alzheimer's research&therapy

REVIEW

Molecular imaging in Alzheimer's disease: new perspectives on biomarkers for early diagnosis and drug development

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Abstract

Recent progress in molecular imaging has provided new important knowledge for further understanding the time course of early pathological disease processes in Alzheimer's disease (AD). Positron emission tomography (PET) amyloid beta (Aβ) tracers such as Pittsburgh Compound B detect increasing deposition of fibrillar Aβ in the brain at the prodromal stages of AD, while the levels of fibrillar Aβ appear more stable at high levels in clinical AD. There is a need for PET ligands to visualize smaller forms of Aβ, oligomeric forms, in the brain and to understand how they interact with synaptic activity and neurodegeneration. The inflammatory markers presently under development might provide further insight into the disease mechanism as well as imaging tracers for tau. Biomarkers measuring functional changes in the brain such as regional cerebral glucose metabolism and neurotransmitter activity seem to strongly correlate with clinical symptoms of cognitive decline. Molecular imaging biomarkers will have a clinical implication in AD not only for early detection of AD but for selecting patients for certain drug therapies and to test disease-modifying drugs. PET fibrillar Aβ imaging together with cerebrospinal fluid biomarkers are promising as biomarkers for early recognition of subjects at risk for AD, for identifying patients for certain therapy and for quantifying anti-amyloid effects. Functional biomarkers such as regional cerebral glucose metabolism together with measurement of the brain volumes provide valuable information about disease progression and outcome of drug treatment.

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Introduction

Alzheimer's disease (AD) is characterized by a slow continued deterioration of cognitive processes. The first symptoms of episodic memory disturbances might be quite subtle. When the patient is assessed for memory problems the disease has most probably been ongoing in the brain for several years and has most probably induced nonrepairable disturbances of important functional neuronal networks and loops of the brain. It is a challenge to test whether some of these changes could be reversed or slowed down with early drug treatment.

The recent progress in AD research has provided new knowledge for further understanding the pathology processes of AD that precede the onset of clinical disease by many years. It is still an open question why some people can cope with AD brain pathology better than others. Do they have greater capacity of neuronal compensation? Is there ongoing neurogenesis in the brain? The resistance toward increased pathological burden especially observed in highly educated subjects might be a sign of increased brain plasticity as well as greater cognitive reserve [1].

Since Dr Alois Alzheimer first described the AD disease, amyloid beta (Aβ) has played a central role in AD pathology. It has not yet been proven that Aβ is the primary causative factor of AD. A puzzling observation from autopsy AD brain studies has been the weak correlation between fibrillar Aβ load in the brain and cognition while the amount of neurofibrillary tangles significantly correlates with the cognitive status and duration of dementia [2-4]. The effects of Aβ in the clinical stages of AD are most probably mediated by the presence of neurofibrillary tangles in the brain [5]. In addition, a sequential cascade of events including oxidative stress reactions, inflammatory processes and neurotransmitter and receptor dysfunction most probably contributes to the impairment of cognitive function [6].

Molecular imaging techniques have rapidly developed during recent years. This development not only allows one to measure brain structural changes in patients

(atrophy, volume changes and cortical thickness) by magnetic resonance imaging, but also to visualize and quantify brain pathology (fibrillar Aβ, tau, activated microglia and astrocytosis) as well as functional changes (cerebral glucose metabolism, neurotransmitter and neuroreceptor activity) by positron emission tomography (PET) (Table 1). Molecular imaging thus provides important insight into the ongoing pathological processes in AD in relation to clinical symptoms and disease progression. An important step forward has been *in vivo* imaging of Aβ pathology in AD patients. Although the histopathological confirmation of diagnosis at autopsy is important, it reflects the end stage of a disease that may have been ongoing for decades.

The new molecular imaging techniques provide possibilities to develop early diagnostic biomarkers for early detection of AD at preclinical stages, as well as for monitoring effects of drug therapy. Recent research has thus also changed the view on incorporating biomarkers into the standardized clinical diagnosis of AD as suggested by Dubois and colleagues [7,8] and the recommendations from the National Institute on Aging–Alzheimer Association workgroups on diagnostic guidelines for AD [9,10].

Table 1. Pathological and functional biomarkers in Alzheimer's disease

Pathological Alzheimer's disease biomarkers
Positron emission tomography
Fibrillar amyloid beta (^{11}C-Pittsburgh Compound B, ^{18}F-flutemetamol, ^{18}F-florbetapir, and ^{18}F-florbetaben)
Tau (^{18}F-FDDNP)
Microglia (^{11}C-PK11195, ^{11}C-DA1106)
Astrocytes (^{11}C-D-deprenyl)
Magnetic resonance imaging (atrophy, hippocampal volume, cortical thickness)
Cerebrospinal fluid (amyloid beta 1–42, tau, p-tau)
Functional Alzheimer's disease biomarkers
Positron emission tomography
Cerebral glucose metabolism (^{18}F-FDG)
Neurotransmitter activity (for example, ^{11}C-CFT, ^{11}C-PMP)
Neuroreceptors (for example, ^{11}C-raclopride, ^{18}F-alanserine, ^{11}C-nicotine)
Functional magnetic resonance imaging, spectroscopy
Single-photon emission computed tomography (cerebral blood flow)

Amyloid imaging in Alzheimer's disease patients

Among the first Aβ PET tracers was Pittsburgh Compound B (^{11}C-PIB) when 16 AD patients were initially scanned in Sweden [11]. The high ^{11}C-PIB retention observed in cortical and subcortical brain regions of mild AD patients compared with age-matched healthy subjects has consistently been confirmed with ^{11}C-PIB in several other studies (for a review see [12-14]). Several other Aβ PET tracers have also been tested in AD and control patients [12,15] although so far ^{11}C-PIB is the most explored. ^{18}F-labeled tracers will probably be more suitable for use in the clinic, with their longer half-life. ^{18}F-FDDNP was the first ^{18}F-PET tracer used for visualizing Aβ plaque in AD patients [16], showing lower binding affinity to Aβ plaques than ^{11}C-PIB but also suggested to bind to neurofibrillary tangles [16,17]. The ^{18}F-labeled Aβ PET tracers ^{18}F-flutemetamol, ^{18}F-florbetapir and ^{18}F-florbetaben have shown promising results in AD patients [18-20].

The PET Aβ tracers quantify fibrillar Aβ in the brain by binding in the nanomolar range to the Aβ peptide [21]. The *in vivo* ^{11}C-PIB retention correlates with ^{3}H-PIB binding as well as levels of Aβ measured in autopsy AD brain tissue [22-25]. ^{18}F-florbetapir PET imaging has also been shown to correlate with the presence of Aβ amyloid at autopsy [26], as well as ^{18}F-flutemetamol PET imaging to amyloid measured in cortical biopsies [27].

A still unknown factor is the relationship between fibrillar Aβ (plaques) and soluble Aβ oligomers. Presently there is no information on how the smaller soluble Aβ oligomers, which are known for triggering synaptic dysfunction [28-30], can be visualized *in vivo* in man with the presently available Aβ tracers. It is therefore a challenge to try to develop PET tracers that can visualize these smaller forms of Aβ in the brain, although the probably lower content of oligomers in AD brains compared with fibrillar Aβ might be a limiting factor. The soluble Aβ oligomers are important since they probably can induce and interfere with the neurotransmission in the brain [30,31].

Longitudinal PET amyloid studies in Alzheimer's disease patients

There are still few longitudinal studies of Aβ PET imaging in AD patients. These studies are important to understand the rate of accumulation of amyloid in the brain and are important for evaluation of intervention in anti-amyloid drugs. A 2-year follow-up study with ^{11}C-PIB in AD patients revealed at group level consistent stable fibrillar Aβ levels in the brain [32]. Two additional 1-year and 2-year follow-up studies confirmed these observations [33,34] as well as a recent 5-year follow-up PET study of the first imaged PIB PET cohort [35]. In the latter study it was evident at the individual level that increased, stable and decreased PIB retention were observed and the disease progression was reflected in significant decline in cerebral regional cerebral glucose metabolism (rCMRglc) and cognition [35]. In a recent 20-month follow-up study, Villemagne and colleagues reported a 5.7% increase in fibrillar Aβ in AD patients [36]. The longitudinal imaging studies mainly support the

assumption that the Aβ levels in the AD brain reach a maximal level at the early clinical stage of the disease, although both increase and decline in later stages of the disease cannot be excluded [12,37,38].

Amyloid imaging in mild cognitive impairment patients

^{11}C-PIB PET studies in mild cognitive impairment (MCI) patients have revealed a bimodal distribution. Both high (PIB$^+$) and low (PIB$^-$) retention of the PET tracer has been demonstrated [39,40]. PIB$^+$ MCI patients seem to have a greater risk to convert to AD after clinical follow-up compared with PIB$^-$ MCI patients [39,41,42]. Figure 1 illustrates high ^{11}C-PIB retention in a MCI patient (PIB$^+$) who later converted to AD in comparison with a non-converting MCI patient (PIB$^-$). PIB$^+$ MCI patients show comparably high^{11}C-PIB retention to AD patients (Figure 1). We recently observed a significant increase in brain ^{11}C-PIB retention in early MCI patients when re-scanned after 3 years [35]. The MCI patients also showed a decrease in rCMRglc while they remained stable in cognitive function at follow-up [35]. Jack and colleagues [34] and Villemagne and colleagues [36] have also reported annual changes in ^{11}C-PIB retention. These findings support a continuous increase in Aβ load in the early stage of prodromal AD [35] (Figure 2).

Amyloid imaging in older subjects without cognitive impairment

High Aβ has been measured in older cognitive normal controls (for a review see [43]). The reported percentage of positive Aβ PET scans varies from 10 to 50% between different cohorts of studied older people without cognitive impairment [44,45]. A possible explanation for variation in percentage of Aβ PET-positive cognitive normal subjects could be age but also genetic background (APOE genotype). Aβ alone most probably does not account for the decline in memory in older people. Further longitudinal studies are needed to investigate to what extent these Aβ-positive older people with normal cognition will later convert to AD [46]. In a recent longitudinal study of 159 older subjects with normal cognition and PIB$^+$, PET showed a greater risk for developing symptomatic AD within 2 to 5 years compared with PIB$^-$ subjects [47].

Relationship between brain amyloid and cerebrospinal fluid biomarkers

There is a strong inverse correlation between accumulations of fibrillar Aβ in the brain as measured by ^{11}C-PIB and levels of $A\beta_{1-42}$ in cerebrospinal fluid (CSF) [39,48-55]. An inverse correlation between ^{11}C-PIB retention and CSF $A\beta_{1-42}$ has been demonstrated in prodromal AD (MCI) earlier than changes in functional parameters (cerebral glucose metabolism, cognition) [54] (Figure 2). Figure 3 illustrates the inverse relationship between Aβ in the brain and the CSF as analyzed with statistical parametric mapping cluster analysis. A positive relationship has also been observed between ^{11}C-PIB retention and levels of CSF tau and p-tau [39,50,51,54]. Which of the biomarkers are most sensitive to detect the earliest pathological signs of the disease is still unclear.

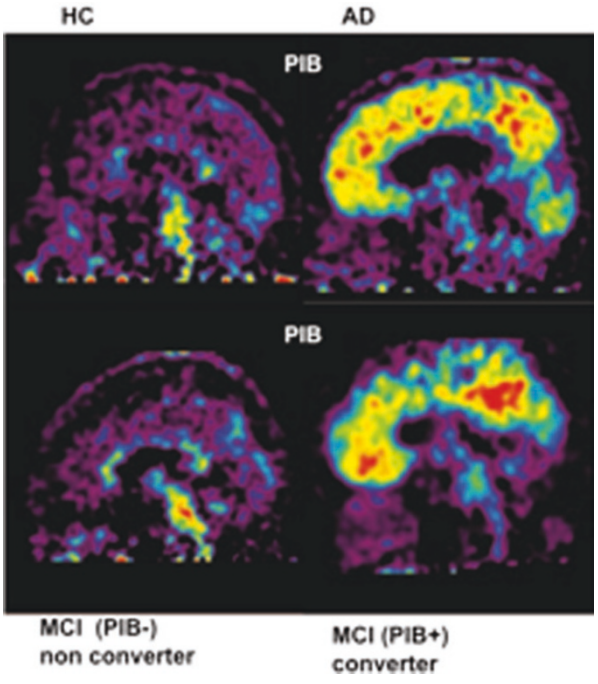

Figure 1. Pittsburgh Compound B retention in the brain. Pittsburgh Compound B (^{11}C-PIB) retention in the brain of a healthy control (HC), an Alzheimer patient (AD), patients with mild cognitive impairment (MCI) who later at clinical follow-up converted to AD, and patients with MCI who did not later convert to AD. PIB$^+$, high Pittsburgh Compound B retention; PIB$^-$, low Pittsburgh Compound B retention. Red, high ^{11}C-PIB retention; yellow, medium ^{11}C-PIB retention; blue, low ^{11}C-PIB retention.

Some data suggest that ^{11}C-PIB PET imaging detects amyloid pathology prior to CSF biomarkers [39,49,54]. Soluble Aβ oligomers might be the most pathogenic in AD. An interesting observation is therefore that AD patients with the APP arctic mutation show no fibrillar Aβ in the brain (PIB-negative) but a reduction of $A\beta_{42}$ in CSF as well as a reduction in cerebral glucose metabolisms by PET [56].

Imaging of inflammatory processes in Alzheimer's disease brain

Inflammatory processes have been suggested to cause the pathological processes of AD [57,58]. Amyloid has been observed to mobilize and activate microglia [59]. Activated microglia are found in autopsy brain tissue at

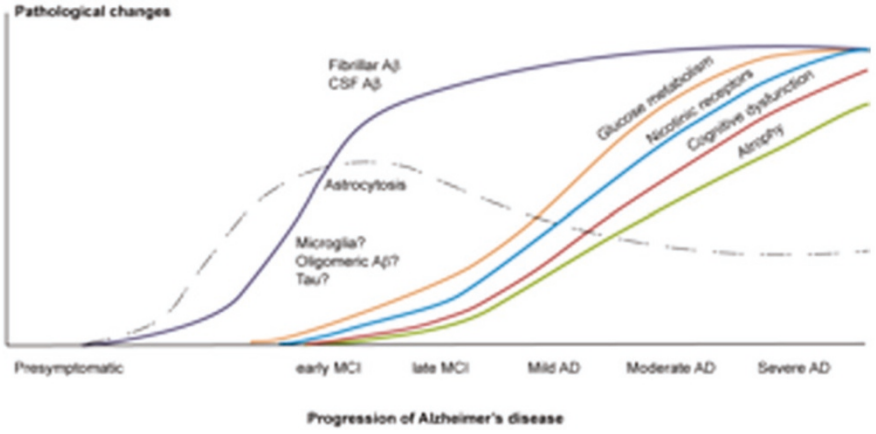

Figure 2. Schematic drawing of changes in pathological and functional imaging markers during progression of Alzheimer's disease. Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment.

sites of aggregated Aβ deposition of AD patients. The peripheral benzodiazepine receptor PET tracer ^{11}C-(R)-PK11195 has been used for measuring the transition of microglia from a resting state to an activated state in the brain. An increase in ^{11}C-(R)-PK11195 binding was described by Cagnin and colleagues in the temporoparietal, cingulated and entorhinal cortices of AD patients as a sign for strong microglia activation compared with controls [60]. Edison and colleagues demonstrated high cortical ^{11}C-(R)-PK11195 binding with reciprocal negative correlation with cognitive performance in AD patients [61]. In some other studies, a lower level of microglia activation was observed in mild AD and MCI [62,63]. ^{11}C-DAA-1106 is a new peripheral benzodiazepine PET tracer that has shown increased binding in several brain regions including the frontal, parietal, temporal cortices and striatum of AD patients compared with age-matched controls [64].

Activated astrocytes participate in the inflammatory processes occurring around the Aβ plaques. An increased number of astrocytes have been measured in autopsy brain tissue from AD patients, especially those with the Swedish APP mutation [65]. A positive correlation has been observed between ^{3}H-PIB binding and GFAP immunoreactivity in autopsy AD brain tissue [25]. It is assumed that synaptic activity might be coupled to utilization of energy through an interaction between astrocytes and neurons where the astrocytes take up glucose and release lactate to neurons [66].

N-[^{11}C-methyl]-L-deuterodeprenyl (^{11}C-DED) has been shown to irreversibly bind to the enzyme monoamino-oxidase B expressed in reactive astrocytes. ^{11}C-DED has therefore been tested as a PET ligand for measurement of activated astrocytes. Increased ^{11}C-DED binding was demonstrated in the brain of patients with Creutzfeldt–Jacob disease [67]. We have recently observed by PET an increased ^{11}C-DED binding in the cortical and subcortical brain regions of MCI patients compared with AD patients and controls [68]. These observations suggest that astrocytosis might be a very early event in the time course of pathological processes in AD (Figure 2). Further studies are needed to explore the relationship between Aβ and inflammatory processes in the early stages of AD.

Imaging of functional changes in Alzheimer's disease brain

Brain glucose metabolism

2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) has been widely used both in research and clinically for measurement of regional changes in rCMRglc in AD [10]. A reduction of rCMRglc is often observed in the parietal, temporal, frontal and posterior cingulate cortices. The decline in rCMRglc is more regional specific compared with the increased ^{11}C-PIB retention in large areas of the AD brain [11,32]. The hypometabolism is often more severe in early-onset AD compared with late-onset AD, while no difference in regional ^{11}C-PIB retention has been observed between early-onset and late-onset AD [69]. ^{11}C-PIB PET seems to detect prodromal AD at an earlier disease stage and better separates between MCI subtypes (amnestic versus nonamnestic) than ^{18}F-FDG [39,58,70]. The decline in rCMRglc follows, in contrast to PIB, the clinical progression of AD and shows a strong correlation with changes in cognition [32,35,58,70]. Figure 3 illustrates the correlation between rCMRglc and episodic memory (Rey Auditory Verbal Learning) and between ^{11}C-PIB and episodic memory (Rey Auditory Verbal Learning) as analyzed with statistical parametric mapping analysis. The ^{18}F-FDG uptake shows more brain regional specific clusters compared with ^{11}C-PIB [54].

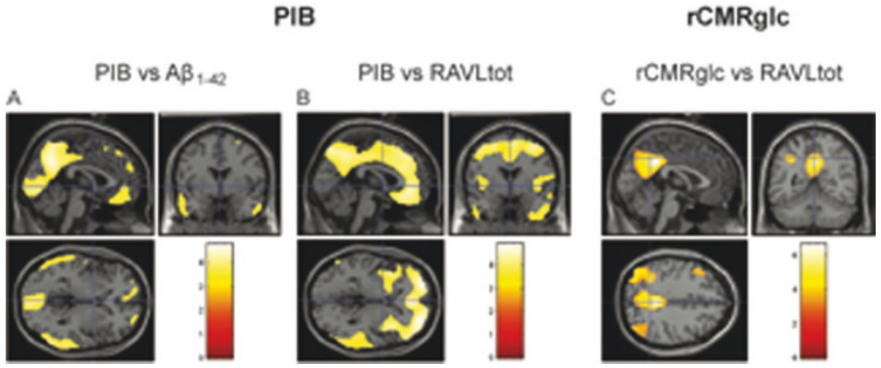

Figure 3. Positron emission tomography measurements, cerebrospinal fluid amyloid beta 1–42 and episodic memory scores. Statistical parametric mapping analysis showing clusters with significant covariance between positron emission tomography measurements versus levels of cerebrospinal fluid (CSF) amyloid beta 1–42 ($A\beta_{1-42}$) and episodic memory scores measured by means of Rey Auditory Verbal Learning (RAVLtot) tests, using data from Alzheimer's disease and mild cognitive impairment patients, at threshold $P < 0.001$, uncorrected for multiple comparisons. **(a)** Areas with significant covariance between Pittsburgh Compound B (^{11}C-PIB) retention and concentrations of $A\beta_{1-42}$ in CSF. **(b)** Clusters with significant covariance between ^{11}C-PIB retention and scores in RAVLtot tests. **(c)** Significant clusters of covariance between regional cerebral glucose metabolism (rCMRglc) and scores in RAVLtot tests. Data from [54].

Neurotransmitter and neuroreceptor imaging

Several neurotransmitters are impaired in AD, especially the cholinergic system but also the dopaminergic and serotonergic neurotransmitter. Several PET tracers have been developed and tested for measuring the different neurotransmitters, enzymes and various subtypes of receptors in AD patients [10]. PET tracers are available for studying dopaminergic, serotonergic and cholinergic systems [12] (Table 1). The cholinergic neurotransmission has so far been the focus for clinical AD therapy. It is therefore worth mentioning that decreases in nicotinic receptors have been demonstrated by PET in AD patients using ^{11}C-nicotine [71] and ^{18}F-fluoro-A-85380 (α4 nicotinic receptors) [72]. The extent of reduction in ^{11}C-nicotine binding correlated with the reduction in level of attention of the AD patients [71]. Presently there is a great interest to develop selective PET tracers for imaging of the α7 nicotinic receptors in the brain since these receptors interact with Aβ and might therefore be a new target for AD therapy [73].

Imaging biomarkers and drug development

Recent progress in molecular imaging and biomarkers indicates that subtle pathological changes indicative for AD disease might be detected decades prior to clinical diagnosis of AD. Differences in the time course are observed between pathological and functional AD imaging biomarkers (Figure 2). PET imaging allows measurement of pathological processes such as deposition of fibrillar Aβ plaques, levels of activated microglia and astrocytosis. There is a need for further exploration of PET tracers visualizing inflammatory processes that might occur at very early disease states (Figure 2). Similarly, there is a great need for PET tracers visualizing the accumulation of Aβ oligomers in different stages of AD (Figure 2). Preclinical data for the new promising PET ligand THK 523 for *in vivo* tau imaging have recently been presented [74]. Additional PET studies are needed to predict with more accuracy the time course for changes in neurotransmitter function including the nicotinic receptors. Brain atrophy changes (magnetic resonance imaging) correlate closely with cognitive decline and disease progression but less with amyloid load in the brain [14,20,75].

The rapid development of molecular imaging will be important not only for early diagnostic biomarkers and early detection of AD [7-9,46] but also to select patients for certain drug therapies and to identify disease-modifying therapies and testing in clinical trials (Table 2). PET imaging biomarkers could thereby play an important role in identifying patients with elevated risk of developing AD. In addition, fibrillar Aβ imaging could (together with CSF $A\beta_{42}$) serve as an inclusion criterion as well as a primary outcome in phase 2 and a secondary outcome in phase 3 drug trials. Measurement of rCMRglc and magnetic resonance imaging atrophy changes are probably most useful for predicting the clinical outcomes of drug therapy.

The multi-tracer PET concept offers unique opportunities in drug trials to study pathological as well as functional processes and to relate these processes in the brain to CSF biomarkers and cognitive outcomes (Figure 4). There is now an increased interest to introduce different biomarkers into clinical trials in AD patients [76], which will be important for all drug candidates in the pipeline for AD trials [77]. Long-term treatment with cholinesterase inhibitors in AD patients has shown significant correlation between the degree of inhibition

Table 2. Clinical implications of molecular imaging in Alzheimer's disease

To increase the understanding of pathophysiological mechanisms
To increase the understanding of time course of disease progression
To understand the differences in time course between pathology and functional changes
To develop diagnostic markers that can predict rate of progression
To enable selection of Alzheimer's disease patients to certain therapy
To measure brain changes after short-term and long-term therapeutic intervention that correlate with clinical symptoms

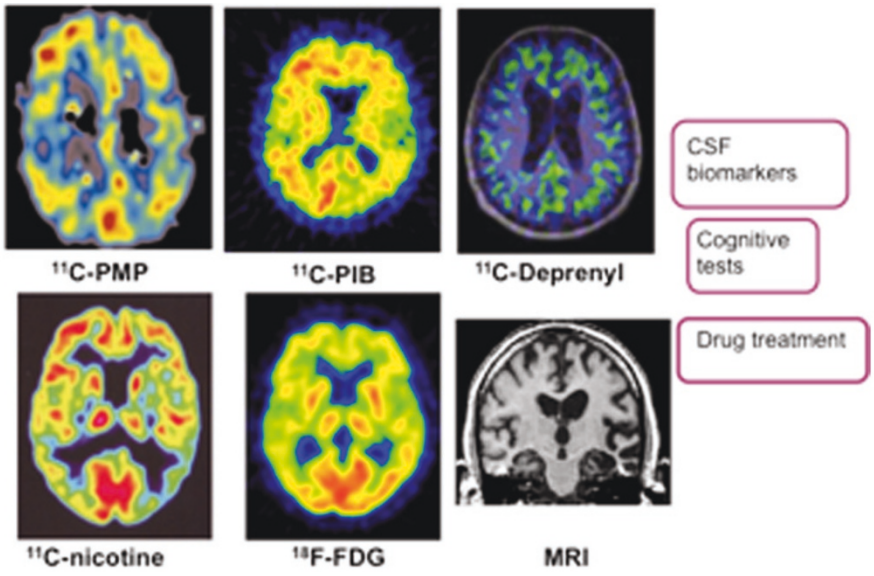

Figure 4. Multi-tracer positron emission tomography concept to study pathological and functional processes in the brain. Multi-positron emission tomography tracer concept applied in drug trials combined with atrophy studies (magnetic resonance imaging (MRI)), cerebrospinal fluid (CSF) biomarkers and cognitive testing. ^{11}C-PMP, acetylcholinesterase; ^{11}C-PIB, amyloid; ^{11}C-deprenyl, astrocytosis; ^{11}C-nicotine, nicotinic receptors; ^{18}F-FDG, 2-[^{18}F]-fluoro-2-deoxy-D-glucose metabolism. Red, high activity; yellow, medium activity; blue, low activity.

of acetylcholinesterase in the brain, the number of nicotinic receptors, rCMRglc and clinical outcome of treatment measured as attentional test performances [78-82]. To evaluate the effect of new disease-modifying therapeutics, imaging of fibrillar amyloid, activated microglia, astrocytosis, tau in addition to rCMRglc and structural brain changes should be applied to determine whether anti-amyloid strategies may clear the amyloid plaques from the brain but also slow down disease progression. A few PET studies in AD patients have shown reduction of brain Aβ measured by ^{11}C-PIB following anti-amyloid treatment [81,83,84] but the disease-modifying effects still have to be proven.

Abbreviations

Aβ, amyloid beta; AD, Alzheimer's disease; ^{11}C-DED, *N*-[^{11}C-methyl]-L-deuterodeprenyl; ^{11}C-PIB, Pittsburgh Compound B; CSF, cerebrospinal fluid; ^{18}F-FDG, 2-[^{18}F]-fluoro-2-deoxy-D-glucose; MCI, mild cognitive impairment; PET, positron emission tomography; rCMRglc, regional cerebral glucose metabolism.

Competing interests

AN is an investigator in clinical trials sponsored by Novartis AB, Jansen-Cilag, Torrey Pines Therapeutics, GSK, Wyeth and Bayer; served on an advisory board for Elan, Pfizer, GSK, Novartis AB, Lundbeck AB, and GE Health Care; served on an advisory board for Elan, Pfizer, GSK, Novartis AB, Lundbeck AB, Merck and GE Health Care; received honorarium for lectures from Novartis AB, Pfizer, Jansen-Cilag, Merck AB, Ely Lilly and Bayer; and received research grants from Novartis AB, Pfizer, GE Health Care and Johnson & Johnson.

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