Achievements in Neuroimaging during the past 25 years

Introduction
From the historical perspective, nuclear medicine contributions to brain imaging started in the 1950s with cerebral blood flow (CBF) measurements determined by the Kety-Schmidt method and inert radioactive gases. Inhalation methods with venous sampling initially allowed hemispheric CBF determination [1]. In the early 1960s, intra-arterial injection methods with externally placed scintillation detectors first demonstrated the possibility of performing regional CBF evaluation [2]. However, these methods were used more as research tools in physiology than for direct patient care. The same was true for the pioneering brain PET studies [3].

At the beginning of the 1980s, brain SPECT for perfusion studies became more amenable to clinical use. The first tomographic images were obtained with krypton-85 and a conventional gamma camera [4]. Even more encouraging, however, was the availability of dedicated tomographic cameras [5] and the first results using a stable radiopharmaceutical: $^{131}$I-IMP [6-8]. However, despite interesting results, neuroimaging was still considered to be a research tool due to the lack of more widely available radiopharmaceuticals. Many nuclear physicians were still "neuroscetics!" As stated at this time by Coleman et al. in their editorial in 1982, "the future of SPECT in studying regional brain function appeared very promising. A compound had to be developed that could be labelled with Tc-99m in a kit form" [9].

This compound was developed in 1984 [10, 11] and introduced by Amersham International precisely 25 years ago on the occasion of the first EANM Milan meeting. HMPAO labelled with $^{99m}$Tc made it possible to perform a tomographic clinical assessment of regional CBF with good sensitivity and spatial resolution using rotating gamma cameras [12]. This can be considered as the landmark representing the beginning of the application of neuro-nuclear medicine in patient care. This advance was further strengthened by the development of PET centres using $^{15}$O-water and the greater availability of $^{18}$F-fluorodeoxyglucose (FDG) for imaging of brain metabolism as well as by the later availability of a second $^{99m}$Tc-labelled SPECT perfusion agent [13].

A brief description of the main achievements accomplished by nuclear medicine imaging in four main domains of neurology follows.

Achievements in stroke: a better understanding of pathophysiology
Given the clinical importance of cerebrovascular disease, which is the third most common cause of death in Europe, it is unsurprising that this was the first area in which nuclear brain imaging gained clinical utility, with its value being particularly evident in the assessment of stroke. Clinical development was also stimulated by the spectacular knowledge obtained from PET research studies on the pathophysiological changes in acute ischaemic stroke. Using $^{15}$O-water PET, fundamental phenomena were identified. For example, in the acute phase of an ischaemic stroke, uncoupling between regional
CBF (rCBF) and oxygen metabolism (CMRO₂) is observed and three different abnormal vascular conditions can be found [14]: (i) irreversibly damaged tissue (low rCBF and CMRO₂), which usually represents the core of the ischaemic area; (ii) an ischaemic penumbra zone surrounding this core, which, though severely ischaemic and not functioning, is still viable (with increased CMRO₂, also called “misery perfusion”) and can be salvaged; (iii) less frequently, a peripheral hypometabolic but viable zone that can receive relatively increased rCBF, called “luxury perfusion”. These types of findings dramatically changed not only the understanding of stroke pathophysiology but also its specific management. For example, it was shown that individual assessment of each subject was important in addition to the rigid time window rules (“time is brain”) for acute stroke treatment. Active recanalisation therapy should be reserved for patients with significant penumbra and avoided in patients who present without hypoperfusion or with extensive irreversible tissue damage [15] since they bear a very high risk of haemorrhage with a very low likelihood of successful recanalisation. Perfusion SPECT, more suitable than PET in the context of emergencies, demonstrated very elegantly that it could provide this relevant information [16-18]. However, the clinical recommendations for clinical use of thrombolysis within 3 h of onset of symptoms left very little space for SPECT imaging. Furthermore, the development of perfusion-diffusion MRI further limited developments of nuclear medicine for this indication.

Achievements in epilepsy: non-invasive localisation of the epileptic zone
Up to 30% of patients with epilepsy develop refractory seizures that are not fully responsive to anti-epileptic medication. Partial epilepsy is the most common type of refractory epilepsy and in a small number of cases, the surgical removal of the epileptogenic zone is the only treatment option. The utility of SPECT and FDG PET has been investigated during the work-up of these patients prior to surgery. When PET was first applied to epilepsy [19], it was anticipated, and subsequently confirmed, that it would provide useful information about brain metabolism relevant to patient management. FDG PET in association with MRI is useful for localisation of the epileptic focus, especially in temporal lobe epilepsy, presenting as an area of hypometabolism. This area is often more extensive than the epileptic focus itself since it shows neuronal loss as well as the epileptic network involved in seizure propagation. FDG PET is also capable of finding small hypometabolic areas when MRI is negative which correspond to subtle abnormalities responsible for the seizures. FDG is a good predictor of post-surgical outcome. Perfusion SPECT is also capable of showing corresponding inter-ictal hyperperfusion [20]. But the unique advantage of the SPECT perfusion tracers is the possibility of injecting them during the seizure, “freezing” the ictal perfusion state and allowing later imaging [21]. Such ictal SPECT has proven its value for presurgical evaluation even if the results are highly dependent on the time of injection with respect to the seizure dynamic. Comparison between inter-ictal and ictal SPECT data is improved by image subtraction and co-registration with MRI data, leading to the so-called SISCOM technique (subtracted ictal SPECT co-registered to magnetic resonance) [22].

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Achievements in movement disorders: diagnosis of the different parkinsonian syndromes

It was in the late 1970s that Garnett and co-workers reported on the successful application of \(^{18}\text{F-DOPA}\) PET for PET imaging of central dopaminergic neurons [23]. This technique was used clinically to demonstrate or exclude dopaminergic cell loss in patients suffering from movement disorders. Another approach to visualise and quantify dopaminergic neurons is the use of radiotracers for the dopamine transporter. Since the late 1980s, studies have shown the possibility of quantifying dopaminergic neurons in vivo by means of PET or SPECT using the dopamine transporter as a marker [24, 25]. In the year 2000, a SPECT tracer for the dopamine transporters \((^{123}\text{I-FP-CIT})\) was licensed to differentiate Parkinson’s disease from essential tremor, and in 2007 the same tracer was also licensed to differentiate Alzheimer’s disease from dementia with Lewy bodies [26, 27].

Shortly after the successful development of central dopamine D$_2$ receptor imaging with PET in humans, initial PET and SPECT studies showed that several movement disorders, such as progressive supranuclear palsy and multiple system atrophy, are characterised by loss of striatal D$_2$ receptors [28]. In the 1990s, a SPECT tracer for dopamine D$_2$ receptors \((^{123}\text{I-IBZM})\) was licensed for clinical studies.

Besides specific D$_2$ receptor imaging, reports appeared in the 1980s that described abnormal brain glucose metabolism in movement disorders such as Parkinson’s disease, multiple system atrophy and progressive supranuclear palsy [29]. Nowadays, FDG PET is frequently used in routine clinical practice in the differential diagnosis of parkinsonism.

Achievements in degenerative dementias: from metabolic patterns to amyloid imaging

Very early on, brain nuclear imaging made a significant contribution to the understanding and the diagnosis of neurodegenerative diseases such as Alzheimer’s disease (AD) which is a major public health issue. Based on the initial knowledge obtained from PET research studies which had identified different metabolic patterns of dementias [30], the advent of SPECT with \(^{99m}\text{Tc-HMPAO}\) 25 years ago and \(^{99m}\text{Tc-ethyl-cysteine dimer}\) in the early 1990s paved the way for wider application of perfusion SPECT in routine clinical diagnosis.

During the 1990s and early 2000s, a huge number of papers highlighted the potential and the limitations of SPECT in the differential diagnosis of dementia. AD was characterised by hypoperfusion in the posterior associative cortex, mainly in the medial temporal lobes, parietal lobes, posterior cingulate and precuneus, often with an asymmetric presentation in the early stages. Meta-analysis of sensitivity and specificity (total accuracy) of SPECT in AD has revealed values between 70% and 80% in comparison to healthy controls, mainly depending on the stage of the disease and the method of data analysis [31]. Since the identification of mild cognitive impairment (MCI; a syndrome that is frequently an intermediary of normal cognition and AD) in 1999 [32], SPECT studies have largely focussed on investigating this area, showing reasonable accuracy for
predicting which MCI patients will convert to AD. SPECT has also consistently revealed hypoperfusion in the frontal and anterior temporal associative cortices [33] in frontotemporal lobar degeneration and its variants, behavioural frontotemporal dementia (FTD) and progressive aphasia.

The last decade has been characterized by the widespread availability of FDG PET, which has greater accuracy than SPECT. This is due to both higher spatial resolution and the intrinsic value of the technique's direct measurement of glucose consumption, which captures early degenerative phenomena at the synaptic level. The diagnostic accuracy of FDG PET approaches 90% in patients with early AD as compared to normal controls and FDG PET is now the standard reference for radionuclide brain imaging in dementia [34, 35]. Furthermore, it has been recognised as a reimbursable procedure by Medicare (U.S.) for the differential diagnosis of AD and FTD. At present, there are ongoing efforts in Europe to register its use to this end, in line with the overwhelming scientific evidence [36]. Statistical analysis at both the group and the individual level has further highlighted the diagnostic potential of FDG PET, and can be performed using free software, such as Statistical Parametric Mapping (SPM) [37] and Statistical Surface Projection (SSP) [38]. The last part of the FDG PET success story is its inclusion as a “biomarker” for the diagnosis of AD before clear symptoms of dementia become evident (“prodromal AD”) under the revised criteria for the diagnosis of AD, virtually written in parallel by the International Psychogeriatric Association [39, 40] and by the National Institute of Aging-Alzheimer Association task force between 2007 and 2011 [41].

The most promising recent development has been the identification of radiopharmaceuticals able to label amyloid in the brain (amyloid PET). The earliest experimental data appeared about 10 years ago and used Pittsburgh compound B (PIB) labelled with 11C [42]. This has been followed by the development of new drugs labelled with 18F [43], which are currently in phase III trials and will soon be commercially available. With these compounds, it is feasible to image brain amyloidosis in the very early stages of AD and possibly in asymptomatic subjects at risk for AD. In fact, amyloid deposition precedes the onset of first cognitive symptoms by a number of years (at least 10). The finding of positive amyloid PET scans in a proportion of “healthy” controls and the still limited follow-up data in these subjects represents a field of uncertainty that will be unravelled in the near future. Moreover, amyloid PET is a potentially powerful method to track the efficacy of drugs that “clean” the brain of amyloid. At present other PET targets such as acetylcholine and serotonin receptors or neuro-inflammation are being actively explored and are likely to add further value to the well-established FDG and amyloid PET tools.

Conclusion
Over the last 25 years, neuro-imaging in nuclear medicine has become well embedded in patient care. It has continually provided unique new information on various neurological disorders such as stroke, epilepsy, Parkinson's disease and degenerative dementias and has contributed significantly to patient management. The current evidence clearly indicates that its role will continue to grow. The heavy health care burden of neurodegenerative diseases unfortunately guarantees that more and more patients will need to
have access to the current techniques of neuro-PET, such as FDG metabolic imaging or amyloid load evaluation. Nuclear medicine is also focusing on psychiatric disorders such as depression and anxiety. Furthermore, the large number of potential new targets for molecular neuro-imaging also guarantees important future developments as well as the development of multimarker and multimodal imaging. Therefore, it is clear that neuro-imaging is rapidly becoming established as the second most common indication for PET imaging after oncology.

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