Molecular imaging techniques using $^{18}$F-fluorodeoxyglucose, amyloid tracers, and, more recently, tau ligands have taken dementia research by storm and undoubtedly improved our understanding of neurodegenerative diseases. The ability to image in vivo the pathological substrates of degenerative diseases and visualize their downstream impact has led to improved models of pathogenesis, better differential diagnosis of atypical conditions, as well as focused subject selection and monitoring of treatment in clinical trials aimed at delaying or preventing the symptomatic phase of Alzheimer’s disease. In this article, we present the main molecular imaging techniques used in research and practice. We further summarize the key findings brought about by each technique individually and more recently, as adjuncts to each other. Specific limitations of each imaging modality are discussed, as well as recommendations to overcome them. A nonvalidated clinical algorithm is proposed for earlier and more accurate identification of complex/atypical neurodegenerative diseases.

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Keywords: Molecular imaging; FDG-PET; Amyloid PET; Dementia; Neurodegenerative diseases; Pathogenesis; Differential diagnosis; Atypical dementia; Alzheimer’s disease

1. Introduction

The term “functional imaging” is widely used to describe a series of approaches to evaluate “brain function” as opposed to “brain anatomy”. Strictly speaking, that distinction is artificial, as all forms of brain imaging are ultimately based on the assessment of properties of cerebral tissues, which vary locally in a way that relates to the “function” of that region. Even direct visualization of the brain by a human observer in the operating or autopsy room can be thought of as functional imaging. Computed tomography and T1-weighted magnetic resonance imaging (MRI), “typical” anatomical imaging approaches, are measurements of the X-ray transmission properties of the brain, which reflect brain’s regional variations in chemical composition, and of essentially the same chemical variations but measured differently through their influence on local magnetic properties of tissues. The “images” thus generated are simply a beautiful way of representing a large number of numerical data about those properties in a fashion that appeals to us because they are similar to our natural visual experience of viewing things. The same principles apply to all medical imaging techniques, including nuclear medicine techniques.

The first applications of radioisotopes to study human function started with nonimaging, radiation counters–based approaches in the 1910s. Planar (2D) imaging techniques began with the development of the rectilinear scanner by Benedict Cassen in 1949 and, especially, with that of the gamma camera by Hal O. Anger in 1959, for studies based on “standard” emitters (i.e., nonpositron emitters). Imaging of positron emitters dates back to 1951. Planar evaluation of
cerebral blood flow (CBF) started with studies by Niels Lassen (for a review, see the study by Lassen et al. [1]). Tomographic (3D) imaging began in 1963 for single-photon emission tomography (SPECT; nonpositron emitters) and 1975 for positron emission tomography (PET) (see the study by Portnow et al. [2] and Hutton [3], respectively). Nowadays, planar imaging is only very rarely used for assessment of the central nervous system in nuclear medicine (brain death studies, assessment of cerebrospinal fluid [CSF] flow).

2. SPECT and PET

For this section, PubMed database was searched for relevant studies using the following keywords: (“Single Photon Emission Tomography” OR “SPECT”) AND (“Positron Emission Tomography” OR “PET”) AND (“Review”) AND (“Neurodegenerative diseases”) AND (“Mild Cognitive Impairment” OR “MCI”). The inclusion of relevant evidence based on personal knowledge or from the reference lists of pertinent articles was admitted. Only articles written in English were included. The final selection of articles was based on relevance, as judged by the authors. The impact factor as such did not affect the selection of the articles included in the analysis.

2.1. Brief review of the basics

SPECT and PET both are emission tomographic techniques. The source of radioactivity (gamma rays) is within the patient who has been dosed with a given radiopharmaceutical. The mathematical processes allowing for the measurement of the 3D distribution in subjects are nevertheless very similar in nature to those used in transmission tomography (computed tomography scanning, where X-rays pass through the body of the subject) and have been known for close to a 100 years through the work of Radon [4]. SPECT and PET both involve the administration (most often intravenously) of radioactive material to subjects. Almost always, radiopharmaceuticals consist of a radioactive atom (the radionuclide) on one hand, which will eventually emit the radioactive signal that will be detected by the scanner, and, on the other hand, a molecule with biological properties that will result in localization of the whole of the radiopharmaceutical (also called radiotracer or radioligand) to a desired target in the body. The nature of the binding-to-target process can be highly variable, sometimes only requiring interactions of low specificity, or at the other extreme involving highly stereospecific recognition of the radiotracer by its target.

The main difference between SPECT and PET resides in the nature of the radionuclide associated with the carrier molecule. That difference has major consequences. The radionuclides used in SPECT imaging are so called single-photon emitters, meaning that they only emit one photon at a time, which will travel in one of any possible direction from its site of emission. Those used in PET obviously emit positrons, small particles with a unit positive charge and the same mass as an electron, which rapidly combine with an electron, resulting in the simultaneous emission of two photons traveling more or less in opposite directions. The detection process for SPECT and PET significantly differs due to the abovementioned properties of the photons being detected. Technically, PET and SPECT cameras present significant differences, which result in performances that are quite distinct. PET cameras used in humans have significantly better spatial resolution, meaning they can measure activity accurately in smaller volumes (Fig. 1). Other technical issues also favor a more accurate detection of the distribution of activity with PET.

SPECT radiopharmaceuticals are most often labeled with technetium-99m, a widely available radionuclide (problems of supply have largely been dealt with) with a reasonable cost and highly desirable physical properties. Other tracers can also be used with SPECT, such as indium-111, iodine-123, or gallium-67. One of the problems with all of those agents is that they can significantly change the biological properties of molecules one links them to, either by their very presence in the complex or through the process used for labeling of the carrier moiety. This limits the number of available SPECT radiotracers. PET radionuclides on the other hand are mostly represented by carbon-11 (¹¹C), nitrogen-13, (¹³N) oxygen-15 (¹⁵O), and ¹⁸F-fluorodeoxyglucose (¹⁸F). The chemical methods used to link them to carrier molecules, and their own chemical nature, have less impact on the biological behavior of the carrier portion of the radiopharmaceutical, and it is possible to label over a thousand different products with positron emitters, many especially designed for studies of the brain [5]. However, most labeling techniques for SPECT agents have been made quite simple, whereas synthesis of PET agents generally requires a specialized radiochemistry laboratory. Furthermore, the half-lives (T1/2; the time for a

Fig. 1. Functional imaging using SPECT (left) and PET (right) of a patient with AD. The red arrows point to bilateral hypometabolism in the parietal lobes. Spatial resolution of SPECT is 8 to 12 mm, whereas that of PET is 4 to 5 mm. Consequently, PET measures brain activity accurately in much smaller volumes than SPECT; hence, providing a significant advantage in the analysis of subtle or focal brain changes associated with degenerative diseases. Abbreviations: SPECT, single-photon emission tomography; PET, positron emission tomography; AD, Alzheimer’s disease.
sample of a given radionuclide to decay to half of its original radioactivity level) of PET tracers tend to be rather short. For instance, carbon-11 has a T1/2 of 20.38 minutes, nitrogen-13 of 9.96 minutes, oxygen-15 of 2.04 minutes, and 18F-fluorodeoxyglucose of 109.8 minutes. This means that with the exception of 18F-fluorodeoxyglucose–labeled tracers, other agents must be used where they have been produced. Because the production of the most frequently prepared positron emitters requires a cyclotron, in addition to the complex radiochemistry facility already mentioned, where the radioactive atoms will be affixed to the desired targeting molecule, the complexity and cost of operation of such a laboratory rapidly become significant. Fortunately, more and more 18F-fluorodeoxyglucose–labeled tracers are available, and those have a long enough physical T1/2 to allow synthesis in a facility equipped with a cyclotron and radiochemistry laboratory with subsequent distribution over a certain distance. The radionuclides used with SPECT have a significant advantage from that perspective, that is, their T1/2 are much longer, typically having values of many hours to days.

Altogether, those physical differences explain why their applications are different. SPECT tends to be more widely used than PET in the clinical world, be it for neuropsychiatric applications or those involving other body organs (i.e., excluding brain) and clinical conditions, because of overall lower cost and greater simplicity. PET is generally found in larger, more specialized hospitals and research centers and reserved for a more limited spectrum of clinical applications; however, in oncology, it has experienced tremendous growth over the past decade because of the widespread availability of 18F-fluorodeoxyglucose (or FDG-PET). In neurology, the spectrum of targets and the actual performance of clinically available tests now favor PET imaging over SPECT. Moreover, recent advances in microfluidics suggest that on-site synthesis of single doses of PET tracers with 18F-fluorodeoxyglucose might make it possible for sites without large radiochemistry laboratories to have access to tracers nowadays only found in academic institutions [6].

2.2. Almost half a century of brain research

PET and SPECT were actually “born” studying the human brain [7,8]. Of course, functional brain imaging with radionuclides largely antedated the arrival of tomographic techniques [9], but they were rapidly replaced by 3D approaches when those became available. Initial studies dealt with glucose metabolism and permeability of the blood-brain barrier and soon with regional CBF measurements [10] using principles developed in the mid-19th century [11]. As availability of radiopharmaceuticals rapidly increased, the number of cerebral targets also did, at least for research purposes. We now have, both with SPECT and, especially, PET, the means to quantitatively assess multiple parameters linked to chemically defined neurotransmission, activity of numerous cerebral enzymes, neural inflammation, deposition of abnormal proteins in brain tissues, and so forth. However, the number of ligands approved for clinical use is much more limited than that available for research purposes.

SPECT tracers for CBF typically are 99mTc-labeled compounds with high lipophilicity, which are administered intravenously. As they travel through the heart and the lungs, those agents are thoroughly mixed with blood, and upon reaching the brain, they will distribute according to regional blood flow. Mostly at the capillary level, they will easily diffuse across the blood-brain barrier into brain tissue due to their high lipophilicity [12,13]. However, once they have entered the brain, they are rapidly and irreversibly transformed into polar components unable to diffuse back into the blood, and therefore, they remain trapped locally, in proportion to regional blood flow; images can be acquired up to a few hours after injection and will still reflect distribution of blood flow at the time of injection. In the vast majority of cases, no actual quantification of blood flow is performed during those studies (relative regional differences are assessed, either visually or with the aid of different statistical approaches). However, flow quantification (mL.min\(^{-1}\) [100 g of tissue]\(^{-1}\)) can actually be achieved relatively easily if the context dictates it (for example, see the study by Matsuda et al. [14] and Laliberte et al. [15]).

PET studies with 18F-FDG rely on the analogous but not identical biological behavior of glucose and 2-deoxyglucose (2-DG) [16]. Its transport across membranes and initial biochemical behavior once it reaches the inside of a cell are largely (although not strictly) the same as those of glucose, with which it competes directly for those processes. Indeed, the first molecular transformation of both glucose and 2-DG is phosphorylation by hexokinase. However, 6-P-glucose then is transformed into fructose-6-phosphate by phosphohexose isomerase, in which the absence of the hydroxyl group in position 2 of 2-DG prevents that reaction from taking place. As there is very limited phosphatase activity for 6-P-DG in the brain (as in many other tissues, allowing for the use of 18F-FDG in multiple organs and diseases), the accumulated phosphorylated tracer is basically trapped intracellularly, with a concentration proportional to that of glucose uptake in the same cell over the time during which 2-DG circulates in the blood (typically about 30–40 minutes, at progressively diminishing concentrations) after its injection. Again, most studies essentially are limited to visual or statistical analysis of the relative distribution of 18F-FDG in the brain. Quantitative measurements of cerebral glucose utilization by the brain (\(\mu\text{mL.min}^{-1}[100 \text{ g of tissue}]^{-1}\)) can be performed based on the work of Sokoloff et al. in animals and humans [8,16].

The importance of regional CBF studies and regional glucose consumption studies rests on the fact that those parameters, which are highly correlated, are also directly linked to the local intensity of glutamatergic synaptic
studies are significantly more widely available and performance of PET is much better than SPECT, and PET to defend the use of SPECT imaging in the differential diag-

availability and high cost of PET scanning made it possible brain-imaging work is conducted. In the past, the limited 2.3.1. Neurodegenerative diseases

easystudyof neurodegenerative diseases and neuropsychiatric conditions. Thus, it is a good indication of the numerous enzymes, neurotransmitter receptors, neurotransmitter transporter systems (both at the cell membrane and synaptic vesicles membrane levels), inflammatory markers, amino acid transporters, protein and neurotransmitters synthesis chains, abnormal protein aggregates, markers of gene expression, apoptosis, and angiogenesis, which we can now study. For each, it is possible to quantitatively assess activity, density, affinity for different ligands, rate of transformation, and so on. Such agents can even be used to assess real-time changes in neurotransmitter concentrations in the brain as it dynamically responds to external challenges by modifying their release [20,21].

2.3. SPECT and PET in neurodegenerative diseases

None of the nuclear medicine techniques for brain imaging are specific for the study of neurodegenerative diseases. Rather, those approaches can all, at one point, be used to further our understanding of normal or pathological function of brain regions. Here, we review some of the most established applications and research results related to neurodegenerative diseases and neuropsychiatric conditions.

2.3.1. Neurodegenerative diseases

This is by far the field in which most nuclear medicine brain-imaging work is conducted. In the past, the limited availability and high cost of PET scanning made it possible to defend the use of SPECT imaging in the differential diagnosis of neurodegenerative disorders. Nowadays, diagnostic performance of PET is much better than SPECT, and PET studies are significantly more widely available and affordable (in many countries, the cost of a SPECT CBF agent is much higher than a dose of $^{18}$F-FDG). For these reasons, PET has become the instrument of choice in nuclear medicine to evaluate cognitive disorders, when indicated [22,23]. Its effectiveness has been repeatedly reviewed and established in influential articles [24,25]. Finally, FDG-PET imaging is an integral part of the revised criteria for the diagnosis of Alzheimer’s disease (AD) (Alzheimer’s disease: The term indicates the presence of Alzheimer’s pathology, leading, according to the current hypothesis, to a neurodegeneration in mediotemporal and temporoparietal areas. The term does not refer to the clinical expression and severity of the disease; see the study by Dubois et al. [26] and McKhann et al. [27]) [27–29] or the behavioral variant frontotemporal dementia (bvFTD) [30].

FDG-PET is a very good marker of neurotransmission intensity and therefore of synaptic integrity [31,32]. Results are a direct reflection of tissue state, efficiently depicting regional anomalies at the synaptic level even if this only implies dysfunction without actual loss. Recent AD criteria have supported its use in staging the disease and labeled FDG-PET a downstream biomarker of degeneration. In one landmark study, it has proved to be a very good marker of AD pathology [33], although recent developments in amyloid and tau imaging have surpassed FDG-PET in that regard (see Sections 3 and 4). Its relationship to the clinical status, however, is not as straightforward. Factors linked to cognitive reserve have a direct impact on the level of tissue dysfunction that will result in a given clinical status [34,35]. However, assessing the nature of the syndrome in combination with underlying symptoms of memory, visuospatial and language dysfunctions, apathy, loss of empathy, or executive deficits can be fruitfully pursued.

In AD, a typical pattern of metabolic reduction primarily involving parietotemporal regions and the precuneus/posterior cingulate complex (PCC) has been described (Fig. 2) [33,36,37]. AD variants such as the “language variant” (also called the logopenic variant primary progressive aphasia [lvPPA] [38]), the “behavioral/ dysexecutive variant” [39], and the “visual variant” (also called posterior cortical atrophy [PCA] [40]) show relatively distinct patterns of focal hypometabolism (Fig. 3A–C). Involvement of the PCC in AD variants and other neurodegenerative diseases is a matter of current investigations by an international group led by the first author of this article. Dementia with Lewy bodies often presents

![Fig. 2. Classic AD pattern of hypometabolism on FDG-PET. Note the bilateral reductions in parietotemporal regions (right > left) and PCC. Note that this pattern that also shows bilateral frontal hypometabolism could be found in the behavioral/dysexecutive variant AD. Abbreviations: AD, Alzheimer’s disease; PCC, precuneus/posterior cingulate complex.](image-url)
with parietal hypometabolism reminiscent of AD, with remarkable sparing of the PCC (also known as the “posterior cingulate island sign”), however, and occipital involvement (Fig. 4) [41–44].

A number of studies have focused on the spectrum of frontotemporal lobar degeneration (FTLD) and showed here again a distinct pattern of hypometabolism in several conditions [30,38,45,46]. The Centers for Medicaid and Medicare Services in the United States issued on September 15, 2004, a decision memo authorizing reimbursement of FDG-PET in patients for whom diagnosis between FTLD and AD was still unclear after a standard

Fig. 3. Patterns of hypometabolism on FDG-PET in AD variants. (A) This 69-year-old male presented with the language variant AD, also called the logopenic variant of primary progressive aphasia (lvPPA). His FDG-PET shows decrease in uptake in the posterior portions of the cingulate gyri and associative polymodal cortices, suggesting underlying AD pathology. Note the severe left-sided posterior temporal anomalies, typical of lvPPA. (B) This 68-year-old male was diagnosed with the behavioral/dysexecutive variant AD based on clinical presentation and a positive amyloid scan. FDG-PET revealed bilateral reductions in parietotemporal regions but sparing of the PCC. As pointed previously, and much to our surprise, this variant of AD does not tend to be associated with significant hypometabolism of the frontal lobes. (C) In the visual variant AD, also called posterior cortical atrophy, the pattern of hypometabolism is typically found in bilateral occipital regions, more pronounced on the right. In the case shown here, the PCC is also affected (right > left). Abbreviations: AD, Alzheimer’s disease; PCC, precuneus/posterior cingulate complex.

Fig. 4. Dementia with Lewy bodies (DLB) presents with several similarities to classic AD on FDG-PET, including bilateral temporoparietal hypometabolism as seen here. However, patient with DLB often show preserved metabolism of the PCC (left arrow). Bilateral hypometabolism of the occipital lobes (right arrow) is another important feature that may be present in DLB but not in classic AD. Abbreviations: AD, Alzheimer’s disease; PCC, precuneus/posterior cingulate complex.
clinical evaluation. Classic bvFTD shows hypometabolism in frontal and anterior temporal regions (Fig. 5) [47], whereas semantic variant primary progressive aphasia is associated with bilateral but usually quite asymmetric (left dominant) anterior temporal lobe hypometabolism (Fig. 6A and B) [48]. Progressive nonfluent aphasia (also called nonfluent variant primary progressive aphasia [nfvPPA]) typically targets the left dorsolateral and dorsomedial prefrontal cortex (Fig. 7) [49]. Recently, authors have attempted to explore FDG-PET patterns in bvFTD phenocopy, a condition reminiscent of bvFTD for which patients show milder symptoms and a much slower course over time [50–54].

Corticobasal degeneration (CBD) is a very heterogeneous neuropathology and can generate a number of clinical phenotypes including corticobasal syndrome (CBS), nfvPPA, bvFTD, executive-motor syndrome, and PCA [55]. The most common pathologic substrates for CBS are CBD, AD, progressive supranuclear palsy (PSP), and FTLD with TAR DNA-binding protein (TDP) inclusions. In practice, FDG-PET findings in CBD-CBS often show asymmetric dorsal frontal and anterior parietal metabolic reduction with or without ipsilateral, striatal, and thalamic hypometabolism, which is most prominent in the hemisphere contralateral to the side of the most affected limbs (Fig. 8) [56]. In CBS cases, FDG-PET imaging can sometimes help predict correct identification of the underlying AD pathology [57,58]. Based on data showing greater visuospatial and memory deficits and temporoparietal-predominant degeneration on neuroimaging in CBS secondary to AD pathology versus FTLD, a group of authors led by Sha and Rabinovici [59] attempted to evaluate the use of modified clinical criteria and visual interpretations of MRI and FDG-PET in predicting amyloid deposition in CBS. Results showed that splitting CBS patients into frontal or temporoparietal clinical variants can help predict the likelihood of underlying AD, but the criteria require further refinement. Most importantly, temporoparietal-predominant neuroimaging patterns appeared sensitive but not specific for AD. Other conditions such as PSP [60], multisystem atrophy [61], amyotrophic lateral sclerosis [62], Creutzfeldt-Jakob disease [63] have been studied, but their distinct patterns remain to be clarified in large cohorts.

2.3.1.1. Atypical complex cases with an uncertain diagnosis

Diagnosis of neurodegenerative diseases can be challenging, particularly in the early stages of the disease, in younger patients, in atypical/unclear presentations, or in patients with comorbid neuropsychiatric symptomatology [64–66]. Delay in treatment due to diagnostic uncertainty, particularly frequent in atypical/unclear degenerative diseases, has important clinical and psychological consequences for patients and their families [67,68]. In tertiary care memory clinics, where the most complex patients are seen, a significant proportion of cases remain unclear despite a comprehensive clinical evaluation. For such atypical/unclear degenerative diseases, further investigation is often undertaken to obtain a clear diagnosis. These complementary evaluations include a detailed neuropsychological evaluation, blood tests, CSF

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**Fig. 5.** Severe bilateral hypometabolism of the frontal lobes (both medially and laterally) in a patient presenting with the behavioral variant of frontotemporal dementia. There is also mild hypometabolism of the temporal lobes (left > right).

**Fig. 6.** (A) The semantic variant of primary progressive aphasia (svPPA) most often presents with a left-sided constellation of deficits. Note the severe hypometabolism in the left anterior temporal areas. However, congruent with progressive contralateral atrophy, right anterior temporal hypometabolism has been reported in many series and may be more indicative of disease progression. By contrast, (B) right svPPA preferentially targets the right anterior temporal lobe and generates behavioral anomalies reminiscent of bvFTD. Abbreviation: bvFTD, behavioral variant frontotemporal dementia.
analysis, MRI, and molecular imaging with FDG-PET. A growing body of evidence indeed supports the value of FDG-PET in the diagnosis of patients with atypical/unclear conditions [24,33,36,69–74]. Importantly, FDG-PET can improve diagnostic accuracy and lead to earlier treatment, better planning for future care, and less suffering for patients and their families. In 2010, a retrospective memory clinic study evaluating the value of FDG-PET in mild cognitive impairment (MCI) (Mild cognitive impairment: This term describes a population with acquired cognitive impairment and no functional disability [75]. This clinical syndrome includes cases with AD biomarker positivity or prodromal AD [about 50%] [see clinical criteria by Dubois et al. [26]], cases with no neurodegenerative disorder [about 35%–40%], and cases progressing to non-AD forms of dementia [about 10%–15%; 76]), typical and atypical/unclear diseases [71], showed that the addition of FDG-PET to the routine memory clinic workup significantly lowered the number of unclear diagnoses from 39% to 16%. FDG-PET was also associated with a change in diagnosis in 29% of patients and a 64% increase in the use of cholinesterase inhibitors (ChEIs), the current drug approved for the treatment of AD. These results were recently corroborated by a prospective study on the clinical use of FDG-PET in 194 patients [69]. In this study, FDG-PET changed the clinical diagnosis in 35%, altered the use of ChEI medication in 17%, and reduced uncertain diagnoses from 30% to 18%.

Recent European Federation of the Neurological Societies (EFNS) guidelines [77] recommend the use of FDG-PET for degenerative diseases showing atypical features and diagnostic uncertainty. However, in a number of cases, equivocal or incongruent FDG-PET results may leave clinicians in an even greater dilemma. Indeed, despite the diagnostic clarification FDG-PET allows in most cases, 18% of patients in the study by Elias et al. [69] and 16% in the study by Laforce et al. [71] remained with an uncertain diagnosis after a first FDG-PET and an extensive diagnostic workup. In these highly difficult cases, very few studies provide guidance about the next steps to take in the investigative process. Given the availability of FDG-PET technology in many centers, some clinicians order a second FDG-PET to look for a progression or clarification of metabolic findings. However, it is not uncommon that the FDG-PET findings are equivocal in this setting. For those cases, a repeat FDG-PET may clarify the diagnosis and prevent treatment delay. We retrospectively assessed the clinical impact of a repeat FDG-PET in 59 patients with atypical/unclear syndromes and inconclusive initial FDG-PET [78]. Changes in primary diagnosis, diagnostic confidence, and management after the second FDG-PET were examined. Conducting a second FDG-PET reduced the number of unclear diagnoses from 80% to 34% and led to diagnostic change in 24% of cases and treatment modification in 22% of patients. Overall, the clinical impact was higher when initial diagnostic confidence was low and the second FDG-PET repeated ≥12 months after the first one. In tertiary care memory clinic settings, when diagnostic incertitude persists despite extensive evaluation and an equivocal FDG-PET, repeating the FDG-PET 12 months later can greatly clarify the diagnosis and improve the care management.

2.3.2. Neuropsychiatric conditions

A significant number of psychiatric diseases affect frontal-subcortical pathways. For decades already, nuclear medicine PET and SPECT imaging involving any of the tracer categories have had already mentioned a profound

Fig. 7. Left prefrontal hypometabolism in a 56-year-old patient presenting with nonfluent variant primary progressive aphasia. Note the relative preservation of right-hemisphere metabolism.

Fig. 8. Right cortical (A), left cortical (B), right medial (C) and left medial (D) view of FDG-PET imaging in a patient with corticobasal syndrome. Note the profound areas of asymmetric hypometabolism (right > left). Amyloid imaging further revealed underlying AD pathology. Abbreviation: AD, Alzheimer’s disease.
impact on how we understand diseases such as schizophrenia, obsessive compulsive disorders (OCDs), depression, and other mood disorders. Exhaustive reviews have been published [79] attesting to the activity in those domains. Although most of that activity contributes to a better understanding of their pathophysiology, some applications are actually entering the clinical realm, for instance by helping to decide whether OCD subjects not responding to therapy might be candidates for anterior cingulotomy [80]. With the rapid developments in deep-brain stimulation for treatment of neuropsychiatric diseases, such applications might multiply very soon.

As pointed out by the Geneva Task Force for the Roadmap of Alzheimer’s Biomarkers, FDG-PET has achieved phases 1 and 2 (rational for use and ability to discriminate AD subjects from healthy controls or other forms of dementia), but phase 3 aims (early detection ability) are only partly achieved, phase 4 studies (routine use in prodromal patients) are ongoing, and phase 5 studies (quantify impact and costs) have not been performed. Specific efforts are needed to complete collecting phase 3 evidence, particularly comparing and combining FDG-PET with other biomarkers, and to properly design phase 4 prospective studies as a basis for phase 5 evaluations.

3. Amyloid imaging

For this section, PubMed database was searched for relevant studies using the following keywords: (“Positron Emission Tomography” OR “PET”) AND (“PIB” OR “Pittsburgh compound b” OR “Pittsburgh compound-b” OR “Florbetapir” OR “AV45” OR “AV-45” OR “Amyvid” OR “Flutemetamol” OR “Vizamyl” OR “GE067” OR “Florbetaben” OR “av-1” OR “BAY94-9172” OR “Neuraceq”) AND (“Review”) AND (“Neurodegenerative diseases”) AND (“Mild Cognitive Impairment” OR “MCI”). The inclusion of relevant evidence based on personal knowledge or from the reference lists of pertinent articles was admitted. Only articles written in English were included. The final selection of articles was based on relevance, as judged by the authors. The impact factor as such did not affect the selection of the articles included in the analysis.

3.1. Brief review of the basics

The advent of amyloid PET ligands has enabled the detection and quantification of amyloid neuritic plaques, a core pathologic feature of AD, in the living human brain. The first tracer specific to amyloid-beta (Aβ) applied in human studies was carbon-11 (11C)-labeled Pittsburgh Compound B (PiB) [81,82]. PiB is an analog of thioflavin-T that, at PET tracer concentrations, binds to fibrillar Aβ deposits with high sensitivity and specificity [83,84]. PiB binds to both extracellular amyloid plaques (composed primarily of the Aβ1–42 peptide [Aβ1–42]) and vascular amyloid deposits (consisting mainly of Aβ1–40 peptides) [85]. At PET tracer concentrations, PiB does not bind to non-Aβ inclusions such as neurofibrillary tangles (NFTs) or Lewy bodies [86–88] or to brain homogenates from patients with non-Aβ dementia [89].

The ~20-minute half-life of 11C, however, limits its use to research centers equipped with a cyclotron and precludes widespread clinical application. A second generation of amyloid tracers labeled with 18F-fluorodeoxyglucose (18F, ~110-minute half-life) has been developed, making it feasible to distribute amyloid tracers to hospitals without an on-site cyclotron. This will greatly enhance the clinical use of amyloid imaging [90]. There are currently three FDA- and European Medicines Agency (EMA)-approved, 18F-fluorodeoxyglucose–labeled, tracers available for clinical use: (1) florbetapir (a styrlypyridine derivative) since 2012 [91]; (2) flutemetamol (a 3-fluoro analog of PiB) since 2013 [92,93]; and (3) florbetaben (a derivative of stilbene) since 2014 [94,95]. These tracers have performed comparably with PiB in clinical populations despite the fact that there is greater nonspecific white-matter uptake in 18F-amyloid tracers [96–98]. All tracers have been validated prospectively by comparing the PET signal with AD neuropathological changes and have shown high correlations between in vivo tracer retention and postmortem measures of fibrillar Aβ [83,91,92,96]. A pooled analysis of neuropathological validation studies of PiB-PET, including a total of 15 autopsy cases with dementia (n = 10) or normal cognition (n = 5) at the time of death, revealed a sensitivity of 73% and specificity of 100% when comparing binary visual reads of PiB-PET images with histopathological presence or absence of amyloid (see the study by Teipel et al. [99] for a review) [83,84,100-104]. One group recently determined the sensitivity and specificity of amyloid PET with florbetaben using neuropathologically determined neuritic plaque levels and showed high sensitivity (97.9%) and specificity (88.9%) in an end-of-life population [105].

3.2. Amyloid imaging in neurodegenerative diseases

3.2.1. Prevalence of amyloid

A recent meta-analysis estimated the prevalence of amyloid PET positivity in a wide variety of dementing syndromes based on 1359 participants with clinically diagnosed AD and 538 participants with non-AD dementia (AD dementia refers to dementia, that is, acquired and progressive cognitive impairment associated with functional disability, as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association [NINCDS-ADRDA] criteria while non-AD dementia refers to non-AD neurodegenerative diseases such as hippocampal sclerosis, frontotemporal lobar degeneration, Lewy body dementia, multiple system
atrophy, and so forth [see McKhann et al., 2011 [27]] referenced to 1849 healthy control participants (based on amyloid PET) and an independent sample of 1369 AD participants (based on autopsy) [106]. Results showed that the likelihood of amyloid positivity was associated with age and APOE4 status. In AD dementia (Mild cognitive impairment: This term describes a population with acquired cognitive impairment and no functional disability [75]. This clinical syndrome includes cases with AD biomarker positivity or prodromal AD [about 50%] [see clinical criteria by Dubois et al. [26]], cases with no neurodegenerative disorder [about 35%–40%], and cases progressing to non-AD forms of dementia [about 10%–15%; [76]), the prevalence of amyloid positivity decreased from age 50 to 90 years in APOE4 noncarriers and to a lesser degree in APOE4 carriers. In most non-AD dementias, amyloid positivity increased with both age (from 60 to 80 years) and APOE4 carrier status (Fig. 9). Studies on AD variants (i.e., lvPPA, PCA, behavioral/dysexecutive variant) have shown that amyloid deposition is more common in lvPPA than in nfvPPA or svPPA, supporting the hypothesis that lvPPA is often associated with underlying AD [107]. Others have detected high PiB binding in patients with PCA, a visuospatial/biparietal clinical syndrome often caused by AD [40,108].

Amyloid PET interpretation is also limited by the fact that it is positive in about 20% of cognitively normal individuals and non-AD dementias, especially when older or when carrying the ε4 allele of the APOE4 gene. When faced with a positive amyloid PET, the probability that the patient actually has AD, in opposition to comorbid amyloid pathology in a non-AD dementia, can be determined by the calculation of its positive predictive value (PPV) [81]. As these calculations cannot be easily made in the day-to-day clinic, we created an evidence-based PPV table (Table 1) [109]. We defined AD as a clinicopathological entity in which the detected amyloid is a primary cause of cognitive impairments. We inferred rates of false positivity (non-AD dementia with comorbid amyloid) and false-negativity (amyloid-negative clinical AD) based on age- and APOE-dependent prevalence estimates of amyloid positivity in normal individuals and AD patients found in large meta-analyses published by the Amyloid Biomarker Study Group. We calculated PPV (true positives/[false positives + true positives]) for a variety of pre-PET probabilities of AD, age groups, and APOE status to produce a PPV table. PPV of PET is higher in young, APOE4 positive patients with high pre-PET probability of AD. In older, APOE4+ patients with low pre-PET probability of AD, positive amyloid PET scans must be interpreted with caution. This PPV table might provide guidance to clinicians and nuclear medicine physicians to interpret positive Aβ PET results for early and differential diagnosis of patients with progressive cognitive impairment.

3.2.2. Alzheimer’s disease

Most studies in AD [26,27,110] have found very high (88%) PiB-PET positivity, with a pattern that closely mirrors the distribution of plaques found at autopsy [105,111]. Tracer binding is diffuse and symmetric, with highest uptake consistently found in prefrontal cortex and PCC, followed closely by lateral parietal and lateral temporal cortex and striatum. Remarkably, there is very little intraindividual variation in the pattern of Aβ deposition across AD patients, even when presenting with extreme clinical phenotypes such as PCA, lvPPA, and behavioral/dysexecutive AD [112–116]. Furthermore, the extent and distribution of Aβ PET retention do correlate only moderately with patterns of neurodegeneration and with cognitive deficits [112,117]. This has led to the suggestion that deposition of Aβ, which is a prerequisite for a definite diagnosis of AD, is the trigger of a cascade of neuropathological events rather than the driver of neurodegeneration and clinical disease progression.

3.2.3. Frontotemporal lobar degeneration

As described previously, FTLD is an umbrella term used for disorders associated with neurodegeneration of the frontal and anterior temporal lobes [118]. Clinical syndromes that fall in the FTLD spectrum include bvFTD, FTD with motor-neuron disease (FTD-MND), semantic variant primary progressive aphasia, and nfvPPA [38,119]. CBS is sometimes included under the FTLD umbrella because of considerable clinical and pathologic overlap [55]. Although most cases of clinical CBS are associated with FTLD pathology (although not necessarily corticobasal degeneration), 25% to 50% of patients are found to have AD as the causative pathology postmortem [55,57,120]. Histopathology in FTLD is heterogeneous,
with most cases featuring tau (Pick’s disease [PiD], corticobasal degeneration, and PSP), TDP-43, or fused-in sarcoma protein inclusions [121,122].

FTLD and AD are the leading causes of early age-of-onset dementia, occurring with similar frequency in patients presenting younger than the age of 65 years [123]. Distinguishing the two during life can be challenging because of clinical and anatomic overlap, and misdiagnosis rates of 10% to 40% are reported even in expert centers [57,124]. Differentiating AD from FTLD is an important clinical use for amyloid PET because Aβ plaques are not part of the FTLD pathologic spectrum (Fig. 10), and the differential diagnosis comes up in young patients in whom age-related amyloid aggregation is less common. Small case series reported low rates of PiB (0%–15%) and flerbetaben positivity (9%) in FTLD [125–127]. Amyloid PET was recently used as a surrogate to AD neuropathology in a study in which splitting CBS patients into frontal or temporoparietal clinical variants helped predict the likelihood of underlying AD [59]. Differentiating AD and FTLD was the focus of one of the largest studies on the diagnostic use of amyloid PET published to date [128]. In 62 AD patients and 45 FTLD patients matched for age and disease severity, PiB visual reads had a higher sensitivity for AD than FDG-PET (89.5% vs. 77.5%), with similar specificity (83% vs. 84%). When scans were classified quantitatively, PiB had higher sensitivity (89% vs. 73%), whereas FDG had higher specificity (83% vs. 98%). PiB outperformed FDG in classifying 12 patients with known histopathology (97% vs. 87% overall accuracy).

### 3.3. An exceptional journey from 2004 to today

An exceptional journey has occurred in the field of amyloid imaging since the publication by Klunk et al. in 2004 [82]. Research using PET amyloid ligands has led to improved models of disease pathogenesis, providing evidence for a long preclinical disease phase in AD, improving subject selection for clinical trials, and stimulating therapeutic trials aimed at delaying or preventing the symptomatic phase of AD [129,130]. Amyloid imaging has served as a secondary outcome measure in AD clinical trials with disease-modifying agents such as the antiamyloid monoclonal antibodies bapineuzumab and solanezumab [131,132]. Brain amyloid reduction and slowing of cognitive decline were found after 1 year of treatment with aducanumab, a human immunoglobulin G1 (IgG1) monoclonal antibody against a conformational epitope found on Aβ [133]. Added value of the technique was also evident in subject selection for clinical trials given an approximate 15% amyloid-negative rate.

Beyond research, amyloid imaging has demonstrated great potential as a diagnostic tool because it allows in vivo detection of amyloid plaques [82]. This stands in contrast to currently available diagnostic imaging techniques in neurodegenerative diseases, which detect the downstream effects of pathology on the brain, such as synaptic dysfunction (FDG-PET) and neuronal loss (MRI)—events that are thought to occur late in the disease cascade [129,134]. Similar to FDG-PET discussed previously, it is now an established technique with data incorporated in the
most recent consensus guidelines for the diagnosis of AD [27] and predementia AD-related conditions [28,135].

As pointed out by the Geneva Task Force for the Roadmap of Alzheimer’s Biomarkers, amyloid imaging has achieved phases 1 (rationale for use) and 2 (discriminative ability) but not phases 3 (early detection ability) and 4 (performance in representative MCI patients) yet. Phase 5 studies (quantification of impact and costs) are going on. Investigations on the use of amyloid PET imaging in routine clinical practice are going on.

4. Tau imaging

For this section, PubMed database was searched for relevant studies using the following keywords: (“Positron Emission Tomography” OR “PET”) AND (“Tau PET” OR “18F-AV-1451” OR “flortaucipir” OR “11C-PBB3” OR “18F-THK523” OR “18F-THK5105” OR “18F-THK5351”) AND (“Review”) AND (“Neurodegenerative diseases”). The inclusion of relevant evidence based on personal knowledge or from the reference lists of pertinent articles was admitted. Only articles written in English were included. The final selection of articles was based on relevance, as judged by the authors. The impact factor as such did not affect the selection of the articles included in the analysis.

4.1. A new frontier

The ability to measure Aβ in CSF or by using PET has offered invaluable insights into the early stages of AD [136–138] and shown great potential as a diagnostic add-on to the clinical workup of patients with cognitive deficits [139]. On the other hand, biomarker studies have shown that the relationships between Aβ pathology and most downstream processes such as glucose hypometabolism, brain atrophy, disease severity, progression, and clinical presentation are modest (for an overview, refer to the study by Jagust [140]). Furthermore, clinical trials applying anti-Aβ monoclonal antibodies have mostly failed to show clinical benefit in AD [141]. Parallel to this, worldwide interest in amyloid imaging has generated great momentum to develop PET tracers that bind to non-Aβ processes such as the microtubule-associated protein tau aggregated as NFTs in AD and other tau-related diseases (e.g., FTLD or chronic traumatic encephalopathy [CTE]). Indeed, tau pathology is known to have devastating effects on synaptic function [142]. Its temporal and spatial distribution correlates strongly with the clinical evolution of AD [143], and postmortem tau aggregates are closely associated with cognitive performance during life [144].

Over the past few years, several promising tau compounds have emerged, including 11C-PBB3 [145]; 18F-AV-1451 (or “flortaucipir”, previously known as T807 [146,147]); and the “THK” series 18F-THK523 [148], 18F-THKS105 [149], and 18F-THK5351 [150]. These tracers have consistently demonstrated good in vivo brain penetration, tracer binding to paired helical filaments of tau in AD brain tissue without labeling Aβ, and deposits as well as patterns of tracer retention on PET scans resembling traditional Braak staging (see the study by Villemagne et al. [45] for a review). 18F-AV-1451 is a novel benzimidazole-pyrimidine derivative with nanomolar binding affinity and more than 25-fold selectivity for PHF-tau over Aβ that has shown promising results [147,151]. In vivo human 18F-AV-1451 scans showed significantly higher retention across frontal, parietal, and temporal cortices and the hippocampus in AD patients than in individuals with MCI and cognitively normal control subjects [147,152]. Cortical retention was comparable with the known distribution of PHF-tau in the AD brain. It showed low retention in white matter and a strong association with disease severity.

In many regards, the advent of tau imaging marked the beginning of an entirely new era with outstanding potential applications. Among them, it is expected to allow the field to recapitulate the pathological studies of Braak and Braak [153]; confirm the various stages of tau deposition; assist in the early and differential diagnosis of AD and non-AD tauopathies; improve prognosis by a more accurate prediction of cognitive decline; study the relative contribution of tau and Aβ pathology to neurodegeneration and symptomatology; and help elucidate the underlying pathology in cognitively unimpaired individuals who present with AD-like neurodegeneration in the absence of Aβ deposition (i.e., “suspected nonamyloid pathology” [SNAP] or “primary age-related tauopathy” [PART]) [46,147,148,154–157]. As stated elegantly by Jagust [158], “Ultimately, tau imaging offers the promise that the relationship between medial temporal tau and neocortical Aβ may one day be disentangled, as well as the relationships of both of these proteins with brain atrophy, hypometabolism, and cognition.”

Yet, challenges associated with the development of tau ligands are not simple. Tau tracers need to pass across both the blood-brain barrier and cell membranes to target intracellular pathology. Also, tau is found at lower concentrations than Aβ and is characterized by different isoforms reflecting alternative splicing with either three (3R) or four (4R) repeated microtubule-binding domains. Tauopathies present a mixture of 3R and 4R tau isoforms (AD: CTE, 3R and 4R; PiD, 3R; PSP and CBD, both 4R). They differ in terms of the regional distribution and morphology of tau aggregates, that is, NFTs, neuropil threads, and dystrophic neurites associated with neuritic plaques in AD [151,159]; Pick bodies in PiD [160]; globule tangles, coiled bodies, and tufted astrocytes in PSP [161]; and astrocytic plaques, coiled bodies, and neuropil threads in CBD [162]. Finally, the ultrastructural characteristics of tau filaments differ across diseases, paired helical filaments (PHFs) in AD versus mainly straight filaments in PiD, PSP, and CBD [163–165]. Good correspondence between in vivo AV-1451 PET imaging and postmortem evaluation was found for CBD [166] and symptomatic MAPT mutation carriers [167–169]. Recently, a group examined in vitro...
binding patterns of PET tracer 18F-AV-1451 and determined strong binding to tau lesions primarily made of PHF in AD brains (e.g., intraneuronal and extraneuronal tangles and dystrophic neurites), but not to a significant extent to neuronal and glial inclusions mainly composed of straight tau filaments in non-AD tauopathy brains or to β-amyloid, α-synuclein, or TDP-43–containing lesions [170]. AV-1451 off-target binding to neuromelanin- and melanin-containing cells and, to a lesser extent, to brain hemorrhagic lesions was also seen and therefore pointed to some off-target binding to bear in mind when interpreting tau PET scans. Other possible unspecific retention sites have been reported with this tracer, both in vivo and ex vivo, in the striatum and choroid plexus [167,171–175].

4.2. Tau imaging in neurodegenerative diseases

4.2.1. Alzheimer’s disease

The recent emergence of tau PET ligands allowed definition of tau tracer retention patterns across the spectrum of normal aging and AD in the living brain. For example, a recent 18F-AV-1451 PET study showed minimal cortical and subcortical uptake in cognitively intact young adults (aged 20–26 years), whereas localized increased uptakes in medial temporal lobe regions (mostly entorhinal cortex and parahippocampal gyrus) were found in cognitively intact Aβ-negative older adults (64-90 y) and extended markedly to inferior and lateral temporal lobe regions in cognitively intact Aβ-positive older adults. AD patients showed additional and more diffuse tracer retention in neocortical areas, involving temporal, parietal, and frontal lobes [172]. Similar findings were reported by other groups with a mild age-related increased tracer uptake in some medial temporal lobe regions (i.e., amygdala, hippocampus) of Aβ-negative cognitively normal subjects, increased retention in inferior and lateral temporal lobe regions of Aβ-positive cognitively normal subjects, and a wider cortical retention in Aβ-positive MCI and AD patients [176,177]. These findings suggest that the presence of NFTs in the inferior temporal gyrus is an early sign of subsequent cognitive impairment and conversion to AD dementia.

Neuropathological studies and animal studies of AD have showed a robust association between tau deposits, decreased cognitive function, and neurodegenerative changes [142,178]. However, brain postmortem examination has long been the only way to assess tau pathology, one of the core neuropathological criteria for the definitive diagnosis of AD [179,180]. Recently, 11C-PBB3 [145] and 18F-THK5105 [149] have demonstrated in vitro binding to tau in the form of NFTs, neuritop threads, and neuritic plaques in AD brain tissue. PET studies showed hippocampal uptake and extensive cortical binding (inferior temporal lobe) that appeared consistent with the widely accepted pathological staging scheme proposed by Braak and Braak [159]. Interestingly, associations were found between tau retention and both cognitive and MRI volumetric measures that were not seen or, to a lower extent, with 11C-PiB [177,181].

Regional tau PET binding, more specifically using 18F-AV-1451, has been shown to recapitulate the topographical distribution of Braak NFTs pathology [172,176,177,182,183] and could be used to objectively estimate Braak stages 0 through VI using a simple algorithm [182]. Therefore, this tau tracer offers a promising tool for the assessment of Braak NFT stage in patients with suspected AD, raising hopes for an in vivo diagnostic technique. In a recent observational case series investigating whether topographic distribution and severity of tau pathology as measured by 18F-AV-1451 retention was associated with clinical phenotype, authors found that PET signal was anatomically representative of both typical and atypical AD variants [181]. In typical amnestic AD (n = 3), higher tracer uptake was constantly seen bilaterally in the posterior cingulate, precuneus, lateral, temporoparietal, and occipital cortices, as well as in the medial temporal and dorsolateral prefrontal cortices in 2 out of 3 patients. In PCA (n = 1), higher tracer retention with right predominance was found in the occipitoparietal and occipitotemporal visual association areas laterally and medially and involved the calcarine fissure and the postcentral gyrus. In lvPPA (n = 1), higher tracer uptake was observed in the left parietal and posterior temporal cortices and in the posterior dorsolateral prefrontal and precuneous cortices bilaterally. Finally, higher tracer binding with right predominance was seen in primary and association sensorimotor (perilobaridic) cortices in CBD (n = 1). These findings are concordant with several other studies [184–188] and provide further evidence that in vivo tau PET imaging accurately reflects clinical

![Fig. 10. Amyloid imaging in AD versus FTLD patients. Contrary to AD and its variants (lvPPA shown here on the top row), conditions grouped under the FTLD spectrum do not harbor amyloid pathology (middle and bottom rows). Abbreviations: AD, Alzheimer’s disease; lvPPA, logopenic variant primary progressive aphasia.](image-url)


4.2.2. Frontotemporal lobar degeneration

In FTLD, 11C-PBB3 has shown in vitro binding to tau inclusions in tissue from patients with a 3R tauopathy (PiD) or 4R tauopathies (PSP and CBD) [145]. Marquié et al. [170] applied 18F-AV-1451 phosphor screen autoradiography, nuclear emulsion autoradiography, and 1H3-AV-1451 in vitro binding assays to the study of postmortem samples from patients with a definite pathological diagnosis of AD, FTLD-tau (PiD, PSP, CBD), FTLD-TDP-43, cerebral amyloid angiopathy, synucleinopathies (dementia with Lewy bodies, multisystem atrophy), metastatic melanoma, brain hemorrhages, superficial siderosis, and controls free of pathology. As stated previously, the authors determined that 18F-AV-1451 strongly binds to tau lesions in AD brains, but not to non-AD tauopathy or to β-amyloid, α-synuclein, or TDP-43-containing lesions. Sander et al. [189] also found high specific binding to AD postmortem brain tissue with 18F-AV-1451. However, they also reported moderate binding in PiD and FTLD with parkinsonism-17 and low but displaceable binding in CBD.

In vivo studies appear to be more encouraging regarding tau PET identification of FTLD disorders [166]. Moreover, different patterns of tau tracer binding could help differentiate between AD and PSP (18F-AV-1451) [190,191] and between AD and CBD [192–194]. Regarding these findings, spatial information provided by tau PET imaging should help the differential diagnosis of AD and non-AD tauopathies, although the possibility of off-target binding, as mentioned earlier, should always be kept in mind.

4.2.3. Chronic traumatic encephalopathy

CTE is a progressive neurodegenerative disease associated with repetitive head impacts [195–200]. Originally described in 1928 in boxers as “punch drunk” or “dementia pugilistica” [201], CTE has been the focus of many recent investigations recruiting, among others, participants from various contact sports such as American football, soccer, rugby, and ice hockey. Large and influential organizations (the National Institute of Health, National Football League, and U.S. Department of Defense) have sponsored further research to elucidate the connection between multiple head traumas and the development of CTE. Interestingly, the pathology of CTE is distinctive from AD and FTLD [196,202–204]. Gross features include atrophy of the cerebral cortex (especially the frontal and temporal lobes), diencephalon and mamillary bodies, and cavum septum pellucidum or septal fenestrations. Microscopically, it is characterized by the deposition of hyperphosphorylated tau (p-tau) as NFTs, astrocytic inclusions, and neurites irregularly distributed around small blood vessels, preferentially at the depths of cerebral sulci [195–197]. In a well-established disease, the tau pathology is most prominent in the frontal and temporal lobes, hippocampus, amygdala, and entorhinal cortex [204–206]. Recent efforts from the Neurologic Injury and Traumatic Encephalopathy project recently funded by the National Institute of Neurological Disorders and Stroke and the National Institute of Biomedical Imaging and Bioengineering should allow the development of clinical diagnostic criteria for CTE [207]. To our knowledge, however, only one molecular imaging study has been conducted in patients with CTE [208], and this should be an area of active research in the future.

4.3. A promising innovation

Tau imaging has already generated both confirmatory data and new insights in major tauopathies such as AD, the FTLD spectrum, and CTE [46]. Moreover, it has helped scientists in the field to refine theoretical models of degeneration. For example, models of biomarker change in AD have hypothesized that Aβ was an initiating event, but recent evidence of neurodegeneration in the absence of Aβ has suggested the possibility of independent and early tauopathy [129]. Current efforts are underway in various centers of the world to scan controls and patients with MCI or AD simultaneously with tau and Aβ PET ligands in an attempt to better understand the complex interplay between the two. An emerging finding from preliminary data so far is that tau accumulates in focal targeted areas of the mesial temporal cortex, whereas amyloid highly diffuses in the brain [182,184,209,210] (Fig. 12). Medial temporal tau depositions may be present before Aβ, but once amyloid starts to accumulate, the degenerative cascade embarks on a faster and irreversible trajectory [172,176,177]. Cortical Aβ and medial temporal tau deposition combined might not be sufficient to induce cognitive impairment, but spreading of tau pathology into isocortical areas has been associated with cognitive impairment [46].

5. Added value of multiple molecular imaging modalities

For this section, we combined the keywords used in the various sections described previously. For example, for the section on FDG-PET and amyloid PET, we combined the keywords used in the section on PET and amyloid imaging. All other criteria remained similar.

Recent efforts, some already cited in previous sections, have combined molecular imaging modalities in an attempt to better understand AD pathophysiology, improve diagnostic accuracy, explore the diagnostic impact of single versus multiple techniques combined, or study the natural history of degenerative diseases over time. By allowing direct comparisons of the diagnostic power of different imaging modalities in identical patient samples, multimodal imaging studies can improve our understanding of
pathophysiological interactions *in vivo* and enable the investigation of the temporal and topographical relations between pathological variables [99]. Using multimodal imaging, one of the most fascinating findings which emerged in AD is the dissociation between the distribution of $\beta$ and patterns of neurodegeneration, in which across AD phenotypes, $\beta$ is deposited relatively symmetrically throughout the neocortex, whereas hypometabolism is more focal and mirrors clinical symptoms [114,211]. The following section will review studies that have focused on FDG-PET and amyloid PET, amyloid and tau PET, as well as combined FDG-PET, amyloid PET, and tau PET in the same endeavor.

5.1. **FDG-PET and amyloid PET**

We need to emphasize here that amyloid imaging is really amyloid plaques imaging and that this nuance is at the core of multiple observations regarding the relationship between FDG and amyloid imaging (see the study by Lehmann et al. [114]).

5.1.1. **Combining both techniques to better predict conversion to AD**

FDG and amyloid PET both better predict conversion from MCI to AD than structural MRI, as shown in multimodal studies [212,213] and in a meta-analysis [214]. Studies comparing FDG with amyloid PET imaging suggest that separately these methods show similar overall levels of predictive accuracy [215,216]. Amyloid PET shows higher sensitivity than FDG, whereas FDG-PET shows higher specificity and greater short-term predictive value [217]. This difference is possibly due to the fact that amyloid load increases a long time before the onset of cognitive symptoms (up to 25 years in familial AD mutations), after which it plateaus in later disease stages [218]. By contrast, FDG-PET shows a more linear correlation with disease progression.

5.1.2. **Combining both techniques to better understand AD**

The relationships between amyloid, metabolism, and clinical phenotype in AD are incompletely understood. Previous studies have yielded mixed results within typical amnestic AD and across different AD phenotypes. For example, in three clinical variants of AD (AD memory, IvPPA, and PCA), clinical syndromes were strongly linked to patterns of glucose metabolism, whereas amyloid PiB-PET binding was similar across clinical phenotypes [107,108,114,219–221]. Using parallel independent component analysis, previous findings from univariate analyses were replicated [114] showing that memory, language, and visuospatial-predominant clinical variants of AD were associated with independent components of glucose metabolism but not with specific patterns of $\beta$-amyloid deposition. FDG and PiB jointly improved the
classification of one variant from others, though the added effect of joint FDG-PiB versus FDG alone was relatively small. Multivariate analyses further revealed an inverse relationship between Aβ deposition and glucose metabolism in the frontal cortex and PCC (Fig. 13), providing insight into the biological interplay between these two biomarkers in key regions of AD-related degeneration [211].

Other authors have explored the link between metabolism and Aβ deposition in AD. Correlations between increased β-amyloid and decreased metabolism have been found in some studies [221–223] but not in others [221,224–226]. Some have suggested that the relationships between amyloid and glucose metabolism vary by brain region and disease state [221,227]. In the first study comparing amyloid retention in early- and late-onset AD, earlier pathological observations could not be replicated in the living human brain as no global and regional differences in amyloid burden were found [112]. In an attempt to understand why early-onset AD presents with a distinct cognitive profile, hence potentially reflecting a different distribution of underlying neuropathology, other authors have examined the relationships between age and both in vivo fibrillary amyloid deposition and glucose metabolism in patients with AD [228]. More specifically, they tested the hypothesis that early-onset AD is associated with more posterior-oriented amyloid load and glucose hypometabolism compared with late-onset AD. As expected, younger AD patients showed more severe impairment on visuospatial function, attention, and executive function composite scores, whereas older AD patients showed a trend toward poorer memory performance. There was no main effect of age for amyloid or FDG-PET, suggesting that overall, the extent of amyloid deposition or glucose hypometabolism did not differ between the groups. Regional distributions of amyloid binding and FDG uptake differed between the groups, however, largely due to increased amyloid binding and decreased FDG uptake in

Fig. 12. MRI (A) and PET imaging of tau (B) and Aβ (C) in two healthy controls, a patient with mild cognitive impairment and a patient with AD. Tau accumulates in focal targeted areas of the mesial temporal cortex, whereas amyloid highly diffuses in the brain (Villemagne et al. [46]). Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography; AD, Alzheimer’s disease.
the parietal cortex of younger patients. Results further suggested that clinical differences between younger and older AD patients are not restricted to topographical differentiation in downstream processes but may originate from distinctive distributions of early upstream events.

Findings using both univariate and multivariate statistical approaches support a recently proposed model postulating that the emergence of heterogeneous AD phenotypes is related to the involvement of specific functional networks that converge in the default-mode network [229]. This model integrates the hypothesis that aggregation of Aβ may be driven by total flow of neuronal activity (yielding diffuse and symmetric patterns of PiB binding throughout “cortical hubs”), whereas tau aggregation may be driven by transneuronal spread, generating patterns of neurodegeneration which coincide with specific functional networks ultimately leading to specific clinical phenotypes [230–232].

5.1.3. Face-to-face versus combined studies of amyloid accumulation and metabolic activity in the diagnosis of atypical patients

The clinical diagnosis of AD has only moderate sensitivity and specificity when compared with the pathological cause of neurodegenerative diseases as determined at autopsy [233]. Misdiagnosis rates are even higher in complex, atypical patients with an uncertain diagnosis, approaching 30% [124]. In a study [128] in which 62 AD patients and 45 FTLD patients matched for age and disease severity were scanned using PiB and FDG-PET, PiB visual reads had a higher sensitivity for AD than FDG-PET with similar specificity and PiB outperformed FDG in classifying 12 patients with known histopathology.

More recently, the field has witnessed a growing number of studies assessing the practical use of amyloid and FDG-PET in the diagnostic process of complex atypical patients with an uncertain diagnosis [139,234,235]. For example, a group of authors evaluated the impact of these tracers on 254 patients and showed that PiB scans were positive in 61% patients with a clinical diagnosis of AD, 28% patients with FTD, 80% patients with Dementia with Lewy bodies, and 30% patients with other neurodegenerative diseases [139]. FDG-PET uptake patterns matched the clinical diagnosis in 58% of AD patients and 33% of FTD patients. PET results led to a change in diagnosis in 25% of patients, and this only occurred when prior diagnostic certainty was 90%. Diagnostic confidence increased from 71% before to 87% after PET. Two-year clinical follow-up in 39 patients showed that PiB and FDG predicted progression to AD for patients with MCI and that the diagnosis of neurodegenerative disease established after PET remained unchanged in 96% of patients. In another study, authors evaluated the effect of amyloid imaging and FDG-PET on clinical decision-making in 140 cognitively impaired patients [234]. Researchers assessed for changes between pre-PET and post-PET clinical diagnosis (from Aβ to non-Aβ diagnosis or vice versa) and AD treatment plan. Altogether, PET had a moderate effect on clinical outcomes. Discordant PiB had a greater effect than discordant FDG, and the influence on diagnosis was greater than that on treatment.

Recently, the Quebec group investigated the clinical use of amyloid PET in the differential diagnosis of atypical cases and its impact on caregivers in the context of a tertiary memory clinic [236]. Using the amyloid tracer 18F-NAV4694 [237–239], they prospectively scanned 28 patients (mean age, 59.3 ± 5.8 years; mean Mini-Mental State Examination, 21.4 ± 6.0) with an atypical syndrome as determined by dementia experts. All patients had a full workup (i.e., history, examination, blood tests, neuropsychology, MRI, and FDG-PET), yet no certain diagnosis could be arrived at after that investigation. Amyloid PET was either positive or negative based on qualitative and quantitative reads by two qualified independent expert nuclear medicine specialists. Physicians rated whether amyloid PET was associated with a change in diagnosis and altered management. They also reported their degree of confidence in diagnosis before and after amyloid PET. Caregivers were met 3 months after having been told of the diagnosis and completed a 21-item Likert scale questionnaire along with a 1-hour interview designed to assess the impact of the amyloid scan. The cohort was 50% amyloid positive and 50% amyloid negative. The interrater reliability was 100%. Amyloid PET was associated with a diagnostic change in 9 of 28 (32%) cases (17.8% changed from AD to non-AD and 14.3% from non-AD to AD). There was a significant increase (44%) in diagnostic confidence after the scan. Altogether, this study corroborated recent findings and suggested an additive role for amyloid PET in atypical cases with an unclear diagnosis despite the detailed workup of a tertiary memory clinic. Amyloid PET increased diagnostic confidence and generated significant alterations in management in almost three-quarters of cases (71.4%), either by a change in medication, additional investigation, referral to other health professional, or enrollment in a clinical trial. Furthermore, the overall process was very well received by caregivers, reducing anxiety and depressive symptomatology, as well as increasing quality time spent with their loved ones.

Lately, the clinical use of amyloid imaging with distinct tracers has been addressed in larger cohorts of patients with cognitive impairment (n = 228 [240]) and suspected early-onset dementia (n = 211 [241]) with diagnostic uncertainty using 18F-Florbetapir and 18F-Flutemetamol, respectively. In the first study, a prescan to postscan change in diagnosis was observed in 62 of 228 (27%) cases. More precisely, 79% of patients with both a previous AD diagnosis and an Aβ-negative scan were subsequently assigned a diagnosis of non-AD, whereas 53% of those with both previous non-AD diagnosis and Aβ-positive scan received a final diagnosis of AD. A prescan to postscan increase (15.2%) in diagnostic confidence of AD diagnosis (i.e., confidence that cognitive impairment is due to AD) was observed in
cases with Aβ-positive results, whereas a decrease (−29.9%) in diagnostic confidence of AD diagnosis was observed in those with Aβ-negative results. This also means that physician’s confidence for their final diagnosis (AD vs. non-AD) was increased in all cases except for those with a prescan diagnosis of AD and discordant amyloid PET results. The use of amyloid imaging resulted in a change in medication for 29% of cases, with initiation of cognition-specific drugs in 65.6% of previously untreated patients with positive scans and discontinuation in 33.3% of previously treated patients with negative scans. In the second study, postscan diagnostic changes occurred in 41 of 211 (19%) patients with early-onset dementia due to disclosure of PET findings inconsistent with results expected after routine diagnostic workup in a tertiary memory clinic. These diagnostic changes included 76% of Aβ-negative cases with an initial diagnosis of AD and 67% of Aβ-positive cases with an initial diagnosis of FTD. PET evidence for amyloid pathology also led to diagnostic changes toward AD in patients with a previous suspicion of other neurodegenerative (11%) and nonneurodegenerative conditions (45%). The overall diagnostic confidence increased from 69% to 88% despite a decreased confidence in 13% of cases (most of them having a prescan diagnosis of AD and discordant PET results).

In this study, the use of amyloid PET ultimately led to altered patient management in 37% of cases, mostly resulting in introduction of AD medication in Aβ-positive cases.

Altogether, these studies point to a considerable clinical impact of both amyloid and metabolic PET imaging on diagnostic confidence, and patient management, especially in early-onset and complex atypical cases with diagnostic uncertainty. To this end, amyloid imaging seems to procure the greatest added diagnostic value, resulting in significant clinical outcomes. However, important issues regarding morbidity, mortality, cost-effectiveness, and social consequences remain to be assessed. These efforts invested toward the development of an improved diagnostic process for atypical neurodegenerative diseases have major implications for a cohort of individuals who are often younger than 65 years and still active in the workforce. Several dementia experts have argued that an accurate diagnosis helps direct therapy (i.e., avoid unnecessary or undesired ChEIs or memantine prescriptions), to determine a better care plan (which considers patient safety and minimizes the risk of preventable complications), and enables patients to participate in legal and financial planning.

5.2. Amyloid and tau PET

Much is expected from combined Aβ and tau imaging studies within the same scientific efforts (Fig. 14). Such endeavors should help confirm whether the presence or concentration of Aβ triggers and accelerates the spread of tau deposition outside the mesial temporal cortex [242]. These pathophysiological processes can further be correlated with the onset of cognitive impairment and conversion into AD to better understand all of the elements that accompany the phenomenon. Combined tau and Aβ imaging should also help clarify whether tau itself is the underlying pathology in cases of AD-like cognitive decline and neurodegeneration, but with no evidence of Aβ deposition [154,243]. Taken together, such efforts will undoubtedly help scientists...
better focus therapeutic targets, whether it is timing of intervention or specificity of proteins to address (e.g., amyloid > tau in the initial phases of the disease vs. tau > amyloid later in the disease). It may very well be that treatments of the future will necessitate a combination of molecules that each target specific proteins [244,245].

5.3. FDG-PET, amyloid PET, and tau PET

A number of cases have been reported in which FDG-PET, amyloid PET, and tau PET were applied within the same paradigm [184,246,247]. Ossenkoppele et al. [115] described a 56-year-old right-handed man with a clinical diagnosis of PCA with suspected underlying AD pathology. In this patient (Fig. 15), amyloid spread throughout the association neocortex but tau was selectively retained in posterior brain regions that were affected clinically and showed markedly reduced PET-FDG uptake. As pointed out by the authors, “…this is in line with neuropathological studies showing that tau (in contrast to Aβ) is disproportionally elevated in brain regions that functionally and structurally deteriorate in PCA compared to relatively preserved brain regions” [248]. FDG-PET and AV-1451 both showed excellent regional specificity in their PCA patient. However, tau radiotracers offer considerable potential added value over FDG, in which they bind to a core element of AD pathology and hence could serve as a dual neurodegenerative and pathophysiological biomarker.

This evidence supports the notion that tau is more closely linked to hypometabolism and symptomatology than amyloid along with current conceptual models of the AD pathophysiological cascade [129]. There may also be differences in metabolic susceptibility to the neurotoxicity of tau across brain regions and individuals. Future studies with larger samples and longitudinal follow-up should explore the relationships between brain metabolism, amyloid binding, and tau aggregation.

6. Summary table of the limitations of molecular imaging

Specific limitations of each imaging modality as well as recommendations to overcome them are listed in Table 2.

7. Molecular imaging as a tool to understand spatial and temporal involvement in neurodegenerative diseases

Several authors have suggested that NFTs and Aβ deposits found in AD are not randomly distributed but have characteristic spatial patterns [159,249–254]. In the early stages of the evolution of AD pathology, NFTs are frequently located in the trans-entorhinal cortex and Aβ in
neocortical regions, particularly in basal regions of temporal and frontal lobe [159,250,253]. Among them, the PCC appears as one of the most metabolically vulnerable regions in early-onset AD [112]. The PCC is a central cortical “hub” that is structurally and functionally interconnected with other heteromodal association regions in lateral parietal, temporal, and prefrontal cortices [255,256]. It plays a central role in episodic memory processes [257,258]. PiB-PET studies of aging have identified the PCC as one of the earliest sites of Aβ deposition [259–264], with elevated PiB binding associated with decreased PCC connectivity at rest [265,266] and aberrantly increased PCC activation during encoding [267]. The PCC is also a site of early metabolic disruption in AD [37], with hypometabolism apparent even in asymptomatic APOE4-gene carriers [268]. Buckner et al. have observed that Aβ pathology and functional and structural changes in AD converge in the PCC and have hypothesized that this may be related to high neuronal activity in the PCC because of its interconnectivity and frequent fluctuation between an activated and deactivated state. This elevated level of activity may predispose the PCC to early Aβ aggregation and render it more vulnerable to Aβ neurotoxicity due to high metabolic stress [255,269,270].

Recently, Sepulcre et al. [271] used stepwise connectivity analysis of PiB-PET to reveal the network properties of Aβ deposits in normal elderly subjects and patients with AD. They found that Aβ accumulation in the medial temporal lobe is associated with accumulation in cortical regions such as orbitofrontal, lateral temporal, and PCC in AD. In normal subjects, there was a predominant association between Aβ deposits in the hippocampus and the midline prefrontal/orbitofrontal regions, even in those with a very low Aβ burden. Moreover, the orbitofrontal cortex, amygdala nucleus, and hippocampus exhibit hub properties in the Aβ network which may be critical to understanding the putative spreading mechanisms of AD pathology in early stages (Fig. 16). Others have found an amyloidogenic predisposition for metabolic vulnerability in the parietal cortex [228] in younger patients with AD. These findings are in line with current theories on the pathogenesis of AD, proposing that Aβ initiates a cascade of neuropathological events that eventually lead to neuronal damage and cell death [272]. As such, disproportionate parietal Aβ accumulation may precede parietal metabolic brain dysfunction in patients with early-onset AD.

Using multivariate analyses in 46 patients with AD variants (AD memory: n = 27; IvPPA: n = 10; PCA: n = 9), we showed an inverse relationship between Aβ deposition and
Table 2
Specific limitations of each imaging modality and recommendations to overcome them

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Main limitations</th>
<th>Recommendations to overcome the limitations</th>
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<tbody>
<tr>
<td>SPECT</td>
<td>1. Poor spatial resolution</td>
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<td></td>
<td>2. Interpretation may be influenced by reader’s experience with dementia</td>
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<td></td>
<td>3. Methodology used to convert raw data may vary from one center to another</td>
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<tr>
<td></td>
<td>1. Use high–spatial resolution SPECT systems dedicated to brain imaging.</td>
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<td></td>
<td>2. Continue medical education (knowledge of the dementing syndromes) for imaging specialists.</td>
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<td></td>
<td>3. Adopt standardized analysis approach (registration to standard templates and use of accepted statistical analysis technology).</td>
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<tr>
<td>FDG-PET</td>
<td>1. Interpretation may be influenced by reader’s experience with dementia</td>
<td></td>
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<tr>
<td></td>
<td>2. Methodology used to convert raw data may vary from one center to another</td>
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<td></td>
<td>3. Although the matching between metabolic pattern and syndrome is very good (see Figs. 2-7), studies with pathologically confirmed or biomarker-confirmed patients are still rare, and findings are not systematically consistent; therefore, the syndrome does not equate the underlying pathology. On the other side, the prognostic value is more clearly demonstrated than its diagnostic value.</td>
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<tr>
<td>Amyloid imaging</td>
<td>1. Expensive technique</td>
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<td></td>
<td>2. Not widely available</td>
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<td></td>
<td>3. Inaccurate interpretation of PET results by clinicians</td>
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<td></td>
<td>1. (a) Selective use of this diagnostic tool in expert dementia centers. (b) Multiple scans can be performed using a single batch of 18F-amyloid PET tracer production.</td>
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<tr>
<td>Tau imaging</td>
<td>1. Research use only</td>
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<td></td>
<td>2. Poor specificity for differential diagnosis of frontotemporal lobar degeneration disorders</td>
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<tr>
<td></td>
<td>1. Efforts are taken to facilitate the transition of tau imaging from a research setting to the clinic.</td>
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<td></td>
<td>2. (a) Development of novel PET tracers with greater specificity for distinct 3R and 4R isoforms of tau. (b) Investigate whether more sophisticated approaches can extract a meaningful signal from tau images in FTLD which can be used for individual patients.</td>
<td></td>
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</table>

Abbreviations: 18F, 18-Fluorine; FTLD, frontotemporal lobar degeneration; 3R, 3-Repeat; 4R, 4-Repeat; SPECT, single-photon emission tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose.


Glucose metabolism in the frontal cortex and PCC (Fig. 13), suggesting a biological interplay in which Aβ may exert both local and remote effects on brain metabolism in AD-related degeneration. Intriguingly, the PiB component in this pair consisted of increased medial frontal and decreased PCC binding. It is important not to misinterpret this finding as evidence of low amyloid in PCC, but rather, it must be interpreted as a dynamic relationship between regional levels of amyloid accumulation (high in the medial frontal cortex and low in the PCC) and brain metabolism. This raises the possibility that variations in amyloid aggregation within key regions of the default-mode network may modulate the pattern of neurodegeneration in AD. Notably, hypometabolism in the prefrontal and occipital cortex typically occurs in advanced clinical stages of AD [273], whereas medial prefrontal amyloid aggregation may be an early event in the AD cascade [272], further underscoring the relative resilience of the prefrontal cortex to AD pathology [224]. Although the reliability and significance of this observation will require further (and ideally longitudinal) study, our observation underscores the complexity of the relationship between amyloid and metabolism, which appears to vary by brain region and disease state [221,227].

8. Future challenges and ethical issues

Pathological substrates causing neurodegenerative diseases are multiple and heterogeneous. Future in vivo imaging techniques will need to account for this and track progression of various proteins across networks in time. We now have three well-validated amyloid ligands and several tau tracers under review for their biochemical and pharmacodynamics properties. Additional ligands for
TDP-43, synuclein, or fused-in sarcoma are needed [213]. Tracers of neuroinflammation and other basic processes that appear to be involved in propagation of disease will also be necessary to capture the full picture of the cascade [274–276], as well as better imaging of neurotransmitter systems (dopamine, serotonin, and acetylcholine), particularly for the differential diagnosis of patients with comorbid psychiatric conditions [277]. We propose that these studies be designed using a large-scale multicenter format (as opposed to small cohorts). As pointed out by the Geneva Task Force for the Roadmap of Alzheimer’s Biomarkers, use of biomarkers has been proposed for diagnosing AD in recent criteria, but some have not been sufficiently investigated to justify their routine clinical use. Future work should focus on phase 3 (early detection ability) and phase 4 (performance in representative MCI patients) paradigms to fulfill phase 5 studies (quantification of impact and costs). Altogether, this multifaceted molecular imaging approach used in combination with advanced algorithms will help us disentangle the links between proteins [278] and serve the ultimate goal which is early and multitargeted therapy of degenerative diseases.

The future also holds many important ethical issues in relation to detecting presymptomatic conditions and early stages of degenerative diseases (e.g., employment and insurance discrimination). Clinicians must consider a fundamental principle of medicine which is nonmaleficence and beneficence [279]. Patient should be offered a comprehensive diagnostic workup including clinical evaluation and imaging that is evidence based. Many authors insist on clearly informing patients and their family members before evaluation, which includes to discuss their expectations and anxiety of having a neurodegenerative disease or to experiment cognitive impairment without knowing the related pathology. After diagnosis of a neurodegenerative disease, patients should be managed by a multidisciplinary team for physical and psychological aspects. This can reduce anxiety both in patients and caregivers. According to Bensaidane et al. [236], the majority of patients do not regret going through complete investigation because it reduces fear of the unknown. Finally, patients’ autonomy, which is a major principle of medical ethics, should be respected through the process of shared decision-making [279].

Cost-effectiveness is a major aspect to consider because molecular imaging can be very expensive; for example, amyloid PET scans cost nearly 4000$ in the United States [280,281]. An examination with high sensitivity and
specificity enhances diagnostic confidence and reduces costs by limiting other tests [236]. Bensaïdane et al. [236] demonstrated the additional value of amyloid PET in patients with unclear diagnosis referred to a tertiary memory clinic. In a cohort of 28 patients, amyloid imaging resulted in diagnostic change in nine patients. Furthermore, it improved diagnostic confidence by 44%. Results supported the idea that an expensive examination can be cost-effective by reducing the number of investigations. We firmly believe that the impact of molecular imaging on prognosis and quality of

![Proposed algorithm for clinicians in tertiary memory clinics faced with complex/atypical cases with unclear neurodegenerative disorders.](image)

CSF studies are equivalent to amyloid imaging, and recently, research showed CSF became abnormal in the earliest stages of AD ahead of the changes seen using amyloid imaging and before neurodegeneration starts [137,138]. *Tau imaging is not available clinically at the moment, and there are no consensus guidelines on its use yet.
life of patients should continue to be explored [236,282,283], particularly in light of promising clinical trials that could modify the course of AD [280].

9. Proposed algorithm for clinicians in tertiary memory clinics faced with complex/atypical cases with unclear neurodegenerative disorders

Fig. 17 presents our effort to provide an integrative algorithm for clinicians in tertiary memory clinics faced with complex/atypical cases with unclear diagnoses. It is based on an expert opinion and should be viewed as a general approach to the diagnosis of complex cases. We acknowledge that any given algorithm is imperfect and that ours should be adjusted to cost-effectiveness issues and local expertise (e.g., many centers in Canada do not have FDG-PET). Use of amyloid imaging should follow recently published appropriate-use criteria. Tau imaging is not available clinically, and there are no consensus guidelines on its use yet; we recommend that this technique be used in expert research centers for the moment. Further development in other radiotracers (synuclein, TDP-43, and so forth) will allow combined use of molecular imaging techniques in the future but only within research boundaries until large-scale studies define their appropriate use. We emphasize that a discussion with patients and families is highly recommended before undertaking any investigation. A multidisciplinary approach is valued at diagnosis and during follow-up.

The top portion of the algorithm is routine practice in typical dementing disorders which can readily be identified using a standard memory clinic approach (i.e., clinical evaluation, laboratory tests, cognitive testing, and structural imaging). When diagnosis is unclear (young onset, concomitant pathologies, atypical presentations, or confounding variables), we suggest to perform an FDG-PET and insist that raw data be processed using a standardized channel as well as interpreted by a nuclear medicine specialist with experience in neurodegenerative conditions. This step can be repeated at a 1-year interval because research has shown that repeating FDG-PET sooner is unlikely to help the process [78]. When diagnosis remains unclear after having performed an FDG-PET, amyloid biomarkers (CSF or molecular imaging) are encouraged assuming proper counseling has been performed beforehand. Amyloid biomarkers (CSF or molecular imaging) are likely to rule in or rule out underlying Alzheimer pathology [138] and alter management (initiation of cholinesterase inhibitor, referral to research projects, specialized speech-language pathology treatments). A clinician’s tool developed by Bergeron et al. [109] can be used at this stage, along with appropriate-use criteria for amyloid imaging, to better define management when facing a positive amyloid PET (what is the probability of a pathologic false positive as well as the probability of amyloid positivity being age-related, comorbid to a primary non-AD dementia–clinicopathologic false positive?). As mentioned previously, tau imaging is not available clinically, and there are no consensus guidelines on its use; therefore, it should be limited to research. Altogether, we believe that this algorithm is one possible approach to the diagnosis of complex/atypical case presenting in tertiary memory clinics.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic Review: We searched PubMed database for relevant studies using SPECT, PET, amyloid imaging, tau imaging, MCI and neurodegenerative diseases as keywords.

2. Interpretation: Molecular imaging techniques using 18F-fluorodeoxyglucose, amyloid tracers and more recently tau ligands have considerably improved our understanding of neurodegenerative diseases. The ability to image in vivo the pathological substrates of these diseases and visualize their downstream impact has led to improved models of pathogenesis, better differential diagnosis of atypical conditions, as well as focused subject selection and monitoring of treatment in clinical trials aimed at delaying or preventing the symptomatic phase of Alzheimer’s disease. We propose a clinical algorithm for earlier and more accurate identification of complex / atypical neurodegenerative diseases.

3. Future directions: Pathological substrates causing neurodegenerative diseases are multiple and heterogeneous. Future in vivo imaging techniques will need to account for this and track progression of various proteins across networks in time. Additional ligands for TDP-43, synuclein, or FUS are needed as well as tracers of neuroinflammation and neurotransmitter systems (dopamine, serotonin and acetylcholine) particularly for the differential diagnosis of patients with comorbid psychiatric conditions. Limitations of each imaging modality need to be considered as well as ethical issues associated with them.

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