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Artificial Intelligence in Neuroimaging: Clinical Applications

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Review Article

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Artificial intelligence (AI) powered by deep learning (DL) has shown remarkable progress in image recognition tasks. Over the past decade, AI has proven its feasibility for applications in medical imaging. Various aspects of clinical practice in neuroimaging can be improved with the help of AI. For example, AI can aid in detecting brain metastases, predicting treatment response of brain tumors, generating a parametric map of dynamic contrast-enhanced MRI, and enhancing radiomics research by extracting salient features from input images. In addition, image quality can be improved via AI-based image reconstruction or motion artifact reduction. In this review, we summarize recent clinical applications of DL in various aspects of neuroimaging.

Keywords: Artificial intelligence; Deep learning; Radiomics; Neuroimaging; Clinical application

INTRODUCTION

Artificial intelligence (AI) augmented by the emergence of deep learning (DL) is rapidly changing lives of humans, let alone those of neuroradiologists. Over the past several years, DL has been applied to many studies at the cutting edge of neuroimaging. It has shown its potential to change the practice in every corner of radiology. By reducing the tedious work of detecting brain metastases (BM) (1, 2) and predicting genetic mutations of glioblastoma and patient survival (3, 4) to improve the quality of images hampered by motion artifacts (5), AI is now ready to give a full play of its ability. In this review, we will focus on four main categories of clinical application of AI in neuroimaging: 1) detection/diagnosis, 2) prediction, 3) image quality improvement, and 4) clinical workflow improvement.

Brief Overview of DL in Neuroimaging

DL refers to the use of more than one hidden layer in a multilayer perceptron (MLP). Universal approximation theorem (6) has proven that all functions are approximatable using MLP. Later, Arpit et al. (7) have shown that DL is capable not because of its high model capacity, but because of its "good" feature extractability. Due to their high representational capacity and generalizable feature extraction, DL models have shown superior performance, particularly in classification tasks with complex high-dimensional data such as autonomous driving (8), diagnosis of retinal diseases (9), and dermatologic diseases (10). Recently, generative models such as cycle-consistent generative adversarial network (cycleGAN) have also shown good performances for other tasks such as image generation. Over the last decade, dedicated DL algorithms for various types of data such as neuroimaging data, time-series data, and graph-structured data have been developed. A more in-depth review focusing on technical aspects of DL has been published previously (11).

Clinical Applications

Many AI papers in the field of neuroimaging are increasingly being published annually. While initial studies mainly focused on exploring the feasibility of AI algorithms, researchers are becoming more interested in clinical applications of AI in neuroimaging. We categorized clinical applications of AI into the following four groups: 1) automated detection or diagnosis, 2) prediction of outcome, lesion extent, disease status, etc., 3) improving the quality of the image, and 4) improving the clinical workflow (Fig. 1).

Detection/Diagnosis

Traditionally, many radiological studies have focused on the detection of lesions and diagnosis. In the field of computer-aided detection (CADe), conventional feature-based models have been suggested for automated lesion detection. However, due to their low sensitivity, their clinical integration has been difficult to significantly improve the performance of radiologists (12). With the help of DL models based on convolutional neural networks (CNNs) have shown near-human performance with high sensitivity, specifically showing a low false-positive rate. Several clinical applications are now commercially available, such as detecting pulmonary nodules on chest radiographs and breast cancer on mammography (13).

In neuroimaging, there are several topics related to the detection/diagnosis using AI-based models, such as detecting BM or providing a differential diagnosis for various neurological disorders. Magnetic resonance imaging (MRI) is the best non-invasive imaging modality for oncologic imaging, such as for BM detection, owing to its excellent soft-tissue contrast. Significant improvement in treatment outcomes of radiation therapy, including stereotactic radiosurgery, makes accurate detection of BM

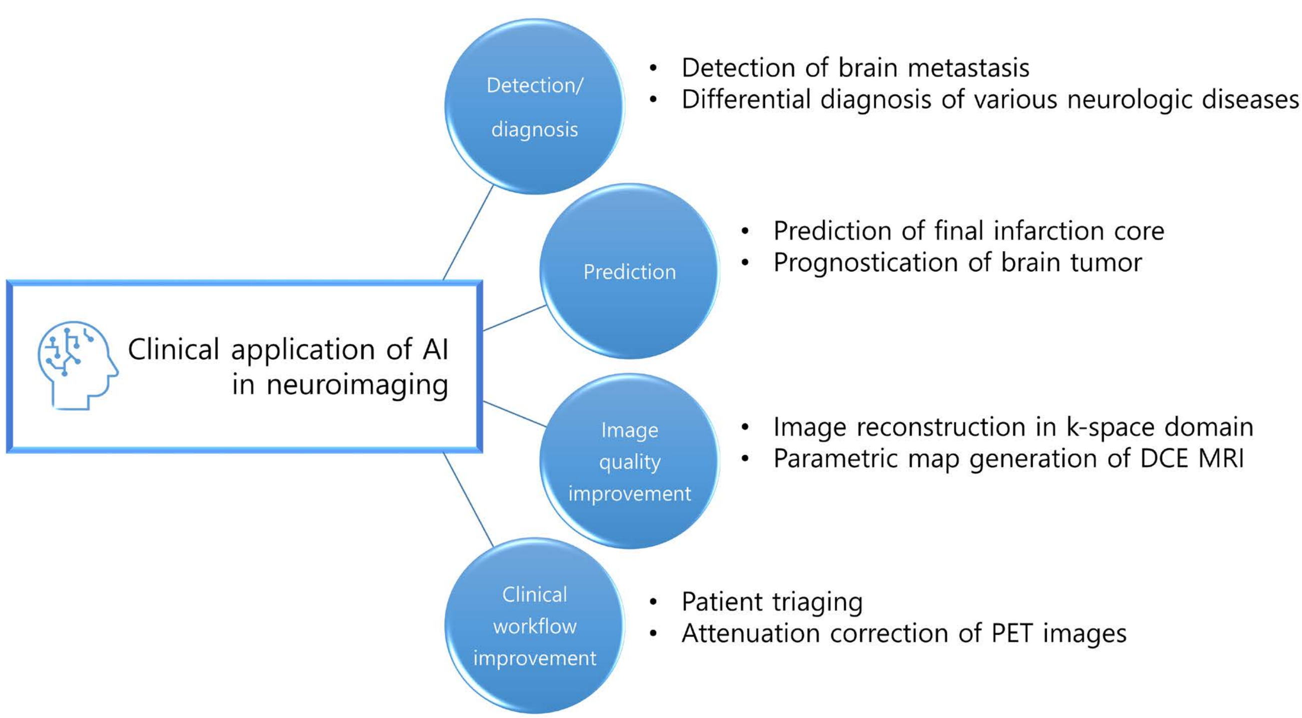

Fig. 1. Graphical overview of main clinical applications of artificial intelligence (AI) in neuroimaging. DCE = dynamic contrast-enhanced; MRI = magnetic resonance imaging; PET = positron emission tomography

more crucial (14, 15). Thus, the need for BM-CADe has greatly increased in the clinical setting. Recently, Zhou et al. (2) have found a sensitivity of 98% for detecting BM ≤ 6-mm using a DL algorithm called single-shot detector by matching a tightly aligned anchor box with the ground truth box. Next, coordinates and prediction confidence of the matching anchor boxes were regressed simultaneously from the pyramidal feature map (16). In addition, it has been shown that a CNN model using multi-sequence data as multi-channel images can detect and segment BM with a high accuracy (17). In a recent meta-analysis and systematic review of 12 related articles, Cho et al. (1) have found that the pooled detectability (or sensitivity) of the BM by AI algorithms is approximately 90%.

After transfer learning, DeepBrainNet, a DL model based on the inception-ResNet-v2 framework trained on more than 14,000 brain MRI scans (18), has shown excellent performances in classification tasks such as diagnosis of Alzheimer's dementia (AD), mild cognitive impairment (MCI), and schizophrenia (19). Interestingly, its performances are better than those of ImageNet-pretrained models. Rauschecker et al. (20) have developed an AI algorithm combining U-Net and Bayesian inference models to classify 19 various neurological diseases. Target diseases include relatively common diseases (such as small vessel ischemic disease and brain tumors) and rare diseases (such as acute disseminated encephalomyelitis and progressive multifocal leukoencephalopathy). The algorithm could provide a correct diagnosis in approximately 90% of test cases, which is higher than that of radiology residents and similar to neuroradiologists (20).

DL can also be applied to diagnose common head and neck diseases on radiographs to reduce the workload of radiologists. A ResNet-based CNN can diagnose maxillary sinusitis on Waters' view radiographs with areas under the receiver operating characteristic curve (AUCs) of 0.88-0.93 (21). This model has been further extended to detect frontal and ethmoid sinusitis using both Waters' and Caldwell's views (22). Similarly, a multi-view DL model for detecting mastoiditis has shown excellent performance in mastoid series with an AUC of 0.97 (23). Interestingly, DL can discriminate skull radiographs of patients with Moyamoya disease from those of controls (24).

Prediction

AI can help predict the outcome or disease status that cannot be determined without an invasive procedure. From a technical standpoint, there is little difference between the prediction task and the classification/regression task because an AI model is generally trained to extract salient high-level features from the input data regardless of whether it deals with future, unknown things or not. Several topics that are suitable for predicting clinically relevant targets of AI among neurologic diseases include acute ischemic stroke, AD, and brain tumors.

To support clinical decisions in stroke management, Yu et al. (25) have used baseline MRI without information on subsequent reperfusion therapy as input to predict the size and location of the infarction core 3-7 days later using an attention-gated U-Net. This may help clinicians select patients who need mechanical thrombectomy by predicting the growth of the infarction. In addition, Ho et al. (26) have proposed a machine learning approach to estimate the time-since-stroke from the stroke protocol MRI. They extracted imaging features using DL-based classifiers from conventional MR sequences and further extended the algorithm by incorporating hidden representations extracted from additional perfusion-weighted MR sequences (26).

Discrimination of MCI from early AD is clinically important because approximately 5-20% of MCI cases convert to AD cases annually. Thus, early appropriate treatment should be initiated to reduce the negative outcome of patients with AD (27). Hence, application of DL for the prediction of conversion from MCI to AD is an active area of research, along with multiple large ongoing clinical trials that gather large-scale multimodal neuroimaging data. According to a systematic review of AI algorithms for AD diagnosis (28), DL models such as CNN and recurrent neural network (RNN) show accuracies of up to 96.0% for AD classification and 84.2% for MCI to AD prediction.

Meanwhile, radiomics, which refers to the extraction and analysis of large numbers of complex features from radiologic imaging data (29), and radiogenomics, which deciphers the relationship between radiomic and genomic information based on the fact that imaging can reflect tumor biology (30), have also shown successful performances in predicting various clinically relevant targets such as grading gliomas, predicting mutation status (31), treatment response (i.e., pseudoprogression vs. true progression) (32), recurrence pattern (i.e., local vs. distant recurrence) (33), prognostication, and survival prediction (4), as well as providing differential diagnosis between other confusing tumorous conditions such as lymphoma (34) and metastasis (35). They can capture intratumoral heterogeneity originating from the biological background of the imaging modality, which is sometimes referred to as "imaging phenotyping." For example, non-small cell lung cancer and head and neck cancer are known to show heterogeneous gene expression patterns believed to be linked to and expressed at the imaging level. Subsequently, radiogenomic analysis has successfully developed and validated the prognostic signature using imaging heterogeneity in other clinically relevant tumors such as glioblastoma.

Recent studies have shown that AI can also be useful in monitoring treatment response of brain tumor on follow-up imaging studies, such as radiomics-based analysis of advanced multimodal sequences using diffuse-weighted or perfusion-weighted MRI (32) and robust feature extraction using DL-based segmentation (31, 36). Moreover, radiomics-based prediction models are evolving from machine learning classifiers, such as support vector machines and random forests, to DL-based models, such as CNN and RNN. For example, Chang et al. (37) have developed a fully automated system to register biopsy sites from neuronavigational crosshairs to preoperative MRI using a CNN. Multimodal imaging measures at biopsy sites are then used to train the network using a cell density counting method applied to pathology images. Choi et al. (31) have found that a CNN hybrid model can extract good features, leading to a better performance in the prediction of isocitrate dehydrogenase (IDH) mutation than the random forest-based classifier or conventional radiomics approach in a fully automated and reproducible manner. In the future, efforts can be made to predict clinically relevant information such as genetic mutations using raw data from imaging phenotypes of complex dimensions or using appropriate DL-based models for each type of dataset, not predefined or manually extracted radiomic features. Interestingly, due to recent progress in radiomics, the term "rawdiomics" has been coined (38). For example, because convolutional filters/kernels in CNN work as a better feature extractor than conventional radiomic features, which are predefined by experts, the DL-based radiomic signature shows a better performance than risk factors comprising only conventional radiomic features in survival prediction (39). Meanwhile, genetic mutation of glioblastoma can also be predicted using sequential data rather than single time-point image data. Specifically, temporal patterns learned from raw time-series data obtained from dynamic susceptibility contrast-enhanced (DSC) perfusion MRI using RNN can predict the mutation status of the IDH gene (3) (Fig. 2).

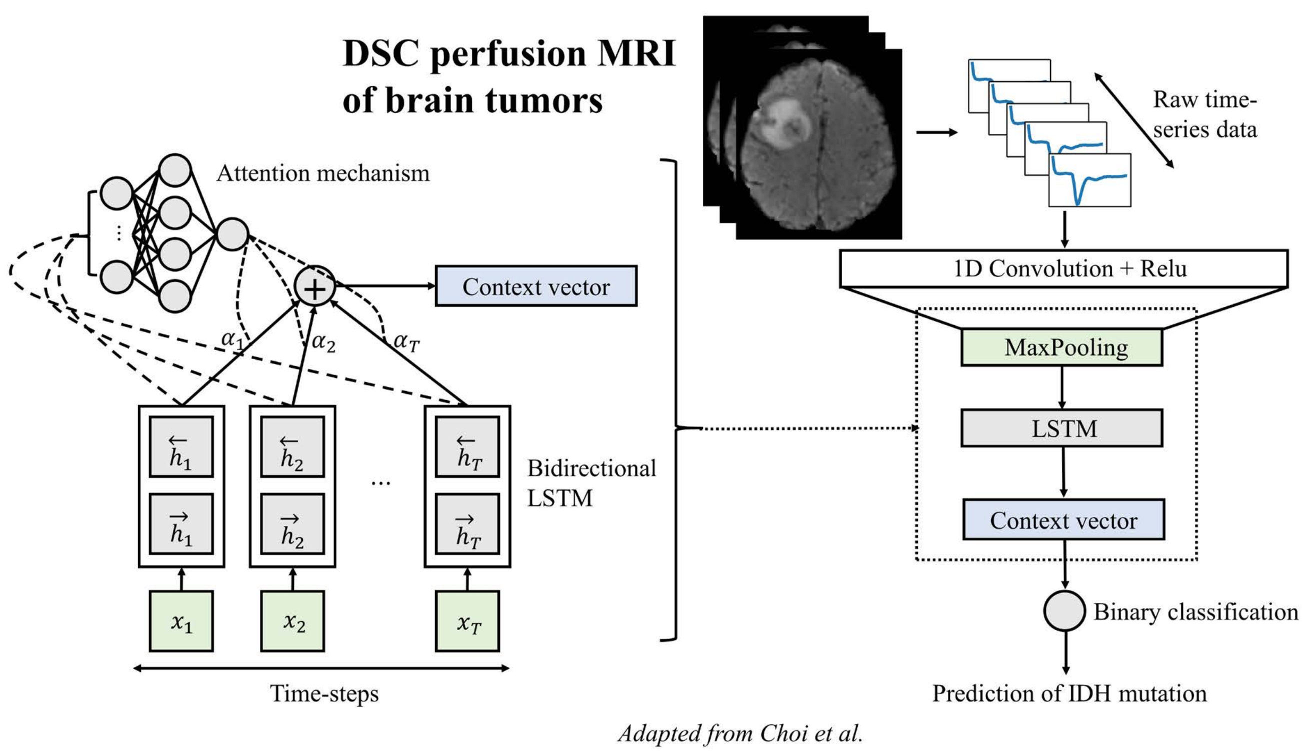

Fig. 2. Exemplary deep learning-based model architecture for predicting genetic mutations in glioma. Adapted from Choi et al. (3). DSC = dynamic susceptibility contrast-enhanced; IDH = isocitrate dehydrogenase; LSTM = long short-term memory; ReLU = rectified linear unit

AI could assist in "integrated diagnosis" of the 2021 World Health Organization classification of central nervous system tumors (40), which includes more various mutations and molecular markers for better stratification of prognosis by filling the gap of spatial and gross morphologic information that genetic information cannot provide. Moreover, because approximately 7-15% of patients are pathologically diagnosed inconclusively, radiomics and/or radiogenomics-based diagnosis may play a major diagnostic and prognostic role in the future (41).

Image Quality Improvement

The quality of images can be improved using AI in various ways, including reconstruction of images from accelerated MR acquisition (42, 43), image co-registration (44), dose reduction (45), contrast conversion (46), improvement of perfusion MRI such as dynamic contrast-enhanced (DCE) MRI (47, 48), and arterial spin labeling (ASL) (49).

Compressed sensing (CS) MRI undersamples the k-space to reduce scan time and aliasing artifacts at the same time. To further mitigate artifacts, a DL based on the k-space can be used to map between the under-sampled and fully sampled k-space or between aliased and full field-of-view images, which is learned by a cascaded CNN using a skipped connection accompanied by an inverse Fourier transform (42). Chung et al. (43) have developed a DL model to reconstruct accelerated images of time-of-flight MR angiography using CS. Using a two-step model that is mainly based on the optimal transport cycleGAN, a type of generative model, the authors found that resultant images showed excellent quality compared to the original vendor images even at an acceleration factor of 8 (43). Recently, the fastMRI challenge was hosted by Facebook AI in collaboration with NYU Langone Health (50), which aimed to have up to 10-times faster scans, making MRI cost-effective by reducing scan time.

For image co-registration, VoxelMorph (51), an early representative co-registration model using a convolutional U-Net, has shown better registration performance than other conventional non-DL-based methods such as Advanced Normalization Tools (52). Recently, Kim et al. (44) have applied cycleGAN to synthesize the deformation field in the registration or CycleMorph, which provides an implicit regularization of deformation and improves topological preservation in image registration.

Computed tomography (CT) perfusion is a widely used modality for diagnosing and planning further management in acute ischemic stroke. However, its radiation dose is quite large due to dynamic acquisition. Dashtbani Moghari et al. (45) have mapped low-dose to normal-dose CT perfusion maps using a three-dimensional generative adversarial network (GAN), which might reduce the radiation dose while obtaining comparable image quality. GAN-based models have already shown significant progress in dose reduction in various fields other than neuroimaging (53). In addition, recent studies have shown that artifacts can be introduced when using vanilla GAN-based models without any additional loss functions. For example, Kang et al. have demonstrated that artificial features without adding cyclic and identity loss may be seen in synthesized CT images by GAN-based models in a DL-based dose reduction study regarding multiphase coronary CT angiography (53, 54).

DCE MRI has become an essential tool for assessing blood-brain-barrier leakage, which is useful for interpreting not only tumors, but also various diseases such as multiple sclerosis, stroke, and dementia (47). Despite the valuable microvascular permeability information it renders, DCE MRI suffers from unreliable parametric maps due to weak arterial input function (AIF), which is based on T1-signal intensity. Choi et al. (50) have shown that the reliability of DCE MRI can be improved using a pix2pix model, replacing the AIF of DCE MRI with that of DSC MRI, which is more robust to noise because of the stronger T2*-signal intensity. In addition to DCE MRI, ASL has been increasingly used in clinical practice because of its noninvasiveness, repeatability, advantages in quantification, and advancements in labeling and readout sequences. Specifically, ASL can obtain contrast enhancement without using a gadolinium-based contrast agent, which may be deposited in the brain parenchyma (55). However, it suffers from an inherently low signal-to-noise ratio (SNR) and sensitivity to motion. Kim et al. (51) have improved the SNR and denoised motion artifacts of ASL using both local and global pathways of a CNN-based model in parallel. Using that model, the mean square errors of cerebral blood flow in stroke regions were significantly reduced compared to those of the conventional averaging method, indicating that the model could successfully reduce image noise.

Lee et al. (46) have developed CollaGAN, which converts an image imputation problem into a multi-domain images-to-image translation task so that a single generator and discriminator network can successfully estimate the missing data using the remaining clean data set. They successfully applied the algorithm to contrast conversion between T1-, T2-weighted, and FLAIR sequences in brain MRI (46). Thus, the model could generate missing sequences among four conventional structural sequences (T1-, T2-, contrast-enhanced T1-weighted images, and FLAIR), which is essential for evaluating brain tumors. Some researchers have attempted to use DL to map between CT and MRI by generating synthetic T2-weighted images from brain CT, which will benefit patients who cannot undergo MRI scan because of medical conditions such as implanted cardiac pacemakers (56), or by generating synthetic CT images from 3D T1-weighted MRI using cycleGAN, which might allow MRI-based planning of radiation therapy (56, 57). However, these pioneering studies still need to be validated to determine whether they are clinically relevant.

Clinical Workflow Improvement

Many studies have applied AI models to improve the clinical workflow, such as the detection of critical findings including intracranial hemorrhage (58-61) and attenuation correction of positron emission tomography (PET) images (62-64). Delayed detection of critical findings such as intracranial hemorrhage, skull fractures, and mass effect on brain CT may lead to irreversible damage to the patient. To address this issue, Titano et al. (58) have developed an automated triaging model to detect urgent neurologic events on brain CT using a natural language processing algorithm and found that it could reduce the time from image acquisition to clinician notification (58-61). Chilamkurthy et al. (59) have also developed a DL model to detect intracranial hemorrhage, skull fracture, and midline shifting using a large dataset containing more than 300,000 brain CT scans and achieved an AUC of 0.92. These models have great potential to be adopted in clinical practice and advance the level of patient care.

For PET/CT or PET/MR, DL-based attenuation correction has shown successful performance (62, 63). CT-based attenuation correction using DL provides quantitatively accurate 18F-FDG PET results with average errors of less than 1% in most brain regions (62). Similarly, MRI-based attenuation correction of DL has shown significantly lower PET reconstruction errors than conventional methods such as Dixon-based soft-tissue and air segmentation and anatomic CT-based template (63). Moreover, because they are both used only for attenuation correction rather than for evaluation of the lesion itself, controversy regarding the generation of pseudolesions can be avoided.

To assess treatment response of glioma, the Response Assessment in Neuro-Oncology (RANO) criteria recommend tracking the sum of products of the two-dimensional diameter of each tumor (65). However, such measurements are subjected to errors and high interobserver variability. Kickingereder et al. (66) have used an artificial neural network (ANN) to mitigate this issue. They found that ANN could perform accurate detection and segmentation of contrast-enhancing and non-enhancing tumors. Furthermore, the time to progression from the quantitative ANN-based assessment was found to be a better surrogate than the RANO-based assessment by central reviewers to predict overall survival in a clinical trial. Similarly, it has been shown that DL could provide an automated treatment response assessment for BM using RANO-BM criteria (67).

AI can also assist in radiation therapy planning by offering automated contouring of tumor volumes on MRI (64). In a multicenter evaluation, AI-assisted contouring can improve contouring accuracy and reduce intra- and inter-observer variations. Moreover, it can reduce the contouring time by approximately 40%.

Future Directions

We have taken a glance at some studies on clinical applications of AI in neuroimaging. We believe that the feasibility exploration phase of applying AI in neuroimaging is almost over. Now it is necessary to obtain high-level evidence to deploy AI models to the current practice. Recently, Park et al. (68) have suggested a methodological guide for evaluating the clinical performance of AI. However, a clear gap is observed between this suggestion and many AI papers in terms of external validation (69). Several meta-analyses and systematic review papers have also pointed out that there is room for improvement in terms of the quality of research (1, 70). To this end, several guidelines dedicated to reporting and quality assessment of AI algorithms such as Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD-ML/AI) and Standards for Reporting and Diagnostic Accuracy Studies (STARD-AI) are underway (71-73). Seeking unmet clinical needs should collaborate with radiologists, clinicians, and DL engineers, which might not be fully appreciated by either alone. To date, only relatively more common diseases have been studied because of many obstacles such as data hunger or shortage. In addition, imaging protocols differ across vendors and hospitals, thus limiting the generalizability of AI algorithms. To overcome these issues, worldwide efforts to build public datasets and standardize imaging protocols and regulatory support are required.

In conclusion, AI has been paving the way for the next level of patient care across the field of neuroimaging, such as detection/diagnosis, prediction, image quality improvement, and clinical workflow improvement. Despite remarkable progress has been made in their performances, AI models should be carefully evaluated and validated before their adoption in clinical practice.

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