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Clinical impact and diagnostic accuracy of ^{18}F(fluorine)-FDG (2-fluoro-D-deoxy-glucose) positron emission tomography/computed tomography (PET/CT) brain imaging in patients with cognitive impairment – a tertiary centre experience in the UK

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Abstract

Aims: This study retrospectively evaluated the clinical impact of brain FDG PET/CT performed in selected patients with cognitive impairment at a tertiary referral centre in the UK. It also assessed the accuracy of FDG PET/CT to correctly establish the diagnosis of Alzheimer's Dementia (AD) in a 'real-world' clinical practice.

Methods and materials: Using an institutional radiology database, a total of 136 patients were identified for inclusion in the study. FDG PET/CT was performed using a standard technique and interpreted by dual-trained radiologists and nuclear medicine physicians. Standardized questionnaires were sent to the referring clinicians to establish the final clinical diagnosis and to obtain information about the clinical impact of FDG PET/CT.

Results: There was a 72% questionnaire return (98/136), with mean patient follow-up of 471 (SD 205) days. FDG PET/CT had an impact on patient management in 81%, adding confidence to the pre-test diagnosis in 43%, changing the pre-test diagnosis in 35%, reducing the need for further investigations in 42%, and resulting in a change in therapy in 32%. There was substantial correlation between the PET/CT diagnosis and final clinical diagnosis with a correlation (k) coefficient of 0.78 ($p < 0.0001$). The accuracy of FDG PET/CT in diagnosis of AD was 94% (CI 87-99), with a sensitivity of 87% (CI 75-92) and a specificity of 97% (CI 87-99).

Conclusion: FDG PET/CT brain imaging has a significant clinical impact when performed selectively in patients with cognitive impairment and shows high accuracy in the diagnosis of AD in a 'real-world' clinical practice.

Introduction

Dementia is a clinical syndrome characterised by neurodegeneration that leads to progressive deterioration in various intellectual domains including memory, language and executive brain function, and usually results in a relentless decline in the capacity for independent living [1]. The commonest cause of neurodegenerative dementia is Alzheimer's disease (AD), accounting for approximately 65% of all cases, followed by vascular dementia, mixed dementia, Lewy body dementia (DLB), fronto-temporal dementia (FTD), and other rare causes. The *World Alzheimer Report* identified that there were 46 million people living with dementia worldwide in 2015, with a total estimated cost of $818 billion, potentially rising to $1 trillion by 2018 [2]. In the UK, it was estimated that in 2015, there were over 850,000 people living with dementia, with a total cost to the economy of £26 billion [3]. Although some recent epidemiological studies have shown that the prevalence of dementia in high-income countries such as the USA and UK may not be rising as historically predicted, it unambiguously remains a problem of worldwide concern with significant implications for economic, health and social care provision [4].

As dementia is an incurable condition, a relatively apathetic approach from medical professionals, health care planners and even patients has traditionally contributed to delays in diagnosis. With increasing recognition of the benefits of primary, secondary and tertiary prevention of cognitive impairment, the role of timely diagnosis is being revisited [5-6]. It is also well-recognised that in the early stages of the disease, especially in younger patients (<65 years) and those with atypical presentations, clinical diagnosis can be both challenging and unreliable [7]. National Institute for Health and Care Excellence (NICE) guidelines state that conventional neuroimaging with computed tomography (CT) and magnetic resonance imaging (MRI) should be used in patients with suspected dementia to exclude other

pathological conditions or to establish a subtype of dementia such as Alzheimer's disease (AD) or vascular dementia [8]. More recently, the first new guidance for AD diagnosis since 1984 emphasized that functional neuroimaging with [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) can be used as a pathophysiological biomarker of AD by depicting reduced FDG uptake in the brain [9]. In recognition of the need to improve diagnosis, strategic clinical networks (SCNs) in the UK have produced specific guidance on the use of conventional and highly specialised neuro-imaging in dementia, which defines the role of FDG PET/CT by judiciously limiting its use to those cases where the patients are relatively young (<65 years), difficult to diagnose, and/or when the knowledge of the precise subtype of dementia would likely influence clinical management (**Table 1**) [10].

Despite the recognition of the utility of FDG PET/CT to diagnose and differentiate between different subtypes of dementia in appropriate cases [11-14], there is currently a lack of evidence looking at the clinical impact of FDG brain imaging in dementia from a referring clinician's perspective, particularly in a UK patient cohort. This study was conducted to primarily evaluate the clinical impact of FDG PET brain scans in patients with cognitive impairment, who did not have a clear diagnosis after initial expert assessment and standard neuro-radiological examinations in a 'real-world' clinical practice. The secondary aim was to assess the accuracy, sensitivity and specificity of FDG PET/CT in diagnosing the commonest cause of neurodegenerative dementia, i.e. AD, when compared with the final clinical diagnosis, in patients presenting with difficult to diagnose dementia at a single tertiary referral centre in the UK.

Methods and materials

Study population

A retrospective review of a prospectively maintained database at the authors' centre showed that a total of 158 patients had undergone brain FDG imaging in a two-year period between June 2013 to June 2015. The inclusion criteria for the study were as follows: patients who had undergone brain FDG PET/CT for the evaluation of cognitive impairment, following a negative brain CT or MRI, and where no specific diagnosis was possible after an expert assessment by a clinician experienced in managing patients with cognitive impairment and dementia. Cognitive impairment was defined clinically for the purposes of this clinico-radiological pathway as an identifiable decline in memory, language, thinking and/or judgement interfering with activities of daily living. There were 22 exclusions, i.e. patients who had a brain PET/CT scan performed for other indications such as epilepsy or tumour assessment, with 136 individuals meeting the inclusion criteria for the study. Patient demographics including name, age, gender, comorbidities, and the referring physician details were collected for all patients. PET/CT reports were retrieved retrospectively from the institutional computerised radiology information system (CRIS™, Healthcare Software Solutions, HSS, Mansfield, UK). Institutional ethical approval was not required at the authors' institution for a retrospective review of an existing standard clinical service, as this was classified as a service evaluation and quality improvement exercise.

PET/CT technique

All PET/CT examinations were performed on a GE Discovery ™ 690 PET/CT scanner (General Electric, GE, Healthcare Ltd, Chalfont St Giles, UK). All patients were asked to fast for a minimum of 6-hours prior to tracer injection. The blood glucose prior to injection was <10 mmol/l in all cases. A standard injection of 250 (+/- 10%) MBq of FDG was

administered, followed by a 30-minute uptake period. The PET protocol used a 10-minute single bed acquisition with the head positioned in an appropriate head restraint. Image reconstruction parameters were as follows: time-of-flight algorithm (Vue Point FX ™, GE Healthcare), with iterative reconstruction involving 24 subsets, 2 iterations and a 3.2mm spatial filter. The CT component of the study was performed with the patient in the same position, using the following parameters: 125 kV, 250 mAs and 3.75 mm slice thickness.

PET/CT reporting criteria

The clinical report was generated following visual PET data review in transaxial, sagittal and coronal planes with and without PET/CT image fusion on a GE Advantage ™ Workstation (GE Healthcare, version 4.5). All cases were dual reported by two of three experienced consultants who are dual-certificated in clinical radiology and nuclear medicine (with 9-years, 7-years and 5-years of independent reporting experience, respectively). Standard and accepted reporting criteria were applied in terms of well-recognised patterns of regional hypometabolism to distinguish between the various causes of cognitive impairment (**Table 2**). In the case of any discrepancy between the two reporters, a consensus was reached before issuing the final clinical read-out. The originally issued clinical report for the PET/CT scan was used for subsequent primary and secondary outcome analysis.

Questionnaires for assessment of final clinical diagnosis and clinical impact

Questionnaires were sent to the referring physicians. The purpose of the questionnaire was to establish the final clinical diagnosis, which could be correlated with the suggested diagnosis from the PET/CT report. Other information such as the referring physician's specialty and questions about the usefulness of the PET/CT report was probed. A Likert scale (1-5) was used to find out how useful the referrer found the PET/CT report for each patient. Following

this, a polar question was asked to see whether the PET/CT scan had an impact on clinical management. If it did, further questions were asked to assess how it had an impact on clinical management, which were the following:

- Did the PET/CT result add confidence to the pre-test diagnosis?
- Did the PET/CT result change the pre-test clinical diagnosis?
- Did the PET/CT result reduce the need for further investigations?
- Did the PET/CT result lead to a change in therapy?

Statistical analysis

All subjects were included in the analysis using the intent-to-treat principle. Statistical analyses were performed using SPSS version 22.0 (IBM, Chicago, IL, USA). The concordance between the final clinical diagnosis and the diagnoses derived from the initial PET/CT report was analysed using the kappa (k) correlation coefficient. The range of plausible values for kappa were between 0 and 1 ($k<0.20$ = poor agreement, $0.21<k<0.40$ = fair agreement, $0.41<k<0.60$ = moderate agreement, $0.61<k<0.80$ = substantial agreement, and $0.81<k<1.00$ = almost perfect agreement). Contingency tables were used to calculate sensitivity, specificity and accuracy of FDG PET/CT for the diagnosis of AD. The final clinical diagnosis was used as the reference standard for these calculations. *P*-values of <0.05 or 95% confidence intervals (95% CI) that did not include 1.0 were considered to be statistically significant.

Results

A total of 136 patients were included in this retrospective study and there were 72 males (53%) and 64 females (47%). The age range was 33 to 88 years with the mean age of males being 64 years (SD 11.8) and females being 66 years (SD 9.9). Referrals were received from four clinical specialties (psychiatry for the elderly, neurology, general psychiatry and care of the elderly) (**Figure 1**). In total, there were 42 individuals with a PET/CT diagnosis of AD, 11 with FTD, 4 with rarer dementias, 1 individual each had a diagnosis of DLB and mixed dementia, and 77 patients had a normal scan with no supportive features of neurodegenerative disease (**Figure 2**).

The completed questionnaire response rate was 72% (98/136), with mean patient follow-up of 471 (SD 205) days. Referring physicians found the PET/CT report useful or very useful in 78% (77/98) of patients. A more objective question showed that in 81% (79/98) the PET/CT report had an impact on clinical management. In 42 individuals (43%), PET/CT added confidence to the pre-test clinical diagnosis and in 34 individuals (35%) it changed the pre-test clinical diagnosis. In 41 cases (42%), PET/CT reduced the need for further investigations. For 31 individuals (32%), the PET/CT report led to a change in therapy. **Figure 3** summarises the referring physicians' responses to the questionnaire.

Of the 98 patients with a confirmed final clinical diagnosis, there was substantial agreement with the diagnosis suggested by the PET/CT report with a kappa coefficient of 0.78 (p-value <0.0001) (**Figure 4 and 5**). There were 14 cases (14/98, 14%) where there was discordance between the final clinical and PET/CT diagnosis. Eleven of these were 'false-negative' cases with normal FDG PET/CT findings, where the final clinical diagnosis was given as FTD (5/11), AD (4/11), and one each of rare dementia (progressive supranuclear palsy) and mixed

dementia. There was one case with abnormal FDG imaging findings that could not be definitively classified into a specific dementia sub-type (clinically diagnosed as FTD), one case which was classified as a sub-type of FTD (logopenic variant primary progressive aphasia, PPA) but was subsequently clinically diagnosed as a linguistic-variant type of AD (**Figure 6**), and only one 'false-positive' case that was reported as possible early AD where the patient's cognitive function subsequently improved and a neurodegenerative cause was ruled out clinically. The discrepant cases are summarised in **table 3**. In the 42/98 (43%) cases that had normal FDG imaging, the diagnosis remained uncertain in 12/42 (29%), and the commonest final diagnoses included psychiatric disorders in 10/42 (24%), mild cognitive impairment in 8/42 (19%), and vascular dementia in 7/42 cases (17%). For the diagnosis of AD, using the final clinical diagnosis as the reference standard, FDG PET/CT had a sensitivity of 87% (95% CI 75-92), specificity of 97% (95% CI 87-99), positive predictive value of 93% (95% CI 80-99), and a negative predictive value of 91% (95% CI 83-95). The overall accuracy of FDG PET/CT in the diagnosis of AD was 94% (95% CI 87-99) (**Figure 7**).

Discussion

The diagnosis of dementia can be challenging, especially in the early stages of the disease, in younger patients (<65 years), in those with atypical presentations, and in patients with substantial psychological overlay [1-2]. It is clear from several longitudinal studies that pathologically proven AD can present with a range of atypical cognitive symptoms and it is not surprising therefore that clinical diagnosis can have an accuracy of less than 70%, and up to 50% of patients can remain undiagnosed until a late stage of the disease [1-2, 15]. Obtaining a timely diagnosis of dementia is important not only in order to allow access to appropriate treatment, but also to enable individuals with dementia, as well as their families, to participate more actively in management decisions, plan for their future, and access support services from statutory and voluntary organisations [5-6]. Failure to make a timely diagnosis can often lead to a lengthy period of follow-up and prolonged and/or repeated neuropsychology assessments, which in the long run can prove expensive, while also generating uncertainty and anxiety for the patient. Identification of the correct sub-type of dementia is crucial as management, course of disease and prognosis vary considerably between the different aetiologies [1-2]. It follows that non-invasive imaging tests that not only corroborate a suspected diagnosis of neurodegenerative dementia, e.g. AD, but also exclude it with a high level of certainty are needed in these challenging cases.

The role of neuro-imaging in dementia has traditionally been to exclude structural causes, e.g. space-occupying lesions and vascular disease. Modern AD imaging guidelines, however, have changed the emphasis of neuro-imaging to a more effective role in identifying dementia sub-types by recognising volumetric MRI, FDG PET and amyloid PET imaging as important imaging biomarkers of the condition [9].

The brain is an obligate glucose user for its metabolic requirements, and glycolytic metabolic activity has been shown to correlate effectively with neuronal and synaptic function [16]. FDG brain imaging is an *in vivo* non-invasive test that can, therefore, demonstrate cerebral glycolytic metabolism as a surrogate marker of synaptic function and neuronal density, which are invariably reduced in neurodegenerative conditions. This is so much the case that FDG imaging in AD has sometimes been referred to as the 'metabolic signature' of the condition [14]. In the classical case, this manifests as a regional pattern of glucose hypometabolism that is demonstrated in the parieto-temporal regions, including the precuneus, with additional reduction in FDG uptake in the posterior cingulate gyri. The posterior cingulate and precuneus regions are often affected in the earliest stages of AD [11]. The involvement of these areas, with regional parieto-temporal hypometabolism, with lesser degree of abnormality in the frontal cortex, and sparing of the primary visual cortex, sensorimotor cortex, basal ganglia and cerebellum effectively defines the 'metabolic phenotype' of AD. Interestingly, as normal glucose metabolism in the hippocampal structures is less than that in the neocortex, small reductions in metabolic activity in the hippocampus are not usually demonstrable on FDG PET in the early stages of the AD [13].

The limited ability of morphological imaging to distinguish between different dementia subtypes is well recognised, as atrophy is often a late sign of the disease [14]. FDG is currently the most widely available imaging biomarker for dementia diagnosis. Over the last decade, convincing evidence has emerged to demonstrate that FDG PET imaging has a 15-20% increment in diagnostic accuracy in AD over the traditional nuclear medicine test of brain perfusion single-photon emission computed tomography (SPECT) [16]. In one of the few high quality head-to-head comparisons between the two techniques, O'Brien and colleagues [17] showed in a cohort of 98 patients (including 30 control patients) that in

differentiating healthy patients from those with dementia, FDG PET had a sensitivity of 85% (95% CI 0.75–0.93) and a specificity of 90% (95% CI, 0.73–0.98), whereas SPECT had sensitivity of 71% (95% CI 0.58–0.81) and specificity of 70% (95% CI, 0.51–0.85). In addition to greater diagnostic accuracy, there are other convincing practical reasons why PET is increasingly replacing SPECT as the functional imaging test of choice in these patients, including superior spatial resolution, less technical variation and shorter acquisition times.

Although there have been multiple studies evaluating the accuracy of FDG PET in diagnosing dementia and identifying its sub-types, there have been very few studies that have evaluated the actual clinical impact of undertaking FDG PET in patients with an uncertain diagnosis of dementia. In a retrospective study of 94 patients presenting to a memory clinic with cognitive impairment and unclear diagnosis who had a PET and were followed up at 5-months and 18-months, La Force *et al* [18] showed that PET was associated with a definable impact on management in 56%, with a change in diagnosis in 29%, confirmation of clinician diagnosis in 16% and had no impact in 28%. In comparison, in the current study conducted in a 'real world' clinical PET service in the UK, it was shown that FDG PET/CT led to a change in the pre-test clinical diagnosis in 35%, obviated the need for further investigations in 42%, led to a change in therapy in 32%, and overall, had an impact on clinical management in 81%, thereby indicating a substantial clinical utility of FDG imaging in selected patients with difficult to diagnose dementia.

There have been a number of studies over the last 15-years that have evaluated the accuracy of FDG imaging in the diagnosis of AD. For instance, Silverman *et al*, in one of the largest multicentre studies of FDG PET imaging of AD in 284 patients, showed that PET had a sensitivity, specificity and accuracy of 95%, 71% and 89%, respectively [19].

Understandably, many of these studies have involved heterogeneous patient cohorts, used diverse inclusion criteria and applied different interpretative methodology, making direct comparisons challenging. In order to mitigate against such factors, Bohnen *et al* applied more stringent criteria which led to the inclusion of 11 suitable studies of FDG PET in the diagnosis of AD in their review, which showed that the accuracy of FDG imaging in AD ranged widely from 68-100% depending on the patient cohort studied, with a large meta-analysis of FDG PET accuracy in AD showing a sensitivity of 86% (CI 76-93) and specificity of 86% (CI 72-93) [16,20]. In the current practical study, it has been confirmed that it is possible to achieve a high level of accuracy (94%, CI 87-99) for correctly diagnosing AD using FDG imaging in a highly selected, relatively young patient population, referred by specialists in dementia care who were unable to find a definite cause for cognitive impairment after thorough clinical evaluation and conventional neuro-imaging.

It is intuitively recognised that patients referred for a complex diagnostic imaging study for dementia may have a mixture of causal pathological factors, and this can make interpretation of FDG studies more challenging when these are undertaken in a highly selected patient cohort [14-15, 21]. This was evident in the current study, where there was a discrepancy between the PET/CT classification and the final clinical diagnosis in 14 patients (14/98, 14%). Interestingly, the majority of these cases (11/14) were, in fact, 'false-negative' on FDG imaging, with a final diagnosis of FTD and AD in five and four cases, respectively. The value of FDG PET extends beyond the differential diagnosis of dementia by providing valuable information about cortical metabolic status. Although a completely normal FDG PET scan does not exclude a diagnosis of dementia, it provides reassuring prognostic information that cognitive function is likely to remain stable for several years after a normal study, e.g. a mean follow-up period of 3 years [19]. Herholz and colleagues also showed in a prospective

longitudinal study of 186 subjects with possible or probable AD that in patients with mild cognitive deficit and a highly abnormal FDG scan at entry into the study, there was almost a five-fold risk of disease progression compared to those with mild metabolic deficit or a normal study [22]. In the relatively small number of suspected AD cases, in a selected and younger patient cohort, who have a normal or equivocal FDG scan at presentation, it may be necessary to pursue a definitive diagnosis, especially if they have progressive symptoms. There is almost certainly a role for the more sensitive amyloid plaque tracers such as Florbetapir-18F, Florbetaben-F18, and Flutemetamol-F18 in such patients [23-25]. For instance, in a pivotal study of 59 end-of-life patients, Clark *et al* compared *in vivo* amyloid plaque imaging using Florbetapir-18F to post-mortem evidence of β-amyloid neuritic plaque density [23]. Florbetapir 18F-PET showed a sensitivity and specificity of 92% (CI 78-98) and 100% (CI 80-100), respectively, in detecting the presence of amyloid plaques. These tracers are now approved for clinical use, and their rational utilisation in highly selected patient groups is advocated by evidence-based guidelines [26]. The authors' proposed algorithm for the evidence-based and rational use of functional imaging in patients with unexplained cognitive impairment and/or suspected dementia is shown in **Figure 8**.

Diagnostic challenge can also arise in phenotypical variants of AD, which are often referred to as 'atypical AD' [7]. These patients can present with focal cortical syndromes, e.g. frontal variant AD and logopenic aphasia, without the classical amnestic symptoms of AD, and there can be overlap with FTD both in terms of clinical assessment and functional imaging deficits on FDG PET. Up to 10% of patients presenting with either AD or FTD on initial clinical assessment can fall into this particularly challenging group [21]. Furthermore, although FTD is a relatively rare cause of neurodegenerative dementia overall, affecting 4-15 per 100 000 <65 years, it is often disproportionately over-represented in the cohort of patients who

encounter diagnostic difficulty and hence are referred for further complex testing [27-28]. Foster *et al* showed in a study of 45 patients with pathologically proven AD (n=31) and FTD (n=14) that if utilized in conjunction with clinical evaluation, FDG PET had an accuracy of 89.6%, sensitivity of 86% and specificity of 97.6% and in correctly distinguishing between the two conditions, whereas clinical accuracy alone was 79% [29]. However, 16% of the scans were rated as normal or non-diagnostic even in patients with pathologically proven dementia. FTD is a clinically and pathologically complex disease, with several clinical variants that include behavioural variant (bv) FTD, semantic dementia, and primary progressive aphasia (PPA), which itself can be further sub-divided into progressive non-fluent aphasia and logopenic variants [27-28]. It is unsurprising, therefore, that FDG imaging may be unreliable in accurately determining the cause of dementia in such complex cases. Moreover, Kipps and co-workers who evaluated 24 patients with a confirmed clinical diagnosis of behavioural variant (bv) FTD showed that in 7 (29%) cases, there was no MRI or PET abnormality [30]. They speculated that some of these may in fact represent 'false-positive' clinical diagnosis rather than 'false-negative' imaging diagnosis, i.e. a non-neurodegenerative phenocopy of bvFTD, and advised caution in making the diagnosis in such cases and recommended careful longitudinal clinical review.

A significant number of patients in the current study had a final clinical diagnosis of a psychiatric disorder (24% of those with a normal FDG scan), and 61% of patients were referred from specialist psychiatric services. It was recognised as early as 1883 that major affective disorder could lead to reversible cognitive impairment, historically referred to as 'pseudo-dementia' [31]. Although this term has certainly fallen into disfavour over recent years, as a more thorough description of cognitive deficits associated with various clinical presentations is preferable, the distinction between functionally related cognitive deficits and

those hastened by neurodegenerative disease can be particularly challenging in the elderly. Misdiagnosis between psychiatric disorders and bvFTD may occur, as some of the symptomatology in bvFTD can be difficult to distinguish from major depressive and obsessive-compulsive disorders [28]. Also, depressive symptoms may also co-exist in up to 40% of patients with neurodegenerative dementia, further adding to the diagnostic dilemma [31]. The present study shows that FDG imaging can be very valuable in such patients by providing supportive evidence of the presence or absence of neurodegenerative dementia, with the proviso that a negative FDG scan does not completely exclude this diagnosis.

Some limitations of this study should be acknowledged. This is a single-centre study, the results of which may not necessarily be applicable in all centres. The retrospective nature of data collection may have led to some post-test bias in clinicians' responses and meant that some data records were incomplete, e.g. it was not possible to obtain objective assessments of the degree of cognitive impairment in all cases. Semi-quantification or statistical mapping using semi-analytical software was not used in this study, which instead relied on the clinical read-out generated by experienced dual-trained radiologists and nuclear medicine physicians. Finally, there was no post-mortem confirmation of the diagnosis, with exclusive reliance on the final clinical diagnosis from a case notes review and questionnaire response. The presence at post-mortem of intra-neuronal neurofibrillary tangles composed of τ-protein and extra-neuronal neuritic plaques with amyloid-β deposition are considered the hallmark of AD. It was understandably not possible in a retrospective study of this nature to obtain a pathological diagnosis. However, this was mitigated by the strengths of the study in that the final clinical diagnosis was formulated by an experienced multidisciplinary team of clinicians after a reasonable longitudinal clinical follow-up of 471 (SD 205) days.

In conclusion, this 'real-world' study into the use of FDG PET/CT brain imaging in a selected patient population in the UK with difficult to diagnose dementia shows that FDG scans had a significant impact on clinical management in >80% of cases. There was a high correlation between the PET/CT classification and final clinical diagnosis, with a kappa of 0.78 (p-value <0.0001), and a high accuracy of 94% (95% CI 87-99) for the diagnosis of the commonest cause of neurodegenerative dementia, AD. It may be possible to improve the sensitivity of functional imaging for the condition further by utilising newer techniques like amyloid plaque tracer imaging in a younger patient cohort where FDG imaging is normal or equivocal, as this does not exclude the diagnosis, and further studies could also evaluate the effect of semi-quantification of FDG uptake by statistical mapping software on the accuracy of scan interpretation. It is clear from this study, however, that the added clarity that FDG PET imaging provides, by either confirming a diagnosis of neurodegenerative dementia and allowing the patient to access support, treatment and relevant services earlier, or providing reassurance that it does not appear to be a neurodegenerative disorder, is of great value in clinical practice. Future studies could attempt to capture the patient experience, and evaluate the benefits of timely diagnosis, or reassurance, from the patient perspective.

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Table and figure legends

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Table 3 – Summary of cases with diagnostic discrepancy between FDG PET/CT findings and final clinical diagnosis.

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Figure 3 – Response to questionnaire exploring clinical impact of FDG PET/CT brain imaging (N=98/136).

Figure 4 – 66-year old with a 2-year history of cognitive decline and non-fluent aphasia. The pre-test diagnosis was uncertain, favouring fronto-temporal dementia (FTD) over Alzheimer's Disease (AD). Selected images are shown: (A) axial FDG PET, (B) sagittal FDG PET, (C) axial unenhanced CT, and (D) axial fused PET/CT. There is symmetric

hypometabolism in both parietal lobes, involving the posterior cingulate gyri (A, *arrows*) and precuneus (B, *arrow*). These are classical findings of AD. Note the absence of any atrophy on the unenhanced CT (C). The patient was commenced on anticholinesterase inhibitor (AChEI) treatment with a good therapeutic response over the next 2-years.

Figure 5 – 46-year-old with suspected behavioural variant fronto-temporal dementia (FTD). Selected images are shown: (A) axial FDG PET, (B) sagittal FDG PET, (C) axial unenhanced CT, and (D) axial fused PET/CT. There is regional hypometabolism in both frontal lobes, involving the anterior cingulate gyri bilaterally (A and B, *arrows*). Note the absence of any atrophy on the unenhanced CT (C). The FDG imaging findings were concordant with the clinical suspicion of FTD, giving greater confidence to the final clinical diagnosis.

Figure 6 – 77-year-old with progressive language disorder, dysphasia and mild memory impairment. The pre-test diagnosis was suspected primary progressive aphasia (PPA) variant of fronto-temporal dementia (FTD). Selected images are shown: (A) axial FDG PET, (B) sagittal FDG PET, (C) axial unenhanced CT, and (D) axial fused PET/CT. There is moderate asymmetric hypometabolism in the left frontal and parietal lobes, with more mild reduction in metabolic activity within the right parietal cortex (A, *arrows*). The left hemispheric defect is shown in the sagittal image (B, *arrow*). Note the striking absence of any atrophy on the unenhanced CT, despite moderately severe metabolic deficits (C). It was felt on the FDG imaging that the appearances were consistent with logopenic variant PPA. However, the final clinical diagnosis was linguistic-variant Alzheimer's disease (AD).

Figure 7 - Receiver operating characteristic (ROC) curve showing graphically the accuracy of the FDG PET/CT diagnosis of AD. The area under the curve (AUC) for AD is 0.94 (95% CI of 0.87-0.99).

Figure 8 – A proposed simplified algorithm for the evidence-based and rational use of functional imaging in patients with unexplained cognitive impairment with negative conventional imaging and no definite diagnosis after expert clinical assessment. *Note: the algorithm assumes that a diagnosis of vascular dementia will be made on clinical grounds and using structural imaging – FDG PET/CT has no role in diagnosing this condition. If the history or signs suggest additional uncertain aetiology, i.e. mixed dementia, then pursue as per algorithm.* Abbreviations: DLB, dementia with Lewy bodies; DaTSCAN™, dopamine active transporter scan; AD, Alzheimer's disease; FTD, fronto-temporal dementia.

Figure 1

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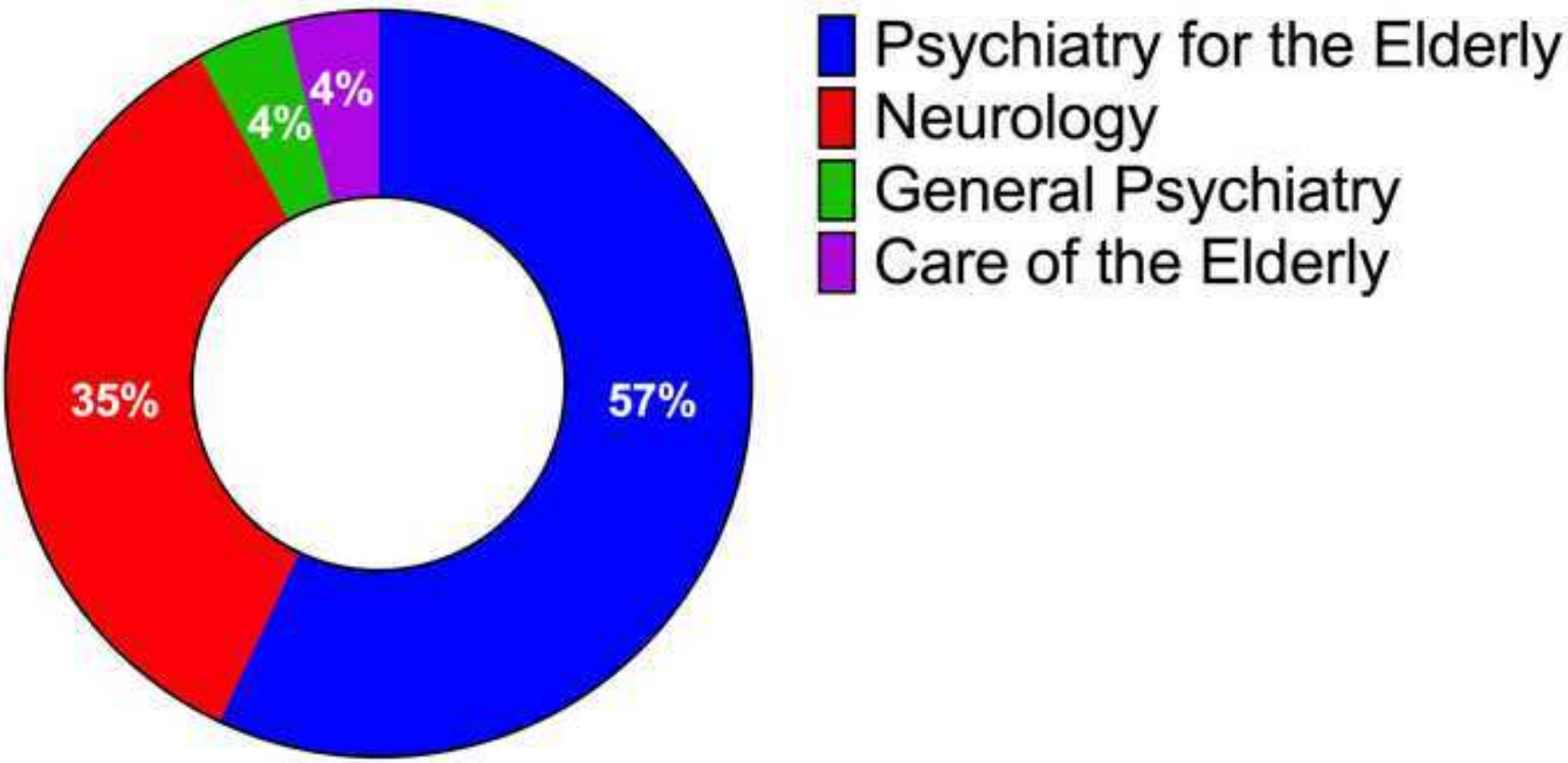

Figure 2

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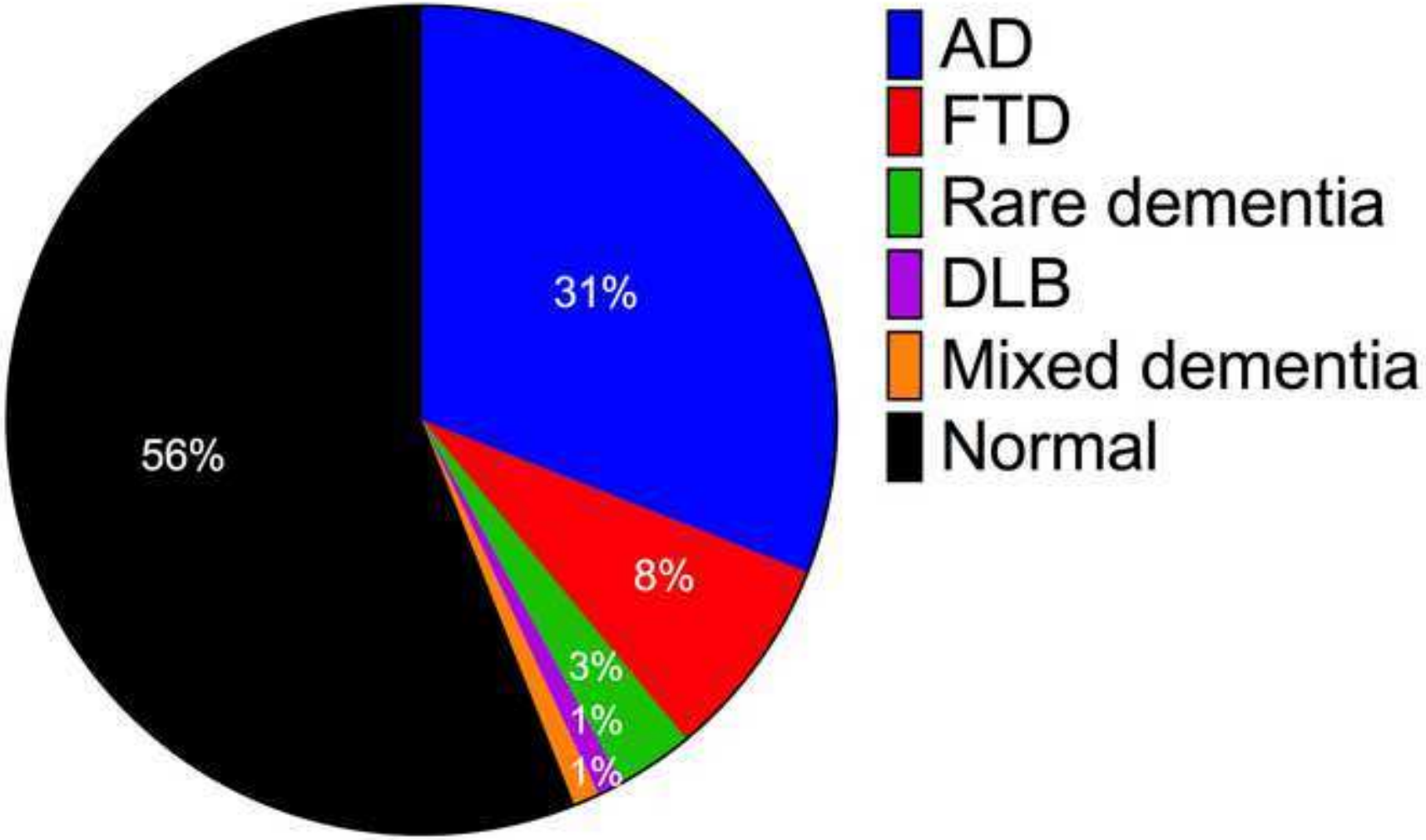

Figure 3

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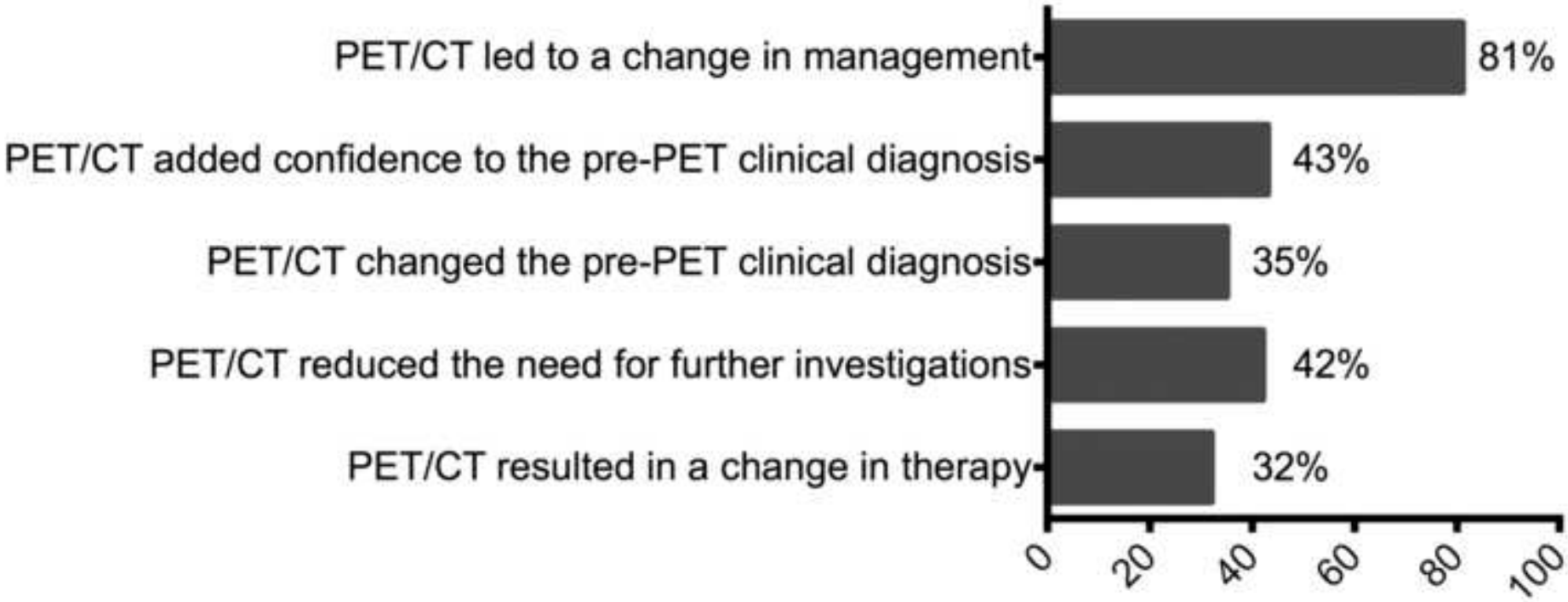

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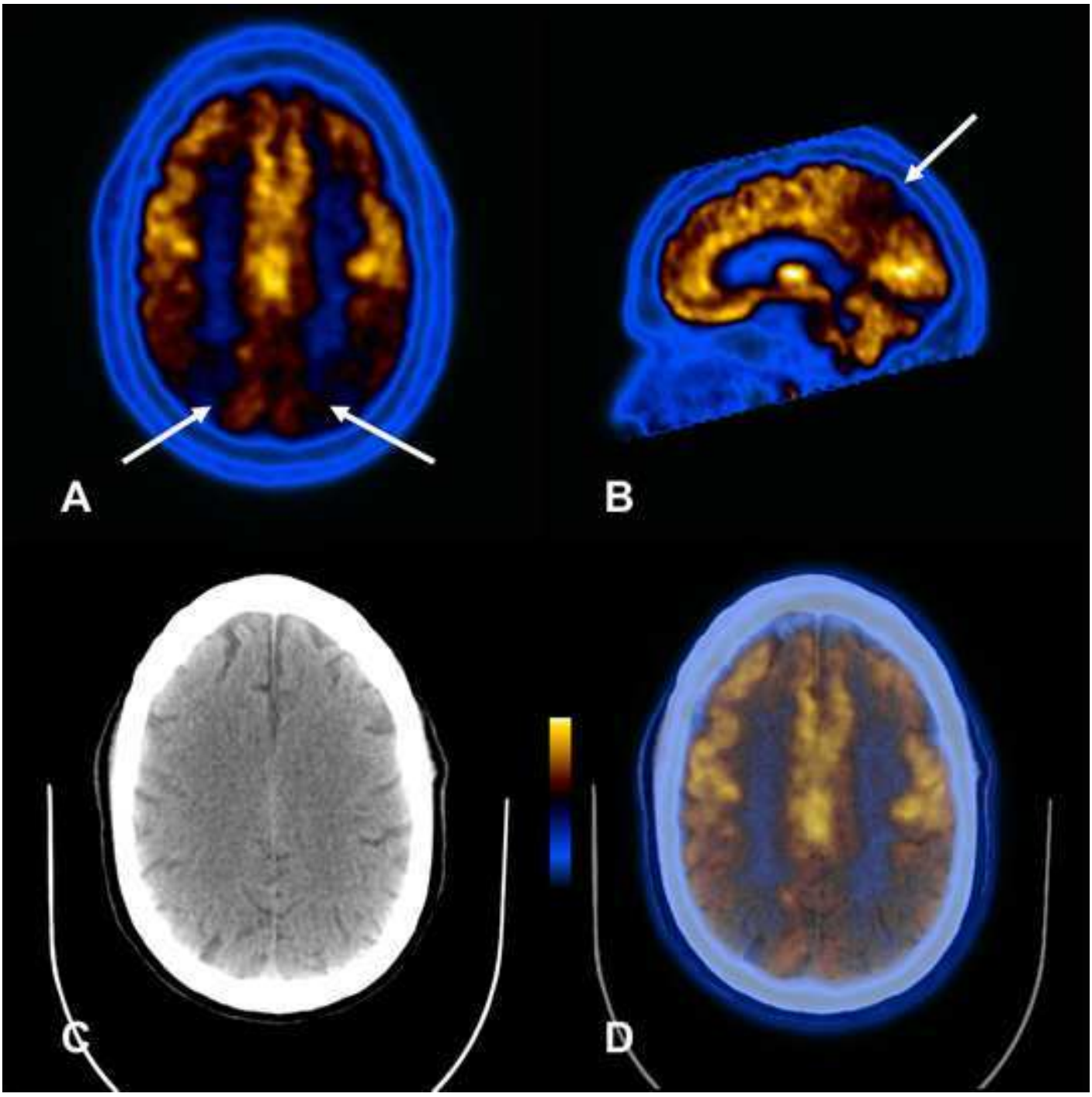

Figure 5

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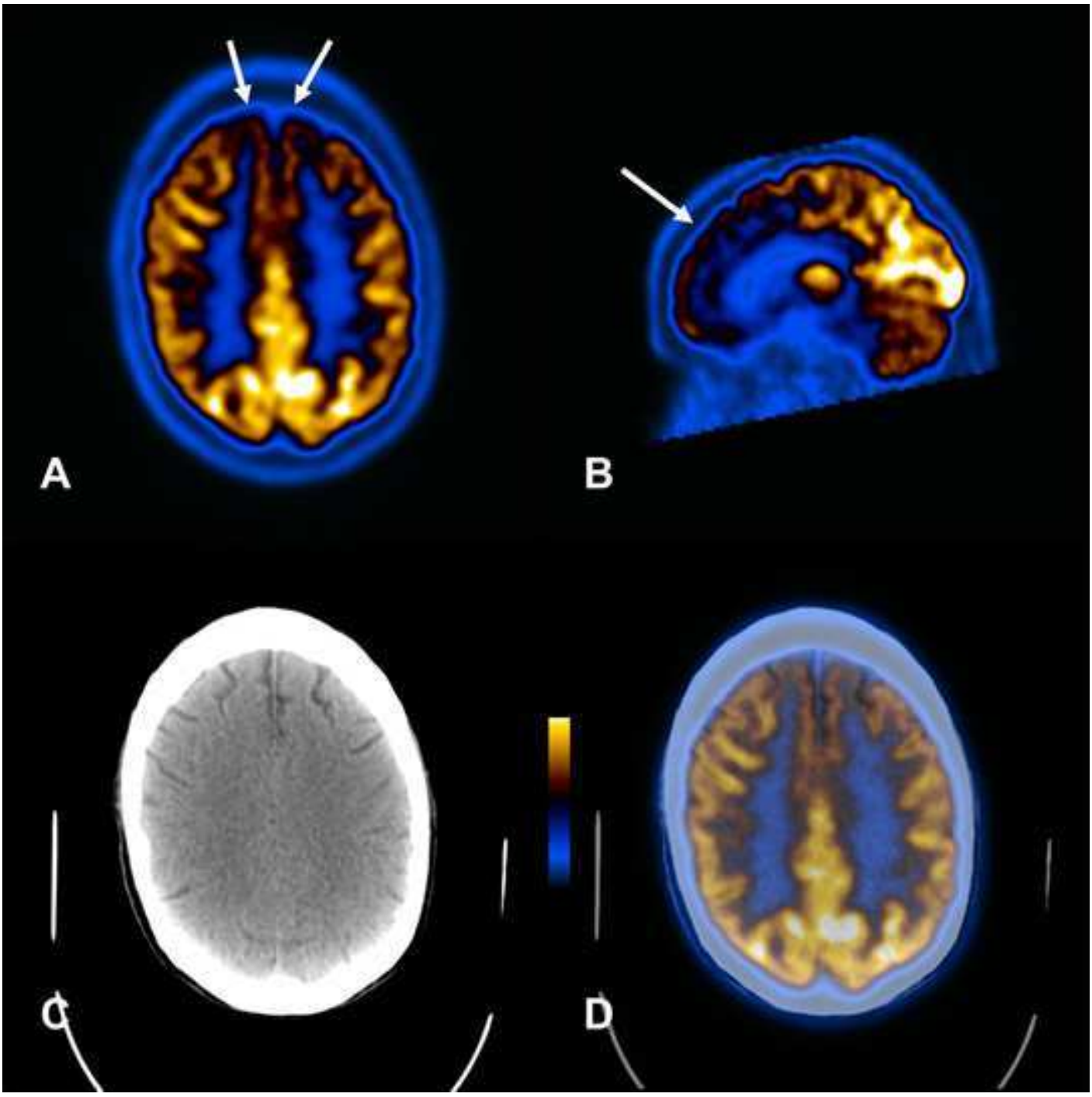

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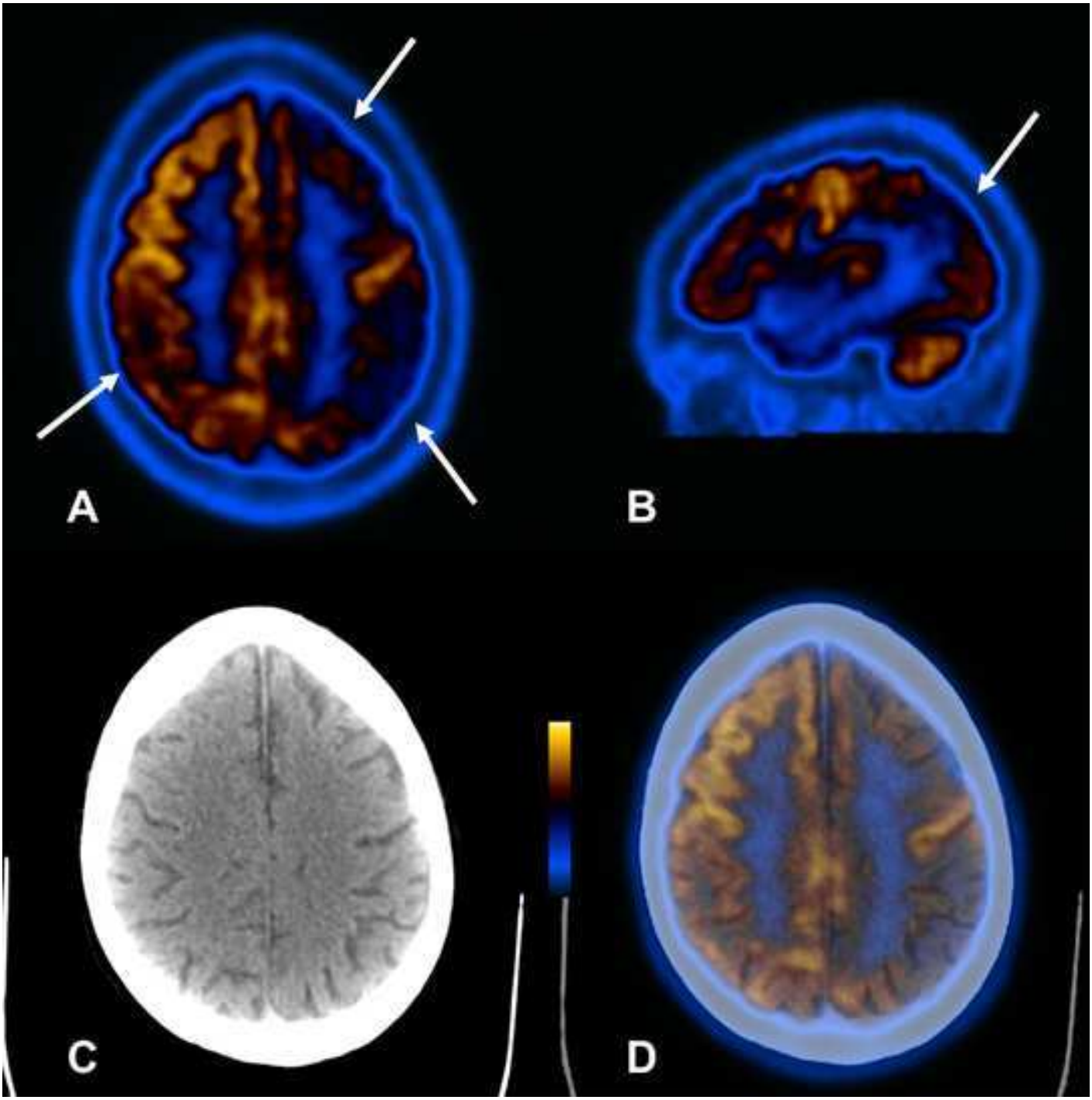

Figure 7

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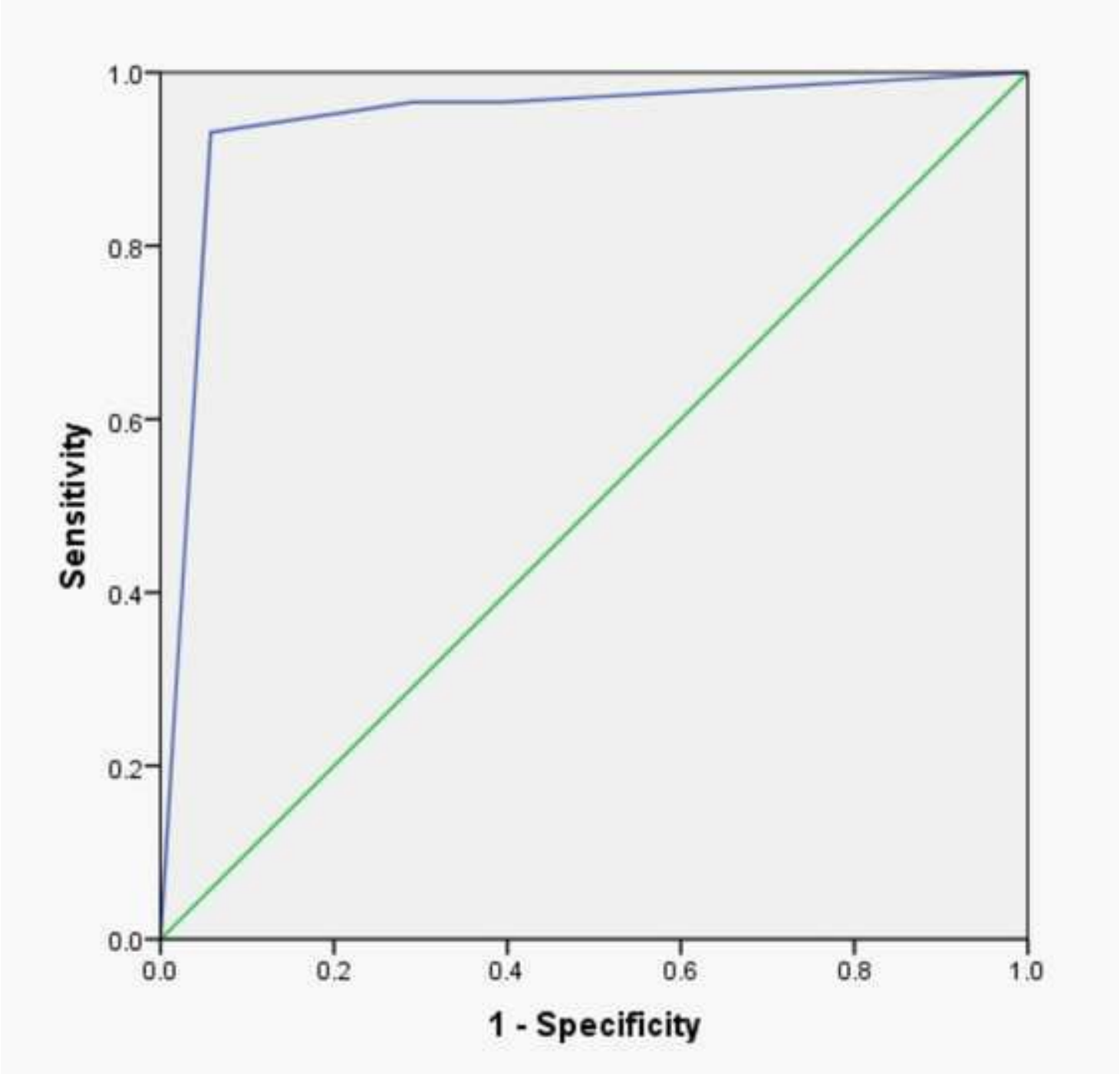

Figure 8

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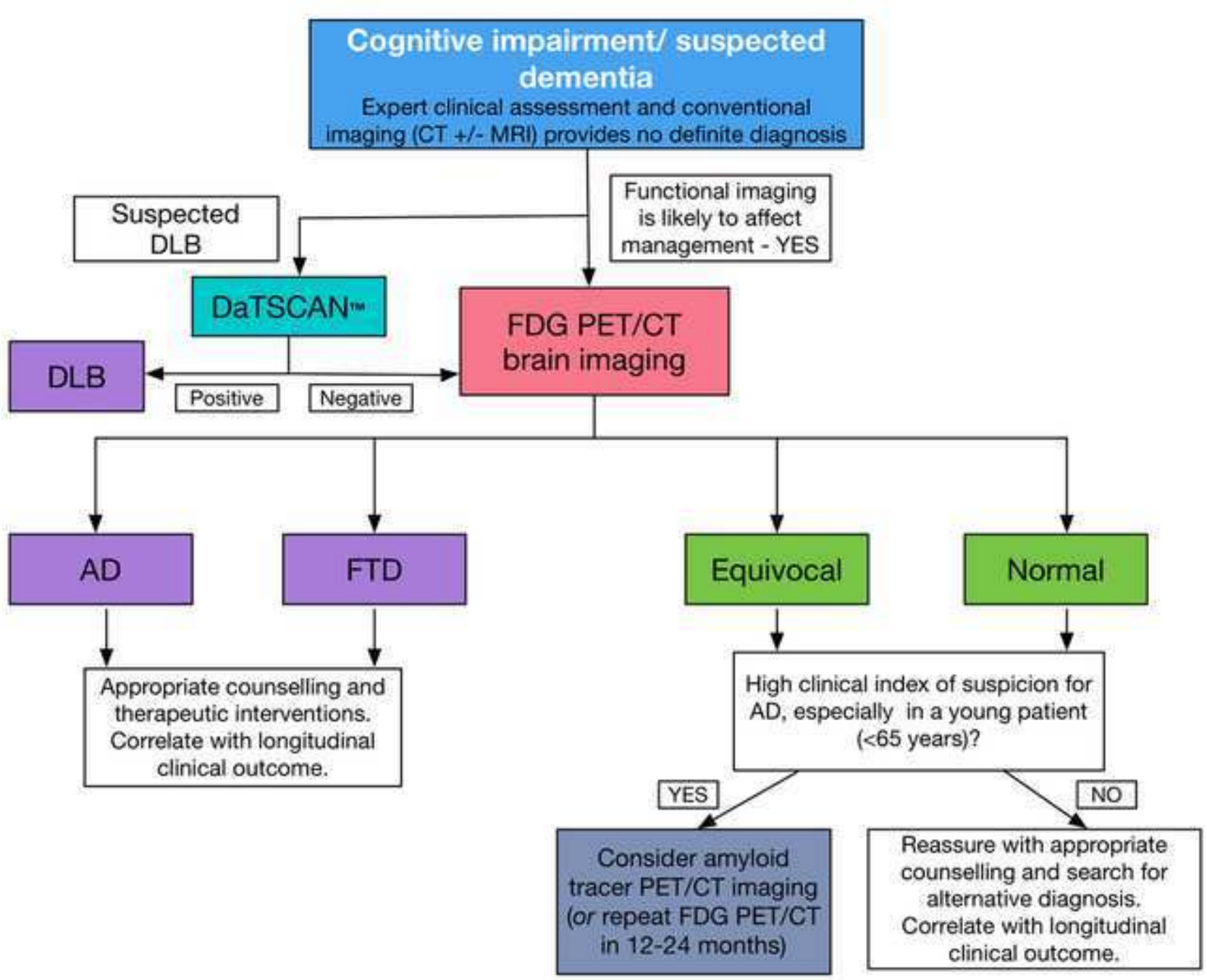

Table 1: Clinical scenarios where FDG PET/CT brain imaging would be indicated in the context of cognitive impairment

- Diagnostic difficulty after history, clinical assessment, structural imaging, and formal cognitive testing
- Early onset dementia (<65 years)
- Clinical uncertainty about subtyping of dementia- especially, differentiating AD and FTD
- Atypical presentation of AD or FTD
- Multiple established psychiatric co-morbidities (depression, schizophrenia, bipolar illness, alcohol-related, learning difficulties) with co-existing and/or new onset cognitive impairment
- Inconclusive formal neuro-psychological assessment

Table 2: Summary of the recognised patterns of metabolic deficit in the main dementia sub-types *

Dementia sub-type	Typical functional deficits	Relative sparing	Additional observations
AD	Posterior cingulate gyrus, precuneus, posterior temporal, posterior parietal. Initial deficits may be asymmetric.	Peri-rolandic sensorimotor cortex, basal ganglia, cerebellum	Later deficits - frontal lobes
FTD	• Classic bvFTD – frontal and anterior temporal cortex, anterior cingulate gyrus. • Semantic dementia – anterior temporal deficit predominates, often asymmetric • lvPPA – left-dominant posterior temporal and parietal • naPPA – inferior frontal, temporo-parietal junction and left peri-Rolandic gyri	Visual cortex	• lvPPA – overlap with AD • naPPA – overlap with atypical Parkinsonism and MND
DLB	Bilateral parietal and posterior temporal (similar to AD), occipital (usually spared in AD)	Less sparing of visual cortex	Abnormal DaTSCAN™
CBGD	Asymmetric sensorimotor cortex, fronto-parietal, basal ganglia (caudate and putamen), thalamus		Abnormal DaTSCAN™
PSP	Mid-brain, caudate, lateral and medial frontal lobes		Abnormal DaTSCAN™
PD-related dementia	Similar to AD	More mesiotemporal and less visual cortex sparing	Abnormal DaTSCAN™

Key: AD= Alzheimer's Disease; FTD= Fronto-temporal dementia; bv= behavioural variant; lvPPA = logopenic variant primary progressive aphasia; na = non-fluent agrammatic; MND= motor neuron disease; DLB= dementia with Lewy bodies; CBGD= Corticobasal ganglionic degeneration; PSP= progressive supranuclear palsy; PD= Parkinson's disease; DaTSCAN™= dopamine active transporter scan (Ioflupane ^{123}I).

* Adapted from various sources, including references 12 and 13.

Table 3: Summary of cases with diagnostic discrepancy between FDG PET/CT findings and final clinical diagnosis

Pt	Age	Gender	Clinical presentation	Referral source	FDG imaging diagnosis	Final clinical diagnosis	Follow-up period (Days)
1	55	M	Behavioural disorder, mild memory impairment	Neurology	AD - mild symmetric parietal hypometabolism	Normal	560
2	77	M	Behavioural disorder	Neurology	Atypical AD - asymmetric left temporal, posterior parietal and frontal hypometabolism	FTD	623
3	67	M	Atypical presentation with Parkinsonism and language difficulty	Neurology	Normal	Progressive supranuclear palsy	567
4	74	M	Memory impairment for 3 years	Psychiatry for the elderly	Normal	AD	511
5	59	M	Behavioural disorder, mild memory impairment	Adult psychiatry	Normal	FTD	434
6	78	F	Memory impairment, low mood	Psychiatry for the elderly	Normal	Mixed Dementia	427
7	63	M	Behavioural disorder, mild memory impairment	Adult psychiatry	Normal	FTD	518
8	51	F	Deteriorating cognitive function	Neurology	Normal	AD	588
9	41	M	Behavioural disorder, deteriorating cognitive function	Adult psychiatry	No specific diagnosis – asymmetric left parieto-temporal hypometabolism and atrophy	FTD	224
10	89	M	Cognitive decline, behavioural disorder	Psychiatry for the elderly	Normal	AD	527
11	70	M	Treatment-resistant	Adult	Normal	FTD	731

			recurrent depressive disorder	psychiatry			
12	67	M	Cognitive impairment	Psychiatry for the elderly	Normal	FTD	539
13	55	M	Short-term memory deficit, language difficulties	Neurology	Normal	FTD	679
14	54	M	Cognitive impairment, word-finding difficulties	Neurology	Normal	AD	624

Key: AD= Alzheimer's Disease; FTD= fronto-temporal dementia; M= male; F= female.

Highlights

1. Dementia remains a problem of worldwide concern with significant implications for economic, health and social care provision.
2. The timely diagnosis of dementia allows patients to benefit from access to appropriate treatment, and allows them to be actively engaged in management decisions.
3. Clinical diagnosis of dementia can be challenging in some patients (young onset, atypical presentation and significant psychological overlay).
4. FDG PET/CT is an important diagnostic tool in these patients.
5. In this study, FDG PET/CT had an impact on management in >80% of these patients and an accuracy of 94% for the diagnosis of Alzheimer's Disease.