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## **Perspectives of the European Association of Nuclear Medicine on the role of artificial intelligence (AI) in molecular brain imaging**

Francesco Fraioli, Nathalie Albert, Ronald Boellaard, Ilaria Boscolo Galazzo, Matthias Brendel, Irene Buvat, Marco Castellaro, Diego Cecchin, Pablo Aguiar Fernandez, Eric Guedj, et al.

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1 **Perspectives of the European Association of Nuclear Medicine on the role**  
2 **of artificial intelligence (AI) in molecular brain imaging**

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## 72 **The current state of AI in nuclear neuroimaging**

73 As for the whole nuclear medicine community, there is great interest in the molecular brain  
74 imaging field to advance the use of AI in research and translation but foremost in daily clinical  
75 routine settings.

76 As seen with previous methodological imaging advancements, the brain is perfect as the  
77 organ of interest to start with testing such new developments. This is not only because multi-  
78 modality image co-registration is much easier for the head compared to other body parts, but  
79 also because large brain image databases are often easily accessible in case of brain imaging.  
80 However, standardization of clinical brain image recording and imaging protocols as well as  
81 efficient dissemination of data will be essential before data from different centers can be used  
82 as input by AI [1]. In this context, it is worth to emphasize that often images are not sufficient  
83 for feeding AI algorithms. There is need to have them annotated, and ideally, additional data  
84 should be associated to the images (patient follow-up, omics, etc.).

85 For these reasons, large validation studies through Consortium datasets have emerged in  
86 molecular neuroimaging including Alzheimer's Disease Neuroimaging Initiative (ADNI),  
87 Parkinson's Progression Markers Initiative (PPMI), and Open Access Series of Imaging Studies  
88 (OASIS). However, more data are still needed for the complete translation to clinical routine  
89 use.

90 Open standard datasets will be essential for the development of AI, even though it may  
91 involve significant costs. One possible cost-efficient solution is to make use of realistic Monte  
92 Carlo simulations techniques for generating in silico neuroimaging datasets, thus allowing for  
93 data augmentation from patient data [2, 3]. Another solution to address this challenge is  
94 federated learning, which allows AI to be trained on decentralized datasets from multiple  
95 hospitals, while ensuring data privacy and security. Federated learning has been already  
96 applied to training of AI models in different brain PET challenges, such as reconstruction,  
97 segmentation, and denoising using brain PET datasets from multiple institutions [4]. An even

98 more recent improvement is swarm learning, which combines federated learning with  
99 blockchain technologies to further ensure the robustness of the learning process [5].

100 As with medical imaging in general, in the case of molecular brain imaging, the process from  
101 data acquisition to diagnosis involves numerous steps (e.g., image acquisition and  
102 reconstruction, image segmentation, extraction of imaging biomarkers, image interpretation,  
103 patient stratification).

104 The next years will show whether AI is, in the case of molecular brain imaging, suitable to  
105 support or even, at least in some applications, replace nuclear medicine physicians. As  
106 examples, rather straightforward binary decisions like positivity vs. negativity in case of  
107 amyloid PET imaging, or rather complex and experience-dependent differential diagnoses like  
108 those obtained by FDG PET imaging in dementia disorders or atypical Parkinsonian syndromes  
109 might be better obtainable in the future by AI.

110

### 111 ***Image acquisition***

112 In the data acquisition stage, deep learning models have been utilized to estimate time-of-  
113 flight (ToF) and improve the quantitative accuracy and diagnostic confidence of PET images  
114 reconstructed without ToF, specifically for brain PET [6]. In tomographic reconstruction, AI  
115 has been employed to enhance the quality of PET and SPECT images by reducing noise and  
116 enhancing image contrast during reconstruction [7]. Deep learning techniques have also  
117 demonstrated effectiveness in providing accurate and generalizable PET attenuation and  
118 scatter correction methods and, interestingly, attenuation correction methods without CT [8].  
119 Finally, generative adversarial networks have been employed for motion correction in brain  
120 PET, effectively addressing the challenge of head motion artifacts. Also, they can be used to  
121 dramatically shorten scan times/activity amounts needed [9].

### 122 ***Segmentation and registration***

123 In post-processing, AI-based segmentation can overcome the time-consuming and observer-  
124 dependent process of manual annotation of brain structures in PET images [10]. AI can also  
125 assist in the registration of neuroimaging data, via the alignment of images from different  
126 imaging modalities or timepoints and learning the mapping between images and different  
127 modalities. Furthermore, AI can facilitate the extraction of meaningful quantitative  
128 parameters from the images, such as improved amyloid PET quantification without non-

129 specific contributions and amyloid PET quantification without using MRI or CT images [11].  
130 Moreover, AI might provide non-invasive estimations of the arterial input function for brain  
131 PET studies, facilitating adoption of absolute quantification in clinical settings [12].

### 132 ***Interpretability analysis***

133 Interpretability is an essential aspect of AI applications in neuroimaging to promote the  
134 development and translation of AI technologies in clinical settings. Clinicians may offer their  
135 clinical expertise (supervision) to identify potential biases, errors, or limitations in the model,  
136 which can be addressed to improve its performance and generalizability [13]. For instance, a  
137 simple supervision can be the role of clinical and imaging experts to check the accuracy of AI  
138 models in the segmentation process. Some other tasks of AI cannot be easily supervised and  
139 require external validation. So-called explainable AI techniques are rapidly emerging to  
140 improve interpretability, including feature visualization, saliency maps, and decision trees.  
141 These can reveal the key features and patterns that contribute to the model's predictions or  
142 decisions. Another approach is to incorporate robustness measures, such as adversarial  
143 training, regularization, and uncertainty quantification, into the AI model to increase its  
144 resilience to various types of noise, artifacts, or uncertainties [14].

145

### 146 **Specific clinical applications**

147

148 Epilepsy is one of the most common neurological disorders characterized by abnormal  
149 excessive firing and synchronization of neurons leading to seizures. The accurate  
150 identification of the epileptogenic foci is essential to avoid misdiagnosis and select the correct  
151 treatment, especially when resective surgery is necessary in drug-resistant epilepsy [15].  
152 While nuclear medicine neuroimaging is a key diagnostic tool, allowing to evaluate metabolic,  
153 neurotransmission, or perfusion abnormalities occurring in people with epilepsy, there is an  
154 increasing need to define accurate computer-aided tools to support clinicians as  
155 interpretation of the scans is highly complex. In this context, AI-based tools pave the way for  
156 solving such tasks, fostered by the exceptional advancement in the models we have witnessed  
157 in the last years. Machine learning (ML) and deep learning (DL) are currently explored for  
158 diverse tasks as cortical lesion localization (mainly for focal cortical dysplasia — FCD), epileptic  
159 focus detection/lateralization and brain region segmentation (e.g., hippocampus), or for the

160 diagnosis and prognosis of different epilepsy types. Still, AI has been mostly applied to MRI or  
161 EEG recordings (especially for seizure identification and forecasting), while their exploitation  
162 in the nuclear medicine-epilepsy field is still in its infancy, with a few studies largely limited to  
163 [<sup>18</sup>F]FDG-PET briefly reviewed in the following.

164 Despite the methodological advancements, AI applications in molecular imaging of epilepsy  
165 are still limited and confined to specific epilepsy types, possibly because of the difficulties in  
166 finding large (and annotated) datasets to train and generalize the complex AI-based models,  
167 the high heterogeneity of patients with epilepsy, and the need to perform patient-specific  
168 fingerprinting for clinical application. Multi-center initiatives, coupled with advanced DL  
169 models (e.g., multi-task CNNs, autoencoders) and data augmentation methods (e.g.,  
170 generative adversarial networks or large simulated databases (3)), might help to overcome  
171 part of such limitations, providing more generalizable models and a precise fine-grained  
172 characterization of inter-individual patient variability to progress towards personalized  
173 medicine.

174 Some recent studies have also underlined the importance of combining multi-modal imaging  
175 data, such as metabolic PET with structural or functional MRI, often leveraging the value of  
176 simultaneous PET/MRI acquisitions [16]. These multi-modal data coupled with AI models can  
177 increase the accuracy in predicting the surgical outcomes and detecting focal epilepsy lesions  
178 such as FCD [17]. All these approaches therefore deserve further investigations for fully  
179 exploiting their potential and exploring their generalizability in the epilepsy workflow.

180 In neurodegenerative and movement disorders, the differential diagnosis can be complex and  
181 is highly dependent on the expertise of the reader. Therefore, AI may help not only in the  
182 (early) differential diagnosis, especially for less experienced readers, but also in the  
183 differential diagnosis of subtypes of dementia or complex cases with non-fully delineated  
184 pattern of presentation. Multimodal imaging with structural and functional information  
185 combined with fluid-based biomarkers is becoming the standard in the diagnostic landscape.  
186 In this multimodal setting, AI can be particularly helpful for feature selection. Moreover, AI  
187 might also give additional clues about the prognosis. However, the biggest challenge in the  
188 field of AI in neurodegenerative disease is the very limited number of available standards of  
189 truth assessments, i.e., autopsies in previously imaged patients. Future studies need to  
190 overcome the lack of validation studies across different centers and the lack of harmonization  
191 of generally accepted AI algorithms to aid in diagnosis across the neurodegenerative disease

192 spectrum. Moreover, all AI models are data-driven, so pre-processing of imaging data plays a  
193 crucial role. Therefore, pre-processing software also needs to be harmonized and validated.  
194 Accommodation of substantial numbers with standard of truth assessments for validation of  
195 AI application in PET imaging of neurodegenerative disorders remains a challenge and may be  
196 solved by large cohorts such as BioFINDER or ADNI [18]. Conversely, PET itself may also be  
197 used as a standard of truth assessment for AI-driven analysis of fluid biomarkers or omics data  
198 with the goal to find cheap and versatile tools for characterization of neurodegenerative  
199 disorders.

200 AI in neuro-oncology is intensively evaluated allowing simplifying steps in the radiomics  
201 pipeline such as tumor segmentation, increasing data comparability between observers and  
202 more importantly extracting new features from the images of brain tumor patients [19]. AI is  
203 currently primarily represented by radiomics analyses, which must be performed according  
204 to the steps described in the Image Biomarker Standardization Initiative (IBSI) guidelines to  
205 ensure standardization of processes [20], providing promising results with good diagnostic  
206 performances in various clinical indications. Some further improvements are nevertheless  
207 required for the generalization of the observed diagnostic performances, by identifying  
208 specific radiomic signatures that are easily transposable across centers. Notably, these efforts  
209 concern the feature repeatability and harmonization through well-defined multicentric  
210 studies. This is particularly meaningful for the field of neuro-oncology since CNS tumors are  
211 rare diseases with a limited number of patients, requiring data collection from different  
212 centers. Studies of PET multi-tracer radiomics analyses and/or combination with  
213 multiparametric MRI and clinical parameters are also encouraged. Another important point  
214 is that diagnostic performance of radiomics models should systematically be compared to  
215 conventional parameters to really appreciate the added value of AI-related methods in each  
216 clinical indication before implementation in clinical routine. Finally, an important effort is  
217 required to make radiomics data accessible at the individual level, providing an additional  
218 clinical tool to assist nuclear medicine physicians in their decisions.

219 Psychiatric disorders are an exciting new field of application where the association of imaging  
220 and clinical data might foster the diagnosis and evaluation of these disorders. In fact, so far,  
221 their assessment relies almost exclusively on clinical interviews using the Diagnostic and  
222 Statistical Manual of Mental Disorders (DSM) nosography. Yet, the DSM reliability is regularly  
223 questioned by its iterative modifications, lack of reproducibility of current diagnoses, and



224 therapeutic resistance of many patients [21]. In this context, more transdiagnostic  
225 approaches are emerging, and PET and SPECT imaging could be particularly relevant to  
226 explore such disorders mainly characterized by dysfunction, in the absence of morphological  
227 lesions, with the possible implementation of various targets such as the perfusion,  
228 metabolism, neurotransmission and neuroinflammation, and especially the individual  
229 application of artificial intelligence tools for precision medicine [22]. In this line, machine  
230 learning classification from controls has suggested accurate performance to identify patients  
231 with attention-deficit and hyperactivity disorder using multimodal serotonergic brain PET  
232 imaging [23], patients with cocaine dependence using brain perfusion SPECT imaging [24],  
233 patients with internet game disorder using metabolic brain PET imaging [25], and patients  
234 with major depression using serotonergic PET imaging or brain metabolic PET imaging, also  
235 demonstrating the value of this last exploration to predict the response of deep brain  
236 stimulation in this context [26]. Machine-learned analysis of [<sup>18</sup>F]FDOPA PET scans of patients  
237 with schizophrenia also showed good performance for identifying treatment responders and  
238 non-responders, with large potential healthcare cost savings [27]. This translation from  
239 research to clinical applications will need more numerous multicentric studies and to be  
240 supported by a paradigm change in psychiatry towards modern approaches of precision  
241 medicine.

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