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Application of advanced brain positron emission tomography–based molecular imaging for a biological framework in neurodegenerative proteinopathies

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Abstract

Introduction: A rapid transition from a clinical-based classification to a pathology-based classification of neurodegenerative conditions, largely promoted by the increasing availability of imaging biomarkers, is emerging. The Framework for Innovative Multi-tracer molecular Brain Imaging, funded by the EU Joint Program - Neurodegenerative Disease Research 2016 "Working Groups for Harmonisation and Alignment in Brain Imaging Methods for Neurodegeneration," aimed at providing a roadmap for the applications of established and new molecular imaging techniques in dementia.
Methods: We consider current and future implications of adopting a pathology-based framework for the use and development of positron emission tomography techniques.
Results: This approach will enhance efforts to understand the multifactorial etiology of Alzheimer's disease and other dementias.
Discussion: The availability of pathology biomarkers will soon transform clinical and research practice. Crucially, a comprehensive understanding of strengths and caveats of these techniques will promote an informed use to take full advantage of these tools.
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1. Introduction

Ever since its introduction 40 years ago, molecular imaging with positron emission tomography (PET) techniques has revolutionized our ability to *in vivo* assess brain pathology and function. For years, the use of PET-based biomarkers, such as regional reductions in brain glucose metabolism or dopaminergic alterations, has been supportive for clinical practice and crucial in research [1,2]. Today, several PET biomarkers are fundamental tools in the diagnostic workup of different neurodegenerative conditions, including Alzheimer's disease (AD), the most common cause of dementia worldwide [3,4].

Concurrently, the clinical neuroscience field has been rapidly moving from essentially a clinical syndromic diagnosis, eventually corroborated by biomarkers, to a pathology-driven, biological definition of neurodegenerative conditions [5]. This shift was likely promoted by the

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increasing availability of both fluid- and imaging-based pathology biomarkers, as well as by increasing evidence of a sometimes-low specificity of clinical diagnosis in predicting pathology at autopsy [6]. It is now widely accepted that the same clinical syndrome, for example amnestic, can be associated with diverse underlying pathologies, ranging from AD to Lewy body disease or frontotemporal lobar degeneration spectrum, including tau and TAR DNA binding protein-43 pathologies. From another angle, it has been also shown that the same underlying pathology can trigger diverse clinical phenotypes. This is the case, among the others, of AD atypical variants, where the pathognomonic signature of plaques and tangles brain accumulation can distribute with different regional patterns and magnitude, triggering different clinical phenotypes (e.g., language-dominant, visual-dominant, frontal/dysexecutive dominant) [7]. In this framework, PET techniques provide a unique ability to *in vivo* evaluate underlying pathology, essentially pushing the field closer to the ultimate goal of a definite diagnosis in a living patient even at a preclinical stage. The importance of this paradigm shift is not limited to research. For instance, this is primarily important also for sound, informed and targeted clinical trials on possible disease-modifying treatments, where presence of disease must be ascertained to test drug efficacy. This is especially relevant as clinical trials are currently moving toward preclinical phases of AD, where subjects are asymptomatic and thus biomarkers play a central role in identifying the neuropathology in individuals at higher risk of clinical progression [8]. In addition, PET-based biomarkers in clinical trials can also be used longitudinally to investigate target engagement and assess whether a drug, for example amyloid-targeting, is actually able to engage and reduce detrimental proteinaceous accumulation.

1.1. PET-based pathology biomarkers

Two main PET techniques are currently available to investigate *in vivo* brain pathology, namely amyloid PET and tau PET [9,10]. The combination of the two, considering the respective properties and limitations (see in the following paragraphs), allows for the identification and tracking of AD course *in vivo*. Other than the diagnostic implications, brain imaging of amyloid and tau can provide unique insights into the AD pathophysiological cascade, for instance by allowing the evaluation of a sequence of pathological events and their interactions. Considering the original amyloid-cascade hypothesis, posing amyloid accumulation as the causative trigger in AD [11], PET molecular imaging techniques have recently allowed its more detailed scrutiny [11]. In addition, *in vivo* imaging of neuroinflammatory responses in the brain fostered the interest in these techniques by an increasingly recognized role of neuroinflammation in the pathophysiological cascade of multiple neurodegenerative conditions, including AD.

1.1.1. Amyloid PET

The term amyloid PET refers to all those PET procedures using radioligands that bind to amyloid plaques in the brain [10]. The first tracer to be introduced, more than a decade ago, was the carbon-labeled Pittsburgh Compound B, or ^{11}C-PiB, which is still the most used in research applications due to very favorable properties [10]. After several years, many other tracers have been developed and tested in humans [10]. Of these, three fluorinated radioligands have also been approved for clinical use by regulatory agencies such as the Food and Drug Administration and the European Medicines Agency, including the ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol [10]. The introduction of this technique revolutionized research in AD, being rapidly implemented into AD research diagnostic criteria [3,4]. The strength of this approach relies on the high consistency between amyloid PET evidence and autopsy tissue evaluation, as shown by multiple PET-to-autopsy studies [12]. This predictive potential is both positive, that is a positive amyloid PET is very likely to be associated with a positive neuropathology examination, and negative, that is a negative amyloid PET, especially in symptomatic phases, is likely to exclude a positive neuropathology examination. The ability to rule in/rule out AD can be particularly useful in specific clinical scenarios, as highlighted by the Appropriate Use Criteria, such as in very early symptomatic phases, in atypical cases, and in specific differential diagnostic settings [13]. One of the most remarkable outcomes of amyloid PET research was, however, the evidence for significant brain amyloid deposition in neurodegenerative conditions other than AD, such as in Lewy body disease, as well as in normal aging [14,15]. Overall, rates of amyloid positivity tend to increase with age, with estimates in cognitively normal subjects ranging from about 30% at age 70 to about 40% at age 80 [14]. This evidence has important implications for both early and differential diagnosis as well as for research practice, emphasizing how the same pathology can be observed across different conditions.

1.1.2. Tau PET

The investigation of brain tau protein accumulation *in vivo* has been available only for few years, but preliminary studies have already highlighted the groundbreaking potential of this technique [9,10]. A crucial difference between amyloid PET and tau PET is indeed the complexity and heterogeneity of the targets. Tau pathology can be extremely diverse, having different structures (e.g., 4-repeat/3-repeat) and conformations (e.g., paired helical filaments, straight filaments, and so forth) [10]. Different tau PET radioligands have been developed and tested in humans, most of which specifically designed to target the tauopathy observed in AD [16]. Preliminary studies with this technique have consistently shown a very significant and extensive cortical tracer

uptake in AD, with notably some variability considering clinical phenotypes and also the age of onset [9]. Consistently, postmortem autoradiographic studies have shown extensive and intense binding of tau PET ligands to paired helical filaments in AD brain tissue specimens [17]. Compared with amyloid PET, for which the available literature is less consistent, tau PET uptake has been shown to correlate with neurodegeneration and cognitive deficits, being also able to accurately track disease progression [9]. Possibly due to the pathological heterogeneity of tauopathies, that is a complex combination of isoforms and morphology, currently available tau PET techniques have provided rather underwhelming results in non-AD tauopathies, such as progressive supranuclear palsy and corticobasal degeneration. Several studies in these conditions have indeed shown significant tracer binding in biologically meaningful regions [18] but, nevertheless, postmortem autoradiographic studies have also shown overall weaker or null staining of the same tracers to non-AD tauopathies or other pathologies, such as TAR DNA binding protein-43 [17]. This discordance between *in vivo* regional patterns of meaningful uptake and *in vitro* weak/null binding of the tracer to the actual pathology is currently under investigation [17], especially in light of the known nonspecific binding some of these tracers show [19].

1.1.3. Neuroinflammation PET

Other than amyloid and tau PET, *in vivo* imaging of inflammatory responses in the brain has recently gained interest in clinical neuroscience research [20]. The majority of research in this field has focused on imaging of microglia activation, mostly targeting the 18 kDa translocator protein (TSPO), an outer mitochondrial membrane protein overexpressed by microglia during activation [20,21]. The application of these techniques has provided unique insights into *in vivo* dynamics of neuroinflammation in various neurodegenerative conditions, often showing significant microglia activation in biologically meaningful, disease-specific regions such as temporoparietal lobes in AD [20]. These techniques have also been used to delineate temporal trajectories of microglia activation along disease course [22], with preliminary applications also to test effects of immunomodulatory therapies, such as in Parkinson's disease and multiple system atrophy [23,24]. While compelling, these studies have nevertheless highlighted the limitations of these techniques. First, TSPO seems to be not an ideal target from the methodological standpoint, given its low-grade expression in the normal brain parenchyma and its endothelial binding, its expression to cell types other than microglia such as astrocytes, as well as a known genetic polymorphism modulating binding of some TSPO radioligands [25]. Additionally, microglia are known to show complex and dynamic types of activation, which can be both beneficial or detrimental [26]. As TSPO seems to be not able to differentiate functional phenotypes, new PET targets are currently under evaluation [27].

1.2. Relationships between pathology and topographical functional biomarkers

The availability of amyloid-, tau-, and neuroinflammation PET techniques has also enabled novel multimodal studies to evaluate *in vivo* the crucial relationships between pathology and functional/topographical markers of neurodegeneration. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG-PET) is the most widely used and validated *in vivo* biomarker of synaptic dysfunction, with a well-known diagnostic and prognostic value in neurodegenerative conditions [2,28]. ^{18}F-FDG-uptake is considered to reflect neuronal/synaptic activity and density [29-31], notwithstanding the possible contribution of other processes influencing the metabolic signal, such as astrocytes' activity [32]. Previous multimodal ^{18}F-FDG-PET/amyloid PET studies have provided evidence for an overall absent or weak relationship between amyloid plaques accumulation and colocalized synaptic dysfunction in AD (among the others, [33-37]). This evidence is consistent with other clinicopathology data showing that the burden of amyloid plaques postmortem correlates weakly with neurodegeneration and/or cognition [38,39]. This is supported by the considerable proportion of amyloid-positive cognitively normal elderly subjects [14]. The fundamental caveat of amyloid PET is that currently available radioligands target only the insoluble amyloid plaques and not the most toxic soluble oligomers. Thus, much of the toxic effects of the oligomers are underestimated. Compared with amyloid PET, preliminary data on tau PET otherwise showed a tight local association between neurofibrillary tau tangles accumulation and brain glucose hypometabolism in both typical and atypical AD [33,34,40-42]. This is also in keeping with the association between regional tau PET signal and clinical status/cognitive deficits found in the AD spectrum (among the others, [43-46]). Both tau PET and ^{18}F-FDG-PET represent crucial tools in providing *in vivo* biomarkers for neurodegeneration. As for neuroinflammation PET, only few studies have evaluated the *in vivo* relationships between microglia activation and brain glucose metabolism [47-49], mostly focusing on AD and on Parkinson's disease and dementia. Overall, the available data show topographical concordance between these biomarkers, with neuroimmune activation detected by PET in AD- and Parkinson's disease and dementia–associated hypometabolic regions and beyond [47-50], possibly predicting the severity of metabolic decline at follow-up [48]. On a technical note, multimodal neuroinflammation/glucose metabolism studies could be partially biased by the locally activated immune cells that by increasing their glucose utilization may attenuate the local cerebral hypometabolism detected by ^{18}F-FDG-PET [51].

1.3. Future applications and caveats

The adoption of a taxonomy of neurodegenerative conditions based on underlying pathology will in the future pave the way to a thorough consideration of PET molecular

imaging techniques as crucial tools. A similar approach will benefit both in clinical practice, for a more accurate early and differential diagnosis, and research, giving unique chances of testing pathophysiological models, comorbidity, and pathology/neuroinflammation dynamic interactions in neurodegeneration. One of the most remarkable implications will be the routine introduction of such pathology evaluations in clinical trials for not only accurate screening of eligible participants but also crucially evaluating whether tested drugs are having an actual effect on pathology burden. The adoption of a research framework for AD based on biological definitions has been just proposed [5], with PET- and fluid-based biomarkers playing a central role for the identification of underlying AD. Parallel to the future availability of new pathology tracers, such as targeting alpha-synuclein, 4R tau, or TAR DNA binding protein-43 pathology, the future holds promise for detailed investigations and redefinitions of the different neurodegenerative conditions. With different imaging markers available, future studies will be able to assess copathology distribution at the whole brain level, possibly tracking its time course and topography. A comprehensive understanding of pathology comorbidities, phenotype complexity, and limits of the available PET molecular imaging techniques, together with the adoption of well-validated quantification approaches, will allow an appropriate and fruitful use of these neuroimaging techniques.

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RESEARCH IN CONTEXT

1. Systematic review: The authors referred to commonly used academic engines (PubMed, Google Scholar) to search relevant literature.
2. Interpretation: Strengths, weaknesses, and potentials of PET pathology biomarkers are recognized and discussed in relation to the study of neurodegenerative conditions and their classification.
3. Future directions: The availability of new PET pathology biomarkers, together with the validation of the currently available, will substantially transform the landscape of clinical and research practice. An informed and appropriate use of such tools will be quintessential to the advancement of the field.

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