REVIEW ARTICLE

PET molecular imaging for pathophysiological visualization in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common dementia worldwide. The exact etiology of AD is unclear as yet, and no effective treatments are currently available, making AD a tremendous burden posed on the whole society. As AD is a multifaceted and heterogeneous disease, and most biomarkers are dynamic in the course of AD, a range of biomarkers should be established to evaluate the severity and prognosis. Positron emission tomography (PET) offers a great opportunity to visualize AD from diverse perspectives by using radiolabeled agents involved in various pathophysiological processes; PET imaging technique helps to explore the pathomechanisms of AD comprehensively and find out the most appropriate biomarker in each AD phase, leading to a better evaluation of the disease. In this review, we discuss the application of PET in the course of AD and summarized radiolabeled compounds with favorable imaging characteristics.

Keywords Alzheimer's disease · Positron emission tomography (PET) · Molecular imaging

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by gradual memory loss and cognitive decline [1]. It is the most common dementia

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worldwide, accounting for 50–60% of all cases (World Alzheimer Report 2018, www.alz.co.uk). Though some population-based studies suggest a decreased incidence of AD in high-income countries [2–5], the prevalence is increasing constantly. Approximately 30 million people are now estimated to live with AD, and the number is projected to triple by 2050 [6]. Despite great efforts have been made to explore the underlying pathological mechanisms and disease-modifying treatments, there is no effective therapy for AD [7], resulting in a substantial burden posed to the whole society.

Diagnosis of AD now depends on clinical phenotypes and some biomarkers suggesting the presence of Alzheimer's pathology [8, 9]. However, in the first panel of diagnostic criteria for AD launched in 1984, due to a lack of reliable means to detect neuropathological changes, only clinical symptoms were focused, and definite diagnosis was hard to make until autopsy [10]. Over the last few decades, with the advancement in structural and functional imaging techniques, the pathological processes of AD are being revealed gradually. While structure imaging biomarkers combining with clinical phenotypes allow a sensitive and specific diagnosis of AD in mid or late stages [11, 12], researchers are gradually moving forward to explore more subtle changes in earlier phases.

Functional imaging, especially molecular imaging, compared with traditional means, is considered as a more

sensitive neuroimaging modality, offering delicate pathophysiological information long before structural changes were presented [13], which may promote traditional pathology to "transpathology" [14]. Positron emission tomography (PET) is a representative technique of molecular imaging, permitting in vivo quantification of radioisotopes in nanomolar to picomolar range [15, 16]. And by using diverse radiotracers, analogs, or substrates of target processes, PET can be used to assess protein binding, receptor availability, transporter systems, signal transduction, and gene expression [15]. Thus, PET presents great potential in AD management, no matter for early diagnosis, disease progression monitoring, or therapeutic effect evaluation [17–19].

The improvements of imaging techniques have led imaging biomarkers to be incorporated into diagnostic criteria of AD. In addition to some biochemical markers in cerebrospinal fluid (CSF), the National Institute on Aging and the Alzheimer's Association (NIA-AA) also introduced a panel of imaging biomarkers into the new guidelines in 2011. Atrophy of mesial temporal lobe on MRI, amyloid-beta deposition on amyloid PET, and hypometabolism on ^{18}F-fluorodeoxyglucose (FDG) PET were used to assess the likelihood that clinical symptoms is due to AD and determine the stage of preclinical AD [8, 13, 20]. After that, the International Working Group (IWG) also proposed an adjusted version of diagnostic criteria for AD, in which the level of Aβ plaques quantified by PET was considered as pathological biomarker of AD, while hypometabolism in ^{18}F-FDG PET and brain atrophy in MRI were regarded as biomarkers of disease progression [9].

These two new guidelines both emphasized the crucial role of imaging biomarkers in advancing preclinical AD research, since this may finally aid the development of disease-modifying interventions. As numerous studies show, clinical signs of most AD patients emerge after an extensive preclinical period, which can reach up to 15–20 years [21, 22]. Over such a prolonged preclinical period, using some non-invasive measures to monitor the occurrence and progression of AD is of critical value. And considering the most fitting indicator may vary in different preclinical phases [13, 23], a range of various biomarkers should be developed and utilized in different stages. In this review, we describe the application of PET as well as its importance in different AD stages and list main categories of PET radiotracers available now (Tables 1 and 2).

Amyloid-beta imaging

Amyloid-beta (Aβ) is a kind of peptide critically involved in AD pathophysiology, as components of the amyloid oligomers, fibrils, and plaques [90]. Aβ derives from amyloid precursor protein (APP), an integral membrane protein

regulating synapse formation [91] and neural plasticity [92], after being sequentially cleaved by β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase complex [93]. And the elimination of the Aβ depends on various clearance systems in brain via degradation, blood–brain barrier transport, interstitial fluid drainage, or CSF absorption [94]. Once the balance of Aβ metabolism is damaged, toxic conformations of Aβ would emerge and trigger pathological processes [95, 96].

There is substantial evidence to support that the accumulation of abnormally folded Aβ is closely related to progressive brain atrophy and cognitive impairment [97, 98]. And many neurological effects presented in Aβ-harbored individuals are similar to those in AD patients [99]. As now dominantly hypothesized, amyloidosis is the initial event of AD, followed by a cascade of pathophysiological processes including the formation of neurofibrillary tangles (NFTs), neuroinflammation, synaptic dysfunction, and eventually neuronal death [100–103]. In subjects with Aβ pathology cognitive intact, those with high Aβ burden often present slightly inferior neuropsychological performance and a higher likelihood of disease progression [104–107]. And as suggested by a longitudinal study, approximately 82% of mild cognitive impairment (MCI) patients presenting Aβ-positive would finally progress to AD during the follow-up period, while the majority of Aβ-negative subjects being cognitively stable [108]. Thus, Aβ burden is a reliable indicator of preclinical AD phase and disease progression.

Currently, two major biomarkers are available to characterize Aβ accumulation: $Aβ_{42}$ in CSF and Aβ burden characterized by PET imaging [93]. CSF $Aβ_{42}$ is quite a specific marker of AD, showing a robust inverse correlation with amyloid load in brain [109], and a good accuracy to differentiate AD from age-matched controls [110]. However, as lumbar puncture is a painfully invasive procedure, it may not be the best method for repeated measurements in longitudinal studies. Instead, amyloid PET allows non-invasive evaluation of cerebral Aβ load. Since amyloid PET shows a similar diagnostic accuracy and higher specificity than CSF $Aβ_{42}$ [111], it could be a better choice for AD research. Thanks to the great effort made in the developing of radiotracers to visualize Aβ in vivo, the field of amyloid imaging has been growing fast. We summarized some radioligands of interest here.

^{11}C-PIB: the first selective Aβ tracer

^{11}C-Pittsburgh compound B (^{11}C-PIB) is the first and one of the most successful selective Aβ tracers after a non-specific radiotracer named ^{18}F-FDDNP, which greatly drives AD researches forward. As a derivative of Thioflavin T, a dye widely used to visualize amyloid in vitro, ^{11}C-PIB could bind to beta-sheet structures, especially fibrillar Aβ

Table 1 PET molecular imaging to study major AD pathophysiology

Pathophysiology	Targets	Radiotracers	Advantages	Limitations	References
Aβ	Fibrillar Aβ	^{11}C-PIB	High affinity for Aβ-fibrils (Ki = 20.2 nM); high sensitivity and specificity; better accuracy than CSF biomarkers for AD diagnosis and progression predicting	Short half-life (20 min)	[24–26]
		^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben	Longer half-life (110 min); high sensitivity and specificity	Appreciable white matter retention may hamper the visual assessment	[19, 27–30]
		^{18}F-AZD4694	High affinity for Aβ-fibrils ($K(d)$ = 2.3 +/− 0.3 nM); high sensitivity and specificity; favorable kinetic profile and relatively low test–retest variability	-	[31–33]
	Prefibrillar Aβ	^{125}I-mAb158	High affinity for soluble protofibrils	-	[34]
		^{124}I-di-scFv-3D6-8D3	Ability to cross the blood–brain barrier and bind to both fibrillary Aβ and soluble aggregates	-	[35, 36]
Tau	Tau	^{18}F-AV-1451	High selectivity and specificity; high affinity to PHF-tau (Kd = 14.6 nM); favorable tracer kinetics; good reproducibility; high accuracy for AD diagnosis; better than ^{11}C-PIB to correlate to the severity of cognitive impairment	The kinetics varies in different disease stages; the uptake curve does not plateau; off-target binding	[37–43]
		^{18}F-AV-680	High selectivity and affinity to PHF-tau; little white matter retention and minimal off-target binding	-	[44]
		^{18}F-THK-5105, ^{18}F-THK-5117	Improved tau affinity and selectivity	Nonspecific binding	[45, 46]
		^{18}F-THK-5351	Favorable pharmacokinetics; higher affinity for tau protein fibrils; lower retention in white matter	Less sensitive and specific to tau and higher off-target binding than ^{18}F-AV-1451; affected by the availability of MAO-B	[47–49]
		^{11}C-PBB3	Good binding affinity; high selectivity; ability to detect a broad range of tau aggregates	Noticeable retention in venous sinuses; instability	[50–52]
Glucose metabolism		^{18}F-FDG	Differentiate AD from healthy subjects and other dementias; predict the conversion from MCI to AD	Susceptible to many external factors; offers less information about disease etiology	[53–58]

Abbreviations: *Aβ* amyloid-beta, *AD* Alzheimer's disease, *CSF* cerebrospinal fluid, *MAO-B* monoamine oxidase B, *PET* positron emission tomography, *PHF* paired helical filament

Table 2 PET molecular imaging for minor AD pathophysiology

Hallmarks	Targets	Radiotracers	References
Neuroinflammation	18-kDa translocator protein	^{11}C-PK11195, ^{11}C-DAA1106, and ^{18}F-FEDAA1106	[59–61]
	MAO-B	^{11}C-DED	[62]
	Phospholipase activity	^{11}C-AA	[63]
Metal ions in amyloid plaques	Metallobiology	^{18}F-CABS13, ^{11}C-L2-b, and ^{18}F-FL2-b	[64, 65]
GSK3		^{11}C-A1070722, ^{11}C-labelling isonicotinamides, and ^{18}F-maleimide-based ligands	[66–69]
Glutamatergic systems	mGluR2	^{11}C-JNJ42491293	[70]
	mGluR1	^{18}F-FITM, ^{11}C-ITMM, ^{11}C-ITDM, and ^{18}F-FIMX	[70]
	mGluR5	^{18}F-FPEB, ^{18}F-SP203, and ^{11}C-ABP688	[71]
Endogenous cannabinoid system	CB1R	^{18}F-MK-9470, ^{18}F-FMPEP-d2, 18F-FPATPP, and 11C-SD5024	[72–75]
	CB2R	^{18}F-labelling 1,3,5-triazine derivatives or ^{11}C-labelling 4-oxoquino-line derivatives	[76]
	FAAH	^{11}C-CURB, ^{11}C-MK-3168, and 11C- FAAH-1906	[77–79]
Cholinergic system	AChE activity	^{11}C-PMP and ^{11}C-MP4A	[80, 81]
	mAChR	^{11}C-MK-6884	[82]
	nAChR	18F-ASEM	[83]
	VAChT	^{11}C-TZ659, ^{18}F-VAT, and radiolabelling benzovesamicol VAChT analogs	[84–86]
Monoaminergic system	5-HT$_{1A}$ receptor	^{11}C-WAY100635 and ^{18}F-MPPF	[87, 88]
	NE	^{11}C-MRB	[89]

Abbreviations: *5-HT* serotonin, *AChE* acetylcholinesterase, *CB1R* type 1 cannabinoid receptor, *CB2R* type 2 cannabinoid receptor, *FAAH* fatty acid amide hydrolase, *GSK3* glycogen synthase kinase 3, *mAChR* muscarinic acetylcholine receptors, *MAO-B* monoamine oxidase B, *mGluRs* metabotropic glutamate receptors, *nAChR* nicotinic acetylcholine receptors, *NE* norepinephrine, *VAChT* vesicular acetylcholine transporter

in plaques with high affinity (Ki = 20.2 nM) [24]. To some extent, ^{11}C-PIB also binds to Aβ oligomers, a neurotoxic form of Aβ gaining increasing attention [112]. Though ^{11}C-PIB was found bind to tau [113] and α-synuclein [114] as well, in the concentrations clinically used, neurofibrillary tangles [115] and Lewy bodies [114] do not contribute to the retention of PIB. These characteristics lead to a sensitive and specific quantification of Aβ burden in vivo.

A robust inverse correlation was observed between ^{11}C-PIB retention and Aβ$_{42}$ level in CSF [116]. And in comparison with CSF biomarkers, PET techniques greatly improved the accuracy of clinical diagnosis [25]. As postmortem studies suggested, the retention of ^{11}C-PIB in PET images is highly correlated to the distribution areas of Aβ at autopsy [117]. Similar to studies conducted by Braak, AD patients mostly show increased uptake in frontal, cingulate, precuneus, striatum, parietal, and lateral temporal cortices. And regions of occipital, sensorimotor, and mesial temporal lobe are usually spared [7]. The striking similarity in the lobes affected and cortices supporting memory function further suggests the importance of amyloid PET in indicating early AD stages [118]. Besides, as amyloid distribution is different in various dementias [119, 120] and AD subtypes [7], the spatial patterns of amyloid deposition measured by PET may help to differentiate AD from other neurodegenerative diseases and determine AD phenotypes.

Additionally, ^{11}C-PIB positive is a sensitive predictor of disease conversion from MCI to AD [26]. With the faster converters commonly showing higher PIB uptake in brain [108], PET presents a better accuracy than CSF biomarker to classify stable MCI and progressed MCI [121]. And the specificity of conversion predicting would constantly increase as the follow-up period elongates [122]. Thus, ^{11}C-PIB PET has been applied to help researchers select subjects of preclinical AD, of which the group is extensively focused on as the target of Aβ-related therapies. ^{11}C-PIB also possesses great potential to assess treatment response, providing much crucial information about the reduction of amyloid burden and its effects on cognitive decline [123].

[18]F-florbetapir, ^{18}F-flutemetamol, and ^{18}F-florbetaben: the second generation of Aβ tracers

Though ^{11}C-PIB possesses plenty of virtues, the short half-life of carbon-11 (half-life of 20 min) limits its access only in PET centers with an on-site cyclotron and experienced carbon-11 radiochemistry technicists. To solve this dilemma, multiple fluorine-18 (half-life of 110 min) labeled radiotracers were developed, including ^{18}F-florbetapir (a.k.a. Amyvid) [27], ^{18}F-flutemetamol (a.k.a. Vizamyl) [28], and ^{18}F-florbetaben (a.k.a. Neuraseq) [29]. They were known

as the second generation of amyloid imaging radiotracers. And to date, these compounds have been approved by the US Food and Drug Administration (FDA). The longer half-life of fluorine-18 enables these tracers to be centrally produced and regionally distributed like ^{18}F-FDG, which may greatly lower the cost and allow AD researches be extensively conducted.

Research using these three tracers have confirmed their high sensitivity and specificity [19]. And mounting evidence has suggested their potential role in amyloidosis early detecting, AD subjects discriminating, and disease progression prediction [7]. In general, results derived from ^{11}C-PIB could mostly be replicated. Although different binding characteristics can be observed both in white matter and grey matter, cortical retention of these tracers was highly correlated with that of ^{11}C-PIB. The strong link between them may allow PET data be transformed and compared in multicenter studies that use different tracers [124].

These tracers have been extensively adopted by researchers around the world, and few drawbacks were reported. But in a minority of subjects, appreciable white matter retention can be observed, which may hamper the visual assessment of clinicians [30]. And according to a study evaluating the effect of concurrent pathologies on the uptake of florbetapir, while other diseases do not affect the tracer retention, Lewy bodies significantly lower the ratio of standard uptake value (SUV), the underlying mechanisms worth further exploring [125].

^{18}F-NAV4694: potentially novel Aβ tracer

^{18}F-NAV4694, formerly known as ^{18}F-AZD4694, is a more novel radiotracer being considered to outperform ligands currently available. In vitro studies of AZD4694 have shown its high affinity for Aβ-fibrils ($K (d) = 2.3 +/- 0.3$ nM). And in brain tissues of AD patients, selective binding to Aβ deposits of NAV4694 can be observed in grey matter, while the non-specific signal in white matter is low [31]. Besides, according to results of clinical validation, ^{18}F-NAV4694 possesses a favorable kinetic profile and a relatively low test–retest variability [32]. When comparing ^{18}F-NAV4694 with ^{11}C-PIB, nearly identical imaging characteristics were reported (Fig. 1) [33]. All these results suggest the tremendous potential of ^{18}F-NAV4694 to be widely applied both in clinical practice and scientific research.

Prefibrillar Aβ imaging

It is worth noting that most radioligands available now are developed to bind to Aβ in insoluble fibrils. However, increasing evidence has suggested that soluble Aβ aggregates are the neurotoxic form of Aβ causing neural dysfunction. Moreover, diffuse plaque pathology in AD patients usually presents

low PIB retention in brain due to the relatively low level of fibrillar Aβ [126]. Soluble Aβ usually better correlated to the severity of AD than amyloid plaques [127]. These results call for agents to visualize soluble oligomers and further investigate their role in AD pathology. In 2003, an antibody-based radioactive ligand, ^{125}I-mAb158, was reported to show high affinity for soluble protofibrils [34]. And recently, some derivatives of this radioligand were described in both diagnostic and therapeutic research. [124]I-RmAb158-scFv8D3 was used to evaluate the distribution of an antibody RmAb158-scFv8D3 in a protofibril-clearing immunotherapy research [36]. And [124]I-Di-scFv-3D6-8D3 was developed with the ability to cross the blood–brain barrier and bind to both fibrillary Aβ and soluble aggregates [35].

Limitations

Although amyloid PET has contributed much to a better understanding of AD pathophysiology, some problems remain unsolved. Histologically determined Aβ deposition was reported to poorly correlate to regional uptake in some PIB negative patients, calling for further postmortem research to evaluate the binding characteristics [128]. As there are some other mechanisms involved in disease progression [129], the dynamic alternation of amyloid pathology and its correlation with other biomarkers should be further explored. Besides, according to some studies comparing amyloid PET and other measures, PET is a sensitive technique to predict disease progression with limited specificity. So other biomarkers such as ^{18}F-FDG metabolism or brain atrophy should be taken into account to improve the prediction specificity [130, 131]. Additionally, different PET centers might apply various protocols to complete Aβ imaging acquisition. Meanwhile, the interpretation of PET images relied on the clinical experience of physicians. Therefore, more standardized approaches involved in image acquisition and interpretation could be helpful to reduce the variation. A guideline or widely accepted protocol could assist physicians to perform a standardized Aβ imaging acquisition and minimize errors produced by operators or PET machines. The combination of visual interpretation and SUVR in Aβ imaging interpretation could establish a semiquantitative analysis system which decreased the variation developed by visual interpretation to some extent [132]. And as studies of prefibrillar Aβ imaging are rather few so far, more research is warranted to develop better prefibrillar Aβ tracers in the future.

Tau imaging

Tau protein is a multifunctional protein mainly locating in axons of central nervous system, playing a crucial role in stabilizing microtubules [133], which is critical for the neuron integrity and axonal transport [134]. Six tau isoforms
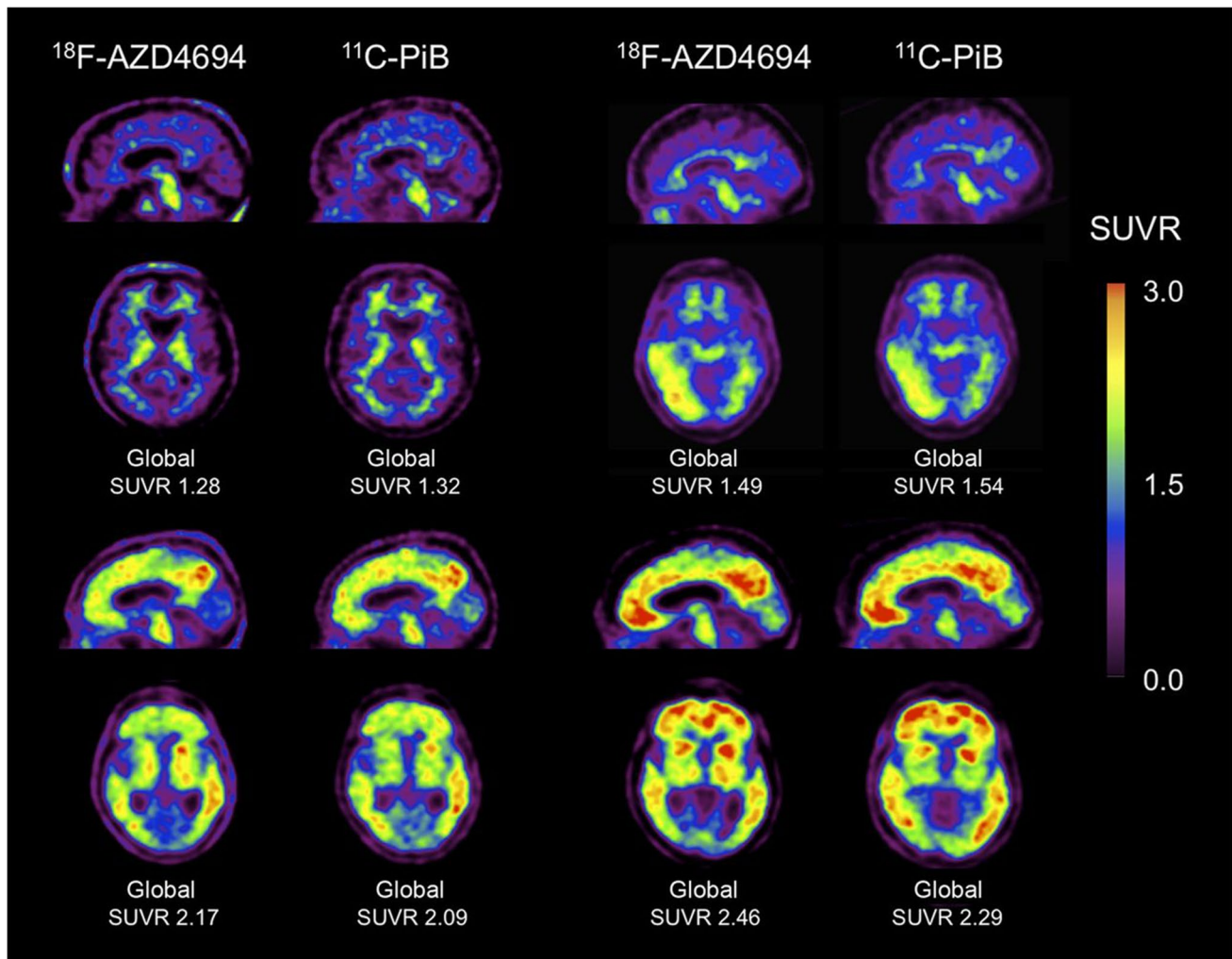
Fig. 1 ^{18}F-AZD4694 and ^{11}C-PiB PET imaging in 4 subjects. Four examples of sagittal and transaxial ^{18}F-AZD4694 images adjacent to same-slice ^{11}C-PiB images in same subject. Top 2 subjects were healthy age-matched controls, and bottom 2 were AD patients. The images showed near-identical appearance and dynamic range of SUVRs of ^{18}F-AZD4694 and.^{11}C-PiB. (This research was originally published in Journal of nuclear medicine: official publication, Society of Nuclear Medicine. 2013;54:880–6. Reprint permission was obtained)

are existing in human brain, generated by alternative mRNA splicing of the microtubule-associated protein tau gene (MAPT). And these isoforms can be classified as either 3 (3R) or 4 (4R) repeated binding domains, which may have different functions in various brain areas [135]. Naturally, tau is unfolded and highly soluble, showing little tendency to aggregate. However, the phosphorylation of tau will hamper the affinity of tau for microtubules and make them disassembled, impairing the function of microtubules. Then, the hyperphosphorylated tau aggregate and result in the formation of paired helical filaments (PHFs) and straight filaments. The neurofibrillary tangles (NFTs) formed by PHFs serve as one of the most essential pathological hallmarks of Alzheimer's disease, derailing neuronal functions and causing cell death [133]. 3R and 4R isoforms are both present

in Alzheimer's disease, while one dominant type is more common in other tauopathies [136].

Though amyloid-beta deposition is considered as the initial event of AD, the lag between the onset of Aβ pathology and the emergence of cognitive decline is usually long. And the correlation between Aβ burden and clinical disease stage gradually weakens after the initial phase of the preclinical stage of AD [13]. Thus, it is necessary to develop another biomarker to evaluate subsequent pathological changes and monitor disease progression. The accumulation of tau could be such an appropriate indicator. Post-mortem studies have shown that the burden of neocortical NFTs is highly associated with cognitive dysfunction [137]. More recent research also further suggest the central role of tau in AD pathophysiology [138]. And the failure of substantial anti-amyloid trials

also strengthens the doubt of amyloid hypothesis, calling for a novel perspective to understand AD pathology [139]. It is of great value to explore the tau protein as a diagnostic or therapeutic target.

Tau in CSF, total tau (t-tau) and phosphorylated tau (p-tau), are widely used as core CSF biomarkers, with CSF p-tau highly correlating with the amount of phosphorylated tau in brain and CSF t-tau reflecting the intensity of neuronal degeneration [140]. But tau pathophysiology is also a biomarker of many other neurodegenerative disease, including corticobasal degeneration (CBD), frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), and Pick's disease. Considering the distribution of tau aggregates differs from each other in these dementias [141], using imaging techniques rather than CSF biochemical biomarkers to visualize the level of tau burden and the spatial distribution seems more anticipated and powerful. Furthermore, it is suggested that the progression of tau deposition in AD follows a stereotypical pattern, with tau deposition limited in the transentorhinal region in early phase, then affecting limbic lobes and finally spreading to neocortical areas [142]. So, tau-targeted PET imaging may better help clinicians staging AD pathology and predicting MCI prognosis as well [143].

However, the developing of tau-binding PET compounds is more challenging than that of Aβ-binding ligands [144]. As tau pathology locates intracellular, binding to tau requires radiotracers to cross both the blood–brain barrier and cell membranes. Moreover, due to the diversities in isoforms and conformations of tau, and a much lower concentration of tau-aggregates than Aβ in brain, ligands used should be much more sensitive and selective. Several series of compounds are available now as potential tau-targeted PET radiotracers, the benzimidazole-pyrimidines derivatives: ^{18}F-AV-1451 (a.k.a. ^{18}F-T807 and Flortaucipir) and ^{18}F-AV-680 (a.k.a. ^{18}F-T808); the quinoline derivatives: ^{18}F-THK-5105, ^{18}F-THK-5117, and ^{18}F-THK-5351; and the pyridinyl-butadienyl-benzothiazoles derivative: ^{11}C-PBB3. In addition to these tracers, some more novel compounds, such as ^{18}F-MK-6240 [145], ^{18}F-RO-6958948 [146], also showed excellent properties for tau imaging, but further researches are needed. These agents are increasingly being used, greatly deepening our understanding of AD tau pathophysiology.

^{18}F-AV-1451 and ^{18}F-AV-680: PHF-tau binding radiotracers

^{18}F-AV-1451 (a.k.a. ^{18}F-T807 or ^{18}F-flortaucipir) was the first promising PET tracer for visualization and quantification of NFT pathology in AD patients. And to date, it has been the most widely used tau-binding radiotracer [37]. According to results of autoradiography and immunohistochemistry staining in human cortical sections, the selectivity of ^{18}F-AV-1451 for tau is 29-fold over Aβ. It also presents high affinity to PHF-tau in the nanomolar range (Kd = 14.6 nM), very low non-specific binding in white matter, and favorable tracer kinetics [37]. Moreover, good reproducibility was reported in a test–retest study, making ^{18}F-AV-1451 PET a powerful means in longitudinal researches [38, 39].

Studies comparing tau PET imaging and CSF biomarkers revealed a significant correlation between tau in CSF and ^{18}F-AV-1451 uptake, especially in some specific cortical regions [147]. And in patients with memorial dysfunction, ^{18}F-AV-1451 is able to distinguish AD from other non-AD neurodegenerative disorders with high accuracy [40]. Abnormally higher cortical retention can be observed in MCI and AD patients compared with cognitive normal subjects, and the elevated binding of ^{18}F-AV-1451 is better correlated to the severity of cognitive impairment than ^{11}C-PIB [148]. Besides, it is suggested that the distribution of tracer retention can be classified into patterns as Braak prescribed (Fig. 2) [149], enabling tau PET to monitor progression of tau pathology and evaluate the cause of clinical symptoms. ^{18}F-AV-1451 positive results can also be observed in preclinical AD patients, with faster increase of tracer retention being observed in the group of high amyloid burden [150], which may further suggest a close relationship between tau and amyloid-beta, making ^{18}F-AV-1451 PET a valuable method to screen and determine subjects in disease-modifying clinical trials. And more recently, international consensus suggested to consider the application of ^{18}F-AV-1451 PET imaging for definitive diagnosis, differential diagnosis, and severity determination of AD [151].

However, this tracer has some limitations. As a study has suggested, the kinetics of this tracer in brain varies in different disease stages, and the uptake curve does not plateau during the typical imaging duration; further dynamic researches are warranted to determine the best timing of scanning for accurately diagnosing [41]. Additionally, in some cortical areas with no tau pathology, off-target binding of ^{18}F-AV-1451 was reported, especially in basal ganglia, substantia nigra, and choroid plexus [42, 43], so more imaging-pathological studies on postmortem materials should be conducted for a better interpretation of PET imaging.

^{18}F-AV-680 is another benzimidazole-pyrimidines derivative showing promise for the tau imaging in AD patients. It also displays high selectivity and affinity to PHF-tau, little white matter retention, and minimal off-target binding. In contrast to ^{18}F-AV-1451, ^{18}F-AV-680 demonstrates a substantial defluorination in rodents, and a faster kinetics in human brains [44]. But studies are warranted to further verify these findings.
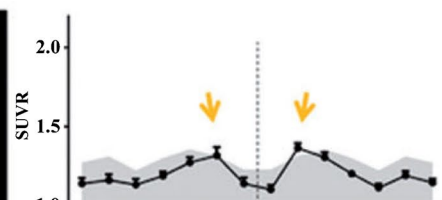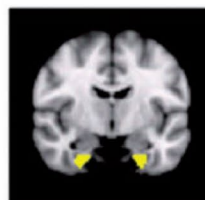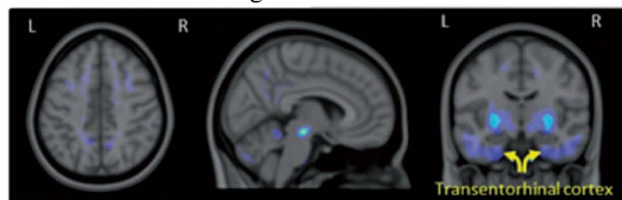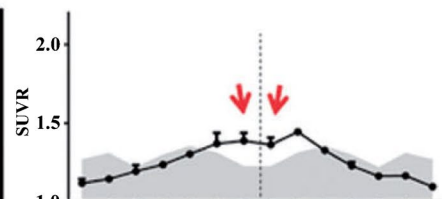
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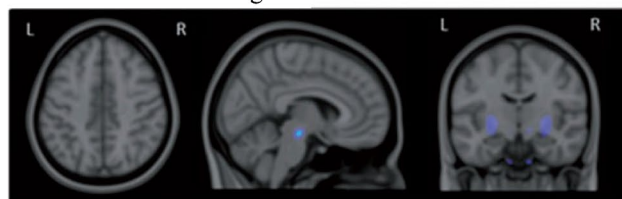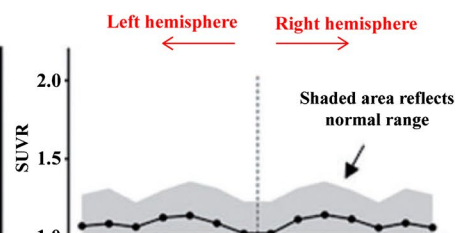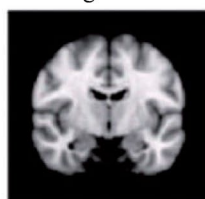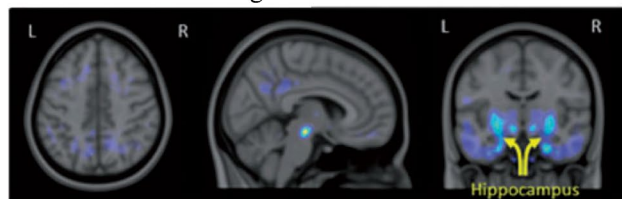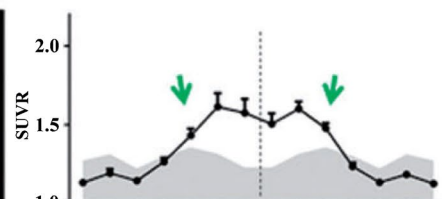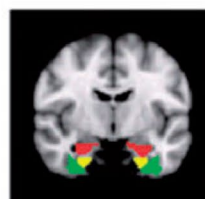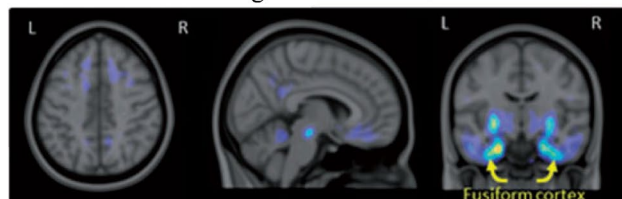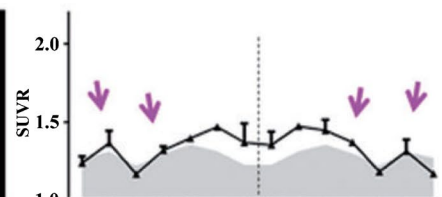
B Estimated Braak stage I

C Estimated Braak stage II
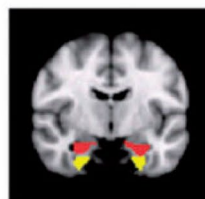
D Estimated Braak stage III
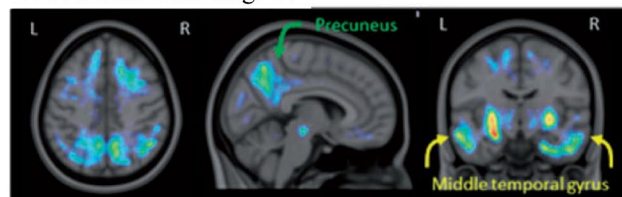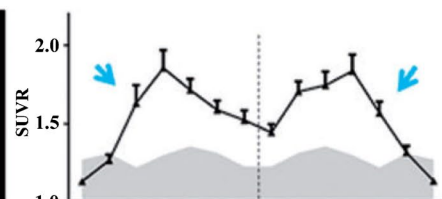
E Estimated Braak stage IV

F Estimated Braak stage V

G Estimated Braak stage VI

Target ROIs

Left hemisphere   Right hemisphere

Shaded area reflects normal range

Transentorhinal cortex

Hippocampus

Fusiform cortex

Precuneus

Middle temporal gyrus

Precuneus

Superior temporal gyrus

Precuneus

Primary visual cortex
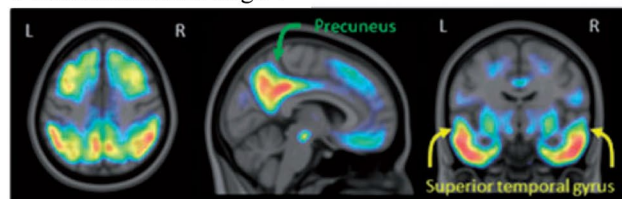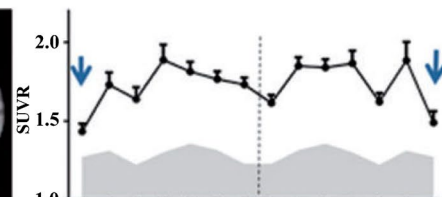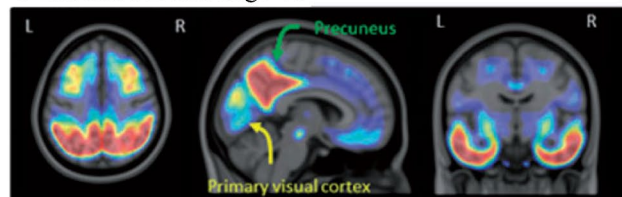
SUVR 1.2   2.0

p e s m f t h h t f m s e p
(left)   (right)

◄**Fig. 2** Average SUVR images of.[18]F-AV-1451 PET scans and region of interest profiles by estimated Braak stage. The regions of interest profiles are as showed "butterfly plots," with the regions of interest from each hemisphere mirrored and ordered mediolaterally, reflecting both the anatomical distribution and order of involvement consistent with disease progressiveness. (This research was originally published in Brain. 2016;139:1539–50. Reprint permission was obtained)

THK series: quinoline derivatives for tau PET imaging

The first ^{18}F-labelling quinoline derivatives created for tau imaging were ^{18}F-THK523, but its clinical application was hampered due to several limitations, including the high white matter retention and relatively low selectivity of tau over Aβ [152]. Then, two new derivatives: ^{18}F-THK-5105 and ^{18}F-THK-5117, were developed to improve the tau affinity and selectivity. These two compounds showed better imaging capability both in vitro and in vivo [45], but nonspecific binding in white matter still existed [46]. After that, ^{18}F-THK-5351 was further developed. Encouragingly, ^{18}F-THK-5351 showed favorable pharmacokinetics, higher affinity for tau protein fibrils, and lower retention in white matter, allowing for better tau visualization [47].

Using ^{18}F-THK-5351, the spatial distribution of retention in AD patients is corresponded to the pattern reported by Braak previously [153]. In AD patients, significant higher retention is observed in association cortices and limbic areas than healthy subjects, and the level of tracer uptake was clearly associated with the cognitive function [154]. And by combining the topology information of tau pathology, various neurodegenerative diseases can be differentiated [155–157]. However, while ^{18}F-THK-5351 seems to target similar binding site with ^{18}F-AV-1451, it is less sensitive and specific to tau of AD and shows higher off-target binding than ^{18}F-AV-1451 [48]. Additionally, the availability of monoamine oxidase B (MAO-B) was reported to affect the uptake of ^{18}F-THK-5351 in brain [49]. So the retention in areas of commonly off-targeted and tissues containing MAO-B should be interpreted with caution.

[11]C-PBB3: a potential tau-targeted PET tracer

Another series of probes, phenyl/pyridinyl-butadienyl-benzothiazoles/benzothiazoliums (PBBs), were also developed as potential tau-targeted PET tracers. And among these derivatives, ^{11}C-PBB3 was the most promising candidate, demonstrating a good binding affinity in the nanomolar range and excellent selectivity for tau over amyloid (40–50-fold) [50]. And compared to other classes of tracers, ^{11}C-PBB3 is the first compound reported to detect a broad range of tau aggregates, binding other tau fibril types as well as AD PHFs [51]. Additionally, ^{11}C-PBB3 has shown the potential to differentiate patients in the AD continuum group

from biomarker-negative individuals and suspected non-AD pathophysiology group [158].

Nevertheless, some shortcomings of this tracer should be overcome in the future. While nonspecific signals of ^{11}C-PBB3 are generally low, retention in venous sinuses is noticeable [50]. And ^{11}C-PBB3 is vulnerable to light due to its structure [52]; the instability will add complexity to its synthesis, purification, and clinical usage. The short half-life of ^{11}C also limits its availability. Besides, a radiometabolite of this tracer could enter the brain and confound the imaging results [159].

Limitations

Now several kinds of ligands have been developed for tau imaging. But as tau proteins are heterogeneous in isoforms and conformations, and the roles of various tau pathologies are elusive, further researches are warranted to better classify these tracers and interpret the binding pattern of each tracer in longitudinal studies. And as quite a few studies have reported off-target retention of these tracers, more imaging-to-postmortem researches should be conducted to validate their binding characteristics. Since tau PET imaging is bound to be applied to monitor disease progression and therapeutic efficacy, reproducibility assessment of these compounds is critical for accurately comparing results. Besides, studies comparing the dynamic change of tau tracer retention and other biomarkers are necessary for a better exploration of the interactions of different pathology, as well as helping determining the best means used for disease evaluation at the right time.

Glucose metabolism imaging

[^{18}F]fuoro-2-deoxyglucose (^{18}F-FDG) is another kind of tracer important in AD research. ^{18}F-FDG is an analog of glucose, with the hydroxyl at C-2 position substituted by fluorine-18. ^{18}F-FDG could reflect the glucose metabolism partly by responding to the hypoxia environment in some tumors, myocardial ischemia, and inflammation [160]. And as the 2-hydroxyl group is necessary for further glycolysis, ^{18}F-FDG phosphorylated cannot be metabolized and is trapped in the cell until radioactive decay [161]. Hence, its retention is powerful to characterize tissues in terms of glucose metabolism. In addition to its extensive application in clinical cancer assessment, ^{18}F-FDG also influences the field of neuroscience profoundly [162].

AD is a progressive neurodegenerative disease, so detecting the occurrence of neural dysfunction and assessing the severity of neurodegeneration are of great value both in researches and clinical practice. Using ^{14}C-deoxyglucose, energy metabolism was reported to closely correlate to

synaptic activation [163]. A literature of studies in recent years also suggest the glucose uptake characterized by ^{18}F-FDG can be used to quantify brain connectivity [164]. Thus, hypometabolism is extensively utilized as a sensitive biomarker to evaluate brain function in AD and other dementias. In the new working criteria developed by NIA-AA, FDG was incorporated as a biomarker to assess the likelihood of AD pathology and stage of preclinical AD [13], while in the advancing diagnostic criteria of AD (IWG-2 criteria) proposed in 2014, hypometabolism was identified as a downstream topographical biomarker [9].

However, hypometabolism in FDG PET is a sensitive but less specific biomarker, affected by age, depression, cognitive reserve, and many other factors [165]. Meanwhile, standardized FDG imaging acquisition protocol including scanning strategy and patient preparation also played an important role in image interpretation of AD patients [166]. Thus, the pattern of hypometabolism distribution across the whole brain should be taken into account when PET imaging results are interpreted. And considering the difficulty on discriminating delicate differences across various regions, using some automated quantitative techniques, like Statistical Parametric Mapping (SPM) and Stereotactic Surface Projections (SSP), may further provide complementary information and improve diagnostic accuracy (Fig. 3) [167–169]. It is reported that in AD patients, decreased glucose uptake in the parietotemporal areas and posterior cingulate cortices is a reliable hallmark of AD [170]. And there is evidence showing that areas presenting hypometabolism in AD patients are similar to those of default-model network [171]. The differences of hypometabolic pattern can also be used to differentiate AD from other neurodegenerative diseases [53–55].

In addition to the role of differentiating AD from healthy subjects and other dementias, another important application of ^{18}F-FDG is to predict the conversion from MCI to AD. A recent study highlighted the ability of hypometabolism in middle and inferior temporal areas to predict the conversion from MCI to AD [56]. And according to a few studies, hypometabolism is the best predictor of AD converting among all biomarkers [54, 57]. All the evidence further suggests us to use FDG-PET measures to specifically rule out synaptic dysfunction and assess disease stages.

By using ^{18}F-FDG, great progress in AD and other dementias has been made, but some insufficiency still exists. Firstly, cerebral FDG metabolism is such a sensitive biomarker that it is susceptible to many external factors. The variability in FDG PET imaging calls for more large-scaled and well-designed studies, to establish reasonable models and interpret PET results more accurately. As reported, SUV measurements might be more reproducible and reliable to interpret FDG PET images derived from PET/CT or PET/MRI, which could allow us to compare and evaluate patient's PET results in a longitudinal time window or with other patient groups [172]. Although semiquantitative means used now greatly improve the diagnostic specificity, its sensitivity is less than visual evaluation by an expert [58]. Thus, visual means and semi-quantitative techniques should be weighed in future researches, and more advanced automated or semiautomated approaches should be developed. Besides, while ^{18}F-FDG has become a powerful compound to measure synaptic dysfunction, it offers less information about disease etiology. To further promote the development of AD research, it seems more reasonable to combine FDG metabolism with other biomarkers and comprehensively understand the underlying pathophysiological mechanism of AD.

Other targets for PET imaging

As the pathophysiology of AD is multifaceted and heterogeneous, the amyloid cascade hypothesis alone cannot fully elucidate it. There are also some other mechanisms proposed to play significant roles in the occurrence and progression of AD. Molecular imaging techniques, especially PET, are of great potential to investigate these pathophysiological processes and help to clarify their relationships with neuronal damage and cognitive dysfunction. We will discuss some other mechanisms involved in AD and list some radioligands targeting these alternations.

Neuroinflammation

Neuroinflammation is regarded as an important participant in AD pathophysiology, though the exact role remains elusive. Some studies have suggested that the inflammation is involved in promoting tau hyperphosphorylation and driving neurodegenerative processes [173], while there is evidence showing its protective role at early AD stages [174]. Currently, numerous PET ligands are available to evaluate neuroinflammation by targeting underlying biological processes [175]. For example, microglial activation could be visualized by quantifying the 18-kDa translocator protein using radiotracers such as ^{11}C-PK11195 [59], ^{11}C-DAA1106 [60], ^{18}F-FEDAA1106 [61], etc. ^{11}C-DED can be utilized to bind monoamine oxidase B (MAO-B) and then measure reactive astrocytosis [62]. And the level of ^{11}C-AA (arachidonic acid) uptake in brain is a reliable biomarker for detecting the upregulation of phospholipase activity [63].

Metal ions in amyloid plaques

High content of metal ions like Zn^{2+} and Cu^{2+} was observed in and around the formation site of amyloid plaques [176]. And these metals are able to mediate the protein aggregation and lead to the formation of amyloid
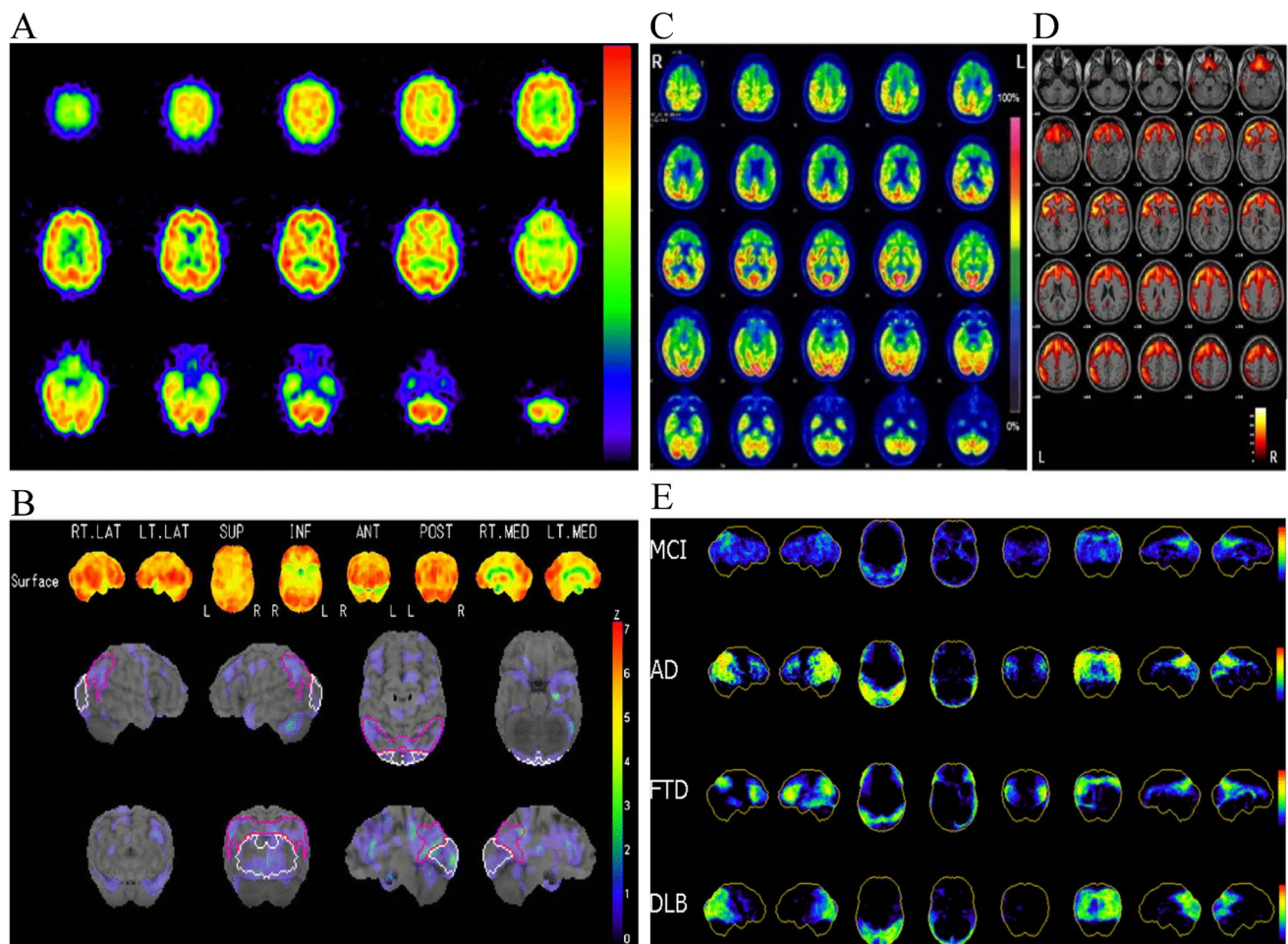
Fig. 3 Examples of SPM and SSP. (**A**) Conventional IMP-SPECT image and (**B**) surface Z score map in a 73-year-old patient with AD. The slightly decreased perfusion in the brain regions of this AD patient was hard to detect by visual inspection, while surface Z score map automated showed brain regions with decreased perfusion and diagnosed this patient as AD. (RT. LAT right lateral, LT. LAT left lateral, SUP superior, INF inferior, ANT anterior, POST posterior, RT. MED right medial, LT. MED left medial, L left, R right); (**C**) Standard clinical display of FDG-PET images ("Standard FDG Images") and (**D**) Voxel-based statistical parametric hypometabolic maps ("SPM Maps") of a patient affected by behavioral variant of frontotemporal dementia. SPM Maps showed the abnormal brain regions more clearly. L=Left, R=right; (**E**) Representative cortical ^{18}F-FDG PET patterns in NL, AD, DLB, and FTD. Three-dimensional stereotactic surface projections (3D-SSPs) and corresponding Z scores showing CMRglc reductions in clinical groups as compared with the NL database are displayed on a color-coded scale ranging from 0 (black) to 10 (red). From left to right: 3D-SSP maps are shown on the right and left lateral, superior and inferior, anterior and posterior, and right and left middle views of a standardized brain image (NL age-matched healthy elderly individuals, AD Alzheimer's disease, DLB dementia with Lewy bodies, FTD frontotemporal dementia, CMRglc cerebral metabolic rate of glucose). (These researches were originally published in Eur J Nucl Med Mol Imaging. 2009 May;36(5):831–40., Neuroimage Clin. 2014;6:445–54. and J Nucl Med. 2008 Mar;49(3):390–8. Reprint permissions were obtained.)

plaques [177]. According to the data, a "Metal Hypothesis of AD" was proposed, and many ionophores and metal-chelators were developed as disease-modifying drugs [178]. The first PET radiotracer discovered to bind metal ions in amyloid plaques is ^{18}F-CABS13, showing promising preliminary results in a mouse model [64]. And in recent years, ^{11}C-L2-b and ^{18}F-FL2-b were synthesized and evaluated to investigate the metallobiology of AD [65], but further researches on the metal-Aβ radioligands are warranted.

Glycogen synthase kinase 3

Glycogen synthase kinase 3 (GSK3) is a wide expressed serine/threonine kinase involved in a range of cellular processes, including apoptosis, glucose regulation, and cell signaling [179–181]. It has been shown that GSK3 activity is associated with the formation of both amyloid plaques and NFTs [182, 183]. And inhibitors of GSK3 were reported to reduce Aβ production and tau aggregation [184]. These evidence encourage the "GSK3 hypothesis

of AD" [185]. Some radiolabeled compounds are now available for GSK3 monitoring [186]. ^{11}C-A1070722 and several ^{11}C-labelling isonicotinamides were developed recently showing better binding characteristics than that synthesized previously [66, 67]. And more recently, glycogen synthase kinase 3β could be visualized by using ^{18}F-labelling maleimide-based and isonicotinamide-based ligands which showed moderate brain uptake [68, 69].

Glutamatergic systems

Glutamate is the most abundant excitatory neurotransmitter in brain, playing a vital role in learning and memory [187, 188]. Glutamate mediates ionotropic and metabotropic receptors (iGluRs and mGluRs, respectively), both of which are implicated in a spectrum of neurodegenerative diseases including AD [189, 190]. During the past decades, a number of radioligands have been developed for imaging iGluRs, but few PET tracers presented favorable in vivo results [70]. In terms of probes of mGluRs, no promising ligands are now available for imaging group III mGluRs (including mGluRs 4, 6, 7, and 8) and mGluR3. However, mGluR2 can be evaluated by a prospective tracer ^{11}C-JNJ42491293. For visualizing mGluR1, ^{18}F-FITM, ^{11}C-ITMM, ^{11}C-ITDM, and ^{18}F-FIMX are clinically useful. And the most widely studied receptor, mGluR5, can be measured in vivo using ^{18}F-FPEB, ^{18}F-SP203, and ^{11}C-ABP688 [71].

Endogenous cannabinoid system

As a few alternations of the endogenous cannabinoid system (ECS) were reported in post-mortem studies [191], the ECS gets increasing attention as a novel target in some AD-therapeutic researches. Though the exact role of ECS in AD remains elusive, accumulating evidence suggests that the activation of cannabinoid signaling could alleviate AD symptoms by reducing excitotoxicity, neuroinflammation, and oxidative stress [192]. Currently, a series of compounds have been developed for the imaging of ECS. ^{18}F-MK-9470 [72], ^{18}F-FMPEP-d2 [73], ^{18}F-FPATPP [74], and ^{11}C-SD5024 [75] are promising imaging tools for ECS researches in terms of type 1 cannabinoid receptor (CB1R). And the availability of type 2 cannabinoid receptor (CB2R) could be measured by several radioligands like ^{18}F-labelling 1,3,5-triazine derivatives or ^{11}C-labelling 4-oxoquinoline derivatives [76]. Fatty acid amide hydrolase (FAAH), the principal catabolic enzyme metabolizing endogenous cannabinoid, could also be detected using tracers like ^{11}C-CURB [77], ^{11}C-MK-3168 [78], and ^{11}C-FAAH-1906 [79].

Cholinergic system

The cholinergic dysfunction has also been found to be crucially involved in the pathophysiology of AD. A few post-mortem studies have suggested the cholinergic alternation in the course of dementia [193, 194]. And by using PET imaging techniques with selective tracers, diverse components of the cholinergic system could be measured in vivo [195]. Specifically, cerebral acetylcholinesterase (AChE) activity could be measured by using ^{11}C-PMP [80] and ^{11}C-MP4A [81]. ^{11}C-MK-6884 [82] and ^{18}F-ASEM [83] can be used to quantify the binding potential of the muscarinic and nicotinic acetylcholine receptors (mAChR and nAChR), respectively. And the imaging of vesicular acetylcholine transporter (VAChT) can be achieved by a series of compounds, such as ^{11}C-TZ659 [84], ^{18}F-VAT [85], and radiolabeled benzovesamicol VAChT analogs [86].

Monoaminergic system

Although the cholinergic system is primarily affected in AD pathology, neurotransmitters of monoaminergic system are also implicated, including serotonin (5-HT), dopamine (DA), and norepinephrine (NE) [196, 197]. And the disruption of the dynamic balance of monoaminergic system may impair the functional neural networks of AD patients involved in affective regulation and executive function [198]. Serotonin 5-HT$_{1A}$ receptor, which is particularly relevant to AD, could be selectively bound by ^{11}C-WAY100635 [87] and ^{18}F-MPPF [88]. And tracers targeting dopaminergic system have been extensively utilized in Parkinsonian disorders [199]. In terms of norepinephrine transporter imaging, ^{11}C-MRB was considered as the most promising ligand [89].

Conclusion

Multiple mechanisms are involved in the pathophysiological processes of AD, so a range of biomarkers are needed in the disease evaluation. The development of PET imaging technique has provided much crucial information about the occurrence and the progression of AD, contributing to the early and differential diagnosis of AD, as well as the assessment of therapeutic response. And the longitudinal scanning could help to clarify the dynamic change of each compound radiolabeled over the course of the disease. Besides, some biochemical processes unexplored could be visualized, which may contribute to the investigation of their role in AD etiology and the elucidation of the heterogeneity of clinical phenotypes. Therefore, PET imaging techniques are essential for the optimal AD evaluation and management in the future.

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest All authors declare no competing interests.

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