PET in Neurodegenerative Diseases

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Positron emission tomography (PET) allows for the in vivo assessment of early brain functional and molecular changes in neurodegenerative conditions, representing a unique tool in the diagnostic workup. The increased use of multivariate PET imaging analysis approaches has provided the chance to investigate regional molecular processes and long-distance brain circuit functional interactions in the last decade. PET metabolic and neurotransmission connectome can reveal brain region interactions.

[18F]FDG-PET | neurodegenerative diseases | Alzheimer's disease spectrum | Lewy bodies disease spectrum | brain metabolic connectivity | brain network analysis

1. Introduction

Positron emission tomography (PET) plays a relevant role as a tool able to provide in vivo biomarkers for neurodegenerative diseases, crucial in the diagnosis process [1]. PET measures different molecular processes underlying the pathophysiology of neurodegenerative diseases [2]. These targets include glucose metabolism of cells throughout the well-established radiotracer [18F] 2-fluoro-2-deoxy-D-glucose (FDG), and a broad range of biological and pathological processes, from neurotransmission to amyloid and tau pathology, with corresponding tracers [1].

The progress in the field of neurodegenerative diseases recently brought about a paradigm shift in approaching brain pathology. Thanks to the emergence of robust methods for quantifying the brain's functional systems [3], the focus of research has shifted from assessing the impact of pathology on local neuron function to investigating the long-distance effect on the interconnected nervous systems [4].

The pathophysiological model of neurodegeneration considers the anatomical and functional relationships between brain regions a relevant subject in neurodegeneration processes [5]. The advent of the "connectivity era" was first characterized by magnetic resonance imaging (MRI)-based brain connectivity analysis due to the wide availability of this tool [4]. Structural connectivity—diffusion tensor images (DTI)—and functional connectivity with functional MRI (fMRI) as well as electroencephalography (EEG) and magnetoencephalography (MEG) allow for the estimation of complex brain networks [6][7]. Recently, a new interest in brain molecular relationships, based on molecular PET data, emerged to define networks throughout radiotracers to detect brain metabolism, neurotransmission, and protein load. Thus, PET-based brain network analysis gradually included brain connectivity measures developed in MRI/EEG/MEG neuroimaging tools [7]. The most diffused molecular and metabolic

connectivity methods are the seed-based correlation analysis [8], the independent component analysis (ICA) [9], and methods based on pairwise covariance of brain regions [10][11].

2. The Role of PET Imaging in Neurodegenerative Conditions

PET represents a unique tool to detect in vivo several pathophysiological processes, including brain metabolism changes, pathological protein load, neurotransmission integrity, and neuroinflammatory responses [2]. The potential of possible future interventions justifies the massive effort of in vivo molecular research to identify early abnormalities, even years before the clinical onset [12]. PET imaging is today a valuable tool in supporting the diagnosis of neurodegenerative conditions in both clinical and research settings [1]. Moreover, PET imaging may represent a useful tool in screening candidates for clinical trials and may serve as a marker of disease activity in monitoring disease progression [2].

[18F]FDG is the most widely used PET radiotracer, currently employed in clinical and research studies [13]. [18F]FDG-PET signal mirrors neuronal oxidative metabolism and astrocytes glycolysis, mostly reflecting synaptic processes [14]. Several neurodegenerative pathological mechanisms lead to synaptic dysfunction and progressive neuronal loss [2]. Indeed, [18F]FDG-PET hypometabolism reveals alterations in a broad range of neurodegenerative conditions since the very early stage [2]. The main challenge in [18F]FDG-PET analysis concerns the signal quantification methods, which influences diagnostic accuracy [15]. Thus, validated and standardized quantification approaches are needed to provide highly accurate results at the single-subject level, such as brain hypometabolism patterns based on comparisons with a large and well-selected dataset of healthy control [16].

PET also allows abnormal protein deposition measures, representing the pathological hallmark of several neurodegenerative conditions, including AD, frontotemporal lobar degeneration (FTLD), and Lewy bodies disease (LBD) spectrum. Especially in AD, tracer growing availability for detecting underlying pathology has produced a shift to an in vivo biological diagnosis [17].

Since the preclinical and prodromal AD phase, in which symptoms of dementia have not been manifested yet, in vivo detection of amyloid and tau pathology has enabled the identification of candidates for clinical trials [18][19]. Amyloid-PET accurately differentiates AD dementia from FTLD [20] and supports AD diagnosis in individuals with atypical clinical onset [21]. However, it is essential to consider that amyloid-PET reveals brain amyloidosis, which is not invariably associated with dementia [22]. About one-third of healthy elderly individuals have pathological cortical amyloid deposition without showing cognitive impairment [23]. The amyloid-PET positivity classification depends on the selected cut-off, which varies on the basis of the applied quantification method, adding further variability in the outcomes [15]. A weak correlation between cortical amyloid burden and cognitive decline emerged [24], likely because currently available amyloid-PET tracers bind fibrillary insoluble amyloid plaques and not the more toxic amyloid oligomers [25]. Additionally worth noting is that amyloid-PET positivity may also be present in neurodegenerative dementia other than AD, including FTLD and dementia with Lewy bodies (DLB) [26][27]. For all

these reasons, using amyloid-PET imaging for screening candidates in clinical trials has been criticized, while the employment of multiple, more specific neurodegeneration biomarkers should be encouraged [1].

Tau-PET imaging, better than amyloid-PET imaging, has the potential to provide staging for AD progression, showing a strict correlation between brain tau protein deposition and measures of atrophy, neurodegeneration, and cognitive decline [28][29]. Moreover, tau pathology correlates with neuronal loss and brain atrophy in tauopathies other than AD [30][31]. However, the selectivity of the currently available tau-PET tracers in non-AD tauopathies still needs further confirmation, and high non-specific binding in subcortical brain structures needs additional care when evaluating tau-PET imaging data [32].

PET imaging allows for the study of brain neurotransmission systems, at both the presynaptic and postsynaptic level, including dopamine, serotonin, noradrenergic, and cholinergic systems [33]. Each neurodegenerative disorder features a prominent disruption in one or multiple specific neurotransmission systems [34]. Specifically, AD patients show a prominent cholinergic depletion; Parkinson's disease (PD) patients dopaminergic, serotoninergic, and noradrenergic impairments; and DLB patients a severe and widely affected cholinergic and dopaminergic systems [35].

The assessment of the dopaminergic system occurs throughout several radiotracers, such as [18F]Dopa, in order to measure dopamine synthesis; [11C]FE-CIT, for the striatal dopamine transporter (DAT); [11C]raclopride and [18F]Fallypride for binding postsynaptic dopamine D2/D3 receptors [35]. PET molecular imaging also allows quantifying the binding of serotonin receptors (5-HTRs), with the development of successful radiotracers for human studies for 5-HT1AR, 5-HT1BR, 5-HT2AR, 5-HT4R, and 5-HT6R [36]. Regarding the noradrenergic system, PET radioligan's target is the noradrenaline transporter (NET) [35]. NET is located presynaptically on noradrenergic neurons and noradrenergic projections, where it is responsible for the re-uptake of noradrenaline [35]. In *post-mortem* tissue, cholinergic cell loss detection passes through the choline acetyltransferase activity (ChAT), the enzyme that catalyzes the synthesis of acetylcholine. Although there are no PET radiotracers for ChAT, there are radiotracers for acetylcholinesterase (AChE) or the vesicular acetylcholine transporter—the latter two being able to map acetylcholine cells in the brain with a good correspondence with ChAT [35][37].

3. Network Analysis of Brain PET Imaging

For the past 20 years, the brain network analysis field has had steady scientific production growth [10][11]. Thanks to fMRI studies' functional connectivity, understanding normal and pathological brain functions has significantly progressed. The first study assessing brain connectivity with data obtained by [18F]FDG-PET dates back to the 1980s [38]. [18F]FDG-PET signal is based on the coupling between synaptic transmission and local glucose consumption, unlike fMRI that detects indirect neural activity, using the amount of oxygen in blood supplying a given brain region. Moreover, the neurovascular coupling—alterations in local perfusion that occur in response to neuronal activity changes—affect fMRI and not [18F]FDG-PET signals. These factors may contribute to the robustness and reproducibility of [18F]FDG-PET connectivity measures. Metabolic connectivity refers to the functional relationships between [18F]FDG-PET measurements in different brain regions. Various analytical

approaches exist to examine such relationships: (i) seed correlation or interregional correlation analysis (IRCA), (ii) independent component analysis (ICA), and (iii) regions of interest (ROI)-based approaches (for a more comprehensive review, also see [10][11]).

3.1. Seed Correlation or Interregional Correlation Analysis (IRCA)

This voxel-based method relies on the *a priori* selection of ROIs or seeds, extracting the average tracer uptake from that region. Then voxel-wise correlations between average uptake in the seeds and the rest of the brain's uptake are calculated [8]. Thus, these steps allow for obtaining the connectivity map of the seeds of interest. The seed can be selected in either a data-driven fashion [39][40][41] or on the basis of an *a priori* hypothesis [42][43]. In the data-driven approach, the seeds resulting from previous data analysis are usually the clusters obtained from the first round of univariate analysis [39][40][41]. On the other hand, the seeds' selection occurs following concrete *a priori* hypotheses [42][43]. The resulting networks have similar topographies to those obtained with resting-state fMRI [44], ensuring a higher discrimination property in some instances.

3.2. Independent Component Analysis (ICA)

The ICA is a multivariate approach based on voxel-wise methods, as well as IRCA. Assuming that the PET signal figured as a mixture of statistically independent components, ICA has its foundation in PET signals' multivariate decomposition across the brain [44]. This method allows for identifying coherent brain networks (for example, the resting state networks) in a data-driven manner without the need to select a specific seed/ROI in advance. However, the number of components to be extracted need to be set by the investigator. The selection of those components with pathophysiological or anatomo-functional meaning is crucial, discarding pure statistical noise components. ICA represents the method of choice for connectivity analysis using fMRI data. Some studies investigated ICA's applicability on [18F]FDG-PET data for large-scale network estimation [44][45][46]. Although the main resting-state networks are identifiable in both two imaging modalities—fMRI and [18F]FDG-PET data—there is a lack of a complete spatial overlap [45][46]. This mismatch suggests that fMRI and [18F]FDG-PET may capture different aspects of network integrity.

3.3. Regions of Interest (ROI)-Based Approaches

ROI-based approaches allow for computing a "connectivity matrix" starting from selecting a set of target regions. ROIs can emerge according to *a priori* hypothesis, i.e., ROIs belonging to a specific anatomo-functional system of interest or a data-driven approach, i.e., ROIs covering the whole brain. Partial correlation analysis and sparse inverse covariance estimation (SICE) are two widely used ROI-based approaches [11]. The former allows for estimating the degree of linear association between each couple of selected ROIs, factoring the contribution of all remaining ROIs. Partial correlation analysis overcomes the limitations of simple correlation analysis, which captures paired information and cannot characterize the effect of multiple interacting brain regions [47]. SICE finds the estimated value of inverse covariance, thereby indirectly providing a measure of partial correlation [4][47]. The advantage of SICE is that it can estimate molecular connectivity even if the number of subjects included in the analysis is less than the number of ROIs (which is relatively frequent in PET studies) [47]. This aspect is essential

for connectome assessment because connectivity studies select many ROIs covering the entire brain. Once the SICE algorithm estimates the whole brain connection matrix, it is possible to calculate the graph theory indexes, e.g., the brain hubs and modules, and changes in node and global network characteristics [48].

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