Wydawnictwo UR 2024
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2024.1.20

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2024; 22 (1): 201–221

REVIEW PAPER

PET and SPECT imaging as a solid guide to detect and discriminate atypical phenotypes of neurodegenerative disorders

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ABSTRACT

Introduction and aim. Atypical or mixed presentations of neurodegenerative disorders may postpone or confound the final diagnosis. Molecular imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) radioligands provide target-specific information and may anticipate the diagnosis by "in vivo" detection of the neuropathological substrate, as Aβ deposition, nigrostriatal dopaminergic depletion or tau inclusions. This concise review will discuss the potential of PET and SPECT imaging as a solid guide to better characterize atypical phenotypes of neurodegeneration in the clinical routine, with the potential to drive personalized interventions, improve cohort uniformity for clinical trials, and serve as biomarkers for targeted molecular therapies.

Material and methods. Literature search was performed focusing on the role of PET and SPECT imaging in assessing atypical phenotypes of neurodegeneration, using the electronic source of database PubMed/MEDLINE and the web-based search engines Google, Google Scholar.

Analysis of the literature. New disease-modifying drugs may increase their effect with early initiation, which is especially important in working persons and younger subjects presenting atypical symptoms. In older individuals, the coexistence of neurodegeneration, age-related changes, cerebrovascular lesions, or depression makes challenging a definitive diagnosis.
Quantitative tools able to measure tracer distribution increase the accuracy of molecular neuroimaging creating topographic maps that compare subject's data with healthy controls databases.

Conclusion. Atypical phenotypes may be associated with quantitative key-pattern allowing a more precise and early diagnosis of the neurodegenerative disorder. Finally, quantitative assessment of the pathological substrates allows us to track the disease process and measure treatment response.

Keywords. atypical phenotypes, neurodegenerative diseases, positron emission tomography, single photon emission computed tomography

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Received: 2.10.2023 / Revised: 1.12.2023 / Accepted: 7.12.2023 / Published: 30.03.2024

Ruffini L, Zilioli A, Cervati V, et al. PET and SPECT imaging as a solid guide to detect and discriminate atypical phenotypes of neurodegenerative disorders. *Eur J Clin Exp Med.* 2024;22(1):201–221. doi: 10.15584/ejcem.2024.1.20.

Introduction

Neurodegeneration is the leading cause of cognitive and physical disability across the globe with an increasing economic burden for patient families and healthcare systems.

According to the latest report by the World Health Organization, the global prevalence of dementia stands at over 55 million individuals, with a yearly increase of nearly 10 million cases.[1]

In the prodromal stage neurodegenerative disorders (Nds) can debut with a continuum of non-specific symptoms and signs postponing a correct diagnosis.[2]

Overlapping symptoms and comorbidities in different diseases may be confounding, especially at an early stage, and makes critical the time-opportunity for new disease-modifying treatments.[3-8]

The clinical phenotype can be the result of multiple different neuropathologies that synergically explain their detrimental role, as it happens in Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and Parkinson-dementia, typically defined by specific complex protein abnormalities, as amyloidoses, α-synucleinopathies, tauopathies, and transactivation response DNA binding protein 43 (TDP-43) proteinopathies. Their presence, conformation and anatomical distribution represent the major hallmark of histopathological diagnosis.[9,10]

The spreading of pathological protein deposition along disease-specific vulnerable neural networks can explain progression and may be associated with specific cognitive phenotype.[11]

Therefore, improving the pathophysiological understanding of the neurodegenerative process allows the development of targeted treatments and disease prevention strategies, while non-pharmacological interventions, such as brain training and physical rehabilitation techniques, may represent potential add-on treatments.

Much effort is currently spent in translational research to develop disease biomarkers that enable early diagnosis, identify subclinical progression, and monitor treatment.

Additionally, studies on the mechanism underlying neurodegeneration move from clinicopathological data to connectome disruption, even suggesting that brain functional connectivity abnormalities might provide "in vivo" signature of molecular pathology.[12]

In a context of such great heterogeneity, the need for precise biological biomarkers is continuously growing and molecular imaging is playing a progressively leading role in the "in vivo" investigation of neurodegeneration. Indeed, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can visualize and measure the pathophysiological processes in the living brain using selective radioligands as imaging probes. PET and SPECT provide target-specific information that can identify distinct patterns related to neuropathological substrates and quantify the rates of the biological processes.

Aim

This concise review will discuss the potential of PET and SPECT imaging as a solid guide for improved detection of atypical phenotypes of neurodegenerative disorders in the clinical routine, including speech difficulties, visual abnormalities, executive, behavioral, and motor functions.

The accuracy of clinical diagnosis remains insufficient and highly dependent on the clinician's experience and level of expertise and the follow-up duration, despite many efforts of experts in determining detailed clinical criteria for a correct diagnosis.[13]

Material and methods

Literature search was performed focusing on the role of PET and SPECT imaging in assessing atypical phenotypes of neurodegeneration, using the electronic source of database PubMed/MEDLINE and the web-based search engines Google, Google Scholar.

The following search algorithm was employed: (A) "atypical phenotypes" AND (B) " Alzheimer's disease " OR "Parkinson' disease" OR "dementia with Lewy bodies" OR "multiple system atrophy" OR "parkinsonism" OR "primary progressive aphasia" OR "corticobasal syndrome/degeneration" OR "progressive supranuclear palsy" OR "posterior cortical atrophy " OR "frontotemporal dementia" OR " amyotrophic lateral sclerosis" AND (C) "PET" OR "SPECT" OR "molecular imaging" OR "DaTscan" OR "FP-CIT" OR "MIBG" OR "amyloid-PET" OR "tau-PET" AND (D) "autopsy validation" OR "neuropathological correlation". The authors did not apply any restriction concerning the publication date. Moreover, the authors screened the bibliography of the included studies searching for additional suitable articles to improve the research. The literature search was lastly updated on September 2023.

Analysis of the literature

PET and SPECT images as quantitative biomarkers of neurodegeneration

PET is the most used technique for the characterization of neurodegeneration profiles, being able to assess neuron glucose consumption, beta-amyloid (Aβ) deposition, and dopamine neurotransmission.[14-16]

Most recently, tracers targeting tau inclusions in the brain have been entering the diagnostic roadmap providing better comprehension of neurodegenerative processes as well as radioligands for neuroinflammation and microglial activation.[17-19]

Dopamine system imaging has become a standard approach in patients with symptoms of dopaminergic neurodegeneration with SPECT radioligands assessing presynaptic (e.g. dopamine synthesis and storage, transporter density) or postsynaptic terminals (i.e. D2 receptors availability).[20]

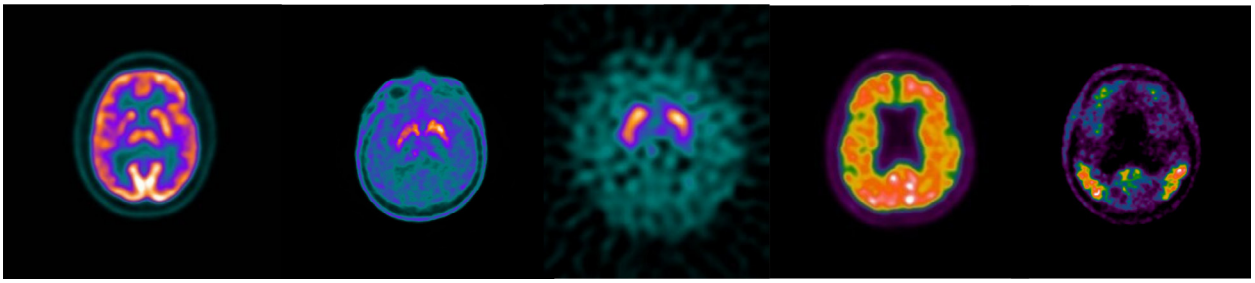


Fig. 1. Representative images of the most used molecular imaging techniques targeting the pathological substrates of neurodegeneration; from the left to the right: glucose consumption (PET with glucose analog [18F]FDG); presynaptic dopamine transporters function (SPECT with [123I]ioflupane also known as DaTscan); nigro-striate synthesis of dopamine (PET with [18F]DOPA); β-amyloid deposition (PET with [18F]flutemetamol); tau protein accumulation (PET with [18F]GTP1)

Highly specific imaging biomarkers and their multimodal combination (Fig. 1) increase diagnostic accuracy and may allow a better patient management, even more when additional symptoms, such as autonomic, pyramidal or cortical sensory disturbances, are present.[21,22]

The diagnosis of atypical variants with high sensitivity and specificity remains a challenge in the differential diagnosis of different neuropathologies. In the context of Alzheimer's disease it's critical to recognize patients with less common syndromes such as the logopenic variant of primary progressive aphasia (PPA) or corticobasal syndrome, because patients phenotypically similar have non-Alzheimer's pathology. On the other hand, the considerable overlap of signs and symptoms for parkinsonian syndromes makes clinical diagnosis challenging.

Extraction of quantifiable features from PET and SPECT images may provide a more precise selection of patients to be included in clinical trials for neurodegenerative diseases with a more aggressive course, as atypical parkinsonian syndromes, with the aim to enrich treatment trial eligibility for disease-specific therapies, such as anti-tau drugs for progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).

The imaging departments are even more frequently asked to assist neurologists and geriatricians in defining the underlying neuropathology of atypical symptoms in clinical and research settings.

Standardization of image acquisition and validation of the used radiotracers represent an ongoing critical challenge to obtain homogeneous and comparable data. The correlation of imaging measures with neuropathology may also improve the identification of at-risk patients and the detection of possible changes resulting from therapy. Therefore, relationships of PET and SPECT results with post-mortem measurements are critical for validating the sensitivity and specificity of imaging biomarkers across clinical phenotypes of neurodegeneration. In Table 1 autopsy validation studies of PET and SPECT imaging biomarkers are reported.[23-59]

To standardize imaging reporting, validated scoring systems have been implemented and visual assessment of PET images with amyloid tracers was the first step to stage amyloid deposition.[60,61] The regulatory authorities require a certified reader training specific for each radiotracer targeting β-amyloid.[60-62]

However, the need for a more precise analysis of regional tracer uptake, especially in the context of atypical patterns, pushed the development and clinical application of quantitative tools to assess biodistribution.

A commonly used approach is the region of interest (ROI)-based analysis with the standardized uptake value ratio (SUVR) calculation between the target regions and the reference region. Pons, whole cerebellum, cerebellar cortex, or cerebral white matter are used as reference regions as they are considered free from abnormal Aβ deposition.[63,64]

More recent methods include the Centiloid (CL) scale and the *z*-scores, both based on SUVR calculation, and magnetic resonance imaging (MRI)-independent indexes have been proposed for quantifying amyloid load across different tracers.[65-67]

Comparison of the subject's data with a database of healthy controls can be used to highlight areas with statistically significant alterations[68,69] and assessment of Z-scores defines the deviation of a sample with respect to the mean of a distribution. Thurfjell et al. demonstrated high concordance of amyloid imaging and an autopsy cohort using a threshold of z=2.0.[63] Z-scores may be calculated for composite cortical regions, individual regions, and at the voxel level obtaining maps due to the underlying statistical calculations (Z-maps) that improve pattern recognition accuracy and facilitate differential diagnosis.[69]

The growing use of quantitative evaluation of PET and SPECT scans in the clinical context increases the probability of reaching a conclusive diagnosis providing information on the extent and regional burden of the neuropathologic features.[70,71]

Objective data from quantification also enable an objective monitoring of the disease process and the biological mechanisms driving tracer accumulation.[64,72,73]

Finally, quantitative measures mainly support the nuclear medicine physician by increasing specificity and

Table 1. Autopsy validation studies of PET and SPECT imaging biomarkers of neurodegeneration*

Imaging biomarker	Tracer	Clinical spectrum	Reference list
Glucose consumption	[18F]FDG	AD/non-AD dementias	23
	[18F]FDG	AD vs FTD	24
	[18F]FDG	AD/non-AD dementias	25
	[18F]FDG	AD	26
	[18F]FDG	AD	27
	[18F]FDG	DLB vs AD	28
	[18F]FDG	DLB, AD, FTD	29
Aβ deposition	[18F]florbetapir	AD	30
	[18F]florbetapir	AD	31
	[18F]florbetaben	AD	32
	[18F]flutemetamol	AD	33
	[18F]flutemetamol	AD/non-AD dementias	34
	[18F]flutemetamol	AD	35
	[11C]-PIB	AD	36
	[11C]-PIB) vs [18F]FDG vs	AD/non-AD dementias	37
	[11C]-PIB	FTD	38
DAT binding	[123I]FP-CIT	DLB	39
	[123I]FP-CIT	DLB	40
	[123I]FP-CIT	DLB/AD	41
	[123I]FP-CIT + [1F]FDG	DLB	42
	[11C]Altropane + [11C]-PIB	DLB	43
	[123I]FP-CIT	CBD	44
	[123I]FP-CIT	DLB/other dementias	45
	[123I]FP-CIT	Parkinsonism (differential diagnosis)	46
	[123I]FP-CIT	MSA/PD	47
Postganglionic cardiac sympathetic denervation	[123I]MIBG	DLB	48
	[123I]MIBG	DLB	49
	[123I]MIBG	DLB	50
Tau accumulation	[18F]flortaucipir	AD	51
	[18F]flortaucipir + [18F] florbetapir	PPA	52
	[18F]flortaucipir	AD, CAA, PiD, PSP, CBD, FTLD-TDP-43, DLB, MSA, HC	53
	[18F]flortaucipir	AD/non-AD, primary tauopathies	54
	[18F]flortaucipir + 11C-PIB	FTD	55
	[18F]flortaucipir	AD/non-AD	56
	[18F]flortaucipir	AD/non-AD dementias	57
	[18F]flortaucipir	AD	58
	[18F]flortaucipir	AD	59

* AD – Alzheimer's disease, DLB – dementia with Lewy bodies, FTD – frontotemporal dementia, MSA – multiple system atrophy, PPA – primary progressive aphasia, PSP – progressive supranuclear palsy, CBD – corticobasal degeneration, PiD – Pick's disease, CAA – cerebral amyloid angiopathy, TDP-43 – frontotemporal lobe degeneration (FTLD)-transactive response DNA binding protein-43, HC – healthy control

diagnostic confidence in reading and interpreting brain scans.[74]

Development and validation of quantitative methods for brain molecular imaging is continuously ongoing even with the support of machine learning and deep learning algorithms.[75-79]

Clinical use of molecular imaging for atypical neurodegeneration

Precise discrimination of neurodegenerative diseases presenting with atypical phenotypes is still challenging in daily clinical practice, especially at the early stages of the disease, but accurate diagnosis is fundamental, because treatment and prognosis vary. Therefore, establishing imaging biomarkers is necessary for early detection and stratification of patients according to the underlying disease. A summary of distinct PET and SPECT imaging patterns of atypical phenotypes of neurodegeneration is reported in Table 2 and 3.[80-121]

The neurodegenerative cascade that accompanies amyloid deposition has been associated with multiple cerebral dysfunctions, mainly affecting executive, behavioral and motor abilities language and visual perception.

In a cause-and-effect relationship, it has been reported that amyloid burden precedes and induces metabolic changes, which could be highlighted by PET with the glucose analog [18F]Fluorodeoxyglucose (FDG) in the early stages of neurodegenerative diseases.[122] Moreover, a temporal ordering of amyloid β and tau lesions spread throughout the brain has been described in Alzheimer's disease, confirming that early accurate diagnosis may provide a window of opportunity for new treatments.[123]

In primary progressive aphasia amyloid-PET may help to predict the underlying neuropathology facilitating differential diagnosis of PPA subtypes, as in the case of the logopenic variant (lvPPA) most commonly associated with AD (Fig. 2a-b).

A recent systematic review of the literature has shown amyloid-PET positivity in 84.9% of lvPPA.[124] Interestingly, in the same study amyloid-PET showed positivity in 54.5% of unclassified PPA suggesting underlying Alzheimer's pathology.[124] On the other hand, PPA can remain isolated for years before the development of impairments in other domains suggesting neurodegeneration and, in these cases, classification of PPA variants may be challenging.

Compared to the amyloid-PET imaging, in which the site of deposition does not correlate with aphasic deficits in terms of topographic correspondence, uptake patterns of tau-PET differ across the PPA variants,[93] allowing differentiation of overlapping clinical profiles.[86]

Moreover, tau-PET burden provides a spatial relationship with cortical regional thickness, showing a greater engagement of the left hemisphere in the majority of patients due to the more common left-lateralized language networks.[87]

Clustering analysis of metabolic images from FDG-PET has been recently used to classify more PPA subtypes than the current recognized ones (non-fluent, semantic, and logopenic PPA) with distinct neuroimaging characteristics and more predictive of clinical course, splitting non-fluent variant into three subtypes, and lvPPA into two subtypes.[91]

Table 2. Summary of distinct patterns in PET imaging of atypical phenotypes of neurodegeneration*

Clinical spectrum	FDG PET	Amyloid PET	TAU PET
Typical AD	Posterior cingulate, precuneus and temporal-parietal associative cortex hypometabolism[80]	Diffuse tracer accumulation across the cerebral cortex, according to Thal's stages[81]	Intense tracer retention in the parietal lobes,(especially precuneus, and posterior cingulate) and mesial basal temporal structures[82]
Frontal AD	Greater medial and orbital frontal hypometabolism compare to typical AD[83]	Diffuse tracer accumulation across the cerebral cortex indistinguishable from typical AD[81]	Classic temporo-parietal tracer retention with potential involvement of frontal areas (>lateral)[84]
Logopenic PPA	Hypometabolism in left, middle. superior temporal areas with less involvement of right medial temporal area and posterior cingulate[85]	Diffuse tracer accumulation across in the cerebral cortex without a clear topographic correspondence[89]	Asymmetric, left greater than right temporoparietal language regions tracer retention[87]
PCA	Bilateral occipitoparietal hypometabolism[88]	Diffuse tracer accumulation across the cerebral cortex[88]	Parieto-occipital tracer retention with less retention compared to typical AD in the hippocampus[88]
bvFTD + ALS	Hypometabolism in frontal association cortex and anterior temporal lobe, usually asymmetric[89] Frontotemporal and insular cortex hypometabolism with the basal ganglia and the thalamus involvement[135]	Until 38% percent of positivity with different grading of binding, increasing with age of the patients. GRN mutation > C90RF72 expansion. Not reported for MAPT mutation[138]	Increased tracer retention in the temporal lobes, temporal white matter, and basal ganglia[90]
Nonfluent PPA	Two main subtypes of hypometabolism: -1: more confined to dominant lobe with involvement of superior temporal and inferior frontal gyri (more related to TDP-43 type A proteinopathy, can evolve to dementia) -2: more medial bilateral frontal lobe involvement (possible evolution to PSP)[91]	10% of positivity (similar or slightly lower than normal individuals)[92]	Accrual in white matter of the prefrontal lobe, including orbitofrontal, inferior, middle and superior regions, and temporal lobe, with greater uptake in the left hemisphere. Involvement even of subcortical grey matter structures, including bilateral thalamus, putamen and globus pallidus[93]
Semantic PPA	Hypometabolism in the whole left temporal lobe, right temporal pole, left thalamus[94]	15% of positivity (similar or slightly lower than normal individuals)[92]	Accrual mainly in temporal pole, inferior and middle temporal gyri, fusiform gyrus, amygdala, parahippocampal gyrus and entorhinal cortex, with left prevalence. TAU Positivity might also be present in TDP-43 proteinopathy (focal TAU or off-target binding?)[93]
CBS	Asimmetric hypometabolism in frontoparietal lobe and striatum[95] -In CBD pathology: > basal ganglia -In AD pathology: > lateral parietal, temporal lobe, posterior cingulate -in CBS-PSP pathology: > medial frontal regions and the anterior cingulate[96]	Percentage of AD pathology ranges from 13% to 24%[97]	Binding in precentral lobe, midbrain, putamen, globus pallidus, thalamus, corticospinal tract with asymmetric feature in CBS-CBD differently from CBS AD and CBS-PSP[95]
PSP	Hypometabolism in medial frontal cortex, striatum and brainstem[95]	Positivity until 40% in patients with clinical features suspicious for PSP[98]	Engagement of subthalamic areas, midbrain, and cerebellar white matter. Involvement of the neocortex in the advanced stages of the disease[95]
MSA	Hypometabolism in cerebellum, putamen and brainstem[95]	Not reported amyloid accrual	Not reported TAU binding, except for retention in posterior putamen perhaps related to interaction with iron deposition[93]
DLB	Hypometabolism in parieto-occipital cortex, temporal lobes, substantia nigra and thalamus. Compared to AD, preservation of medial temporal areas and posterior cingulate metabolism ("cingulate island sign")[95]	High Aβ values are observed until 60% of the DLB patients, often reflecting mixed pathology. The amount of B-amyloid uptake is lower in "pure" AD cases compared to the patients affected by an AD/DLB pathology[99]	In "pure" DLB not differences of accrual compared to controls[100]

* AD – Alzheimer's disease, PPA – primary progressive aphasia, PCA – posterior cortical atrophy, FTD – frontotemporal dementia, ALS – amyotrophic lateral sclerosis, CBS – corticobasal syndrome, PSP – progressive supranuclear palsy, MSA – multiple-system atrophy, DLB – dementia with Lewy bodies

Speech difficulties may also represent an early marker of motor abnormalities in Parkinson's disease (PD).[125]

Recent data have shown that uptake of [123I]FP-CIT (DaTscan), a radioligand with high binding affinity for presynaptic dopamine transporters (DATs), is lower in the striatum ($p<0.001$), caudate ($p=0.003$) and putamen ($p=0.003$) in Parkinson's disease patients with speech difficulties than in patients without speech abnormalities.[126]

Figure 3 shows the DAT-SPECT of a subject with speech abnormalities, akinetic phenotype and autonomic dysfunction.

A challenging common presentation in the spectrum of Lewy body disorders including PD and DLB is autonomic dysfunction. In patients with PD autonomic dysfunction is associated with a more rapid disease progression and shorter survival and may include orthostatic hypotension, bladder disturbances, gastrointestinal malfunction, cardiovascular dysregulation and sexual dysfunction.[127]

Severe cardiac sympathetic degeneration occurs in DLB, but not AD, offering a potential target for molecular imaging. Scintigraphy with [123I]meta-iodobenzylguanidine (MIBG), an analogue of norepinephrine that

Table 3. Critical outcomes of SPECT imaging biomarkers in differentiating clinical presentations of neurodegeneration*

Clinical spectrum	[123I]FP-CIT (DAT imaging)	[123I]MIBG (sympathetic innervation)	[123I]FP-CIT + [123I]MIBG (combined imaging)
PD	Differential diagnosis from Parkinsonism with authopsy validation[46] Differentiation of PD and MSA[47]	Differentiating PD from other neurodegenerative parkinsonism[50,112] Differentiation of PD and MSA[118]	Differentiating PD from other neurodegenerative parkinsonian syndromes[121]
DLB	Specificity of 90.4% for excluding non-DLB dementia (101) Loss of striatal DAT binding more intense in the putamen than in the caudate (43,101) Class I evidence that [123I]-FP-CIT accurately identifies patients with DLB (40,102,103) Authopsy validation[39,40,41,43,46]	High sensitivity and specificity of MIBG myocardial scintigraphy for differentiating PD from other neurodegenerative parkinsonism in both early and delayed imaging phases[112] Class II evidence that reduced cardiac uptake of 123I-MIBG accurately identifies patients with DLB and cardiac sympathetic denervation[113] Early and delayed H/M ratio strongly correlate with residual cardiac sympathetic nerve fibers[114,115] 3-year follow-up of 133 patients confirms high correlation between abnormal cardiac MIBG and clnical diagnosis of DLB with early and delayed H/M ratio 2.51 and 2.20[116,117]	Sensitivity and specificity of combined techniques in differentiating DLB from AD 96.1 and 90.7 %, respectively[120,121]
MSA	Severe decrease DAT binding and higher asymmetry in MSA-P than in MSA-C[104-107] Higher striatal uptake in MSA-C variant (probably due to predominant degeneration of ponto-cerebellar rather than nigrostriatal pathways)[106,108]	MIBG scintigraphy distinguish between PD and MSA, and between AD and DLB (H/M ratio 1.77 with 94% sensitivity and 91% specificity)[116] Most MSA patients show a normal myocardial MIBG uptake (118) MSA-P patients show a mild cardiac sympathetic dysfunction without any correlation to disease duration[119]	
PSP	More intense decreased DAT binding compared to PD and MSA-P in both caudate and putamen (higher putamen/caudate ratio)[104,105,109,110]		
CBS	Mild-to-moderate reduction of striatal presynaptic dopamine uptake with greater uptake asymmetry compared to PD[111,44,110]		

* PD – Parkinson disease, DLB – dementia with Lewy bodies, MSA – multiple-system atrophy, MSA-P – MSA with predominantly parkinsonian signs, MSA-C – MSA with cerebellar features, PSP – progressive supranuclear palsy, CBS – corticobasal syndrome, DAT – dopamine transporte, [123I]FP-CIT – [123I]*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane), [123I]MIBG – [123I]metaiodobenzylguanidine

assesses the post-ganglion peripheral autonomic nervous system, has been used as a non-invasive method to assess myocardial sympathetic nerve damage. The DLB Consortium consensus report recommends MIBG scanning as a biomarker of DLB.[128] Calculation of MIBG uptake using the heart-to-mediastinum (H/M) ratio provides a semiquantitative diagnostic index for distinguishing DLB from AD with high specificityand an autopsy study has validated the diagnostic accuracy of MIBG cardiac scintigraphy for DLB revealing that residual cardiac sympathetic fibers strongly correlate with H/M ratios.[114,116,129] A recent paper has provided a Class I evidence that cardiac MIBG scintigraphy using the H/M indicator may also distinguish mild cognitive impairment with Lewy bodies from mild cognitive impairment due to AD.[130]

In Figure 4, the assessment of cardiac autonomic innervation with MIBG-SPECT in subjects with DLB and AD is represented.

Low MIBG uptake associated with autonomic dysfunction (mild memory disorder, constipation/postural hypotension, depression/anxiety, visual hallucination/psychosis, REM sleep disorder) may detect PD very early in the pre-motor phase according to the multiple Braak stages on the pathological accrual of α-Synuclein.[131,132]

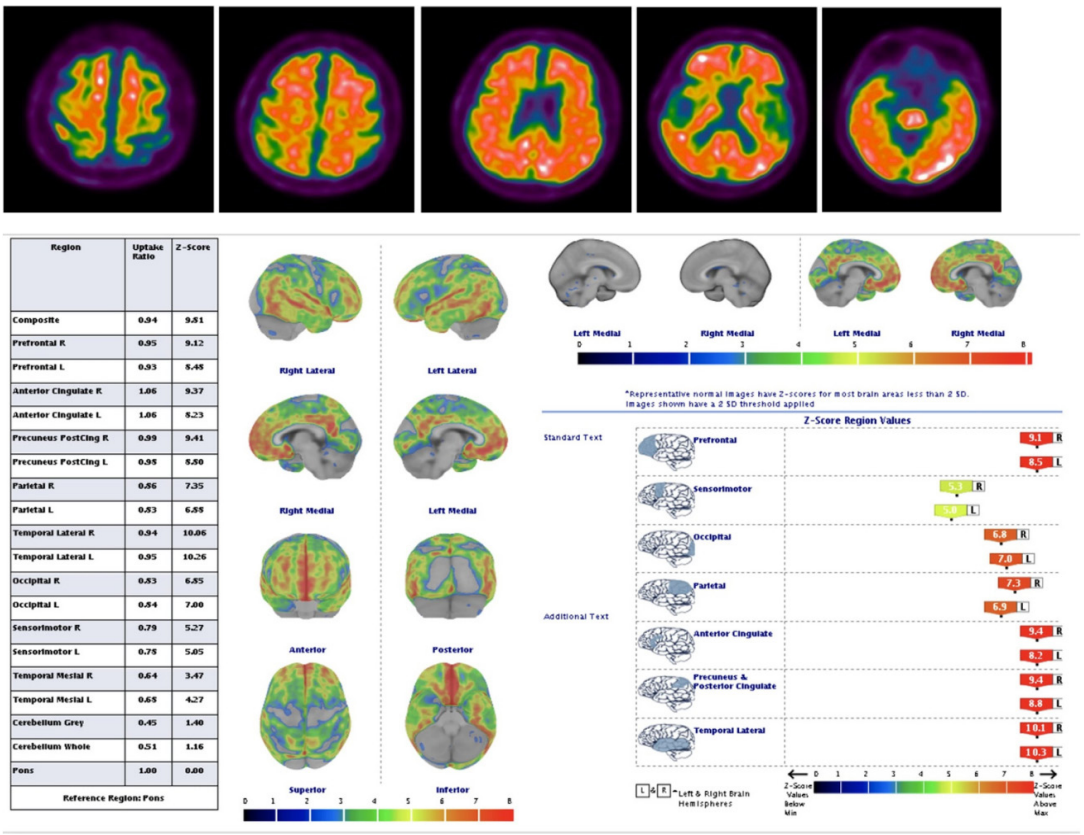
Accumulating evidence shows that Lewy body disorders affect central and peripheral autonomic nervous systems requiring the combination of both [123I]FP-CIT and MIBG imaging to provide early and accurate diagnosis and appropriate treatment.[120,121]

An additional topic in the diagnostic work-up of patients with DLB is distinguishing them from those with AD or mixed pathology. The role of amyloid-PET imaging in this clinical context is established and lower amyloid tracer uptake accurately distinguishes cases with DLB.[96] However, high Aβ values are observed in up to 60% of the DLB patients, often reflecting mixed pathology. Interestingly, the amount of β-amyloid uptake is lower in "pure" AD cases compared to the patients affected by an AD/DLB pathology, with lesser involvement of the occipital regions in the former.[133]

Challenging fields are continuously emerging in the world of neurodegeneration with a high need for reliable imaging biomarkers supporting clinical features to reach a correct diagnosis and prognostic assessment (Table 2, 3), especially for disorders with more aggressive courses as atypical parkinsonism and amyotrophic lateral sclerosis (ALS). PET and SPECT imaging are increasingly used in these settings with earlier onset, faster progression, and poor response to treatment, aiming to resolve the initial diagnostic uncertainty.

In Multiple System Atrophy (MSA) FDG-PET shows a reduced metabolism in the cerebellum,

A



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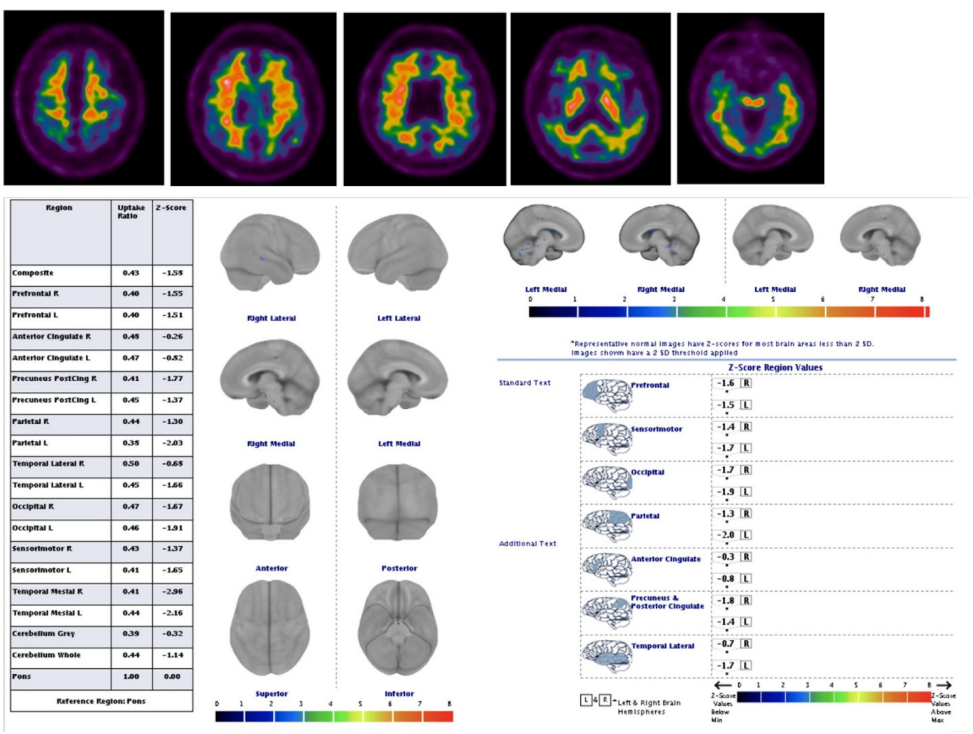

Fig. 2. Amyloid-PET with [18F]flutemetamol in subjects with primary progressive aphasia (PPA) – A): A case of semantic variant of PPA with negative amyloid-PET: representative axial sections show low retention of the tracer in the cortical grey matter confirmed by the Z-score images obtained from quantitative analysis, B): A case of logopenic PPA with positive amyloid-PET suggesting underlying Alzheimer's pathology: representative axial sections show diffuse increased retention of [18F]flutemetamol in the cortical gray matter and Z-score images show all pixels with a deviation above the mean of the normal controls in number of standard deviations (cut-off value +2 SD); quantitative analysis was performed using CortexID Suite, GE Healthcare®, pons as reference region

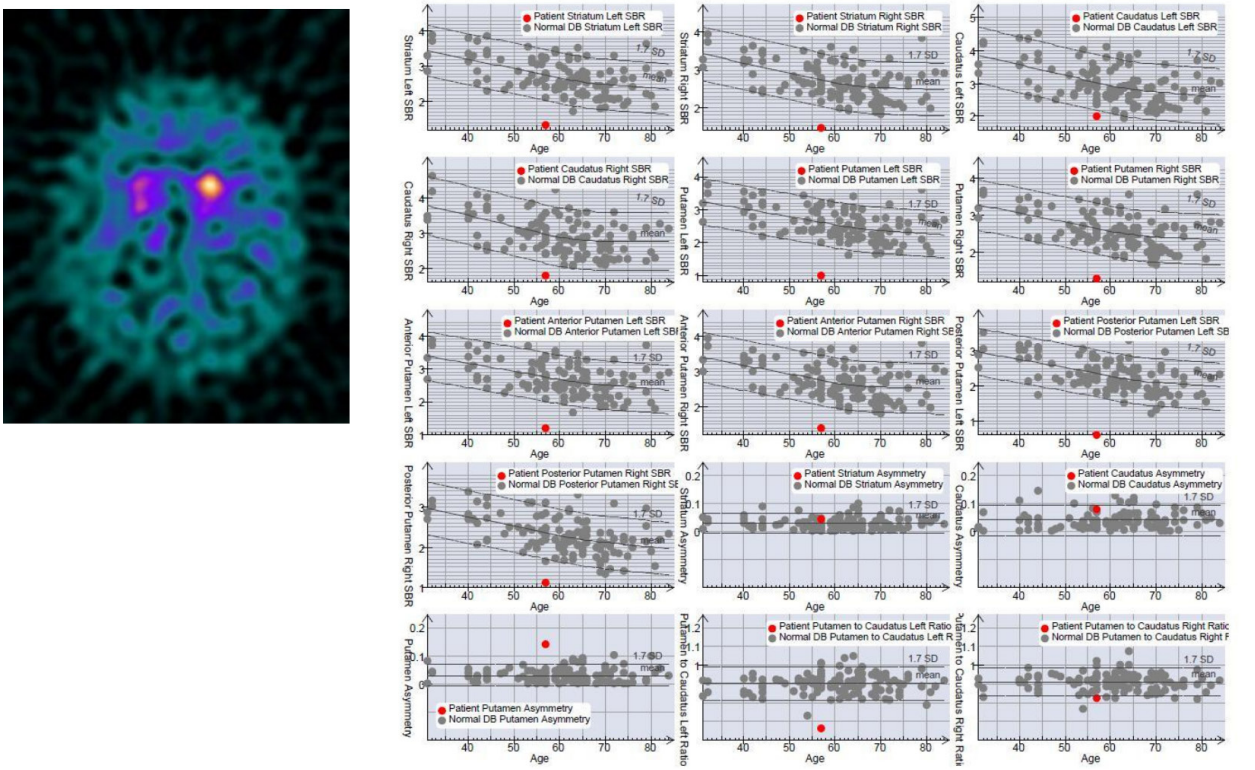

Fig. 3. Visual and quantitative analyses of DaTscan SPECT in a patient with Parkinson disease associated with speech abnormalities, akinetic phenotype and autonomic dysfunction, axial section shows reduced [123I]FP-CIT uptake in the right caudate and in both the putamen, quantitative assessment of tracer uptake (DaTQUANT software, GE Healthcare®) confirms the visual findings, but also indicates reduced uptake in the left caudate compared to normal controls

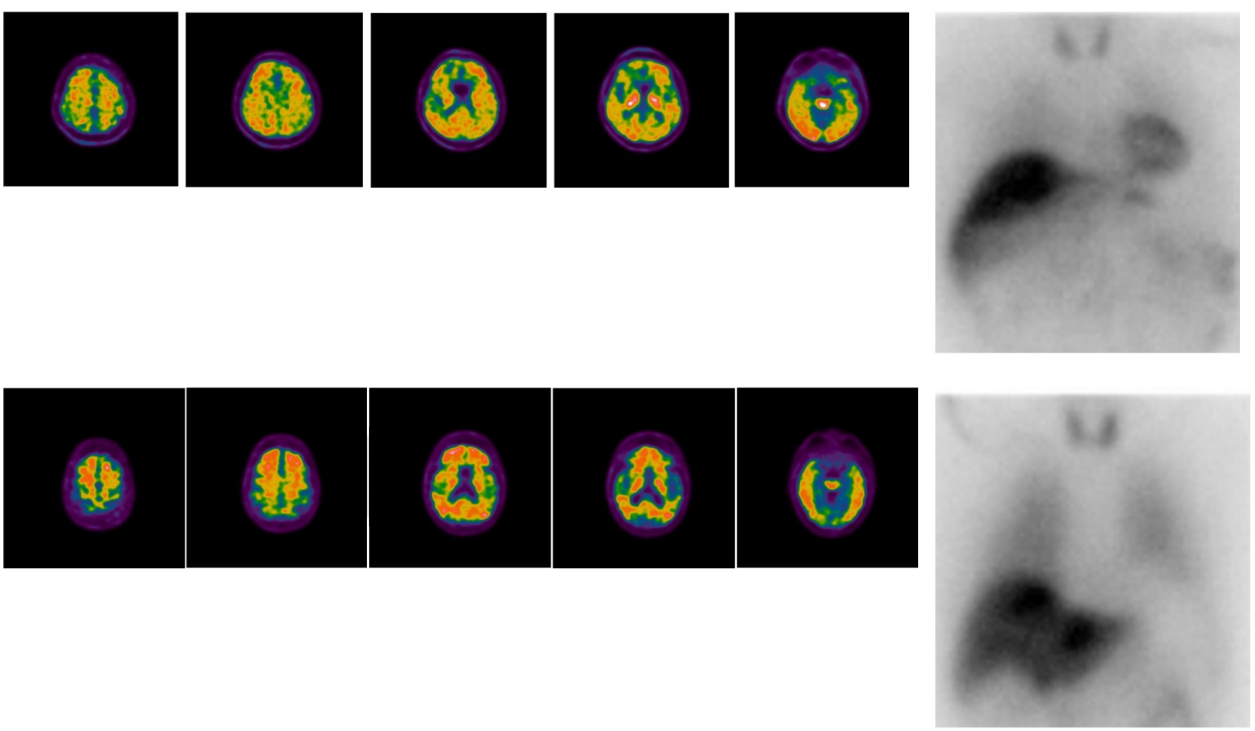

Fig. 4. Assessment of autonomic dysfunction in the differential diagnosis of DLB from Alzheimer's disease. Amyloid deposition, evaluated with 18F-Flutemetamol PET, is increased in both cases with a global z-score +5.30 SD in the AD subject (upper axial PET images) and +5.16 SD in the DLB case (lower axial PET images), cardiac MIBG uptake is intense in the AD case (upper static image) with H/M uptake ratio 2.4, obtained 15–20 min after tracer administration, while in the DLB case (lower static image) MIBG uptake is dramatically reduced with H/M uptake ratio 1.2, reflecting the myocardial sympathetic nerve damage, quantitative software for amyloid-PET analysis: CortexID Suite, GE Healthcare®, cut-off value +2 SD, pons as reference region

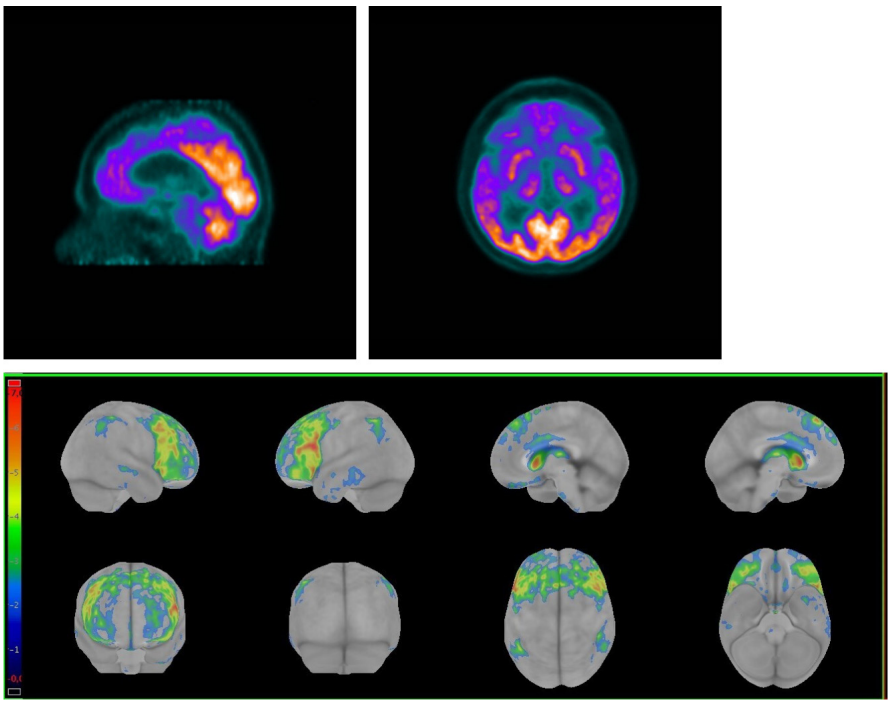

Fig. 5. Metabolic pattern of amyotrophic lateral sclerosis on FDG-PET. Representative sagittal and axial PET images (upper pictures) show hypometabolism in the prefrontal and premotor cortex associated with symmetric relative hypermetabolism in the occipital cortical pole and in the cerebellum, z-score images (lower picture) confirm significant hypometabolism in the prefrontal and premotor cortex showing all pixels with a deviation below the mean of the normal controls in number of standard deviations (cut-off value -2 SD), quantitative software: CortexID Suite GE Healthcare®, pons as reference region

putamen, and brainstem regions compared to PSP, in which the medial frontal cortex, prefrontal areas, striatum, and brainstem are preferentially involved.[95,133] In Corticobasal Syndrome, the critical element is the asymmetric decrease of brain metabolism, engaging mainly the frontoparietal lobe and striatum.[95,96] In PSP patients, the tau-PET may show the engagement of the subthalamic areas, midbrain, and cerebellar white matter with the further involvement of the neocortex in the advanced stages of the disease.[95] Moreover, FDG-PET may be used as a gatekeeper method to select patients candidates to the second level or more expensive imaging as tau-PET.[133]

Recent studies have also shown the diagnostic value of FDG-PET in identifying ALS from controls with most discriminating hypometabolism in the prefrontal and premotor cortex and relative hypermetabolism in the occipital cortex, cerebellum, upper brain stem, and medial temporal cortex).[135-138] Metabolic pattern of ALS on FDG-PET imaging is presented in Figure 5.

A higher mortality rate has been revealed in the presence of extensive frontotemporal hypometabolism.[136,137] A precise definition of neurodegeneration pathophysiology could shorten the period from symptom onset to diagnosis and allow earlier interventions.

An additional source of diagnostic uncertainty that patients with neurodegenerative disease frequently experience are visual alterations and neuropsychiatric symptoms (NPS) that may be mistaken for a psychiatric disorder.

Visual symptoms can present as independent and early signs of neurodegenerative disease and they may determine a challenge in the patient's life including repeated appointments with eye specialists, eventual unnecessary surgeries (e.g., cataract removal) and diagnosis delay.

A recent survey among neuro-ophthalmologists demonstrated that at least 5–10% of new patients referred to them had a previous diagnosis of a neurodegenerative disease. For new patients without a diagnosis of neurodegeneration, visual complaints were attributed to undiagnosed neurodegenerative disease in more than 5% of cases.[139]

Interestingly, 40% of the interviewed neuro-ophthalmologists indicated the lack of tools to assess visual dysfunction due to neurodegeneration as a barrier to a specific diagnosis.[139]

In these cases the quantitative assessment of glucose metabolism, amyloid deposition or tau accumulation may guide accurate diagnosis and patient management providing information about regional, particularly occipital, involvement in FDG, amyloid- or tau-PET.

Recently, dysfunction of visual contrast sensitivity has been strongly associated with cerebral deposition of amyloid plaque and tau protein, primarily in temporal, parietal and occipital brain regions.[140] In Figure 6, am-

Fig. 6. Alterations in visual contrast sensitivity and cerebral deposition of β amyloid, representative left sagittal images of amyloid-PET with 18F-flutemetamol in two subjects with dysfunction of visual contrast sensitivity; in one case (left picture), Aβ accumulation was detected by PET in the occipital lobes (right z-score +7.61 SD, left +9.76 SD) suggesting Alzheimer's disease-related pathophysiology; in the second case (right picture), amyloid-PET showed a normal tracer retention in the occipital lobes (right z-score +1.70 SD, left +1.81 SD), quantitative software: CortexID Suite GE Healthcare®, z-score cut-off value +2 SD, pons as reference region

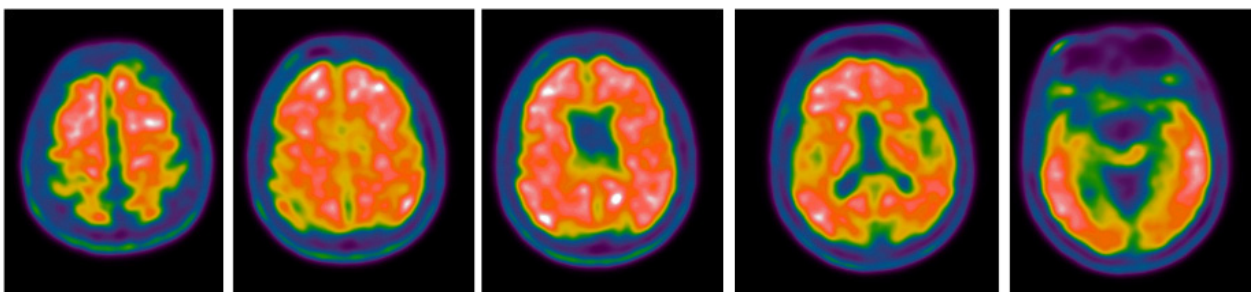

Fig. 7. Neuropsychiatric symptoms associated with elevated Aβ deposition and cognitive decline as early markers of Alzheimer's disease, representative axial sections of amyloid-PET with [18F]florbetaben in a patient with anxiety, depression and cognitive impairment show diffuse elevated Aβ deposition in the examined cortical regions, visual assessment of brain amyloid-β plaque load (BAPL) was graded as score 3, according to the method described in Barthel et al.[57]

yloid-PET images are presented in subjects with visual contrast sensitivity alterations.

In posterior cortical atrophy (PCA), the paradigmatic neurodegenerative disease impairing visuospatial perceptions and mainly due to Alzheimer's disease pathology, FDG-PET hypometabolism in occipital regions correlates with a highly regional concordance with hyper-fosforilated tau accrual. In contrast, the amyloid burden is more diffuse along the neocortex, although a possible link between amyloid deposition in the primary visual cortex and the onset of visuospatial impairment has been suggested.[88,141]

Furthermore, the phenotypic PCA heterogeneity can be disentangled, through the assessment of glucose metabolism, highlighting the primary involvement of either the right or left hemisphere and the ventral or dorsal visual streams.[142]

The presence of NPS is an independent risk factor for cognitive impairment, faster decline and poorer outcomes in functional status and quality of life.[143,144] Among NPS, delusions and delirium are the most associated with worse cognitive and functional outcomes.[145] Neuropsychiatric symptoms and cognitive decline are both signs of similar brain pathologies; thus it is crucial to investigate the underlying pathway linking NPS to neurodegeneration.

Assessment of amyloid deposition with PET might help in selected cases of NPS with slight cognitive deficits. In cases of major depression with episodes of transient amnesia, a normal amyloid-PET might contribute to confirming a psychiatric disorder, especially when the clinical history is suggestive of depression, but neuropsychological assessment has shown some cognitive deficits.

Recently, great attention has been paid to the relationship between depressive symptoms and neuroimaging biomarkers, such as glucose metabolism or amyloid deposition, that appear distinctly related.[146]

Touron et al. have shown that preclinical depressive symptoms are associated with glucose hypometabolism in the brain areas particularly susceptible to AD, such as the hippocampus, amygdala, the precuneus/posterior cingulate cortex, the medial and dorsolateral prefrontal cortex, insula, and the temporoparietal cortex, and in-

dependent of amyloid-PET results as shown in the previous studies.[147-149]

Older adults with cognitive impairment are at risk of having or developing NPS and even slight levels of depressive symptoms are associated with the increased risk of cognitive decline.[150,151]

The Mayo Clinic Study of Aging has demonstrated that subjects with regional glucose hypometabolism (measured with FDG-PET) and depression (Beck Depression Inventory-II ≥13) had a more than threefold increased risk of incident MCI.[152]

The risk was also significantly elevated for participants with anxiety (Beck Anxiety Inventory ≥10) and glucose hypometabolism.

On the other side, a recent systematic review has shown that NPS, particularly depressive and anxiety symptoms, are associated with higher Aβ deposition, as presented in Figure 7.[153]

Longitudinal studies have shown that baseline Aβ deposition and NPS have a synergistic interaction in the very early stages of AD[154]: greater baseline cortical amyloid and increased depressive symptoms are associated with more significant cognitive decline over time.[155,156]

No association was revealed between NPS and tau pathology.[153]

A small percentage of people with dementia also experiment with early behavioral changes – such as a disregard for social norms or loss of empathy – that can lead to a mistaken diagnosis (i.e. behavioral variant of frontotemporal dementia instead of a variant of AD), also due to the lack of standardized clinical criteria for this AD phenotype.[157] Assessment of brain glucose consumption with FDG-PET may identify the metabolic pattern of the behavioral subtype of AD (bvAD).

Hypometabolism in the frontal regions distinguishes frontal variant (bvAD) from typical AD, while it largely matches typical AD in the posterior cingulate cortex, precuneus, and lateral temporoparietal regions.[158]

The frontal-hypometabolism pattern in bv-AD can be highly comparable to behavioral frontotemporal dementia (bv-FTD), leading to a significant risk of misdiagnosis considering the clinical features' resemblance. To obtain the correct diagnosis, the amyloid-PET takes a lead role for its high negative predictive values since the absence of pathological β-amyloid rules out AD diagnosis with great sensibility and specificity.[159] A large series of pathologically confirmed FTD reported Aβ deposition in 38% of patients with bvFTD and increased progression with age, suggesting a role for amyloid imaging in clinical assessments of FTD syndromes.[81]

In a high percentage of cases, estimated at around 12.5%, an overlap between FTD and motoneuronal disease occurs, and a more significant number of FTD patients also show subtle motor system involvement.[38,160] Recently, in such overlap conditions, an increase in glucose metabolism has been observed along the brainstem with a shorter survival if this occurs in the medulla oblongata.[161]

Mild behavioral impairment (MBI) is emerging as a novel marker of preclinical Alzheimer's disease.[162] Higher β-amyloid tracer uptake resulted strongly associated withMBI in normal elderly individuals, specifically in the neocortex, including the frontal cortex, followed by the striatum, according to the sequential stages of hierarchical amyloidosis in AD.[163,164]

No significant associations have been demonstrated with tau-PET uptake, suggesting that in cognitively normal elderly MBI is not associated with tau-PET signal, according to the observation that considerable tau aggregation is rarely observed in cognitively normal older individuals, but it is present in dementia due to AD.[163-165]

At different stages of neurodegenerative disorders, motor symptoms may be present, including bradykinesia, extrapyramidal rigidity or spasticity. Less severe motor disorders such as gait slowing may occur at an early stage of dementia and alterations in dual-task performance (walking while simultaneously performing another task) is often present in elderly people with MCI.[16,166]

Motor and cognitive disorders may coexist in PD, ALS, PSP or CBS, and motor impairments are often associated with worse cognitive decline. Data from the DEMPARK/LANDSCAPE study have demonstrated that less severe cognitive deficits are present in tremor-dominant PD rather than in the akinetic variant.[168]

In genetic FTD motor severity appears strictly related to time course and the affected gene.[169]

Multimodal molecular imaging may improve diagnostic accuracy in the motor-cognitive phenotype setting, detecting the disease's key neuropathological correlates. Tau imaging can detect tau aggregation in PSP and corticobasal degeneration (95) as well as DAT imaging is the most accurate marker for PD.[170] Cardiac adrenergic imaging with MIBG-SPECT may provide the diagnosis of pre-motor PD in patients presenting with mild memory impairments and other non-specific symptoms as autonomic dysfunction, sleep disorder, depression or anxiety, visual hallucinations.[112]

A systematic meta-analysis including 74 studies, 2323 patients with PD and 1767 healthy controls, has shown glucose hypometabolism on FDG-PET in the bilateral inferior parietal cortex and left caudate nucleus, respectively related to cognitive deficits (inferior parietal cortex) and motor symptoms (caudate nucleus).[171] In the same study, FDG-PET hypometabolism outperformed results of structural MRI in identifying functional brain abnormalities in PD.

Actual challenges for molecular imaging of neurodegeneration

Pattern overlaps

Throughout recent years, pattern overlaps between ND's phenotypes have gained increasing attention. A recent study on 895 autopsy cases from patients with neurodegenerative disease measured regional aggregation of β-amyloid, tau, α-synuclein, and TDP-43.[172] Authors identified 6 disease clusters reflecting primary tauopathies, AD typical coexistence of amyloid-β and tau pathology, TDP-43 proteinopathies, synucleinopathies, tau-α-synuclein copathology, and minimal cerebral pathology.

The same proteins can represent risk factors for different NDs implying an overlap between them at a subcellular level. On the other side, the cells and the fold of protein aggregates involved in the disease process can also overlap between multiple diseases.

Molecular neuroimaging allows us to detect and monitor *in vivo* the ND hallmarks, their anatomical distribution and the interrelationships of the underlying molecular and cellular processes, disentangling pattern overlaps of neurodegeneration.

Co-pathologies suggest that NDs might share common pathogenic pathways as shown by the genome-wide association studies (GWASs).[173,174] Genetic overlap between neurodegenerative diseases is more frequently studied in pairwise investigations, and more recently across multiple neurodegenerative disorders.[174-176]

The case of tau-directed imaging

The composition of tau aggregates and their geometric arrangements may vary in disease subtypes, while it is constant in patients with the same disease.[177-180,10] Tauopathy is classified by the type of tau isoforms present in the neurofibrillary tangles, differing in the number of carboxy-terminal repeating domains (3R or 4R).[181] While AD is associated with both 3R and 4R forms, 4R tau is abundant in CBD and PSP, 3R in Pick's disease and three subtypes (3R, 4R or 3R/4R) are present in FTD.[182,181,177]

In addition to tau isoforms, distinctive folds in the tau fibrils characterize AD (paired helical filaments » straight filaments) and non-AD tauopathies as PSP (straight filaments; rare twisted filament), CBD and Pick's disease (straight filaments >> twisted filament).[183]

Therefore, awareness of these differences is relevant in molecular imaging with tau-directed radioligands.

Among the first-generation of tau PET radiotracers, the pyridoindole derivative[18F]-flortaucipir was the first radioligand approved for clinical use by the FDA on May 2020.[184]

However, off-target binding to white matter or other neural structures (i.e. in the striatum and choroid plexus) and low affinity for tau fibrils in non-AD tauopathies such as PSP and CBD,[185] pushed the development of second-generation tau PET tracers, including [18F]-RO-948, [18F]-MK-6240, [18F]-PI-2620, [18F]-JNJ-311, [18F]PM-PBB3, and [18F]-GTP1.[186]

A post-mortem radioligand binding study on second-generation tau PET tracers PI2620, MK6240 and RO948 in AD, CBD and PSP has shown different binding properties of the different tracers, suggesting the potential for development of pure selective 4R tau PET tracers.[187]

A recent in-depth analysis of the binding mechanism across 10 first- and second-generations PET tracers using multiple approaches (i.e. molecular dynamics, docking, and metadynamics simulations) has demonstrated that MK6240 binds better to tau aggregates in AD than in CBD and PSP, and that CBD2115, PI2620, and PMPBB3 represent 4R tau binders.[188]

Fluid and imaging biomarkers for neurodegeneration

Currently, several fluid biomarkers including beta-amyloid, tau protein, neurofilament light chain, alpha-synuclein and glial fibrillary protein, can differentiate different neurodegenerative diseases. The best-validated fluid biomarkers derive from CSF, but blood-based tests may are improving in accuracy and predictive value especially for the ratio of amyloid-beta 42/40 (Aβ 42/40), pTau, and NfL.[189-191] Serum biomarkers may enable much broader accessibility of testing, in light of lower costs and less invasive collection. However, as of yet no single biomarker allows for definitive diagnoses.[192] Integrating information from imaging and fluid biomarkers in a "composite tool" may increase sensitivity and specificity of diagnosis, especially in screening at-risk subjects.[193] Considering that false positive results are expected using blood tests for AD in general population, a positive result is likely to require a definitive confirmation through PET imaging able to detect region specific findings differentiating similar disease phenotypes in a non-invasive fashion. Moreover, in prodromal disease stages, molecular imaging may allow to assess not only the presence but also the location and the stage of the pathological and therapeutic target. In the case of tau imaging, the regional PET signal may allow to identify the different tauopathies.

Finally, a unique advantage of molecular imaging is the quantitative capability which allows to estimate the specific disease hallmark that may be monitored during treatment intervention also in the early phases.

When conducting molecular imaging in atypical phenotypes

Suggesting a standardized sequence for the utilization of PET and SPECT techniques in the context of atypical neurodegenerative disorders is a complex task.

We propose that within the spectrum of disorders potentially linked to AD-related pathology (such as pri-

mary progressive aphasias, behavioral disorders, and posterior cortical atrophy, as discussed in our review), the assessment with PET-amyloid should be consistently performed following the initial diagnostic workup, including clinical and neuropsychological evaluation, and structural imaging. The PET analysis enables a precise diagnosis, ensuring access to clinical trials and specific pharmacological treatments. Moreover, recent evidence suggests that early acquisition-phase PET-amyloid acquisition resembles the corresponding FDG-PET images, allowing the assessment of neuropathology and brain metabolism in a single PET scan.[194] However, it is important to consider the potential decrease in specificity of the PET-amyloid for individuals above 75 years and the presence of amyloid pathology as incidental or co-pathology.[195]

In this regard, FDG-PET remains a key tool in differentiating neurodegenerative dementias from psychiatric disorders and maintains a relevant role in the early stages of neurodegenerative disorders, especially in conditions where atrophy is not yet significant and cannot be detected by conventional neuroimaging methods.[196,197]

The anticipated widespread integration of quantitative analyses in routine clinical practice shortly (i.e., DaTscan SPECT and tau PET) will enable the assessment of prognosis for various pathologies at the time of diagnosis. This consideration is crucial, given that the high costs associated with these methods do not allow for their repeated application throughout the progression of the pathology on a large scale.

Conclusion

This concise review summarizes the current use and potential role of Molecular Imaging techniques such as PET and SPECT in discriminating atypical phenotypes of neurodegeneration and it may represent a quick guide to choosing the best imaging method in this heterogeneous clinical setting.

PET and SPECT radioligands targeting the key neuropathological substrate of neurodegenerative disorders could anticipate the time for a correct diagnosis when atypical symptoms or signs may be confounding. This issue is crucial in working persons and younger subjects with an early-onset of the disease, especially if they have the chance for the effect of new modifying-disease drugs. Delaying disease progression and symptoms by even a few years can highly impact the quality of life of patients, as well as their families and caregivers.

The application of new treatments requires patient screening in the prodromal phase to provide neuropathological target detection, such as cerebral Aβ deposition, tau inclusions, or α-synuclein accumulation, and to monitor treatment effects especially at the subclinical level. On the other hand, precise staging and diagnosis of neurodegenerative diseases may assist patient care and management in daily clinical practice. Moreover, the utilization of objective imaging techniques providing an "in vivo" quantitative assessment of specific disease targets, provides an accurate diagnosis in older individuals where the coexistence of cerebral age-related changes, cerebrovascular lesions, depression and neurodegenerative diseases may increase the complexity of the diagnostic process. In this heterogeneous context, a multilevel approach is needed and a strong cooperation between primary care physicians and specialized centers for personalized patient care is needed.

One potential limitation of our review is the need for more detailed technical description of the radioligands used for PET and SPECT imaging, but it was outside of our goal as well as an in-depth analysis of quantitave methods to process acquired images.

An additional limitation could be the narrative approach of this review. However, our purpose was to deepen the understanding in the research area of molecular imaging of atypical presentation of neurodegenerative disorders focusing on existing debates, previous studies conducted on the topic, and latest applications available, summarizing their results so that they are easily translatable into clinical practice.

A big effort should be made in the future to provide an "imaging continuum" able to assess and integrate all the aspects of neurodegeneration, from pathology substrates to functional connectivity, facing the challenge to stratify patients for an appropriate allocation of new arriving treatments.

Radioligand landscape will be probably enriched by tracers of neuroinflammation and synaptic density, while the diffusion of hybrid PET/MRI scanners, as well as advanced imaging protocols could install a precision medicine approach for a comprehensive workup of neurodegenerative disorders with atypical presentation.

Declarations

Funding

This research received no external funding.

Author contributions

Conceptualization, L.R. and M.S.; Methodology, L.R. and A.Z.; Software, F.M.; Validation, M.S., M.S., F.L.; M.M.; Formal Analysis, M.S., S.M.; Investigation, V.C.; Data Curation, S.M., F.M; Writing – Original Draft Preparation, L.R. And A.Z.; Writing – Review & Editing, L.R., M.S.; Visualization, G.B. T.G. C.C..; Supervision, L.R. and M.S.

Conflicts of interest

No conflicts of interest to disclose.

Data availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Ethics approval

The review figures are derived from scans of patients included in the following protocols approved by the Ethical Committee of our institution (345/2019/OSS*/AOUPR and 666/2021/FARM/AOUPR).

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