the DMN is most widely studied for its involvement in Alzheimer's disease, it is also known to play a role in schizophrenia, autism, hyperactivity disorder, epilepsy, and multiple sclerosis. In Alzheimer's disease, two main DMN structures, the posterior cingulate cortex (PCC) and the hippocampal formation, have been the focus of much research. These two regions are both implicated in the early stages of the disease. Specifically, the hippocampal region is typically the first area to atrophy, while the PCC is found to be significantly hypometabolic in early stages of the Alzheimer's process. These structural and functional changes compromise the connection between the two regions. These findings imply that connectivity changes could be early signs of Alzheimer's disease. [8]

Section 4 "Cognitive Impairment"

Cognitive function categories, often described as "domains", include executive control, decision making, working memory, long-term memory, attention, speech and language[9]. The risk for cognitive impairment increases with age, especially for memory, attention, and executive control[9]. One study described neuropsychological assessments in 70-90 year olds without dementia at baseline and after a 2-year follow-up; researchers found that across all subjects, there was a decline in multiple cognitive domains examined (memory, executive function, attention/processing speed, and global cognition) and 14% of subjects developed mild cognitive impairment (MCI) or dementia[10]. There are approximately 47.5 million people with dementia, worldwide, and 7.7 million new cases every year[11]. It is important to identify impairments earlier in order to increase quality of life, delay onset of debilitating symptoms that cause loss of independence in patients, and potentially prolong or prevent the institutionalization of patients[12;13;14]. The US National Institute on Aging (NIA) recommends early screening for dementia in order for physicians to plan long-term care accurately, treat the underlying health condition, and provide caregivers and patients with ample time and resources to prepare mentally, financially, and physically for lifestyle changes. Caring

for patients with cognitive impairments is costly. In 2016, it was estimated that $236 billion dollars was spent on caring for Alzheimer's alone in the US. [15] According to a study funded by the US National Institutes of Health NIA, the average total healthcare cost of $287,000 or $183,000 for Medicare beneficiaries was determined per person with probable dementia five years before death[16]. Rattinger et al.[17] reported that an increase in severity of dementia led to greater costs of care amounting to 6% higher per point lost in Mini-Mental State Examination (MMSE) scores. Furthermore, cost of care increased over 2-fold for patients diagnosed with mild dementia, 5-fold for moderate, and 6-fold for severe dementia. Addressing dementia earlier often leads to the slower progression of dementia symptoms and severity, which could provide financial relief to patients and their caregivers[18;19]. Primary care physicians are often the first responders to patient and family complaints of cognitive decline, making their role important in recognizing and responding accordingly[20;21;22]. PET has proven to be a useful tool in determining the underlying disorders linked to cognitive impairment, especially those related to neurodegenerative diseases (Ref. Table 1).

Table 1. Optimal combinations of PET targets and MRI sequences to assist with the diagnosis of specific neurodegenerative diseases

Disease	**Imaging Modalities**	**Characteristic Findings**
Alzheimer's Disease	FDG-PET; Amyloid-PET; MRI (T2 FLAIR and T1 3D GRE)[3]	FDG-PET: hypometabolism in parietal, temporal, and posterior cingulate cortices (early stages); relative sparing of primary sensorimotor and primary visual cortex' sparing of striatum, thalamus, and cerebellum Amyloid-PET: loss of distinctive gray-white matter border[23] MRI: mesial temporal lobe (especially hippocampus and entorhinal cortex) atrophy; tempoparietal cortical atrophy[24]
Frontotemporal Dementia	FDG-PET; MRI (FLAIR and T1 3D GRE)[3]	FDG-PET: hypometabolism found earlier and/or with greater initial severity in frontal cortex, anterior temporal and mesiotemporal areas than in the parietal and lateral posterior temporal cortex; relative sparing of primary sensorimotor, posterior cingulate, and visual cortex[23] MRI: atrophy in ventromedial frontal cortex, bilateral posterior orbital frontal regions, bilateral insula, anterior cingulate cortex, dorsolateral frontal cortex, and premotor cortex[25]
Vascular Dementia	FDG-PET; MRI (FLAIR, T2/SWI, and DWI)[3]	FDG-PET: hypometabolic foci affecting cortical, subcortical, and cerebellar areas[23] MRI: lacunar infarcts; abnormalities in cerebral white matter[26]

Dementia with Lewy Bodies	FDG-PET; MRI (FLAIR and T1 3D GRE)[3]	FDG-PET: similar to Alzheimer's Disease, but less sparing of occipital cortex[23] MRI: generalized decrease in cerebral volume most marked in frontal lobes and parietotemporal regions; enlargement of the lateral ventricles; relatively focal atrophy of the midbrain, hypothalamus, and substantia innominate; hippocampi remain normal size[27]
Parkinson's Disease	FDG-PET; Dopamine-PET; MRI (T1, T2 multiplanar, and T2/SWI)[3]	FDG-PET: similar to Alzheimer's Disease, but less paring of visual cortex; in early, untreated Parkinson's Disease, basal ganglias may appear hypometabolic[23] 18F-dopa-PET: low putamen Striatal dopamine receptor (D2) sites: normal or up (untreated); normal or low (treated) MRI: substantia nigra shows loss of normal swallow tail appearance[28]
Huntington's Disease	FDG-PET; MRI (T1, T2, and T2/SWI)[3]	FDG-PET: early hypometabolism in caudate and lentiform nuclei; gradual development of diffuse cortical hypometabolism[23] MRI: caudate head atrophy causing enlargement of frontal horns, which is measured by (frontal horn width/intercaudate distance) and (intercaudate distance/inner table width)[29]
Primary Progressive Aphasia (PPA): (ref. table 3 For subtype details)	FDG-PET; MRI	FDG-PET: left frontal hypometabolism; left anterior temporal hypometabolism; left temporal-parietal hypometabolism[30] MRI: left posterior frontoinsular atrophy; anterior temporal atrophy; left posterior perisylvian and inferior parietal atrophy[31]

Section 5 "Memory"

Memory problems, a common form of cognitive impairment may entail decline in ability to recall details that interferes with daily activities. Some form of memory impairment is seen in about 1 in 3 people over the age of 70 in the US[32]. Memory loss is commonly associated with Alzheimer's diseases (AD). AD is a neurodegenerative disorder, associated with beta-amyloid plaques and tau tangles in the brain. Treatments for AD include cholinesterase inhibitors, memantine, and medications that treat subsequent symptoms, such as changes in sleep patterns and behavior or depression. Studies have also shown that good diet, exercise, and mental stimulation help delay symptoms in patients with AD. Non-AD disorders that affect memory include various

types of dementia (vascular or neurodegenerative diseases such as frontotemporal dementia or Lewy Body Disease), hippocampal sclerosis, traumatic brain injuries, and epilepsy[33].

FDG-PET can identify early onset of AD, before a distinct pattern of symptoms manifest, and, it is the preferred imaging modality with respect to overall accuracy in evaluating patients with possible AD[34]. Early onset and late onset AD also can have distinct metabolic features[35].

The Metabolic Cerebral Imaging in Incipient Dementia (MCI-ID) trial involves examination of early and long-term value of imaging brain metabolism, through a prospective multi-center randomized study of the impact of PET in patients undergoing evaluation for mild cognitive problems[36]. Prior to an interim analysis of data acquired through May 2013, 63 subjects (each at least 65 years old) were enrolled of whom 59 underwent a baseline FDG-PET brain scan as well as neuropsychological testing. Forty-three of those subjects completed the study by undergoing repeat neuropsychologic testing plus medication prescription data collected every 6 months for 2 years (Ref. Table 2): 24 were randomized to immediate release of PET results to their managing physicians and the other 19 randomized to a 2-year delayed release of PET results to their managing physicians. It was found that immediate release of PET findings was associated with earlier prescription of AD-drugs for patients with AD-like brain metabolism (Ref Fig. 2), with over three times as many being prescribed cholinesterase inhibitors (most commonly donepezil) within the first year after PET.

Table 2: Demographic Data for all subjects, and completing subjects, in MCI-ID trial

	All Subjects (n=63)	**Subjects with analyzed medication data (n=43)**
Age		
Av ± SD	74.54 ± 6.69	74.60 ± 6.51
Median	75	75
Range	65-90	65-90
Sex		
Male	37 (59%)	27 (63%)
Female	26 (41%)	16 (37%)
PET pattern		
AD-like	21 (36%)	18 (42%)
non-AD-like	38 (64%)	25 (58%)

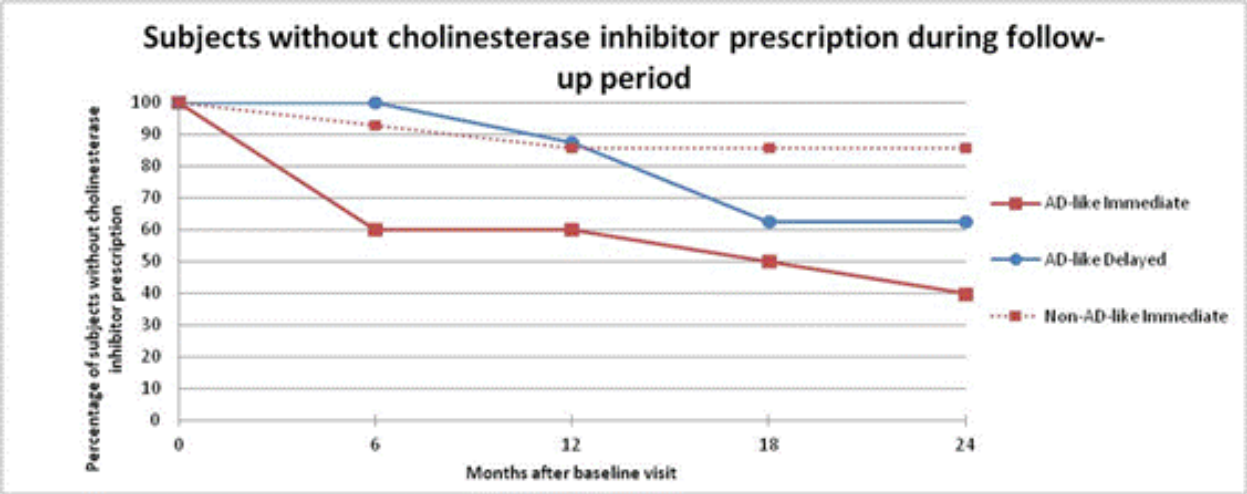

Fig. 2: Immediate release of PET findings associated with earlier prescription of AD-drugs for patients with AD-like brain metabolism.

Furthermore, over the 2 year follow-up period, subjects with AD-like patterns of brain metabolism who were prescribed AD-targeted medications within the first year of follow-up did significantly better than those who were not, on tests of both memory and executive function (Ref. Table 3, Figure 3).

Table 3: Rate of change in the ADAS-Cog Memory Subscale, MMSE, and Trail Making Part B test scores for patients with PET scans AD-like who were prescribed and not prescribed AD medications in the 1st year of follow-up (a). Rate of change in the ADAS-Cog Memory Subscale, MMSE, and Trail Making Part B test scores for subjects with non-AD-like PET who were prescribed and not prescribed AD medications in the 1st year follow-up (b).

Rate of Change in Test Scores for AD-like Subjects Prescribed or Not Prescribed AD Meds in 1st Year Follow-up				
	All AD-like	AD Meds in 1st year	No AD Meds in 1st year	p value
ADAS-Cog Memory Subscale	+0.82 pts/yr	-3.3 pts/year	+2.9 pts/yr	0.02
MMSE	-1.04 pts/yr	+1.63 pts/yr	-1.93 pts/yr	0.02
Trail Making Part B	+39.6 sec/yr	-5.7 sec/yr	+62.3 sec/yr	0.0004

(a)

Rate of Change in Test Scores for non-AD-like Subjects Prescribed or Not Prescribed AD Meds in 1st Year Follow-up				
	All non-AD-like	AD Meds in 1st year	No AD Meds in 1st year	p value
ADAS-Cog Memory Subscale	-1.43 pts/yr	+0.57 pts/yr	-1.68 pts/yr	N.S.
MMSE	-1.75 pts/yr	-1.70 pts/yr	-1.76 pts/yr	N.S.
Trail Making Part B	+13.6 sec.yr	+1.70 sec/yr	+15.1 sec/yr	N.S.

(b)

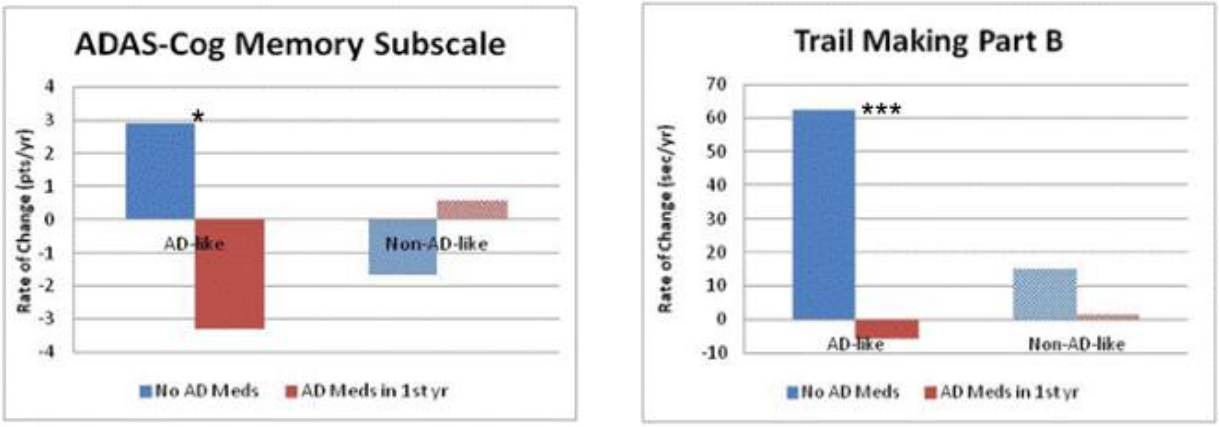

Fig. 3: Over the 2 year follow-up period, AD-like subjects who were prescribed AD-targeted medications (**red** solid bars) within the first year of follow-up did significantly better than those who did not receive AD-targeted medications (**blue** solid bars) on tests of memory (*Left panel*, lower score=better memory), and executive function (*Right panel*, lower score=better executive function) while those with non-AD like patterns did not benefit from early prescription of the drugs. *p=0.02 and ***p=0.0004

FDG-PET was thus able to not only detect AD-altered brain metabolism and distinguish it from metabolic patterns found for other causes of declining cognition, but also provide clinically meaningful

therapeutic guidance that significantly impacted cognitive outcomes.

PET has also been used to study microglial activation in early AD. Microglia appear to play a particularly active immunologic role in the brain[37]. A continuous increase in microglial pro-inflammatory mediators is neurotoxic, such that systemic inflammation may trigger neurological disorders. In AD, amyloid plaques can activate microglia leading to inflammatory changes[38]. The microglia can potentially delay AD progression by helping clear amyloid plaques and secreting neuroprotective growth factors and anti-inflammatory cytokines, or become hyperactive over time causing greater damaging inflammation. Investigators are currently trying to better define microglia (normal state or activated) at different stages of AD[37;38].

In one study, 96 participants (64 with AD and 32 controls) had undergone PET with both the amyloid-imaging agent Pittsburg compound B and with the microglial-labeling agent F-DPA PET-714 tracer[38]. Of the 64 subjects with AD, 38 were classified with prodromal AD and 26 with AD dementia. Subjects were classified as high, mixed, and low affinity binders. After 2 years of follow-up, researchers further ranked the 30 high + mixed binders with AD into slow and fast decliners (n = 10 and n=20, respectively) (Ref Fig 4).

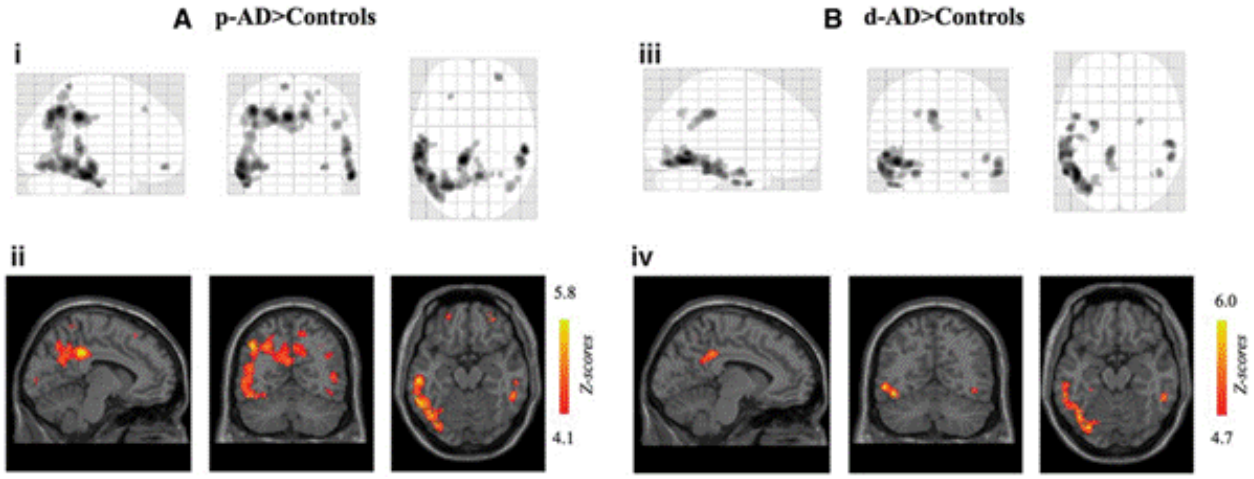

Fig. 4: Statistical parametric mapping analysis of ^{18} F-DPA-714 binding (SUVr) between (A) patients with prodromal Alzheimer's disease (p-AD) and controls and (B) between Alzheimer's disease dementia (d-AD) and controls, in the combined High Affinity Binders (HAB) + Mixed Affinity Binders (MAB) group. (**i** and **iii**) 'Glass brain' representations and (**ii** and **iv**) sagittal, coronal and axial views (x = 65, y = 44 and z = 37) with corresponding z-values. Significance threshold set at P <0.05 family-wise error (FWE) corrected, with *TSPO* genotype as covariate.

Reproduced directly from reference[38]: Lorraine Hamelin et al., *Early and protective microglial activation in Alzheimer's disease: a prospective study using ^{18} F-DPA-714 PET imaging*, Brain, 2016, Volume 139, Issue 4, Pages 1252-1264, by permission of Oxford University Press)

Protein binding correlated positively with grey matter volume, Pittsburgh compound B binding, and Mini-Mental State Examination scores. There was also greater protein binding in slow decliners vs. fast decliners.These findings further support that microglial activation emerges in early AD (prodromal and potential preclinical stage) and may serve as a protector from declining clinical progression of early AD[38].

Recently, there has been a stronger push towards using a multimodal approach

clinically, encompassing PET and other diagnostics tools to identify AD-type decline early, and distinguish it from other causes of memory impairment. One study compared the sensitivity of FDG-PET, MR morphometry via structural MRI, diffusion tensor imaging, derived fractional anisotropy, and memory testing via RAVLT in diagnosing memory impairment in 44 MCI patients and 22 controls, individually versus all imaging modalities combined. After comparing the results of each modality, researchers determined 100% accuracy in diagnosis when all methods were combined, while no method was entirely accurate alone[39].

Section 6 "Executive Function"

Executive function governs an individual's ability to control his or her actions and self-awareness. Deficiencies in executive function can lead to the loss of ability to multitask, the ability to plan and initiate, verbal fluency, and the ability to process/store/retrieve information. Because these skills are so essential to everyday life, impairments significantly hinder the patient's quality of life. Frontotemporal Dementia (FTD) is a neurodegenerative disorder typically associated with loss of executive functions. There are multiple types of FTD. Behavioral-variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA) are relatively common examples. Researchers often refer to bvFTD as "FTD" and groups SD and PNFA as Progressive Primary Aphasia (PPA). Typically, cell death occurs in anterior temporal and/or frontal lobes[40]. Non-neurodegenerative disorders associated with impairments in executive function include obsessive-compulsive disorder, attention deficit hyperactivity disorder, Autism, and Tourette's syndrome. PET has been shown to help confirm presence of FTD and distinguish it from other neurodegenerative disorders, such as AD.

Foster et al.[41] examined 45 patients that had undergone FDG-PET at the University of Michigan and had dementia and autopsy confirmed diagnoses of AD (31 cases) or FTD (14 cases), without other pathological complications. Six neurologists used 5 different methods (review of clinical information, diagnostic checklist, clinical information + checklist, transaxial FDG-PET scans, and FDG-PET stereotactic surface projection (SSP) metabolism and statistical maps) to rate each case as AD or FTD and their degree of confidence (very confident, somewhat confident, uncertain). The six raters and 45 subjects totaled 270 observations for each measure. Researchers found that the overall accuracy increased from 79% with initial clinical diagnosis to 90% with FDG-PET info ($p=0.03$). Furthermore, PET significantly increased the diagnostic accuracy of FTD ($p=0.01$). Scan ratings changed in 42 (16%) of the scans after the addition of FDG-PET; of these 42 changes, 34 (81%) corrected the earlier misdiagnosis.

Along with determining decline in executive function due to FTD, PET can also be used to examine cognitive dysfunction in high level processing, associated with exposure to chemotherapy. The National Cancer Institute predicts that 1,685,210 new cases of cancer will be diagnosed in the US in 2016, and 595,690 patients will die from it[42]. With cancer patients living longer, physicians have had a greater chance to understand the long-term effects of the cancer and its treatments. Many patients report cognitive decline after undergoing chemotherapy.

In an early study in this field, researchers gave formal cognitive testing to 28 breast cancer patients 6 months following cancer treatment and compared their results

to that of the normal population. They found that 75% of the patients scored below the expected level (-2SD on one or more of the cognitive measures[43]. In a more recent study, Ganz *et al.*[44] prospectively studied 189 breast cancer patients who completed neuropsychological testing. Twenty-three percent of the participants had higher memory complaints and 19% had high executive function complaints. Further analysis revealed a significant correlation between high memory complaints and the combination of chemotherapy plus radiation therapy[44].

Silverman *et al.*[45] investigated brain metabolism and blood flow in 16 right-handed women that underwent chemotherapy for breast cancer and 8 women that never received chemotherapy. The subjects performed control and memory related tasks while undergoing [O-15] water PET scans to determine cerebral blood flow due to cognition, and [F-18] FDG- PET to evaluate resting brain metabolism. Researchers found that patterns of cerebral blood flow in the frontal cortex and cerebellum during short-term recall was significantly altered in patients who underwent chemotherapy. They also found that cerebral activation in the interior frontal gyrus was significantly different in controls compared to in subjects that underwent chemotherapy[45].

In another study, 33 breast cancer patients who had completed initial treatment (23 with chemotherapy and 10 without) underwent FDG-PET evaluation, cognitive impairment assessment, and serum measurements for pro-inflammatory cytokine markers (IL-1ra, sTNF-RII, CRP, and IL-6) at baseline and one year after treatment. Cognitive complaints and cytokine levels correlated with metabolism in medial prefrontal cortex and anterior temporal cortex in patients that had undergone chemotherapy, but not in chemotherapy-naive subjects[46].

Section 7 "Language"

In the past, much of our understanding of language in the brain came from observations of individuals with brain lesions or diseases. Largely based on this lesion data, researchers concluded that language processing is strongly lateralized to the left cerebral hemisphere in most people, and involves a network that includes frontal, temporal, and parietal lobes[47]. However, studies reveal that somewhere between 5% and 30% of individuals have language networks that have right-sided or bilateral language function. [30;48]

Deficiencies in speech range from stuttering to apraxia and/or may be related to conditions such as strokes, autism, ADHD, oral cancer, or dementia. Primary Progressive Aphasia (PPA) is a cognitive disorder that is caused by neurodegenerative disease, and involves the gradual loss of language function. It is usually the result of degeneration of brain tissue related to speech and language. Initially, patients with PPA experience confusion over common words. As PPA worsens, verbal communication is deeply affected and patients even lose the ability to understand speech. An important clinical feature of PPA is that it is unaccompanied by other significant cognitive dysfunction in its early stages, meaning that patients with PPA may still live their normal lives. Memory and perception is affected in later stages. There are three main subtypes of PPA: Semantic Variant PPA, Logopenic Variant PPA, and Nonfluent/Agrammatic Variant PPA**.** They are associated with different neurodegenerative profiles and accompanied by different clinical features (Ref. Table 4). In a recent study[30], 44 FDG PET scans were analyzed, by statistical parametric mapping and visual analysis methods. The raters were

blind to clinical information and answered a standardized questionnaire that accounted for the quality of each scan, the presence of PPA, which subtype of PPA, and the underlying disease. Researchers found that agreement between PPA and control and variants of PPA except nonfluent/agrammatic PPA, was high, with accuracies of over 90 percent achieved[30]

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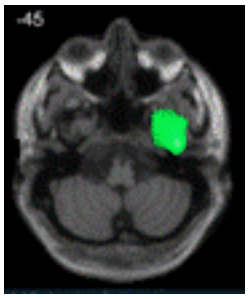
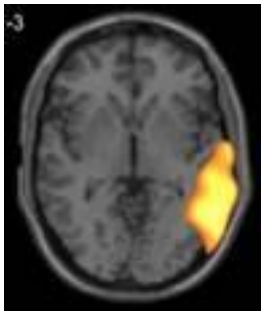
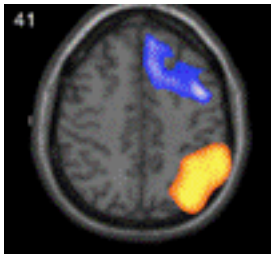
Table 4: Key clinical features, associated neurodegenerative diseases, PET and MRI findings, and MRI images with highlighted regions of hypometabolism of PPA variants (Adapted from: Bonner et al. and Matias-Guiu et al.).

Primary Progressive Aphasia (PPA) Variant	**Clinical Features**	**Associated Neuro-degenerative Disease**	**PET and MRI Characteristic Findings**	**Scans**
Semantic Variant PPA	-impaired single word comprehension and retrieval -three or more of: poor object and/or person knowledge; surface dyslexia: spread repetition; spared motor speech	FTLD-TDP	FDG-PET: left anterior temporal lobe, especially superior, middle, and inferior temporal gyri, hypometabolism; in some cases, corresponding regions in the right hemisphere can be affected, but to a lesser extent[30] MRI: anterior temporal lobe atrophy[31]	 The green color highlights hypometabolism on an MRI in Semantic Variant PPS.
Logopenic Variant PPA	-impaired repetition of phrases and sentences -three or more of: speech sounds errors; spared motor speech; spared single word comprehension and object knowledge; absence of agrammatism	AD	FDG-PET: left parietotemporal, especially middle, inferior, and superior temporal gyri, and supramarginalis and angularis gyri hypometabolism[30] MRI: left posterior perisylvian and inferior parietal cortical atrophy[31] Amyloid imaging PET: most commonly is positive for this PPA variant only	 The yellow color highlights hypometabolism on an MRI in Logopenic Variant PPS.

Nonfluent/Agrammatic Variant PPA	-grammatical simplification and errors in language production -effortful halting speech with speech sound errors -two or more of: impaired syntactic comprehension; spared content word comprehension; spared object knowledge	FTLD-tau	FDG-PET: left frontal, especially middle and inferior frontal, and precentral gyri hypometabolism[30] MRI: left posterior frontoinsular hypometabolism[31]	 The blue color highlights hypometabolism on an MRI in Nonfluent/Agrammatic Variant PPS.

Section 8 "Limbic Encephalitis"

Limbic encephalitis can cause various symptoms including memory loss, seizures, confusion and altered personality/behavior. There are two major types of encephalitis: infectious encephalitis due to direct invasion via virus or infectious agent (i.e. HSV-1) and autoimmune encephalitis due to an individual's own immune system attacking the limbic region. Paraneoplastic limbic encephalitis (PLE) and non-paraneoplastic limbic encephalitis (NPLE) fall under autoimmune encephalitides, secondary to autoantibodies. In NPLE, patient have similar clinical symptoms as PLE but no tumor. Clinicians can order blood tests for these antibodies to confirm their presence. Using PET, physicians can detect underlying malignancy and visualize the location of subsequent tumors that go undetected by other means[49;50].

In a retrospective study completed by Kristensen et al.[51], researchers studied 137 patients who were referred from 2009-2013 with suspected Paraneoplastic Syndrome (PNS). Their resulting PET/CT scan reports were compared to a final follow-up of average 31 months later in patients who did not have an immediate positive scan for cancer, and accuracy for identifying malignant causes of symptoms was 82% [51]. In another retrospective study, 42 patients with clinically suspected PNS were studied in relation to histological findings, PET/CT results, and PNS antibodies to examine the value of PET/CT for identifying intrinsic malignancy in presence of PNS antibodies[52]. Overall accuracy for identifying or excluding PNS exceeded 90% [52].

Section 9 "Dopaminergic Function and Central Motor Disorder"

The dopaminergic system plays a substantial role in the regulation of movement, motivation, and cognition. Disorders of that system have been identified in Parkinson's disease, Huntington's disease, tardive dyskinea, schizophrenia, depression, addiction and many other conditions. The ability to image and study this system through PET has opened the doors for greater understanding, more accurate diagnosis, and improved therapy. [53;54]

Dopaminergic neurons are concentrated in the substantia nigra and ventral tegmental area of the brainstem, and innervate the forebrain. There are five subtypes of dopaminergic receptors, each with slightly varying actions. The two most well understood, and highest density receptors include D1 and D2, both of which

are involved in positive regulation of behavioral activity. D3. D4, and D5 are all characterized by their inhibitory actions. D2 and D3 are concentrated in the limbic regions, and are known to be related to drug dependence and addiction. D4 has been found to be involved in schizophrenia. Abnormal alterations of the synthesis, transport, and receptor density of dopamine all have substantial implications in the development of these neurological and psychiatric disorders. High-affinity and selective PET-tracers have been developed for these targets[53]. Synthesis targeting tracers include 6-[18F]FDOPA and 6-[18F]FMT, while transport targeting tracers include 11C/18F-labeled tropane analogues. Selective and high-affinity PET radioligands have also been developed to investigate the postsynaptic role and density of receptor subtypes D1, D2, and D3. Such D1 ligands or tracers include [11C]SCH 23390 and [11C]NNC 112. Developed D2/D3 ligands are [11C]raclopride and [18F]fallypride. In conjunction with the information provided by the dopamine-specific tracers, FDG-PET can also assess the parallel functional consequences of changes in dopaminergic activity. [53;54]

In order to accurately assess altered dopaminergic function, it is necessary to understand how the system appears in a healthy brain, and normal changes that occur simply due to aging. Dopamine cells are predominantly located in the midbrain. The neurons originating in substantia nigra project to the dorsal striatum. This neuronal group is primarily involved in movement initiation and execution. The ventral tegmental area contains the dopamine neurons that are particularly involved in reinforcement, motivation, mood, and thought organization and project to the limbic, and limbic connected regions. Such brain structures include the nucleus accumbens, orbital and cingulate cortices, amygdala, and hippocampus. Lastly, dopaminergic neurons originating in the retrobulbar area terminate in the hypothalamus, and are responsible for regulating pituitary hormone secretion.

While normal aging does increase an individual's chance of developing a neurodegenerative disease, there is an important distinction between brain dopamine changes as a result of normal aging and changes due to the presence of a disorder. Aside from the use of dopaminergic PET scans for clinical evaluations, they have been a valuable research tool. PET has clarified that it is not unusual for healthy elders to exhibit a mild decline in cognitive function associated with changes in the dopaminergic system. This effect is largely credited to several aging-related features of the dopaminergic neuronal system, demonstrated for example through a reduction in available D2 receptors in the caudate nucleus, putamen and frontal cerebral cortex. [55]

Antonini's and Leenders' experimental results further cement this D2 dopaminergic aging pattern. The researchers used PET to scan two age groups of healthy individuals using radiotracer [11C]-Raclopride (D2 antagoinst). It was discovered that uptake of the tracer in the caudate nucleus and putamen in the older group of subjects was, on average, 20% and 26% less, respectively, than uptake in the younger age group. Dopamine transporter studies have also identified age-related declines in the caudate nucleus and putamen. There is an average of 6.6% decline in dopamine transporters each decade of life beginning at age 18, and occurring nearly linearly through age 88. [56;57;58]

((18)F-DOPA) PET tracer has been particularly helpful in aiding early diagnosis of idiopathic Parkinson's disease (PD), a

neurodegenerative disorder caused by progressive loss of dopaminergic neurons in the basal ganglia and distinguishing it from other Parkinsonian syndromes. Early in the course of the disease, PD can be difficult to distinguish from Parkinson's plus syndromes and other movement disorder processes. This is the case because, in addition to an overlap in clinical features, traditional imaging techniques (CT, MRI) are not capable of providing valuable diagnostic information until advanced disease stages when morphological alterations become detectable. ((18)F-DOPA) tracer targets presynaptic dopamine function, marking dopamine neuronal metabolism. This tracer is sensitive to changes occurring in the brain even prior to expression of PD symptoms. Basal ganglia, especially posterior putamen, uptake of ((18)F-DOPA) in PD has been found to be reduced compared to controls. Additionally, PD patients exhibit a more accelerated loss of dopaminergic neurons, as compared to normal controls. This tracer thus provides information in diagnosis of disease in pre-clinical stages, as well as monitoring of disease process, and response to therapy. [23;59]

In the near future, hybrid PET/MRI systems may play an increasing role in the early diagnosis of PD[59]. This technology will allow near-simultaneous assessment of both primary neurodegenerative and cerebrovascular-related or other structural changes in brain tissue. [23]

Section 10 "Amyloid Imaging"

Neurodegeneration, or neuronal loss, is directly related to cognitive decline. Senile plaques and neurofibrillary tangles, abnormal protein structures within the brain, are often associated with dying neurons. Sticky clumps of protein, Amyloid-beta make up senile plaques. Amyloid PET identifies plaques not only in Alzheimer's Disease, but also in other brain disorders, as well as in normal aging (Ref. Fig 5). As a result, the presence of amyloid alone does not confer a diagnosis of Alzheimer's Disease, though the absence of it is considered to make the diagnosis unlikely. Amyloid-beta plaques are not found as a result of frontotemporal dementia or pure vascular dementia. [6;60]

Amyloid imaging and autopsies have revealed that amyloid-beta plaque buildup occurs in many well-functioning people as a result of normal aging. This accumulation of plaque can begin in middle-aged people, or even earlier, and has been found to be correlated with minor memory issues. Autopsies revealed that over 20% of elderly men and women have buildup of amyloid-beta plaque, despite having had normal memory throughout their lives. While it is widely agreed that the presence of plaques alone is not justification for an Alzheimer's diagnosis, it remains largely unclear as to whether plaques in cognitively functioning people is necessarily an indication of early stages of Alzheimer's disease. The Harvard Aging Brain Study aimed to determine whether amyloid presence can be accepted as a method of pre-diagnosing Alzheimer's disease. In this study, 87 cognitively normal older adults and 32 adults diagnosed with mild Alzheimer's disease underwent MRI and PiB-PET scanning. It was discovered that the cognitively normal subjects who had amyloid-positive scans also tended to have similar, but less severe, structural changes as those with mild AD. Interestingly, the structural changes were most evident in brain regions that are involved in the Default Mode Network, representing of highly connected brain structures known to be implicated in the early course of AD. [61]

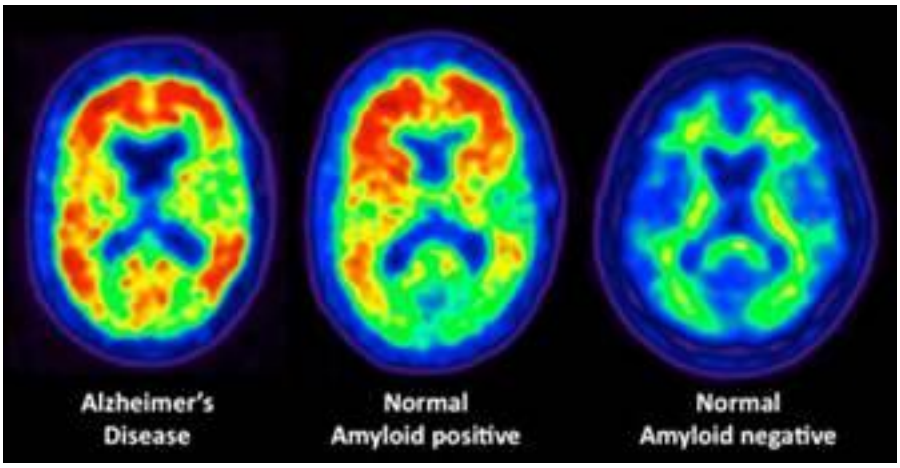


Fig. 5 These PET scans show amyloid plaque in red and orange. The leftmost scan shows amyloid plaque build up in a patient with Alzheimer's Disease. The middle image shows an individual with amyloid plaque but no cognitive problems. The rightmost scan shows a cognitively normal individual with no amyloid plaque present. [62]

To date, three F18 labeled tracers have been approved by the FDA for clinical use in amyloid imaging, including flutemetamol (Vizamyl), florbetapir (Amyvid), and florbetaben (Neuraceq). All three F18-labeled tracers have high nonspecific white matter uptake, creating a discrete white matter pattern in scans of healthy brains. In Alzheimer's, the scan shows a loss of this distinctive gray-white border, and a resulting loss of the normal white matter pattern. This can be taken as evidence of the presence of cortical amyloid plaques. Interpretation of certain scans can be clouded by image noise, atrophy, and image blur. In the case of those issues, it may be useful to co-register the PET image with a CT or MRI scan, if available. This co-registration allows for comparison of PET radioactivity with the gray matter anatomy, as seen in the structural image. [60;61]

Imaging Dementia – Evidence for Amyloid Scanning (IDEAS)[60] is an ongoing, large-scale study employing Amyloid-PET imaging to determine if the generated images have the capacity to aid physicians in the treatment of Alzheimer's disease, and if in fact that treatment actually results in significantly better outcomes. With a budget of approximately $100 million, the study is expected to span over the next four years and is led by the Alzheimer's Association, and managed by the American College of Radiology and American College of Radiology Imaging Network.

Section 11 "Development of new PET tracers: Neuroinflammation, Tau Imaging, and Other Agents"

As alluded to previously, during the neuroinflammatory response, increase in glial activation is linked to an increase in translocator protein expression, making it a useful target for measuring neuroinflammation imaging via PET with various radioactive tracers, including F-DPA-713, F-DPA-714, and PK-11195.

Tau tracers are also under development, though many challenges remain. Because tau aggregates are intracellular, tracers may need to not only cross blood-brain barrier, but also plasma cell membranes. To make matters more complex, there are 6 isoforms of tau, each with a different phenotype. Furthermore, tau will aggregate in white matter, nonspecifically. Despite these challenges, many scientists are currently developing tau-binding radiotracers for PET. [63; 64; 65]

In the future, additional radiotracers that are disease-specific and/or directly therapy-guiding will likely find increasingly widespread use in clinical brain PET studies.

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