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EDITORIAL

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

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The current state of AI in nuclear neuroimaging

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

As seen with previous methodological imaging advancements, the brain is perfect as the organ of interest to start with testing such new developments. This is not only because multi-modality image co-registration is much easier for the head compared to other body parts, but also because large brain image databases are often easily accessible in case of brain imaging. However, standardization of clinical brain image recording and imaging protocols as well as efficient dissemination of data will be essential before data from different centers can be used as input by AI [1]. In this context, it is worth to emphasize that often images are not sufficient for feeding AI algorithms. There is need

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to have them annotated, and ideally, additional data should be associated to the images (patient follow-up, omics, etc.).

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

Open standard datasets will be essential for the development of AI, even though it may involve significant costs. One possible cost-efficient solution is to make use of realistic Monte Carlo simulations techniques for generating in silico neuroimaging datasets, thus allowing for data augmentation from patient data [2, 3]. Another solution to address this challenge is federated learning, which allows AI to be trained on decentralized datasets from multiple hospitals, while ensuring data privacy and security. Federated learning has been already applied to training of AI models in different brain PET challenges, such as reconstruction, segmentation, and denoising using brain PET datasets from multiple institutions [4]. An even more recent improvement is swarm learning, which combines federated learning with blockchain technologies to further ensure the robustness of the learning process [5].

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

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

Image acquisition

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

Segmentation and registration

In post-processing, AI-based segmentation can overcome the time-consuming and observer-dependent process of manual annotation of brain structures in PET images [10]. AI can also assist in the registration of neuroimaging data, via the alignment of images from different imaging modalities or timepoints and learning the mapping between images and different modalities. Furthermore, AI can facilitate the extraction of meaningful quantitative parameters from the images, such as improved amyloid PET quantification without non-specific contributions and amyloid PET quantification without using MRI or CT images [11]. Moreover, AI might provide non-invasive estimations of the arterial input function for brain PET studies, facilitating adoption of absolute quantification in clinical settings [12].

Interpretability analysis

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

Specific clinical applications

Epilepsy is one of the most common neurological disorders characterized by abnormal excessive firing and synchronization of neurons leading to seizures. The accurate identification of the epileptogenic foci is essential to avoid misdiagnosis and select the correct treatment, especially when resective surgery is necessary in drug-resistant epilepsy [15]. While nuclear medicine neuroimaging is a key diagnostic

tool, allowing to evaluate metabolic, neurotransmission, or perfusion abnormalities occurring in people with epilepsy, there is an increasing need to define accurate computer-aided tools to support clinicians as interpretation of the scans is highly complex. In this context, AI-based tools pave the way for solving such tasks, fostered by the exceptional advancement in the models we have witnessed in the last years. Machine learning (ML) and deep learning (DL) are currently explored for diverse tasks as cortical lesion localization (mainly for focal cortical dysplasia — FCD), epileptic focus detection/lateralization and brain region segmentation (e.g., hippocampus), or for the diagnosis and prognosis of different epilepsy types. Still, AI has been mostly applied to MRI or EEG recordings (especially for seizure identification and forecasting), while their exploitation in the nuclear medicine-epilepsy field is still in its infancy, with a few studies largely limited to [^{18}F]FDG-PET briefly reviewed in the following.

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

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

In *neurodegenerative and movement disorders*, the differential diagnosis can be complex and is highly dependent on the expertise of the reader. Therefore, AI may help not only in the (early) differential diagnosis, especially for less experienced readers, but also in the differential diagnosis of subtypes of dementia or complex cases with non-fully delineated pattern of presentation. Multimodal imaging with structural and functional information combined with fluid-based biomarkers is becoming the standard in the diagnostic landscape. In this multimodal setting, AI can be particularly helpful for feature selection. Moreover, AI might also give additional clues about the prognosis. However, the biggest challenge in the field of AI in neurodegenerative disease is the very limited number of available standards of truth assessments, i.e., autopsies in previously imaged patients. Future studies need to overcome the lack of validation studies across different centers and the lack of harmonization of generally accepted AI algorithms to aid in diagnosis across the neurodegenerative disease spectrum. Moreover, all AI models are data-driven, so pre-processing of imaging data plays a crucial role. Therefore, pre-processing software also needs to be harmonized and validated.

Accommodation of substantial numbers with standard of truth assessments for validation of AI application in PET imaging of neurodegenerative disorders remains a challenge and may be solved by large cohorts such as BioFINDER or ADNI [18]. Conversely, PET itself may also be used as a standard of truth assessment for AI-driven analysis of fluid biomarkers or omics data with the goal to find cheap and versatile tools for characterization of neurodegenerative disorders.

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

Psychiatric disorders are an exciting new field of application where the association of imaging and clinical data might foster the diagnosis and evaluation of these

disorders. In fact, so far, their assessment relies almost exclusively on clinical interviews using the Diagnostic and Statistical Manual of Mental Disorders (DSM) nosography. Yet, the DSM reliability is regularly questioned by its iterative modifications, lack of reproducibility of current diagnoses, and therapeutic resistance of many patients [21]. In this context, more transdiagnostic approaches are emerging, and PET and SPECT imaging could be particularly relevant to explore such disorders mainly characterized by dysfunction, in the absence of morphological lesions, with the possible implementation of various targets such as the perfusion, metabolism, neurotransmission and neuroinflammation, and especially the individual application of artificial intelligence tools for precision medicine [22]. In this line, machine learning classification from controls has suggested accurate performance to identify patients with attention-deficit and hyperactivity disorder using multimodal serotoninergic brain PET imaging [23], patients with cocaine dependence using brain perfusion SPECT imaging [24], patients with internet game disorder using metabolic brain PET imaging [25], and patients with major depression using serotoninergic PET imaging or brain metabolic PET imaging, also demonstrating the value of this last exploration to predict the response of deep brain stimulation in this context [26]. Machine-learned analysis of [^{18}F]FDOPA PET scans of patients with schizophrenia also showed good performance for identifying treatment responders and non-responders, with large potential healthcare cost savings [27]. This translation from research to clinical applications will need more numerous multicentric studies and to be supported by a paradigm change in psychiatry towards modern approaches of precision medicine.

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