Review

Molecular imaging in neurodegenerative forms of dementia

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SUMMARY: *Cognitive dysfunction and dementia are a common consequence of several types of neurodegenerative disorders. Yet, there are numerous challenges in the differential diagnosis of neurodegenerative forms of dementia, which have hampered the successful implementation of clinical trials and development of new disease-modifying therapies. One of the main issues is represented by patients' heterogeneity at different levels, from the molecular and pathological aspects, to the presentation of overlapping and often mixed clinical phenotypes and syndromes. Different molecular brain imaging techniques such as PET or SPECT represent important diagnostic tools for investigating and tracking the brain pathological changes in neurodegenerative disorders leading to dementia. Molecular imaging also promises to revolutionize our understanding of the complex and often shared pathological pathways underlying different neurodegenerative forms of dementia and to disentangle the clinical phenotypes via neurobiologically meaningful biomarkers. I review the most important, significant, and up-to-date results from molecular imaging research (PET and SPECT studies) in neurodegenerative forms of dementia including amnestic Alzheimer's disease, its prodromal stage of mild cognitive impairment, atypical forms of Alzheimer's disease, frontotemporal lobar degeneration syndromes, Parkinson disease with cognitive impairment, and dementia with Lewy bodies. Overall, past and more recent research has clearly demonstrated the value of using molecular imaging techniques to guide the differential diagnosis in neurodegenerative forms of dementia. Future studies should assess the potential utility of molecular imaging to empower clinical trials via unravelling the patient-specific pathological and clinical heterogeneity.*

KEY WORDS: *Alzheimer's disease, Frontotemporal dementia, Parkinson's disease, PET, Neurodegeneration, SPECT.*

INTRODUCTION

Dementia can be caused by several different forms of neurodegenerative conditions which cause irreversible and progressive dying of the neurons in the central nervous system[4,49,59]. These syndromes usually affect elderly people, although in some cases (e.g., genetic forms) young adults can suffer from devastating forms of dementia driven by neurodegenerative disorders[8]. Although classified as distinct diseases, the clinical presentation and underlying molecular etio-pathogenesis can overlap in apparently different disorders including Alzheimer's disease, frontotemporal dementia, and Parkinson's disease[5]. The complexity of the clinical spectrum in these diseases and the multifaceted nature of the underlying pathology makes sometimes the differential diagnosis amongst these neurodegenerative disorders difficult[7].

Novel and established molecular imaging techniques have thus the potential to guide the clinical diagnosis

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Progress in Neuroscience 2019; 4 (1-4): 41-52. *ISSN: 2240-5127*
doi: 10.14588/PiN.2019.Passamonti.41

LIST OF ACRONYMS AND ABBREVIATIONS: **3R/4R** = 3 repeat/4 repeat (tau); **1C-PiB** = 11C-labeled Pittsburgh compound-B; **AD** = Alzheiemer's Disease; **ALS** = Amyotrophic Lateral Sclerosis; **APP** = Amyloid Precursor Protein; **bvFTD** = behavioural variant of the FrontoTemporal Dementia; **CBD** = Cortico-Basal Degeneration; **CBS** = Cortico-Basal Syndrome; **DAT** = Dopamine transporter; **DLB** = Dementia with Lewy Bodies; **FDG** = Fluoro-Dexosi-Glucose; **FTLD** = FrontoTemporal Lobar Degeneration; **lvPPA** = logopenic variant of primary progressive aphasia; **MCI** = Mild Cognitive Impairment; **MRI** = Magnetic Resonance Imaging; **PCA** = Posterior Cortical Atrophy; **PD** = Parkinson Disease; **PDD** = Parkinson Disease Dementia; **PET** = Positron Emission Tomography; **PNFA** = Progressive Non-Fluent Aphasia; **PPA** = Primary Progressive Aphasia; **PS1** = PreSenilin 1; **PS2** = PreSenilin 2; **PSP** = Progressive Supranuclear Palsy; **SPECT** = Single Photon Emission Computed Tomography; **TDP-43** = TAR DNA-binding protein 43.

and in some circumstances can offer new insights into the etio-pathogenesis of these conditions[36,63]. A promising and emerging application of molecular imaging is also that of providing reliable biomarkers that can be employed to stratify patients in clinical trial to provide objective assessment tools to track the disease evolution and the potential utility of new treatments, even before an effect detectable at the clinical level[36,63]. Patient heterogeneity in molecular, pathological, and clinical terms is usually high and it is one of the main drivers of null results in clinical trials. Stratifying single patients via the use of neuro-imaging techniques that characterize the degree of their pathological complexity and heterogeneity holds the promise of empowering clinical trials that aim at halting or reverting the devastating effects of neurodegenerative disorders.

☐ ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

❐ Typical forms of Alzheimer's disease

Alzheimer's disease and its prodromal stage of mild cognitive impairment are the most common neuro-degenerative forms of dementia, which affect around 53 millions of people around the world in 2018. It has also been estimated that every 65 seconds someone in the USA develops Alzheimer's disease[2].

The typical age of onset of AD is around 65-70 years and the most commonly reported symptoms in the typical form of AD are represented by episodic memory deficits[22]. In less typical forms of AD language and semantic impairment, as well as prominent problem in executive functions have been reported[22]. Although the current criteria for the diagnosis of AD are inherently clinical in nature[49], there are continuous attempts to develop reliable diagnostic tools for an early diagnosis of AD. This is particularly true for the complex clinical spectrum of MCI which in some cases (around 10-15%) covert into AD in around 4.5 years[43].

The AD's spectrum of disorders has two molecular hallmarks that can be assessed via advanced molecular imaging techniques: the amyloid burden and the presence of the abnormal accumulation of the tau protein[66]. Hyper-phosphorylated tau contributes to form the characteristic neurofibrillary tangles observed *post mortem* in AD[66]. The causal links between amyloid deposition, abnormal tau accumulation, and neurodegeneration are not fully resolved, although the progression of the neuronal dying follows a specific pattern that is described in the Braak staging system[11]. In early forms of AD, the cellular loss is localized to the medial temporal regions including the amygdala, hippocampus, entorhinal, and para-hippocampal cortex[11]. This neurodegenerative pattern also explains the early presence of episodic memory impairments. More recent studies have extended the early stages of AD to include other sub-cortical regions and brainstem areas such as the basal forebrain nuclei and the locus coeruleus, in which early signs of AD-related pathological changes can be detected even before damage to the medial temporal lobe system[3].

The next stage in the pathological and clinical progression of AD is represented by the involvement of the neocortex, in particular the posterior regions such as the temporo-parietal cortex[11]. The primary sensory/motor regions such as the visual cortex remain relatively spared from the AD-related neuro-degenerative processes even at relatively late stages of the disease[66]. One of the main challenges of the molecular imaging in AD and related disorders is to tackle its molecular and clinical heterogeneity to provide reliable measures that quantify the degree of amyloid and tau pathology. These measures could be used to personalize new disease-modifying treatment that target the amyloid and/or tau burden.

❐ Atypical forms of Alzheimer's disease

A relatively small proportion (around 5%) of patients with AD display an early-onset of the disease (before 65 years of age)[8]. In these cases, genetic mutations in

the APP, presenilin (PS1 or PS2) gene can be detected[8]. The clinical spectrum of these inherited conditions can vary, although they tend to share the classic AD pathological features at the post-mortem level (amyloid plaques, neurofibrillary tangles)[22].
Another form of atypical AD is represented by the PCA[14]. Although the post-mortem characteristics of PCA highly resemble those of AD pathology, at the phenotypic and clinical level the predominant syndrome is characterized by severe deficits in visuo-spatial skills, difficulty in orientation, and constructional apraxia[14].
The logopenic variant (or logopenic aphasia) is part of the PPA spectrum of diseases which spans clinical and pathological features with the frontotemporal lobar degeneration syndromes as well as AD[28]. The main clinical features of AD-related forms of logopenic aphasia are the presence of impaired word retrieval and sentence repetition in the absence of motor speech abnormalities or agrammatism[28].
AD-related pathology can also lead to parkinsonian disorders such as the CBS, a complex and pathologically heterogeneous condition which can be caused by AD or frontotemporal related pathology[27]. At the clinical level, patients with CBS often display a parkinsonian syndrome which is associated with cortical deficits including apraxia, speech disorders (agrammatism, progressive non-fluent aphasia), alien limb features, and sensory cortical loss (astereognosis and agraphesthesia)[27]. The CBS cases with underlying AD pathology are not distinguishable from those affected by FTD-related pathological changes[27]. This is thus a condition in which the molecular imaging plays a fundamental role for the differential diagnosis of the underlying pathological causes of this neurodegenerative disorder.

☐ MOLECULAR IMAGING IN ALZHEIMER'S DISEASE AND RELATED DISORDERS

❒ Fluoro-Dexosi-Glucose positron emission tomography

In the past, one of the most widely used molecular imaging techniques to assess patients with AD-related disorders has been represented by the FDG PET imaging. FDG PET assesses the degree of regional glucose metabolism and consequently is an indirect measure of perfusion, brain atrophy, and function. FDG PET studies in AD have consistently demonstrated abnormal decrease in the glucose metabolism in posterior regions including temporo-parietal cortices, posterior cingulate cortex, and medial temporal lobe regions such as the amygdala and hippocampus[12,37,50]. Longitudinal studies using FDG PET have also found that AD progression is related to decline in glucose metabolism in posterior cortical regions, consistently with the clinical syndrome of AD[1,67]. FDG PET imaging has also been valuable in demonstrating significant changes in metabolism in elderly individuals at risk to develop AD due to genetic factors or the presence of mild cognitive impairment[67]. The main limitation of the use of FDG PET in assessing AD-pathology is constituted by its inability to distinguish the effect of regional atrophy or vascular changes over and above the metabolic effects. FDG PET is also not suited to quantify the underlying molecular pathology of AD, namely amyloid deposition and tau burden.

❒ Amyloid PET tracer

The ^{11}CPiB PET tracer has revolutionized the molecular imaging of AD and has allowed to track for the first time *in vivo* a critical pathological aspect of AD[30,35]. As expected from post-mortem research, patients with AD and some forms of MCI which are likely to convert to AD, display increased binding of the ^{11}CPiB PET tracer in several brain regions including the frontal, temporal, and parietal lobes[20]. The ability of the ^{11}CPiB PET tracer to identify AD pathology is elevated and around 96% of the AD patients are found to display positive ^{11}CPiB PET scan[33]. Even more importantly, longitudinal studies using ^{11}CPiB PET have revealed that MCI patients with positive ^{11}CPiB PET scan are more likely to convert to AD[16]. Likewise, individuals at high risk of developing AD due to genetic mutations show increased amyloid burden with ^{11}CPiB PET[61]. However, the ^{11}CPiB PET has shown limited ability to characterize the phenotypic complexity in AD[54]. In other words, there is poor correlation between the ^{11}CPiB PET signal and the clinical disorder of AD, in terms of localization of the clinical syndromes and in terms of regional deficits in glucose metabolism[54]. In other words, the amyloid burden that is quantified by the ^{11}CPiB PET tracer can be diffused or scattered to several regions of the brain, even those which might not have immediate clinical relevance at the

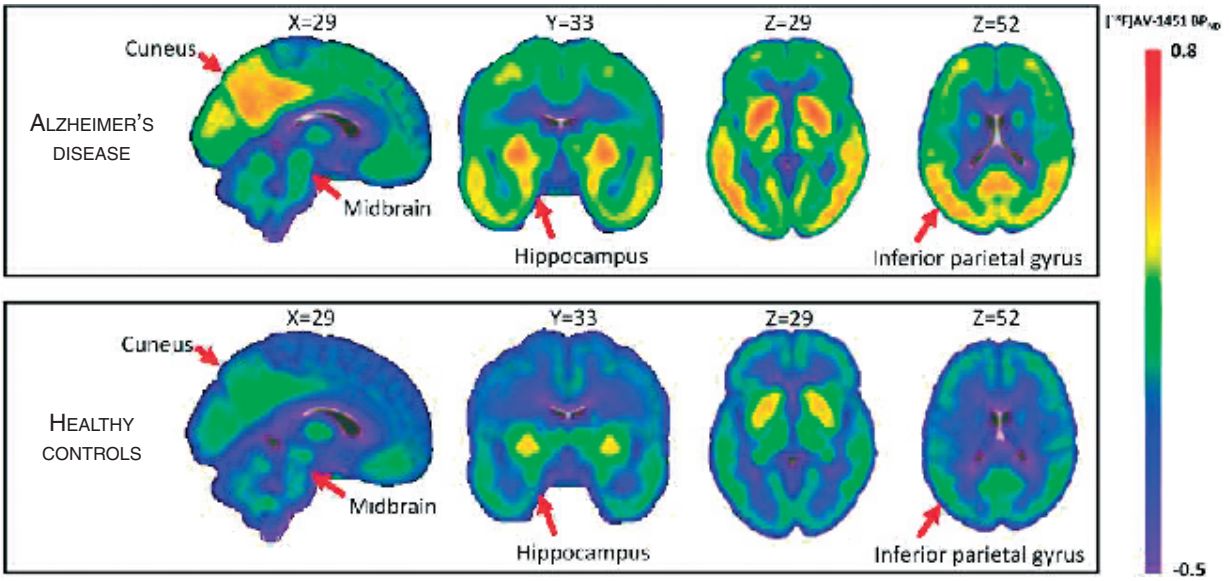

Figure 1. Mean [18F]AV-1451 positron emission tomography map in each group. Note the overall high [18F]AV-1451 binding in the basal ganglia in both groups including controls. Patients with Alzheimer's disease pathology showed increased [18F]AV-1451 binding in the medial temporal lobe regions and other cortical areas, relative to controls[65].

symptomatologic and clinical level[54]. The correlation between the amyloid burden detected via 11CPiB PET tracer and glucose hypometabolism, brain atrophy, and disease progression is also modest[54].

❒ Tau PET tracers

More recently, new and promising compounds, which bind to the tau protein, have been developed. These include 11C-PBB3; 18F-AV-1451 (or "flortaucipir", previously known as T807), and the "THK" group including 18F-THK523, 18F-THK5105, and 18F-THK535[47]. All these ligands have shown a good ability to tack the pathological accumulation of the tau protein in AD and have been able to detect the typical AD evolution described in the Braak staging system[71] (Figure 1). The advent of tau imaging in AD therefore represents an important milestone for the development of new disease-modifying clinical trials that aim at targeting the tau protein[71]. The novel tau tracers show good clinico-pathological correlations and are able to discriminate amongst the less typical form of AD syndromes including PCA, logopenic variant of AD, and CBS[72]. There is also evidence that tau PET tracers are able to reveal the age-dependant accumulation of tau seen in elderly individuals and in monitoring the various stages of deposition of the tau described by Braak and Braak[46,65]. Nevertheless, there are limitations of these new PET tau tracer which are almost related to their 'off-target' binding properties[38]. Another issue regards the specificity of these tau tracers to different iso-forms of the tau protein[52]. This is an important issue as AD and non-AD dementia (e.g., FTLD syndromes) are characterized by different iso-forms of tau, namely the 3R and 4R[17]. More specifically AD-related tau accumulation is characterized by a 3R/4R mixture, while in FTLD syndromes, one isoform is usually prevalent over other ones[17]. The chemical complexity of the tau isoforms thus represents a challenge to characterize the tau burden in neurodegenerative disorders. Off-target binding to neuromelanin or iron-related components such as microhaemorrhagic lesions in the striatum or the choroid plexus have also been reported for some of the tau tracer[38]. A better understanding and characterization of the possible unspecific pattern of binding of these newly developed tau tracers is thus urgently warranted before these novel tools can be fully implemented in the clinical practice.

☐ FRONTOTEMPORAL LOBAR DEGENERATION

❒ Clinical spectrum of FTLD syndromes

The FTLD spectrum of disorders is an overarching

neurodegenerative condition that includes clinically heterogeneous diseases such as the PSP, CBD, PPA, and the bvFTD[13,28]. The clinical phenotypes of these conditions can be very variable although some behavioural features such as apathy, impulsivity, behavioural dys-inhibition tend to be present to a certain extend in all of these conditions, while the language disorders or the severe parkinsonism and balance problems tend to be more evident in the PPA and PSP, respectively[13,28]. As discussed before, around 1/3 of the cases with CBS display AD-related pathology while the remaining part are caused by FTLD-related pathology[27]. At the molecular level, the FTLD disorders is highly heterogenous and in many cases the pathology overlaps across the clinical spectrum[41].

The bvFTD is most often caused by tau pathology such as that observed in Pick's disease, although abnormal accumulation of the TDP-43 can also be a feature[41]. Patients with bvFTD have highly significant behavioural problems including severe personality changes, abnormal appetite, and obsessive compulsive symptoms[58,68].

Some cases of with bvFTD also display motor neuron diseases resembling ALS[6]. At the post-mortem level, TDP-43 pathology is present while genetically there is an high rate of mutation in the C09orf72 gene, which is hypothesized to play a key role in intra-cellular membrane traffic including exocytosis and endocytosis[32].

The PPA syndrome is divided in three forms (i.e., semantic dementia, PNFA, and logopenic aphasia), two of which are caused by FTLD-related pathology (semantic dementia and PNFA) and one of which by AD-related pathology (logopenic aphasia)[24]. At the clinical level the semantic form of PPA is characterized by anomia, deficits in single words comprehension, and only later in the course of the disease by behavioural features similar to those described in the bvFTD[24]. Of note, the majority of the cases of patients with semantic dementia show pathological accumulation of the TDP-43 protein, although rare cases witch Pick's related tau pathology have been reported[29].

PNFA's clinical picture is characterized by non-fluent aphasia, apraxia of speech, and agrammatism with no problems in sentence repetition or understanding[24]. Pathologically, PNFA can be caused by tau or TDP-43 pathology[25].

❒ Molecular imaging in FTLD syndromes

■ **FDG and amyloid PET tracer.** Given the molecular, pathological, and clinical complexity of FTLD syndromes there are at the moment limited molecular imaging studies and consequently few assessment tools to tackle the heterogeneity of the pathologies underlying FTLD syndromes. Despite these limitations, FDG PET studies have consistently found that the glucose metabolism is significantly reduced in patients with FTLD syndromes especially in fronto-temporal cortices[21]. More specifically, patients with logopenic aphasia due to AD have been reported to show reduced FDG metabolism in the left temporo-parietal areas[42] (Figure 2). A high rate of positivity at the amyloid PET in these patients also confirmed *in vivo* the underlying AD-related pathology[48]. On the opposite side, patients with the bvFTD variant have been found to have reduced FDG metabolism in the prefrontal cortex, consistently with their clinical syndrome of disinhibition and behavioural dysregulation[15].

FDG PET is also able to identify the functional neuroanatomy in semantic dementia by showing reduced glucose metabolism in the left anterior temporal pole, a key 'hub' region involved in semantic knowledge[34]. Furthermore, patients with semantic dementia typically show negative amyloid PET scan, which is consistent with their underlying pathology (TDP-43 accumulation)[70]. Likewise, patients with progressive non-fluent aphasia show reduced FDG metabolism in the left anterior insula[51]. In some of the cases of patients with PNFA (10%), amyloid positivity has been detected which emphasizes the molecular complexity of the FTLD clinical phenotype[64]. For those cases of patients with FTD and motor neuron disease, FDG PET is able to reveal hypometabolic patterns that encompass the frontal and temporal lobes[31].

To summarize, FDG PET in FTLD syndromes is capable of characterizing the clinical spectrum of FTLD, although, similarly to AD-related disorders, FDG PET is not able to discriminate between regional atrophy and metabolic effects, which remains the main limitation of this technique. Discriminating AD from FTLD could also be challenging with FDG PET especially in those cases in which the clinical symptoms overlap. In this context, the ^{11}CPiB PET tracer can

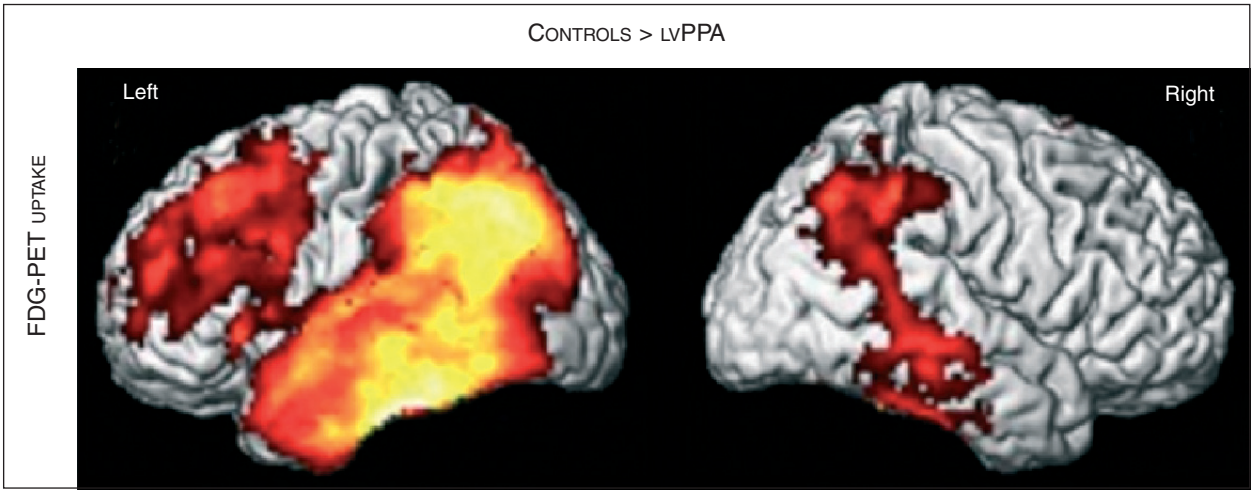

Figure 2. Patients with the logopenic variant of primary progressive aphasia due to Alzheimer's disease pathology show reduced FDG-PET binding (reflecting decreased glucose metabolism) in temporo-parietal regions, especially in the left hemisphere[42]. Legenda: L = left; R = right;

play an important role. Even in some tertiary centres, there is still a rate ranging between 10% to 40% of misdiagnosis between AD and FTLD syndromes but new techniques combing FDG PET and MRI have shown that it is possible to achieve an accuracy of up to 92% in the differential diagnosis between FTLD syndromes and AD[15] (Figure 3). The use of ^{11}CPiB PET tracer can help differentiating between AD and FTLD, although some studies have reported a low rate (9-10%) of PiB positivity in small series of FTLD cases, depending on the clinical phenotype[64]. In any case, a recent study in n = 62 AD patients and n = 45 FTLD cases showed that the sensitivity of PiB in discriminating between the diagnoses was higher than FDG PET (89.5% *vs* 77.5%), although both techniques showed comparable specificity (83% *vs* 84%)[60].

- **TAU TRACERS.** There is accumulating evidence that tau tracers such as C-PPP3 bind to tau inclusion in post-mortem tissue from patients with PSP or CBD. However, there are also data showing that another commonly used tau tracer such as AV-1451 display significant 'off-target' binding to neuromelanin, and iron-related components which have not been fully resolved[38]. *Post-mortem* studies also found that although AV-1451 specifically binds to AD-related tau pathology, there is little binding of the same tracer to non-AD tau pathology as that observed in FTLD syndromes[44]. Other recent study confirmed the strong AD-related binding of the AV-1451 PET ligand and reported only moderate binding of the same compound to pathological tissue from patients with FTLD syndromes including CBD and PSP[45]. Nonetheless, my recent research was able to demonstrate that AV-1451 PET is able to discriminate between two clinically very different types of tauopathies, namely AD and PSP[17]. There is also evidence that AV-1451 PET binding recapitulates the pathological hallmarks seen in FTLD syndromes and in genetic carriers of mutations linked to FTLD syndromes[9-10]. Hence, despite the off-target binding the regional specificity offered by the AV-1451 PET tau imaging might still provide valuable information to help the differential diagnosis between AD-related and FTLD syndromes over and above the presence of off-target binding[17].

☐ PARKINSON'S DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES

❒ CLINICAL SPECTRUM OF PDD AND DLNB

Parkinson's disease with dementia and dementia with Lewy bodies are two linked parkinsonian syndromes caused by the abnormal accumulation of the alfa-synuclein protein which can be identified in the Lewy-bodies, the characteristic pathological hallmark of PD and DLB[69]. The boundaries between PDD and DLB are not well defined, although at the clinical level the

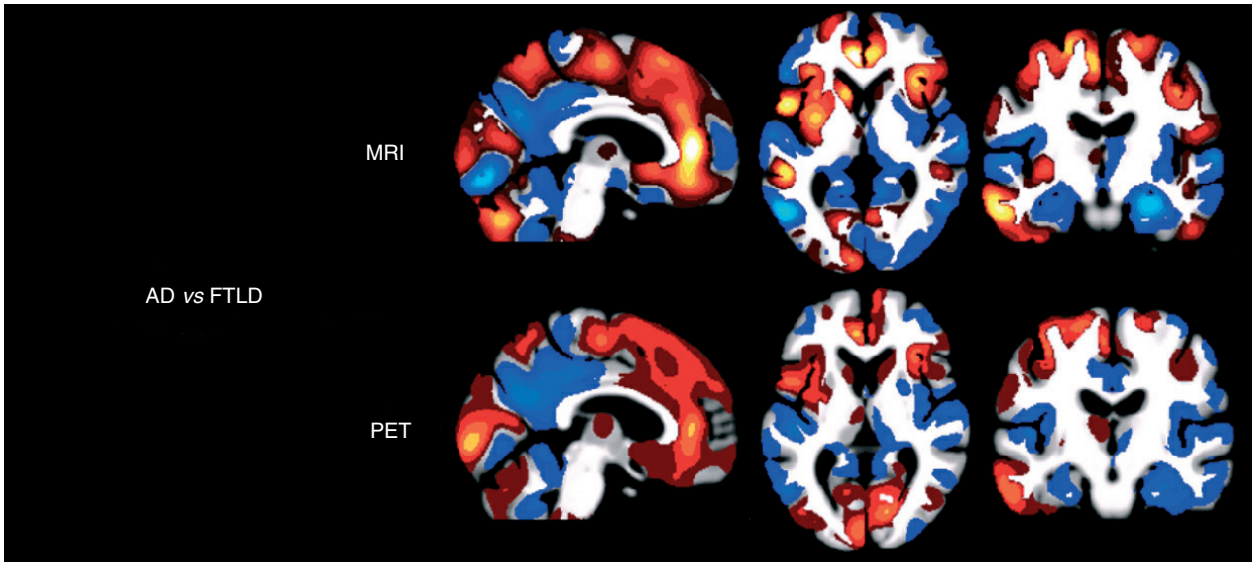

Figure 3. The combined use of MRI and PET with the FDG-PET radioligand provided the highest accuracy for detection and discrimination of patients with AD relative to those with FTLD. The regions in red are the most discriminative for FTLD patients, while the blue regions are the most discriminative for AD patients in terms of MRI and PET signal.

presence of early cognitive symptoms (including visual hallucinations) is recognized as an important clinical discriminant between DLB and PDD, in which the cognitive symptoms typically develop later in the course of the disease and usually after the full manifestation of the motor disorder[39]. A part for the temporal evolution of the cognitive problems in PDD and DLB, the clinical features of these disorders are highly overlapping. It has been estimated that up to 70% of patients with Parkinson's disease develop at a certain stage of their disease trajectory some cognitive dysfunctions. Typical cognitive problems include visual hallucinations, deficits in visuo-spatial skills, impairments in executive functions such as attention or working-memory, and speech difficulty (e.g., reduced verbal fluency). At the pathological level, PDD and DLB can also be characterized by amyloid accumulation and more recently the potential presence of tau pathology in PDD and DLB has also been recognized[19]. This implies that the complexity of the molecular pathophysiology in PDD and DLB can span over other common neurodegenerative disorders including AD and FTLD syndromes. The lack of clear clinical and pathological 'borders' across PDD, DLB, AD, and FTLD syndromes represents thus a diagnostic challenge which will become even more pronounced when new therapeutic options targeting different molecular pathways will be available for these conditions[19].

❒ Molecular imaging in PDD and DLB

Consistently with the clinical spectrum of these disorders, past SPECT and FDG PET studies have reported decreased perfusion and glucose metabolism in posterior cortical regions in PDD and DLB[56]. These regions include the occipital and temporo-parietal regions as well as the basal ganglia, cerebellum, and frontal cortices[56]. Interestingly, there was a relative sparing of the medial temporal lobe areas in terms of FDG PET metabolism which is in keeping with the less pronounced episodic memory problems displayed by these patients especially when compared to those with AD[56]. Decreased FDG PET metabolism in posterior visual cortices also related to frequency and severity of visual hallucinations which supports the clinical utility of FDG PET in tracking the symptomatology of PPD and DLB[18]. Likewise, decreased SPECT DAT binding in the basal ganglia has been found to correlate with cognitive symptoms in patients with PDD and DLB, while reduced dopaminergic transporter binding in the putamen was found to relate to the severity of motor problems[62].
Around 40% of patients with DLB have also been found to display positive amyloid PET scan[23] (Figure 4). The specificity of the positivity of the amyloid scan for cognitive problems in DLB is further corroborated by the fact that PD without dementia show a less significant binding of the ^{11}CPiB PET

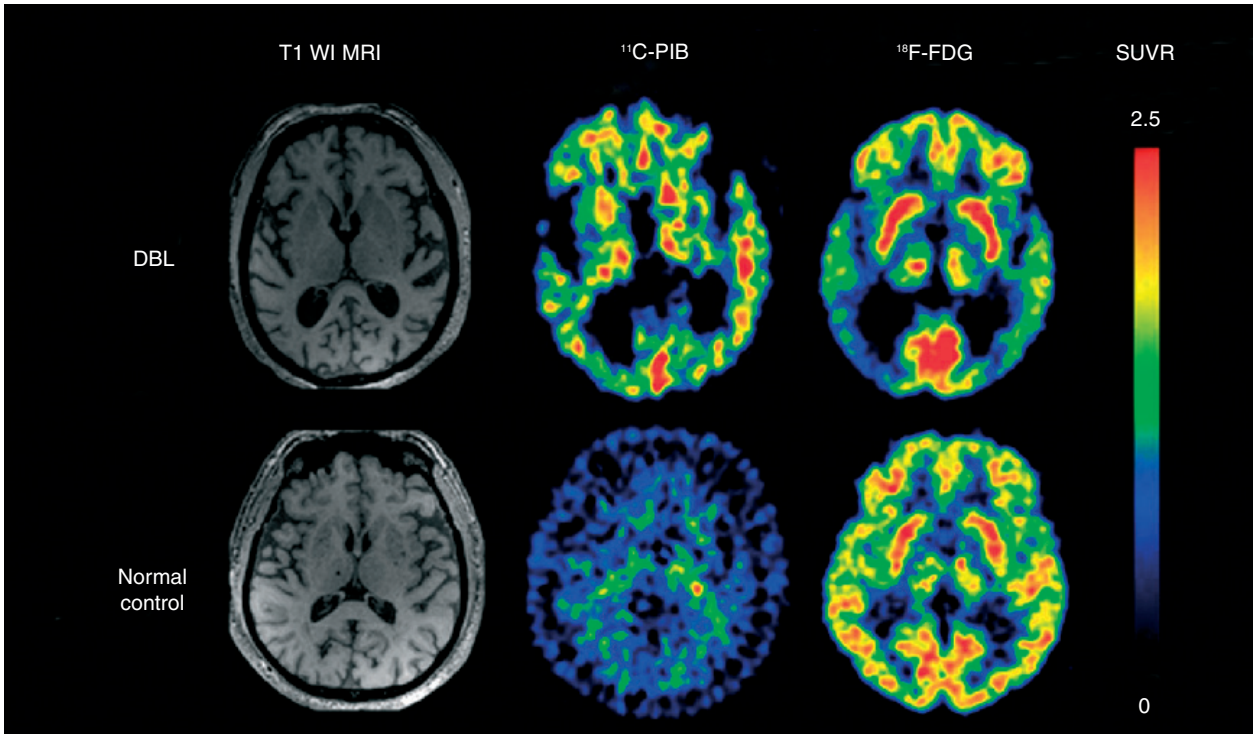

Figure 4. Structural MRI, amyloid (^{11}C-PIB) and FDG PET scan in a patients with dementia with Lewy bodies relative to a normal control. While the MRI scan do not show prominent changes the amyloid and glucose metabolism PET scans are able to show amyloid accumulation in the DLB patient and reduced glucose metabolism in occipito-parietal regions which is consistent with the clinical syndrome (*Modified from Liu et al., 2018*[40]).

tracer[57]. While new PET tracers for the main pathological hallmark of PDD and DLB (alpha-synuclein) remain under-develop, some recent studies have shown that PET tau tracers such as AV-1451 might have some clinical utility in detecting the typical neurodegeneration in the substantia nigra that characterize these disorders[68]. Although this effect seems to be dependent on the 'off-target' binding properties of the AV-1451 tracer (i.e., 'off-target' binding to neuromelanin)[26]; it might be possible that the AV-1451 tracer may still offer some useful information and insight to help developing new in vivo biomarkers for PDD and DLB[26].

☐ MOLECULAR IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF NEURODEGENERATIVE FORMS OF DEMENTIA

As highlighted several times throughout this review, the presence of overlapping clinical and pathological features in the neurodegenerative disorders that lead to dementia syndromes poses a challenge to the differential diagnosis amongst these conditions and inevitably confound the patient selection in clinical trials targeting distinct molecular pathways.

A promising way of addressing and tackling such complexity is to use advanced and novel molecular imaging biomarkers that can reliably quantify *in vivo* the specific pathological changes associated with different neurodegenerative disorders.

In the near future, I envisage the use of biomarkers like PET with amyloid and/or tau tracer to provide a good discrimination between AD-related and FTLD-related syndromes. Atypical forms of AD including patients with cortico-basal syndrome will be better characterized by the combined use of tau and amyloid tracers. The use of well-established markers of nigro-striatal degeneration (DAT SPECT) or glucose metabolism (FDG PET) remains invaluable to characterize the presence of dopaminergic deficits and areas of hypometabolism and to complement the more novel PET biomarkers. Due to space limitations, this review does not describe the attempts and effort to validate other important neuroimaging

measures in dementia and neurodegenerative disorders, including structural and functional MRI. These techniques are less expensive and less invasive alternatives of PET and SPECT biomarkers and are more indicated to assess the level of atrophy and functionally-relevant effects of the neurodegenerative processes. In the future it is possible that new and multi-modal markers will be develop by integrating large arrays of measures including clinical, MRI-based, and molecular imaging-derived biomarkers. This highly complex set of data holds the promise of providing a more powerful characterization of the patient's specific clinical, pathological, and brain features that would enable the development of personalized therapies alongside individualized health care for improved prognostication, therapies, and clinical management. Sophisticated algorithms based on machine learning approaches and artificial intelligence methods have been recently implemented in the revolutionary field of Precision Medicine applied to neurodegenerative conditions, although their utility in the everyday clinical practice remains to be ascertained and fully tested[53].

□ CONCLUSION

Molecular imaging studies in neurodegenerative conditions leading to dementia are highly informative regarding the clinical, pathological, and brain features underpinning an overlapping group of clinical disorders. Advanced imaging techniques hold the promise to improve the differential diagnosis across these conditions and can be helpful to track the disease progression or monitor the potential effects of disease-modifying therapies. An improved stratification of patients based on objective and reliable measures that are able to quantify the molecular complexity of each neurodegenerative disorder is urgently needed to de-risk and empower upcoming clinical trials.

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Disclosure. *The Author declare no conflicts of interest.*