THE QUARTERLY JOURNAL OF

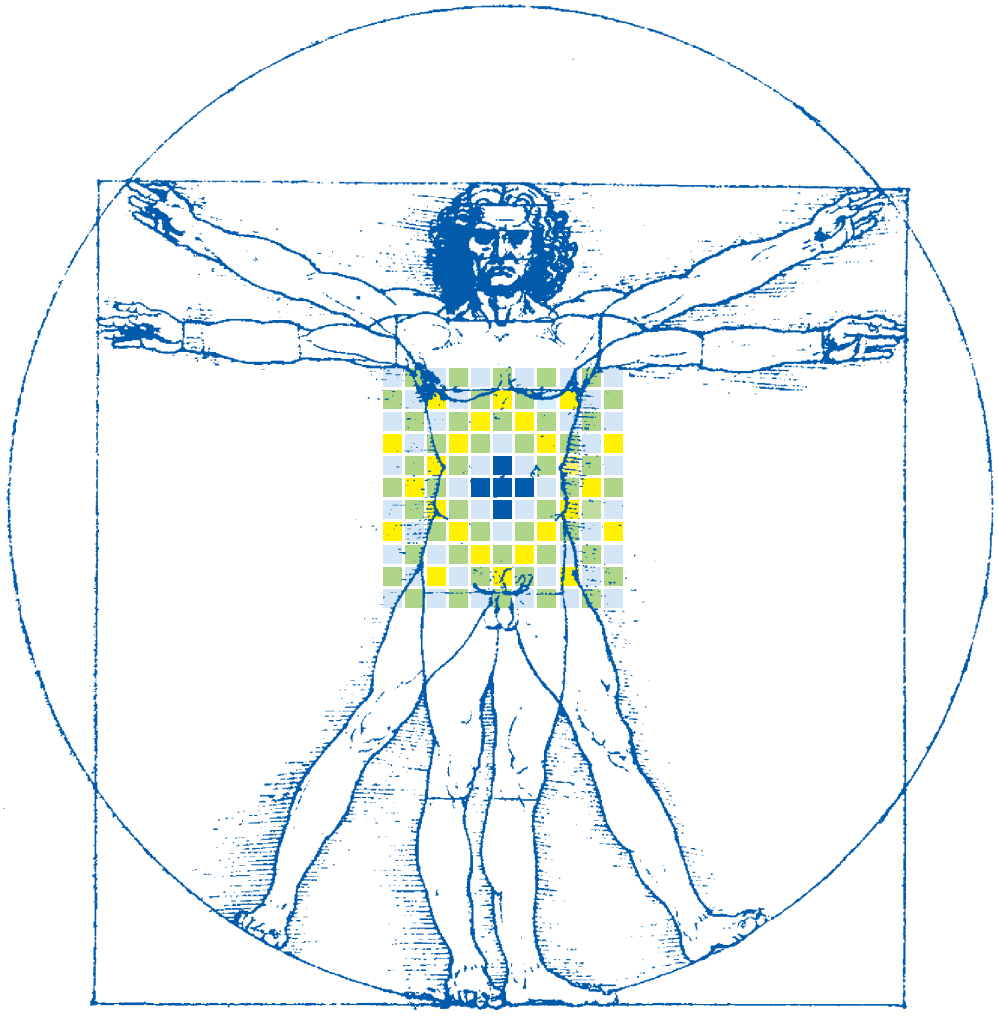
NUCLEAR MEDICINE AND MOLECULAR IMAGING

AFFILIATED TO

THE SOCIETY OF RADIOPHARMACEUTICAL SCIENCES

THE INTERNATIONAL RESEARCH GROUP OF IMMUNOSCINTIGRAPHY AND THERAPY (IRIST)

VOLUME 58 - No. 4 - DECEMBER 2014



PUBBLICAZIONE PERIODICA TRIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A. P. D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 1824-4785 TAXE PERÇUE

PUBLISHED BY MINERVA MEDICA

PET IN NEURODEGENERATIVE DISORDERS

Guest Editor: M. Pagani and G. Capriotti

EDITORIAL

Q J NUCL MED MOL IMAGING 2014;58:329-31

Functional imaging in neurodegenerative disorders: past, present and future

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[…] we are like dwarves perched on the shoulders of giants, and thus we are able to see more and farther than the latter. And this is not at all because of the acuteness of our sight or the stature of our body, but because we are carried aloft and elevated by the magnitude of the giants […]

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The present monographic issue of the Quarterly Journal of Nuclear Medicine and Molecular Imaging is dedicated to the role of functional imaging in the broad field of neurodegenerative disorders, with a special focus on some of the most relevant topics of the last decades, of the present time and of the near future. Functional neuroimaging is close to reach the time in which it will be routinely implemented in clinical practice and in which the principles of "molecular imaging" will aid clinical diagnosis disclosing the fine extra- and intracellular deposit of protein aggregates and neuroinflammation markers. The almost simultaneous advancement in nuclear medicine techniques, *i.e.*, PET-MRI, along with the development of new tracers and the implementation of more and more sophisticated image analysis software will assign to neuroimaging a preeminent role in the diagnostic algorithm both in neurological and psychiatric practice.

To reconnect with the introductive quote by Bernard of Chartres, from our point of view nuclear medicine has also "giants and dwarves". The undisputed ruler in nuclear medicine for the past decades and of our present time is ^{18}F-FDG-PET, which is undoubtedly one of our giants. It still plays a key role in brain imaging, and most certainly it will in the near future.

Karl Herholz in his review aims at providing a valuable guidance to physicians reading brain ^{18}F-FDG-PET scans in neurodegenerative disorders by describing the criteria for data acquisition and reconstruction protocols. The characteristic findings of Alzheimer-related hypometabolism are described and compared with other related pathological conditions. This complete review gives also tips on how to display the scans as well as a detailed description of the patterns of ^{18}F-FDG distribution in the most common dementing disorders. It is an exhaustive compendium for all physicians interested in neuroimaging.

FDG-PET and MRI have extensively been used to investigate the functional and anatomical changes, respectively, occurring in patients with amyotrophic lateral sclerosis (ALS).[1] The review by Quartuccio *et al.* describes how PET, which has not been used yet in clinical routine for the evaluation of patients with ALS, can be used as a potential tool in the diagnostic algorithm of the disease. Recent studies [2, 3] suggested a possible role of FDG-PET as ALS biomarker highlighting the need, common to all neuroimaging

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studies, of recruiting large cohorts of patients, irrespectively if in a single center or in a multicenter study. This will result in robust statistics and will contribute to reliably describe metabolic patterns typical of neurodegenerative disorders to be used as biomarkers in clinical practice.

^{18}F-DOPA could also be considered a giant having been the most widely used ^{18}F-labelled tracer for dopaminergic imaging for several years.[4] Despite the "seniority" of ^{18}F-DOPA the radiopharmaceutical is seldom used in the clinical daily practice. The aim of Darcourt and colleagues in their review is to demonstrate that ^{18}F-DOPA is now mature for the purpose. The old debate about adaptive changes occurring in early stages of Parkinson's disease (*i.e.*, up-regulation of the AADC enzyme), which could lead to an underestimation of the nigro-striatal loss in the early phases of the disease,[4] is described in detail with the authors coming to the conclusion that the sensitivity of ^{18}F-DOPA, is comparable to that of DaT imaging and therefore ^{18}F-DOPA can be considered mature for the diagnosis of parkinsonian syndromes in clinical routine.

The topic of the review written by Arnaldi *et al.* is the premotor phase of Parkinson's disease (PD). The main non-motor symptoms of PD, such as hyposmia, mood alterations, REM sleep behavior disorder (RBD) and constipation, are described.[5-8] Amongst them, RBD, given its low prevalence in the general population, is depicted as the best target for the identification of PD in the pre-motor phase, especially if present in association with other non-motor symptoms of PD.[9] The correct identifications of PD patients in the pre-motor phase could facilitate the development of neuroprotective and neuromodulatory strategies in early stages of disease. The role of dopaminergic and non-dopaminergic imaging, as well as the study of cortical functions in pre-motor PD is described in the paper and, as a new future perspective, the authors introduce to the readers a very active area of research which is oriented to the development of specific radioligands for the imaging of α-synuclein.

The importance of the cholinergic system in the pathogenesis of AD and PD is extensively reviewed by the group of Sabri in Liepzig. The focus of Meyer *et al.* is basically oriented to the role of PET and SPECT in imaging the most abundant subtype of nicotinic acetylcholine receptors (nAChRs), the α4β 2 subtype, which is expressed on the postsynaptic side of the cholinergic neurons and plays an important role in cognitive functions.[10, 11] The authors also examined the relationship between nAChRs availability, cognitive impairment and motor/non-motor symptoms in AD and PD respectively. Future directions of research in the imaging of the cholinergic system are oriented to the development of new radioligands targeting the α4β 2 subtype with more favorable characteristics, or to other interesting subtypes of nAChR, such as the α6 subunit, which plays an important role in the modulation of the dopaminergic system, and the α7 subunit.

A new interesting perspective on disclosing the neurobiology of neurodegenerative disorders is given by the group from Fukui. Okazawa and colleagues describe oxidative stress and mitochondrial dysfunction as the most probable molecular mechanisms involved in the neuronal impairment of several neurodegenerative disorders. The ability of some PET radioligands, the most promising being Cu-labeled ATSM, of imaging *in vivo* the pathophysiological changes occurring in the brain areas exposed to oxidative stress is very intriguing as well as the possibility to investigate such conditions from a novel point of view. Despite only a few studies have been conducted in this field so far, this is a very interesting direction for research in the near future.

We end the overview with the paper dedicated to Aβ and tau imaging in dementia, the very hot topic in neuroimaging of the present time and definitely of the near future. Several efforts have been made in the last decade to develop tracers allowing *in vivo* visualization of the two pathological hallmarks of AD, namely extracellular amyloid plaques [12] (consisting of insoluble fibrillary β-amyloid peptides) and intracellular tau aggregates, the neurofibrillary tangles (NFT). Zwan and colleagues, of the group of Villemagne in Melbourne, describe the long path which led to the development of PET selective Aβ radiotracers, selective tau radiotracers and also non-selective pan-amyloid tracers, showing affinity for both Aβ plaques and NFT. While several studies have already been published on Aβ imaging, which is already moving into clinical practice, little has been written so far on the most recently developed tau radiotracers and the debate about their clinical utility and the preference torward either of them has just started.

Functional imaging in the field of neurodegenerative disorders will most likely see progresses in leaps and bounds in the near future, we can't wait to see them and to come to know who will be the next "giant".

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