
Molecular Imaging of Alzheimer's Disease Using PET

Research indicates that positron emission tomography (PET) aids in assisting specialists in the early and differential diagnosis of Alzheimer's disease (AD). In this article, Dr. Rosa-Neto and Mr. Leuzy discuss how PET reveals critical information on various aspects of the brain physiology altered by dementia.

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Molecular Imaging Techniques

Molecular imaging of the brain aims to quantify various biological processes via the modeling of interactions between a molecular probe and a molecule of interest naturally occurring in a living organism. Brain molecular-imaging techniques such as positron emission tomography (PET) and single photon emission tomography (SPECT) allow clinical investigators to record and analyze such interactions in vivo. PET and SPECT associated with specific molecular probes are sensitive to

detecting biological processes in the order of pico-molar (10^{-12}), however these techniques have limited spatial resolution. In contrast, magnetic resonance imaging (MRI) has a tremendous spatial resolution (sub-milliliter range) but lower sensitivity (micro-molar; 10^{-6}) relative to PET and SPECT (Table 1). Together, these techniques reveal critical information with regards to the alterations in the brain's anatomy and physiology witnessed in dementia, as well as canalizing diagnostic methods and therapeutic interventions.

The Nature of PET Imaging

The goal of a PET study in dementia is to quantify important biological processes altered in the brains of patients with dementia, such as glucose metabolism, cerebral blood flow, the availability of neuroreceptors and the detection of disease-related molecules (*i.e.*, amyloid deposits, tangles, inflam-

mation).¹ PET is a complex evaluation requiring expertise in many fields such as nuclear medicine, radiochemistry, imaging, kinetics and neuroscience. A PET scan likewise encompasses various activities such as:

1. production of a radioisotope;
2. synthesis of a radiopharmaceutical;
3. data acquisition;
4. imaging reconstruction; and
5. estimation of a biologically relevant outcome by the analysis of the brain radioactivity distribution maps recorded during the course of the study (Figure 1).

The production of a radioisotope is generally obtained with a particle accelerator known as a medical cyclotron (Figure 1A), which produces a beam of high-energy protons or deuterons directed against a target consisting of the nuclei of stable atoms. This process results in transmutation of the target nucleus into a short-lived positron-

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emitting radioisotope (Figure 1B). Spontaneous decomposition of the produced radioisotope occurs within a specific half-life ($[^{15}\text{O}]$, two minutes; $[^{11}\text{C}]$, 20.4 minutes and $[^{18}\text{F}]$, 109.8 minutes). The product of decomposition of these radioisotopes is an anti-electron, known as a positron. Once produced at the cyclotron facility, positron-emitting radioisotopes are chemically incorporated into radiopharmaceuticals (Figure 1C). Positrons emitted by the radioisotope present in the radiopharmaceutical collide with surrounding electrons. The resultant collision between the emitted positron and any electron located in its vicinity releases the rest-mass energy of the two particles ($E = mc^2$) as two high-energy photons (gamma rays) of 511 keV each. The photons are released at an angle of 180 degrees. If this annihilation event occurs within the PET field of view, a ring of detectors converts the coincident photons into light, which is subsequently amplified by photo-multipliers. Finally, the events computed by the scanner are analyzed by algorithms, which reconstruct the data as maps of the radioactivity concentration in the brain as a function of time (Figure 1F).

PET records the interactions between radiopharmaceuticals and molecules of interest. In essence, PET is a technique that computes patterns of spatial-temporal distributions of positron-emitting radioisotopes in the brain or any other part of the body

(Figure 1F). With few exceptions, positron-emitting radioisotopes administered to dementia patients are associated with molecular probes called radiopharmaceuticals (Figure 1C), and thus, one may assume that the distribution of radioactivity recorded by the PET camera refers to the distribution of the radiopharmaceuticals in the brain or any other organ. The use of mathematical models allows for the extraction of biologically relevant information from the spatial-temporal distributions of positron-emitting radioisotopes recorded during the PET scan. However the mathematical models

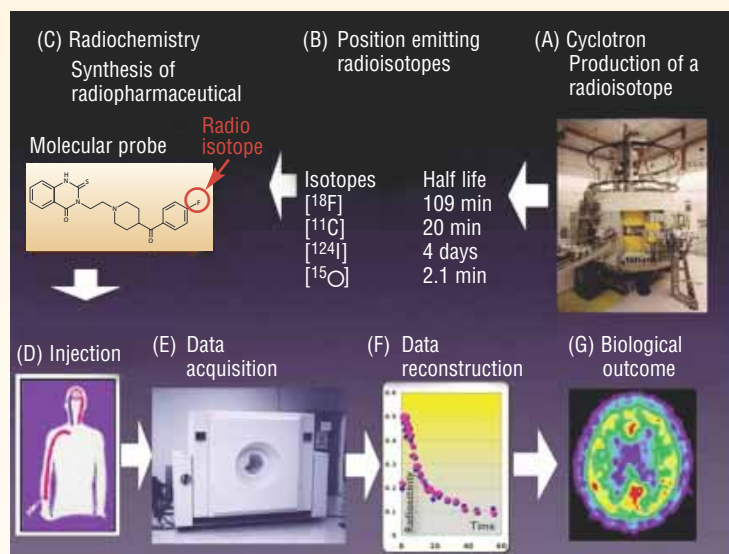
provide accurate results if:

1. the radiopharmaceuticals specifically interact with only one molecule of interest in the brain during the time frame of the PET scan; and
2. the radiopharmaceuticals are in “tracer concentration” (minute doses incapable of causing any pharmacologic effect).

Typical biological outcomes of interest for clinical research in dementia include the biodistribution of pharmaceuticals, the identification of disease-related molecules and the estimation of rates of molecular transport and energy metabolism.

Figure 1

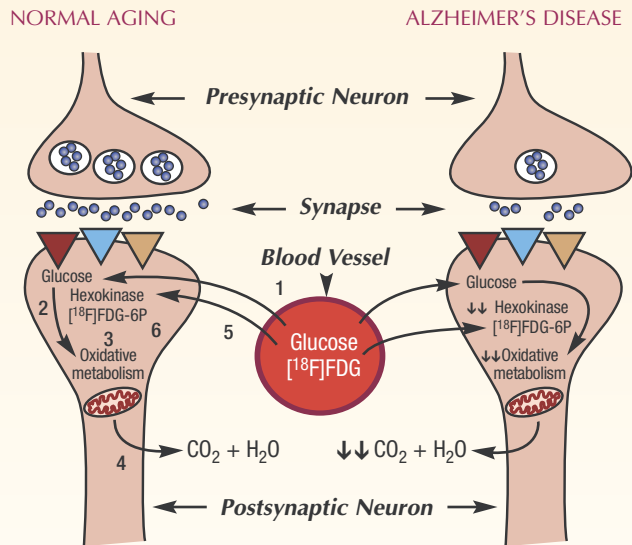
Overview of the Procedures Involved in a PET Scan



Production of radioisotopes for PET scans requires short-lived positron-emitting radioisotopes. Thus, a cyclotron (A) and radiochemistry unit must be located near the PET scanner to ensure the rapid delivery of short-lived positron-emitting radioisotopes (B) required to label radiopharmaceuticals (C). A radiochemistry unit is required for the synthesis of radiopharmaceuticals and for quality control of PET radiopharmaceuticals. The PET scan requires the venous injection of a trace amount of the molecular probe (D). The PET (E) camera records the dynamic distribution of radioactivity (F) during the time-course of a study. Images of radiopharmaceutical concentrations in the brain are reconstructed using sophisticated methods. Further processing of PET images will eventually provide biologically relevant outcomes (G). The biologically relevant outcomes are frequently expressed using colour scales, which are numerical representations of a biological process for every single voxel of the brain.

Figure 2

Schematic Representation of [¹⁸F]FDG Uptake in the Brain in Normal Subjects and Patients with AD



The glucose in the blood is transported from the vessel to the brain cells (1) where it undergoes anaerobic (2) and oxidative (3) metabolism resulting in energy, CO₂ and H₂O (4). Because energy and glucose consumption are linked with cell function, glucose metabolism is accepted as an indicator of brain function. In a PET study, glucose metabolism is measured after the venous injection of a tracer dose of [¹⁸F]FDG. Once injected, [¹⁸F]FDG is transported from the blood vessels to the brain cells (5). PET quantifies the amount of [¹⁸F]FDG-6P accumulated in the brain cells, as the hexokinase-mediated phosphorylation of [¹⁸F]FDG prevents any subsequent egress of [¹⁸F]FDG-6P from these cells (6). [¹⁸F]FDG concentrations in the brain tissue and plasma are used to calculate a biologically relevant outcome called the cerebral metabolic rate of glucose. The cerebral metabolic rate of glucose provides an estimate of the brain's glucose-consumption rate. Low synaptic activity imposed by AD pathology (7) reduces glucose metabolism and consequently reduces [¹⁸F]FDG accumulation in AD patients (right) compared to normal controls (left).

PET Imaging Outcomes of Interest for Alzheimer's Disease (AD)

Post-mortem studies indicate that the pathophysiologic process involved in AD begins long before the clinical symptoms develop.^{2,3} Thus, due to its high sensitivity and noninvasive nature, PET can identify the presence of the pathological molecules. Indeed, a number of imaging studies using longitudinal designs have shown the potential of PET to detect presymptomatic or prodromal AD in a population

with elevated genetic risk and in subjects with mild memory impairment.⁴⁻⁸ In general, PET studies on AD focus on the quantification of abnormal metabolic changes, the detection of disease-specific abnormal proteins (tau and amyloid deposits) as well as declines in neurotransmission.^{9,10} PET associated with various molecular probes has the potential to diagnose and monitor disease progression and treatment. Table 2 summarizes several PET radiopharmaceuticals applied to AD research.

Imaging abnormal cerebral blood flow and metabolism in AD.

Pioneer studies of brain metabolism performed by Kety and Lassen^{3,10} in the mid 1950s showed that a global decline of brain perfusion and metabolism is present in patients with dementia. The advent of tomographic imaging revealed that cerebral blood flow and metabolic consequences of dementia are not widely diffused through the brain; rather they are associated with a major dysfunction of certain brain regions (Figure 2 and 3).^{11,12}

Brain regional glucose metabolism is typically estimated using the PET and the molecular probe 2-fluoro-2-deoxy-D-glucose ([¹⁸F]FDG), which is an analogue of glucose normally consumed by the brain.^{13,14} In brief, the accumulation of [¹⁸F]FDG in a given brain region is proportional to its glucose metabolic rate (Figure 2).^{13,15} In typical cases of AD, declines of brain glucose metabolism (hypometabolism) and cerebral blood flow initially occur in the posterior parieto-temporal cortex and posterior cingulate cortex (Figure 3).^{11,12,16} During the evolution of AD, metabolic declines progressively spread to other brain regions initially spared during the early phase of the disease. The hypometabolism revealed by PET in AD patients possibly reflects several pathological processes underlying AD pathology, such as loss of synaptic activity, gliosis and deposits of amyloid

Table 1

Summary of Molecular Imaging Modalities Utilized in the Investigation of Patients with AD

	PET	SPECT	MRI
Sensitivity	Pico-molar concentration	Pico-molar concentration	Micro-molar concentration
Typical anatomical resolution	5 mm ³	10 mm ³	Less than 1mm ³
Quantification	Absolute	Semiquantitative outcome	Semiquantitative outcome
Typical radioisotopes utilized	[¹⁸ F]FDG, [¹¹ C], [¹⁵ O]	[^{99m} Tc] [¹²³ I]	None

plaques.¹⁷⁻¹⁹ Recent studies also link the hypometabolism in the posterior parieto-temporal cortex and posterior cingulate cortex with various vulnerability factors for AD, such as the presence of the genetic polymorphism for the apolipoprotein E epsilon 4.¹²⁻¹⁴ Furthermore, several independent studies strongly suggest that PET [¹⁸F]FDG is sensitive in detecting the presence of hypometabolism in the brain several years before the onset of AD symptoms.^{15,16} Thus, the quantification of brain metabolism in AD has potential clinical relevance, since an early diagnosis of AD allows for early interventions with disease-modifying therapies, which aim to delay the onset and progression of AD.

Today, a PET [¹⁸F]FDG is typically indicated by a specialist for patients with a documented cognitive decline of at least six months and a recently established diagnosis of dementia, meeting the diagnostic criteria for AD. Although the accuracy of a PET [¹⁸F]FDG as a diagnostic tool for AD may be superior to a baseline clinical evaluation,⁵⁵ the diagnostic value

of a PET [¹⁸F]FDG is limited since regional hypometabolism is not a specific finding of AD. PET associated with radioligands designed to target specific aspects of AD neuropathology constitutes a research field with high translational value.

Imaging brain pathology in AD. Advances in radiochemistry permits the use of new radioligands specifically designed for the quantification of pathological aspects of AD. Much attention has been given to imaging of amyloid deposition^{26,31} and neuroinflammation^{19,43,44} associated with AD. Imaging brain pathology using PET may have important impact on disease-modifying therapies as this therapeutic approach focuses on specific mechanisms such as the formation of amyloid plaques, neuroprotection and neurorestorative approaches.

Imaging disease-related abnormal molecules. Progressive accumulation of abnormal protein aggregates including amyloid or tau deposits are pathological hallmarks of AD. Abnormal amyloid deposits in AD brains are found as neuritic plaques, amyloid

angiopathy and diffuse amyloid deposits. The amyloid cascade hypothesis of AD predicts that the neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of progressive abnormal amyloid deposition.²²⁻²⁴ Thus, quantifying the amyloid burden (amyloid accumulated) in the brain of AD patients may aid in the diagnosis and monitoring of disease progression.^{35,55} Another important application for imaging disease-related abnormal proteins is to improve the specificity and accuracy of the diagnosis of AD and predementia states.

Though several PET molecular agents for amyloid plaques have been tested, the [¹¹C]PIB and the [¹⁸F]FDDNP have thus far proved to be the most effective radiopharmaceuticals in the demonstration of AD pathology.^{26,27} While [¹¹C]PIB seems to be more specific to amyloid deposits, it has been suggested that [¹⁸F]FDDNP has an affinity for amyloid and tangle pathology. Preliminary studies indicate that these lead compounds exhibit high binding in brain areas affected by AD pathol-

ogy, such as the frontal, temporal and parietal lobes. However, deposition in the brain is not unique to clinically apparent AD and has been found in normal aging as well as in patients in the presymptomatic stages of AD.²⁸⁻³¹

The concept of amyloid imaging is currently being tested and hopefully PET imaging using amyloid agents will be available for clinical purposes in the near future.

Imaging neuroinflammation in AD. [¹¹C]PK11195 is a radiopharmaceutical that selectively binds to the peripheral benzodiazepine receptor present in the activated microglia, which is a cell involved in brain inflammatory responses. In vivo studies carried out in various degenerative diseases, including AD, indicate that the inflammation is an active process underlying AD. The binding of [¹¹C]PK11195 is enhanced

in the entorhinal cortex, hippocampus and posterior cingulate cortex in patients with AD. In fact, neuroinflammation, as revealed by high [¹¹C]PK11195 binding, was also present in AD patients with a mild clinical presentation of the disease.^{19,43,44} The clinical value of inflammation and amyloid imaging techniques is still under evaluation.

Imaging abnormal neurotransmission in AD. Abnormalities in various neurotransmission systems such as those utilizing serotonin, glutamate and acetylcholine, have been described extensively in AD. In vivo quantification of such abnormalities may help clinical researchers to understand the mechanisms underlying AD and to propose new therapeutic targets, the exploitation of which will hopefully translate into improved quality of life for AD patients.

Imaging cholinergic neurotransmission. Declines in cholinergic neurotransmission have significant clinical relevance since the mechanisms of action of three FDA-approved medications for the treatment of AD aim to enhance brain acetylcholine neurotransmission through the inhibition of acetylcholinesterase (AChE), the enzyme responsible for the breakdown of acetylcholine. In fact, post-mortem studies in AD patients indicate important declines in cholinergic innervation as well as a global reduction of acetylcholine synthesis capacity. These findings, together with the degeneration of the nucleus basalis of Meynert, strongly support that acetylcholine neurotransmission is impaired in AD. However, it has been argued that in vivo quantification of presynaptic cholinergic neurotransmission in AD patients

Table 2

Summary of PET Molecular Agents Utilized in AD Research

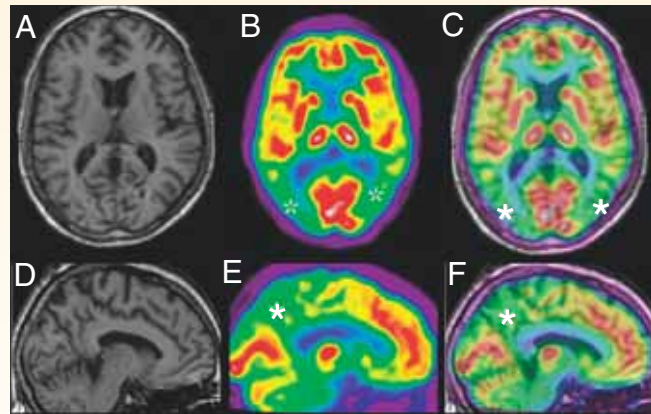
	Biological Process of Interest	Molecular Agents	Typical Findings in AD
Metabolism (References: 12,16-18, 48-52)	Glucose metabolism	[¹⁸ F]FDG	Hypometabolism
	Oxygen metabolism	[¹⁵ O]O ₂	Hypometabolism
	Cerebral blood flow	[¹⁵ O]H ₂ O	Reduction of blood flow
Pathology (References: 19,21 17,18,25,26,29,30)	Neuroinflammation	[¹¹ C]PK11195	Inflammatory changes
	Amyloid plaques	[¹¹ C]PIB	High amyloid load
	Amyloid plaques + tangles	[¹⁸ F]FDDNP	High amyloid load
Neurotransmission (Hippocampus/cortex) (References: 2,35,36,41-44,53,54)	Serotonin 5-HT _{1A}	[¹⁸ F]MPPF	Low binding
	Serotonin 5-HT _{2A}	[¹⁸ F]altanserin [¹⁸ F]setoperone	Unchanged Low binding
	Dopamine D ₂	[¹¹ C]FLB	Low binding
	GABA	[¹¹ C]flumazenil	Unchanged
	Acetylcholinesterase (AChE) activity	[¹¹ C]PMP, [¹¹ C]MP4A	Reduction of AChE

using PET is of limited value due to peculiarities of the cholinergic neurotransmission.³¹ Therefore, it is expected that eventual progress in radiochemistry would allow adequate quantification of cholinergic neurotransmission in the living human brain. Studies using [¹¹C]physostigmine, [¹¹C]methyl-4-piperidyl-acetate ([¹¹C]MP4A) and [¹¹C]methylpiperidin-4-yl-propionate ([¹¹C]PMP) confirm the declines in cholinergic neurotransmission reported by post-mortem studies; some of these studies found correlations between cholinergic dysfunctions and cognitive deficits of AD patients.³⁰⁻³⁶ Cholinergic, muscarinic and nicotinic receptors have been studied in patients with AD, however the interpretation of these studies is limited due to the low specificity of most muscarinic and nicotinic neuroreceptors. In brief, studies using radiopharmaceuticals such as [¹¹C]nicotine suggest a decline in cholinergic nicotinic receptors in AD; studies with the muscarinic receptor radiopharmaceuticals [¹¹C]benztropine, [¹¹C]-N-methyl-4-piperidyl benzilate and [¹⁸F]A85380 also indicate declines in acetylcholine neurotransmission in AD.³⁸⁻⁴⁰ So far no PET radiopharmaceutical could properly quantify the presynaptic aspects of cholinergic neurotransmission.

Imaging serotonin and dopamine neurotransmission in AD. In contrast to cholinergic radiopharmaceuticals, most of the current serotonergic and dopaminergic PET

Figure 3

Typical Declines of Brain Glucose Metabolism in AD Patients



This is a composite plate showing an MRI (A,D), a PET [¹⁸F]FDG (B,E) and the combination between PET and MRI images (C,F) obtained from a patient (female; 70 years of age) with the diagnosis of probable AD. Note that in the fusion images (C,F), the MRI add spatial resolution to the PET. The indication (*) shows the posterior temporoparietal junction (B,C) and the posterior cingulate gyrus (E,F), which are areas typically hypometabolic in AD.

molecular agents allow for selective, reliable and accurate quantification of various aspects of serotonin and dopamine neurotransmission. Serotonin 5-HT_{1A} receptors are abundant in brain regions affected by AD. Although there are conflicting results regarding the 5-HT_{1A} binding in the hippocampus of patients with predementia, it seems that AD patients have substantial declines in hippocampal 5-HT_{1A} receptor binding.^{41,42} Declines in hippocampal dopamine D₂ receptor binding are also reported in AD patients.⁵¹ In contrast, hippocampal and neocortical binding of gamma-aminobutyric acid (GABA) receptors remains unaltered in AD.^{52,53} Information regarding the availability of serotonin 5-HT_{2A} receptor is conflicting and remains to be clarified.⁵⁴⁻⁵⁶ In the striatum,

while dopamine D₂ receptors are unaffected by AD, dopamine D₁ receptors are slightly decreased.⁵⁷ Together these findings highlight the role of hippocampal dopamine and serotonin neurotransmission in the etiology of AD, however further research is necessary in order to evaluate the clinical significance of these findings.

Future directions of PET imaging in AD

Certainly, the main mission of imaging in AD is the development of new techniques capable of accurately diagnosing predementia states. Moreover, new radiopharmaceuticals for imaging cholinergic presynaptic terminals, imaging agents for glutamate synaptic function and efficient molecular probes for tau protein are amongst the

important goals to be achieved by radiochemistry research. However, it is possible that single-mode imaging methods may not provide sufficient diagnostic accuracy for pre-AD dementia. Thus, multimodal imaging diagnostic platforms with multiple molecular probes may constitute an alternative for the current single-mode imaging methods.

Conclusions

Current literature indicates that only PET [¹⁸F]FDG has clinical relevance in assisting specialists in the early and differential diagnosis of AD.

Molecular imaging of AD patients using PET associated with various radiopharmaceuticals provides valuable information regarding the numerous

aspects of the neurobiology of dementia. Furthermore, PET has potential research applications such as early diagnosis, following the evolution of certain biomarkers during the course of dementia, and in monitoring treatment efficacy. Hopefully these research applications will be rapidly translated into benefits for patients living with AD.

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