Is there Still a Place for Perfusion SPECT in the Diagnosis of Dementia?

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Abstract: Although research interest within functional imaging has moved towards applications of MRI, such as BOLD and perfusion imaging, there is a wealth of clinical experience in emission tomographic imaging techniques that make the use of these modalities relevant for the decades to come. This review touches upon the technical and practical issues that distinguish SPECT from PET, describes perfusion and metabolic changes observed in the dementias, compares the clinical utility of the two techniques, and reports data on clinical sensitivity and specificity, as well as diagnostic head-to head comparisons in dementia, and specifically Alzheimer's disease. While few centres have a genuine choice between PET and SPECT, either appears to be good enough to help with the differential diagnosis of dementia in difficult cases.

Keywords: Single photon emission tomography, positron emission tomography, dementia, Alzheimer's disease, mild cognitive impairment, diagnosis.

INTRODUCTION

Radionuclide-based imaging, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), have been available for the diagnosis of dementia since the second half of the last century, but their impact on daily diagnostic practice has been limited. Opinions differ about the relative advantages of PET and SPECT in the diagnosis of the dementias [1-4]. Of the industrialised countries, particularly Europe and Japan still use SPECT frequently for diagnostic purposes in dementia [5], in general the US literature tends to ignore clinical SPECT and expects FDG-PET to be available.

Intrinsic Limitations of SPECT

In contrast to PET where the physics of positron annihilation provide directional information that helps with the three-dimensional reconstruction of the activity map, in SPECT collimators are used in order to focus the signal onto the detector(s). In contrast to PET where the physics of positron annihilation provide directional information that helps with the three-dimensional reconstruction of the activity map, in SPECT collimators are used in order to focus the signal onto the detector(s). This directional filtering only allows for a small proportion of emitted photons to be detected, which limits the sensitivity of SPECT, in addition scattered photons are excluded with energy filters. In contrast to quantitative attenuation modelling with transmission scans in PET, attenuation is often ignored in SPECT or resolved making the assumption of homogenous attenuation in the head. SPECT gamma emitters with half-lives of 6-12 hours are employed, so that the tracers can be generated commercially some distance from the scanner. The long half-life of the radioactive label makes only a limited numbers of exposures possible. The gamma emitting nuclei (^{123}Iodine and ^{99m}Technetium) are large and tend to change the pharmacology of the tracer after substitution (Table **1**). This requires a repetition of the pharmacological development work necessary to describe binding characteristics, and may explain the limited number of SPECT-ligands commercially available.

Table 1. Some Common Perfusion Tracers for SPECT

Tracer	Isotope-Mode
Hexamethylpropyleneamine oxime (HMPAO)	^{99m}Tc- SPECT
N-isopropyl-p-iodoamphetamine (IMP)	^{123}I-SPECT
Ethylene cysteinate dimer (ECD)	^{99m}Tc-SPECT

Image Analysis Methods

Images are usually analysed qualitatively using visual inspection, or quantitatively with a variety of semi-automated methods [6]. Qualitative visual assessment of PET scans can be reliable (intra-observer $\kappa = 0.56$; inter-observer $\kappa = 0.51$) [7], as can be SPECT [8, 9], particularly if well defined classification criteria are used [10, 11].

Typically for research purposes, but occasionally also in a clinical context, regions of interest (ROIs) are superimposed over the brain activity map, often following the underlying structural anatomy. Mean uptake values are averaged within these regions and compared within or between subjects [12]. Quantitative methods, such as the automated multi-ROI programme 3DSRT [13, 14], statistical parametric mapping [15-17], discriminant function analysis [18-20], three-dimensional stereotactic surface projection [21] and neural network analysis [22-26] have been added to the research tools available in PET and SPECT. Adding structural information from MRI or CT improves clinical and research interpretations of functional scans [19, 27-30]. Fig. (**1**) shows an example of visual and quantitative analysis of SPECT and how this can be helpful in an unusual case.

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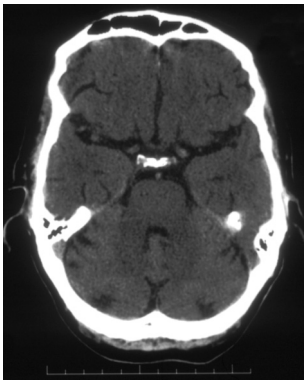
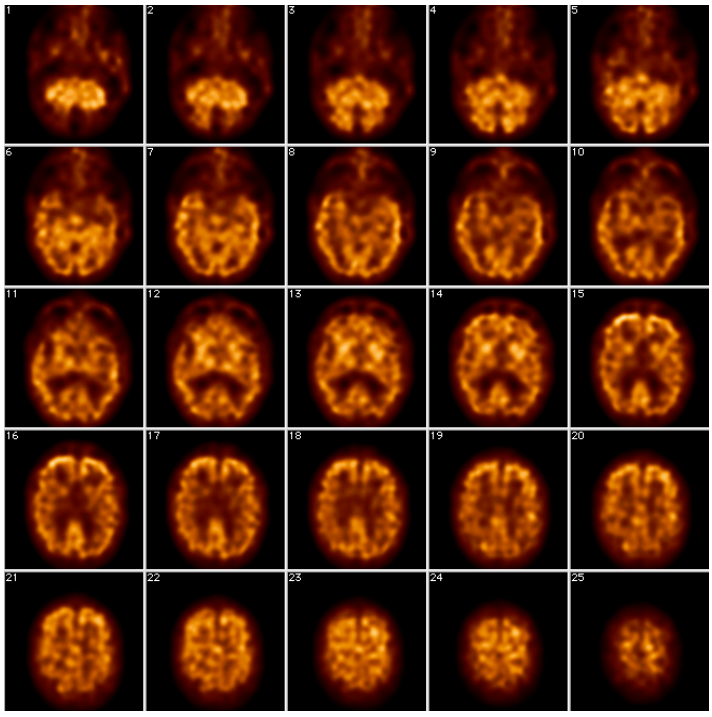
1876-388X/10

(**a**)



(**b**)



(**c**)

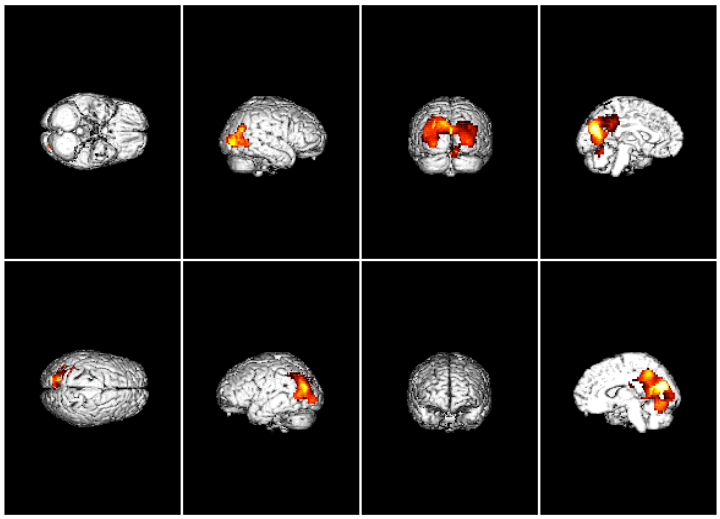


Fig. (1). A 81 year-old man with a clinical diagnosis of 'frontal lobe dysfunction' showing no evidence of significant atrophy on brain Computed Tomography (**a**) but evidence of Alzheimer-type neurodegenerative pattern on both visual (**b**) and voxel-based quantitative (**c**) analysis.

The Practical Scope of Clinical PET and SPECT in Dementia

Before discussing the clinical use of perfusion and metabolic imaging in dementia, it will help to reflect on the possible roles such imaging can play, in order to identify the kind of evidence necessary to support its use. Aspects of the use of imaging include stage of the disease, differential diagnosis, the need to predict prognosis and treatment response, and clinical setting, i.e. usual grounds for referral, such as the presence of symptoms, signs, screening, or treatment resistance. An important factor is the availability and efficacy of alternative diagnostic methods, as well as the nature of conditions that affect patients alternatively to, or concurrently with, Alzheimer's disease (AD), as well confounders, such as age. On theoretical grounds very early diagnosis may be the ideal, as potential treatments may be most effective when brain damage is minimal. However, for economical and practical reasons patients are very unlikely to be screened using imaging methods. Detection before the appearance of symptoms is, therefore, unlikely. 'Dementia' is a clinical diagnosis and crucially depends on impairments of activities of daily living [31]. As it is the gold standard *in vivo*, it is more sensitive than, for example, a typical screening scale, such as the mini mental state examination (MMSE [32]). Clinical judgement makes it possible to diagnose early dementia in people of varying backgrounds, ranging from a university professor with a MMSE score of 29 out of 30 to a person with Down's syndrome whose MMSE score has always been in the "dementia range". It also allows for the exclusion of conditions, such as depression, that may present with both memory impairment and reduced activities of daily living scores. The myth of psychiatrists' inability to differentiate depression from dementia in old age is mainly propagated for the benefit of research funding agencies. Most imaging will therefore take place after a clinical diagnosis of dementia or at least mild cognitive impairment (MCI) has been made.

Patterns of Perfusion-SPECT Abnormalities in the Dementias

The above implies that the purpose of imaging will be mainly the differential diagnosis of the causes of dementia [33]. From this point of view, a specific imaging modality that has some affinity with the causal mechanism of the dementia in question will be the ideal approach. Examples for this are imaging of the dopamine transporter in dementia of the Lewy body type [34] or amyloid imaging in AD [35]. While this strategy seems to bear fruit for the dopamine transporter tracer, Alzheimer's plaques are found in a substantial part of the brains of non-demented older people [36], so that some non-demented people have positive amyloid scans. Functional imaging, in particular with tracers that mirror brain perfusion or glucose uptake, will reflect brain function (at rest) and to some extent anatomical changes, such as atrophy, although the resolution of these imaging modalities tend to be lower than that of structural scans. Images will therefore in general rather reflect the pattern of impairment than be directly associated with diagnosis. Moreover, Alzheimer's and vascular dementia can occur together so that mixed imaging patterns are likely to be found in a significant proportion of patients. The natural history of symptoms in AD varies in terms of symptoms and clinical signs, so that a variable pattern of brain changes may be expected. At an advanced stage, most dementias tend to involve large portions of association cortex, so spatial patterns of reduced perfusion or metabolism that help differential diagnosis may disappear.

AD initially presents with posterior cingulate [37, 38] or medial temporal [39-42] reductions in brain activity, followed by bilateral posterior temporo-parietal reductions [10, 20, 43-47]. Patients with mild cognitive impairment and temporo-parietal association area, posterior cingulate, or hippocampal reductions in blood flow or glucose metabolism are more likely to go into progressive cognitive decline [48]. Later, prefrontal activity reductions appear. Herholz and colleagues have suggested computing a ratio of association cortex to primary sensory-motor cortex activity as a diagnostic index for AD [49]. Patients, who initially present with functional impairment and reduced activity of anterior parts of the brain, have a variety of underlying pathologies, ranging from Pick's to tauopathies, to ubiquitin, and microvacuolar type histology [50]. In vascular dementia patchy lesions of brain perfusion are often asymmetrical in distribution, or localised in "watershed" regions of the brain. Patients with Lewy-body dementia show little difference in perfusion patterns from AD, although occipito-temporal changes have been described [51, 52].

Sensitivity and Specificity

In order to estimate the sensitivity and specificity of an imaging method, a "gold standard" has to be available that provides, so to say, the denominators of the formula. While dementia is a clinical diagnosis, the differential diagnosis is even more dependent on 'soft' items of information. Formal diagnostic criteria exist, such as the NINCDS-ADRDA criteria for AD [53], the NINDS-AIREN criteria for vascular dementia [54], and revised criteria for dementia with Lewy bodies [55]. Interestingly, such criteria are usually not very sensitive, but show high specificity compared with post mortem criteria. Should functional imaging then be designed to reflect the distribution and severity of brain cell loss, or patients' functional impairment, their symptoms and signs? By the time the brain histology is known, a number of confounding factors will have intervened: additional illness and treatment, and selection bias with low uptake of post mortem examinations. For this reason, the significance of abnormalities in MCI, usually defined as subjective and objective cognitive impairment without functional impairment, are difficult to assess: unless brains come to pathological examination shortly after the scan, intervening illness is likely to blur the picture. At best, patterns of hypoperfusion in MCI patients that are typical of AD will predict later conversion to dementia [56-59]. Of greatest interest is, of course, whether imaging can inform treatment decisions. Without any specific effective treatments, "predictive validity" means follow-up within 2-3 years to confirm clinical diagnosis, and that (hopefully) imaging results at baseline predict clinical outcome. Using data pooled from 27 studies, we found that SPECT successfully discriminated between healthy elderly controls and AD with a pooled sensitivity of 77% against a pooled specificity of 89% [60]. Used in addition to structural imaging, functional imaging appears to increase diagnostic sensitivity in AD, with blood flow and metabolism first affected in posterior cingulate gyrus and precuneus, then advancing to medial temporal structures and parieto-temporal association cortex [61]. Entorhinal cortex and hippocampal metabolic

reductions have been used to discriminate cognitively normal volunteers from subjects with mild cognitive impairment with a diagnostic accuracy of 81%, and from AD using the temporal neocortex with a diagnostic accuracy of 100% [62]. Similarly, the ratio of deoxyglucose uptake in association cortex over primary sensory-motor cortex of patients with mild cognitive deficits predicted progression to AD [49]. As AD advances, bilateral parieto-temporal perfusion deficits become more frequent and severe [63] with a reported odds ratio (OR) of 5.2 (95% CI 1.1-24.4) for moderate AD (MMSE:10-17) and an OR of 17.0 (95% CI 3.1-94.2) for severe AD (MMSE<10).

Pathological Confirmation of Scan Diagnosis

Increasingly, patient cohorts are followed up till post-mortem. The advantages and disadvantages of pathological diagnosis as a "gold standard" have been discussed above. While diagnostic verification by 3 year clinical follow-up suggested that regional brain metabolism was a sensitive indicator of AD [64], pathological verification in the same study confirmed a sensitivity of 94% (91 out of 97 subjects) and a specificity of 73% (30 out of 41 subjects) compared with other patients presenting with dementia. Overall diagnostic accuracy of 55 patients who presented with questionable or mild dementia was 89% [64]. In a diagnostically challenging group of patients, sensitivity and specificity of PET compared with a histological diagnosis of AD were 93% and 63%, respectively; sensitivity and specificity of the clinical diagnosis of probable AD versus histology were 63% and 100%, respectively, so that the overall diagnostic accuracy of PET at 82% was better than clinical diagnosis at 73% [45]. Two comparable SPECT studies with pathological verification of AD reported sensitivities of 86% and 63% against specificities of 73% and 93%, respectively [65, 66].

Follow-Up Studies

Longitudinal functional imaging studies suggest that patients with more severe temporo-parietal perfusion or metabolic deficits show a more rapid cognitive and general decline over time [67, 68]. Patients with MCI, who initially show regional cerebral blood flow (rCBF) decreases in the posterior cingulate, parietal and precuneus regions, subsequently show additional abnormalities in the hippocampus and parahippocampus when a clinical diagnosis of AD can be made [37, 69]. Specific neuropsychological abnormalities that occur during the natural history of single AD patients, can be predicted by early metabolic asymmetries in their association cortices [70]. This hints at compensatory mechanisms in the brain that allow normal psychological function, when abnormalities can already be discovered in strategic brain regions [71]. Such compensatory plasticity may be responsible for the observation that pre-morbid IQ and word reading ability are inversely correlated with metabolism in AD [72]. Longitudinal studies during treatment are of course of particular interest, but are in their infancy, mainly due to the state of development of treatments in AD [43].

Guidelines and Consensus Statements

Parieto-temporal deficits in PET/SPECT of AD and widespread irregular lesions in vascular dementia have been generally acknowledged [73], but guidelines do not recommend the routine clinical use of SPECT [74, 75]. Similarly, there is little evidence to support a role for PET in the clinical evaluation of patients with suspected or established dementia [76]. The American College of Radiology recommends functional imaging for cases that are difficult to diagnose [77]. More recent consensus statements concur that imaging techniques have an important role to play in the diagnosis and assessment of dementia and specifically AD [78-82]. In the UK, both English and Scottish guidelines recommend imaging, in particular SPECT, for the differential diagnosis of difficult cases [83, 84].

SPECT *vs* PET

Whole brain correlations of abnormal tracer uptake between PET and SPECT in the same subjects were relatively modest (r=0.43), with higher correlations in the temporo-parietal and posterior cingulate association cortices [4]. In the same study, PET with statistical parametric mapping (SPM) discriminated better between healthy volunteers and patients with AD than SPECT. Using temporo-parietal reductions as a diagnostic criterion, Messa and colleagues compared PET and SPECT in participants with probable AD and normal controls, and determined a sensitivity of 100% for PET and 90% for SPECT [85]. Ishii and colleagues compared F-18-FDG-PET with IMP-SPECT in patients with DLB; reductions of tracer uptake were found in posterior parietal and to a lesser extent in occipital cortex, with PET appearing to be more sensitive to abnormalities [86]. Clinical utility in predicting outcome appears greater for FDG-PET than for SPECT [87, 88], although opinions about their respective merits differ [1-3].

CONCLUSON

The choice between PET and SPECT then appears to be marginal but clearly in favour of PET. In real life, few clinicians will have the choice between the two, so that the decision will be more between functional scan and no functional scan. From the above data it seems that SPECT is a creditable alternative to ^{18}FDG-PET. While perfusion MRI is being used in research to good effect, its clinical availability as an alternative imaging modality will require more time to be established in most places [89].

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