

Positron Emission Tomography Imaging in Dementia

a report by

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Positron emission tomography (PET) utilises biologically active molecules in micromolar or nanomolar concentrations that have been labelled with short-lived positron-emitting isotopes. The physical characteristics of the isotopes and the molecular specificity of labelled molecules, combined with the high detection efficacy of modern PET scanners, provide sensitivity for *in vivo* measurement that is several orders of magnitude higher than with the other imaging techniques. While the very short half-lives of ^{15}O (two minutes) and ^{11}C (20 minutes) limit their use to fully equipped PET centres with a cyclotron and radiopharmaceutical laboratory, ^{18}F -labelled tracers (half-life 110 minutes) can be produced in specialised cyclotron centres for regional distribution to hospitals running a PET scanner only.

Glucose is the main energy supply for the brain. Its metabolism maintains ion gradients and glutamate turnover and is closely coupled to neuronal function at rest and during functional activation.¹ Its measurement by ^{18}F -fluoro-2-deoxy-D-glucose (FDG) is based on phosphorylation of the tracer by hexokinase, which is the pivotal first step of that metabolic pathway. Typically, PET images are obtained 30–60 minutes after tracer injection, when FDG uptake is approximately proportional to glucose metabolism, and actual measurement times can be as short as five to 10 minutes. Under resting conditions (awake, but without external stimulation), normal grey matter displays two to four times higher glucose metabolism than white matter. There is a moderate reduction of cerebral glucose metabolism with age, mainly affecting the frontal association cortex.² Significant regional reductions of glucose metabolism indicate impairment of synaptic function, and the technique is therefore applicable to all types of dementia.

There is growing interest in imaging amyloid deposits, the pathological hallmarks of Alzheimer's disease (AD). There are now several PET tracers for *in vivo* amyloid imaging that allow longitudinal studies of amyloid deposition to clarify whether amyloid deposition is a cause or consequence in the pathophysiology of AD.^{3,4} Furthermore, the degeneration of major neurotransmitter systems can be demonstrated *in vivo* by using appropriate PET tracers. Impairment of the cholinergic and dopaminergic neurotransmission is of particular diagnostic interest. By these means, PET can detect early stages and differentiate between various types of dementia, and also monitor progression and the effect of therapeutic intervention.

Alzheimer's Disease

Over more than 20 years, multiple studies have demonstrated that glucose metabolism and blood flow are impaired in temporal–parietal association cortices, with the angular gyrus usually being located at the centre of the metabolic impairment.⁵ The frontal association cortex may also be involved, but variably and usually to a lesser degree. The affected association cortices are those that become myelinated last during brain maturation and are also prone to cortical amyloid deposition.⁶ There may be a distinct hemispheric asymmetry, which usually corresponds to the predominant cognitive deficits

(language impairment in the dominant and visuospatial disorientation in the sub-dominant hemisphere). In contrast to other dementia types, in AD glucose metabolism in the basal ganglia, primary motor and visual cortex and cerebellum is usually well preserved. This pattern generally reflects AD clinical symptoms, with impairment of memory and associative thinking, including higher-order sensory processing and planning of action, but relative preservation of primary motor and sensory function.

Voxel-based comparisons with normal reference samples clearly show that the posterior cingulate gyrus and the precuneus are also impaired at an early stage of AD.⁷ This is usually not directly obvious by mere inspection of FDG PET scans because metabolism in that area is above the cortical average in normal brain at a resting state,⁸ and with the beginning of impairment it returns to the level of the surrounding cortex but does not stand out as a hypometabolic lesion. Thus, this important diagnostic sign is easily missed by standard visual interpretation of FDG PET brain scans. On the background of sufficient numbers of FDG PET scans in normal controls it is becoming increasingly standard to base the interpretation of patient studies not merely on visual interpretation of the tracer distribution, but also on quantitative mapping with reference to an appropriate normal sample.^{9–15}

The pattern of metabolic impairment can vary considerably among individual patients. It is typically more pronounced in patients with onset of the disease before 75 years of age than in patients who develop AD at later ages.^{16,17} The degree of metabolic impairment in frontal association cortices varies and is typically seen in more severely affected patients and in patients who are carriers of the apolipoprotein E4 allele.¹⁸ There are AD patients with very pronounced focal impairment of occipito-temporo-parietal association areas, which may correspond to the clinical syndrome of posterior cortical atrophy.¹⁹

Normal ageing and AD cause significant atrophy, including in those brain areas that are also hypometabolic on FDG PET.²⁰ Regional atrophy will cause underestimation of regional glucose metabolism on PET scans due to partial volume effects, depending on scanner resolution. The magnitude of this effect has been estimated in several studies. They concluded that the metabolic reduction in posterior neocortical association areas cannot be explained completely by atrophy-related partial volume effects,²¹ while there



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is typically more severe hippocampal atrophy on MRI than apparent hypometabolism on PET scans.²²

Longitudinal studies have demonstrated that the severity and extent of metabolic impairment in temporal and parietal cortex increases with dementia progression, and frontal reductions become more evident.^{23,24} The reduction of metabolism is in the order of 16–19% over three years in association cortices, which contrasts with an absence of significant decline in normal control subjects.²⁵ Asymmetrical metabolic impairment and associated predominance of language or visuospatial impairment tends to persist during progression.^{26,27} Based on these observations, FDG PET can serve as a biomarker in therapeutic trials.^{28,29} When monitoring change due to disease progression over one year using standard neuropsychological testing by mini-mental state examination (MMSE) and Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog), one typically obtains coefficients of variance (COV) around 100% for these changes, whereas PET measurements are subject to about 50% COV, thus doubling t-scores and reducing the required sample size by about 75% at the same study power.^{30,31}

Mild Cognitive Impairment

Mild cognitive impairment (MCI) can progress to AD, but MCI patients may also remain stable over many years, develop mixed or vascular dementia or even remit. There is considerable interest in whether PET would allow a reliable diagnosis of AD at this early stage before clinical manifestation of dementia. Impairment of regional cerebral metabolic rate of glucose consumption (rCMRglc) has been observed in individuals at high risk of AD due to family history of AD and possession of the apolipoprotein E (ApoE) ϵ 4 allele,^{32,33} even at a completely asymptomatic stage, and this abnormality is seen decades before the likely onset of dementia.³⁴ In middle-aged and elderly asymptomatic ApoE ϵ 4-positive individuals, temporo-parietal and posterior cingulate rCMRglc declines by about 2% per year.³⁵

The first study noting the predictive power of posterior cingulate metabolism in patients with severe memory deficits for predicting progression was performed by Minoshima et al. in 1997.⁷ This observation was followed by several studies indicating a high predictive power with sensitivity and specificity above 80% for prediction of rapid progression,^{36–41} which is clearly superior to ApoE ϵ 4 testing. Mesial temporal metabolic impairment has been observed as a general feature in patients with memory impairment,^{42–44} and hippocampal metabolic impairment appears to predict development of MCI in cognitively normal subjects.⁴⁵

Amyloid

The first tracer used to label A β -amyloid selectively *in vivo* was ¹¹C-labelled thioflavin analogue, named for convenience Pittsburgh compound B (¹¹C-PIB).⁴⁶ Dynamic scanning provides quantitation of binding potential, while a relatively simple and practical method of quantitating uptake in a clinical setting is based on scans obtained approximately 60 minutes after intravenous injection of the tracer, with the cerebellum as an unaffected reference region.⁴⁷ Since its introduction, this tracer has been used by multiple research groups and has been consistently proved to provide high sensitivity in detecting amyloid plaques and vascular amyloid in the human brain *in vivo*.^{48–50} In normal subjects, some unspecific binding is observed, mainly in white matter – which probably is due to the compound's lipophilicity – whereas in patients with AD, specific binding mostly in the

frontal, temporal and parietal association cortices typically exceeds twice the background level. Follow-up studies with ¹¹C-PIB in AD indicate that there is no further increase of tracer uptake during progression of the disease.⁵¹

When used in tracer amounts, ¹¹C-PIB is specific for amyloid and does not bind to neurofibrillary tangles.⁵² Its clinical specificity for AD is currently being studied and it has been shown that patients with frontotemporal dementia or semantic dementia do not show increased ¹¹C-PIB binding.^{53,54} Findings in patients with MCI are heterogeneous: some show intensely increased binding, like AD patients, while others are within normal limits. First results from follow-up studies of up to 18 months indicate that some patients with increased binding may indeed progress to AD.⁵⁵ As to be expected from previous *post mortem* findings, increased amyloid binding has also been observed in some cognitively normal elderly volunteers.⁵⁶ It remains to be determined whether increased ¹¹C-PIB uptake in elderly individuals who are cognitively normal represent false-positive findings or a pre-symptomatic stage of AD that could become clinically manifest up to a decade later.

An alternative ¹¹C-labelled tracer is the stilbene derivative SB-13,⁵⁷ which appears to have similar properties to ¹¹C-PIB without obvious advantages. ¹⁸F-labelled tracers could have the practical advantage of becoming more widely available from commercial providers, even for PET centres without their own cyclotron. Recently, a series of stilbene derivatives have been labelled with ¹⁸F and evaluated as amyloid ligands, demonstrating satisfactory specific amyloid binding to non-specific binding in AD for compound AV-45.⁵⁸ A related compound, ¹⁸F-BAY94-9172 (formerly known as AV-1), demonstrated 100% sensitivity and 90% specificity for AD in 15 patients with mild AD, 15 healthy elderly controls and five individuals with frontotemporal lobar degeneration.⁵⁹

Another tracer, the anthracyclin derivative ¹⁸F-FDDNP, has different characteristics and binds to neurofibrillary tangles as well as amyloid plaques with less affinity and specificity than PIB.^{60,61} Binding to amyloid competes with some non-steroidal antiplogistics.⁶² While providing a generally somewhat less favourable signal-to-background ratio, it also detects neurofibrillary tangles, which appear in the hippocampus in the earliest stages of AD⁶³ and differentiates persons with mild cognitive impairment from those with Alzheimer's disease and those with no cognitive impairment.⁶⁴

Cholinergic System

Impairment of cholinergic neurotransmission is characteristic of AD, and may be even more severe in dementia with Lewy bodies (DLB).⁶⁵ Tracers for imaging nicotinic receptors, which are of particular interest because of their largely pre-synaptic location, are ¹¹C-nicotine⁶⁶ and ¹⁸F-A-85380.⁶⁷ Reduced binding has been observed in the cortex with ¹¹C-nicotine,^{66,68} and mostly in the thalamus with ¹⁸F-A-85380⁶⁹ in AD.

The most important degrading enzyme for acetylcholine in the human cortex is acetylcholine esterase (AChE), which is present in cholinergic axons and relatively few cholinergic neurons. As the cholinergic axons degenerate, AChE activity is also reduced.⁷⁰ Labelled analogues of acetylcholine that are also substrates for AChE can be used to measure and image its activity *in vivo*. These are ¹¹C-N-methyl-4-piperidyl-acetate (MP4A, also known as AMP),⁷¹ which is 94% specific for AChE in human brain, and ¹¹C-N-methyl-4-piperidyl-propionate (MP4P, or PMP).⁷² There have been several studies measuring AChE activity, all of which found a reduction of cortical activity in AD^{73–76} and even in MCI,⁷⁷ most severely

affecting the temporal cortex. This technique has also been used to measure drug-induced AChE inhibition in AD patients, which for all currently available cholinesterase inhibitors at standard clinical dose is in the range of 30–40%.^{78–80}

Fronto-temporal Lobar Degeneration

This group of diseases comprises fronto-temporal dementia (FTD) as the most frequent manifestation with mostly behavioural symptoms and also more focal degenerative processes such as progressive aphasia, progressive apraxia and semantic dementia with various histopathological features (including Pick bodies in some cases) but absence of amyloid plaques.⁸¹ In FTD, cerebral glucose metabolism is impaired mostly in the frontal cortex, especially in the mesial frontal cortex.⁸² Frontolateral and anterior temporal cortices are often also severely impaired, and this impairment is related to the clinical symptoms of aphasia or semantic memory deficits and may be very asymmetric.^{83,84} Milder metabolic impairment often involves posterior association cortices as well.⁸⁵ The regional pattern of predominantly frontal impairment usually allows clear distinction from AD, although there may be overlap as AD can involve frontal regions as well and FTD may not spare the temporo-parietal cortex. It has recently been shown in a series of 45 patients with pathologically confirmed diagnosis that FDG PET can discriminate FTD from AD with more than 85% sensitivity and specificity.⁸⁶

Semantic dementia, which is clinically characterised by a failure of semantic memory, typically shows severe metabolic impairment of the anterior parts of the left temporal lobe,^{87,88} often also extending into basolateral parts of the frontal lobe.⁸⁹ The main metabolic deficits in progressive aphasia are typically located in the language areas of the left hemisphere.⁹⁰ There is considerable overlap of metabolic deficits with FTD, especially as these diseases progress.

Dementia with Lewy Bodies

DLB is clinically characterised by fluctuating consciousness, possible parkinsonian motor features and impairment of visual perception, including hallucinations. The latter are the likely correlate of the reduction of glucose metabolism in the primary visual cortex that has been described with FDG PET in DLB, in addition to an impairment of

posterior association areas, like in AD.⁹¹ In contrast, metabolic activity in the primary visual cortex is usually well preserved in AD, but in practice the distinction may be difficult as metabolic activity in that area is subject to considerable variability and depends on examination conditions (eyes open or eyes closed). A recent analysis of diagnostic discrimination reported a relatively low accuracy of 73% for discrimination between DLB and AD.⁹²

A more reliable feature to differentiate DLB from AD is the impairment of dopamine synthesis and transport,⁹³ which can be assessed with 18F-fluorodopa⁹⁴ and tracers for dopamine transporters.⁹⁵ A deficit of dopamine synthesis similar to PD has been found in DLB, even at a stage when parkinsonism may not yet be prominent,^{93,96} while it is normal in patients with AD. In contrast to the cholinergic impairment, which is severe in DLB but only mild in PD without dementia, the dopaminergic deficit does not appear to be related to dementia.⁹⁷

Summary

Brain PET using FDG is a firmly established technique for demonstration of regional functional impairment in neurodegenerative disease. AD is associated with typical regional impairments of posterior cortical association areas, including the posterior cingulate gyrus, which are closely related to clinical symptoms. Thus, FDG PET facilitates very early diagnosis before clinical manifestation of dementia and can provide monitoring of progression and treatment effects. DLB shows metabolic impairment similar to AD but involves additional metabolic impairment of primary visual cortex. Predominant impairment of frontal and anterior temporal regions is seen in FTD: primary progressive aphasia and semantic dementia. New perspectives for specific molecular imaging have been opened by tracers for imaging amyloid that appear to be very sensitive even in the detection of pre-clinical AD cases. As amyloid deposition is also found in a proportion of cognitively normal elderly people, confirmation of its pathological significance remains to be demonstrated by long-term follow-up studies. Tracers for imaging nicotinic receptors and for measuring local acetylcholine esterase activity demonstrate cholinergic impairment in MCI, AD and DLB. The impairment of dopamine neurotransmission that is characteristic of DLB can be demonstrated by ¹⁸F-fluorodopa PET. ■

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