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Advancing Therapeutics through MRI Contrast Agents: Current Status and Future Prospects

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ABSTRACT

Introduction: In recent years, magnetic resonance imaging has emerged as a highly promising method for the detection of severe illnesses. Its remarkable spatiotemporal resolution and user-friendliness have made it an essential clinical diagnostic instrument. However, there are situations in which poor contrast in MRI poses difficulties that need the use of contrast agents. Researchers have worked hard to improve the accuracy of viewing sick body regions by combining MRI with other imaging modalities to maximize its synergistic potential and altering the contrast agents.

Aim of work: To elaborate the approach of contrast agents design and maximize their suitability for smart applications such as MRI imaging. Furthermore, we highlight the significance of using diverse artificial intelligence instruments, including deep learning and machine learning, in order to investigate the potential applications of MRI for illness detection in the future.

Methods: The MEDLINE database's electronic literature was searched using the provided search terms: Advancing, Therapeutics, MRI, Contrast, Agents. The search was limited to publications between 2020 and 2024 in order to identify relevant material. Relevant search terms were utilized on Google Scholar to locate and explore relevant scholarly articles. The selection of papers was guided by certain inclusion criteria.

Results: The study's included papers were released between 2020 and 2024. The study was organized into several sections with particular headers in the discussion section.

Conclusion: This review discussed the basic knowledge of MRI contrast agents, their sensible design, and their constraints. We stress the need for more attention to be paid to commonplace MRI contrast agents in their discussion of case studies and contemporary occurrences. They also emphasize the significance and constraints of AI methods for processing images, such machine learning and deep learning. According to the assessment, these AI methods may open the door to a future imaging system.

Keywords: Advancing, Therapeutics, MRI, Contrast, Agents

INTRODUCTION

In the field of biomedical engineering, studies and advances in technology spanning the bench to the bedside have resulted in some creative breakthroughs. Magnetic resonance imaging (MRI) is one of the best instances of this (Wald et al., 2020). Yamanakkanavar et al. (2020) claim that by showing internal inflammation, tumors, soft tissues, blood vessel images, tissue perfusion, and the characterization of sick regions, MRI aids in the diagnosis of several disorders. However, as compared to other imaging modalities like computed tomography (CT) and X-rays, etc., it offers better noninvasiveness, less toxicity (when it comes to contrast chemicals), and preserves bio- and cytocompatibility. Actually, MRI aligns protons in any biological sample using powerful magnetic fields, then utilizes the longitudinal (T1) or transverse (T2) relaxations of those protons to create pictures. For a high contrast, high quality MR picture, the water molecules must be polarized as much as feasible. But the contrast gets faint when it comes to the brain or other internal organs (Daksh et al., 2022).

Here, magnetic materials have been created by scientists to improve the MR signals' contrast. T1-based agents and T2-based agents are the two major categories into which MRCAs may be divided (Molaei, 2023). While each of these organizations' contrast agents (CA) are equally crucial for imaging, their mechanistic techniques vary somewhat from one another. T2-weighted MRCAs utilize a transverse signal for relaxation, whereas T1-based MRCAs utilize a longitudinal signal. When administered intravenously, both of these classes exhibit increased magnetic resonance contrast from a diagnostic perspective. Gadolinium (Gd^{3+})-based MRCAs have advanced significantly during the last several decades among the different MRCAs (Dekker et al., 2023). Gd^{3+} possesses seven unpaired electrons due to its massive spin quantum state, which makes it advantageous for magnetic applications. Specially, 60% of Gd-based MRCAs may be efficiently used in neurological MRI, while approximately 40% of them might be used for full-body MRI (Costelloe et al., 2020).

Nevertheless, new observations suggest that Gd-based MRCAs may be toxic in several human body areas and may induce nephrogenic systemic fibrosis (NSF). Additionally, using these CA in individuals with acute liver or renal disorders may be risky (Lersy et al, 2020). In actuality, using Gd-agents for renal imaging is also not recommended. Therefore, it is imperative that these obstacles be removed. In this regard, the development of substitute CA has been essential in recent years. Due to their significant spin polarization, transition metal ions, in addition to lanthanides (Gd^{3+}, Dy^{3+}, and Eu^{3+}), may also be productive in this field (Gupta et al., 2020). Fe^{3+} and Mn^{2+} are now preferred options for T1 MRCAs in this case. Shorter Mn-Hwater bond lengths and a significantly large number of single electrons in the valent states are characteristics of Mn^{2+} CAs. Mn-complexes are useful for neuroimaging because they may effectively traverse the blood-brain barrier via cerebral capillaries, the olfactory nerve, or cerebrospinal fluid. Recently, a number of organizations have produced several intriguing Mn^{2+} MRCAs for imaging various human body areas. The majority of these investigations confirmed that Mn-based compounds may help MRI in the near future and may be able to mitigate the toxicity of Gd^{3+} (Zheng et al., 2022).

The field of CAs has largely been taken over by the unexpected increase of Mn^{2+} MRI CAs, leading to the publication of several review papers in recent years. Notably, throughout the last five years, more than 3000 publications have been published annually worldwide, indicating a clear need for more study in this area. While for MRI imaging Mn-based MOFs were suggested by Xue and colleagues, the review papers (Iki et al., 2023) show the general advancement and need of Mn-based CAs in MRI. Here, they provided an overview of the most recent advancements in MOF-mediated theranostic platforms, which can also administer chemotherapy (Xue et al., 2023).

However, researchers are making progress in the efficient CAs targeting of the cells and organs. Notably, by building up within the targeted organs/cells, these targeting tactics might intensify the contrast. Due to their stability and other drawbacks, the majority of these targeting strategies are still on the bench. Numerous image-processing methods have emerged here, demonstrating tremendous promise in the field of molecular imaging. The picture quality has reached a new level thanks to techniques like AI, or more specifically, machine and learning data science (Li et al., 2022). The MRI CAs' logical design has been examined in this paper. Their targeted tactics and limitations have received particular attention. Since then, several methods of image processing have been explored that have the potential to greatly enhance picture quality. It has also been shown that many recent examples highlight the relatively recent developments in digital molecular imaging. Our goal is to validate our knowledge of MRI CAs and image processing tools, as achieving so will undoubtedly make this modality a cutting-edge tool for identifying and treating crucial illnesses.

AIM OF WORK

To elaborate the approach of CA design and maximize their suitability for smart applications such as multimodal imaging. Furthermore, we highlight the significance of using diverse AI instruments, including deep learning and machine learning, in order to investigate the potential applications of MRI for illness detection in the future.

METHODS

Using various keywords (Advancing, Therapeutics, MRI, Contrast, Agents), scientific websites (Google Scholar and Pubmed) were searched to retrieve all relevant publications. A set of selection criteria was used to determine which papers were chosen. After reviewing each paper's abstracts and significant titles, we eliminated case reports, duplicate articles, and articles without complete text. The reviews that this study looked at were released between 2020 and 2024.

RESULTS

Studies on the advancing therapeutics through MRI contrast agents between 2020 and 2024 were considered in the current investigation. Consequently, the review was published under several topics in the discussion section, including MRI Contrast Agents, Targeting diseases with MRI CAs and Future of MRI Imaging.

DISCUSSION

1. MRI Contrast Agents

These days, contrast chemicals are used to guide about one-third of MRI procedures (Akbas et al., 2023). Up till now, Gd^{3+} has emerged as the most used CA in clinical settings. However, new studies show that in order to improve visibility and bioavailability, substitute contrast ants such Fe^{3+} and Mn^{2+} are required (Geraldes et al., 2021). In actuality, the body's protons from its fat or water content align with the magnetic field and relax as a result, promoting a signal. Such magnetic polarization in a typical MRI, however, is dependent on a number of variables, and all protons cannot be aligned instantaneously by the external field. As a result, CAs are highly sought after when doing thorough and impulsive MRI. It has been shown that materials with a high number of unpaired electrons in their valance shell create a considerable amount of spin-polarization as well as an enhanced magnetic moment (Rahmati & David, 2024).

These CAs may be categorized into four types based on biophysical and biochemical perspectives: paramagnetic, superparamagnetic, transfer-based, and direct detection based and chemical exchanges. For the last several decades, para- and superparamagnetic contrast compounds have been among them (Caspani et al., 2020). These two groups include the majority of clinical contrast compounds, including iron, gadolinium, manganese, etc. Gadolinium-based CAs were historically employed more than other forms of MRCAs. Approved in 1988, gadolinium diethylenetriamine pentetic acid had been the very first clinically approved CA (Setia et al., 2024).

Because of their interactions with the environment, spins lose energy when the external magnetic field approaches, and T1 relaxation occurs. The CA accelerates energy depletion by interacting with water molecules as well as the ions of metal in its core. T1 CAs work best when their rotational motion matches the frequency of Larmor (42.58 MHz T^{-1} for hydrogen protons), resulting in the most efficient energy transfer (Jeon et al., 2021). The protons of hydrogen lose energy and regain their initial magnetic moment quicker when they react to the CA, which lowers the water molecules' fast tumbling motion to an approximate frequency that is similar to the Larmor frequency. A net decrease in magnetization is seen by the T2 relaxation in the plane of transverse motion (Ouyang et al., 2022). A small magnetic moment is produced by the first net alignment to the magnetic field that surrounds them. This magnetic moment then transforms to the net phase coherence that represents their precessions in the transverse plane. Different processes affect T2 relaxation, but the precessional motion of these spins towards decarbonization is promoted by all actions leading to T1 relaxation. CAs also alter T2 by introducing localized disparities into the magnetic field. There are areas where the applied longitudinal field and the Larmor frequency diverge due to the induced fields. The net transverse magnetization falls because spins are out of phase as a result of the realignment brought on by the precession of hydrogen protons (Antwi-Baah et al., 2022).

Smaller doses of CAs with substantial limits of detection (LOD) are preferred. When it comes to MRIs, relatively little CA (at the μM level) is required. Most of the time, nevertheless, the amount that is given may be a little bit high, that causes concerns about safety and potential toxicity. This clarifies that only a limited number of MRCAs have been approved by the Food and Drug Administration in USA. Designing CAs that can both perform better and have few or no negative effects is thus imperative (Yang et al., 2023).

An MRI is a crucial diagnostic tool for any irregularities seen in the human body's interior. Deep-seated infections, illnesses of the vasculature, inflammatory diseases, neurological disorders, and cancers may all be effectively detected by it. As a result, this technology may be used to quickly and quantitatively diagnose any illness. However, magnetic resonance imaging CAs do more than only help with illness diagnosis, they also serve as theranostic modalities and image-guiding for therapeutic and surgical systems. In one instance, Li and associates created a self-assembling peptide which incorporates vancomycin with a Gd-complex to detect and eliminate S. aureus infections in vivo. In this case, the Gd-complex served as the MRI imaging probe that was conjugated with the antibiotic vancomycin. That complex's peptide increased the longitudinal relaxivity rate following self-assembly owing to π-π stacking. The theranostic agent's unusual structural properties, particularly those that would impede molecular rotation and increase the period that Gd-chelates would decrease. This might explain its high relaxivity value (Li et al., 2021). Furthermore, Xiu and his group showcased a system that is generated from MnO_2 NP and has the remarkable capacity to photograph bacterial biofilm (Xiu et al., 2020). By using bacterial microenvironment-responsive MRI, the authors of this work have effectively extended the T1 relaxation duration of the Mn^{2+}-based MRI agent. The CA reaches its maximum relaxation after 8 hours of subcutaneous injection and concurrently decreases after 24 hours, signifying the kidneys' elimination of the sample (Xiu et al., 2020).

Tumor diagnosis has also made use of MRI imaging. Zhao and his colleagues used MRI to effectively find liver cancers. Because the Gd-based CAs are toxic, liver MRIs are difficult to conduct. The authors of this study did not use any CAs to image tumors using MRI. By bridging the blood-brain barrier, MRI may effectively identify brain malignancies in addition to liver cancer (Zhao et al., 2020).

The ability to examine the vascular architecture and its functioning is made possible by the substantial advancements made in MRI technology for medical imaging. Low-field MRI (<3 T) provides low-contrast images and has considerable spatiotemporal resolution problems. However, there are hardly any CAs for ultra-high field MRI (>7 T), which makes it difficult to easily assess disorders of the vasculature. To bridge this gap, researchers have started focusing on iron-based dual T1-T2 CAs lately. A T1-T2 dual-mode iron oxide nanoparticle-based CA, for example, has been proven by Wang et al. to be useful for the identification of vascular disorders under UHF-MRI. These NPs have a promising pharmacokinetic profile and are effective in this sector due to their ultrasmall core size. The 7 T MR angiography's detection limit may be extended by using this CA for pictures with diameters as small as 140 μm (Wang et al., 2021). Similarly, a number of CAs based on Gd and transition metals have shown promise as agents for MRI-mediated vascular imaging. To transfer into clinics, additional research is necessary to maintain reasonable excretion levels and minimal toxicity (Kalman et al., 2020).

Additionally, the use of MRI in the prediction of inflammatory illnesses and neurodegenerative disorders has been investigated. Because of the images' great contrast and spatiotemporal reactivity under these circumstances, clinics should strongly consider using this diagnostic modalities. MRI CAs are frequently coupled with NIR-II emitters to offer efficient in vivo NIR-II imaging-guided MRI. Li et al. (2021) discovered glioblastoma utilizing Fe-based metal-organic framework (MOF) nanoparticles alongside NIR-II fluorophore. The tumor-targeting AE105 peptide was subsequently added to the nanoparticles. The nanoplatform may pass across the blood-brain barrier, and the peptide specifically targets the overexpressed urokinase NIR-II provides these benefits by combining high MRI penetration depth, detection sensitivity, and spatiotemporal resolution, all of which are required for precisely describing cancer cells. Numerous studies have demonstrated that doping Mn into CuS nanoparticles improves T1/T2 MRI contrast and exhibits considerable NIR absorption, making it appropriate for PA imaging (Gawi Ermi, 2021). Mn nanoparticles combined with CuS and surfaces covered with PEG or bovine serum albumin possess the ability to dramatically improve PA as well as MRI signals in the target cells. Yang et al. created nanoscale metal-organic particles (NMOPs) using Mn and the NIR dye IR825 and covered them with a PEG functionalized polydopamine, or PDA, coating to achieve good contrast in T1-weighted MR imaging. Biodistribution and tumor treatment were monitored with an 808 m laser. After 60 days of administering the nanoprobe, a relaxivity r1 of 7.48 mM^{-1} s^{-1} was found at 3.0 T (Zhu et al., 2023).

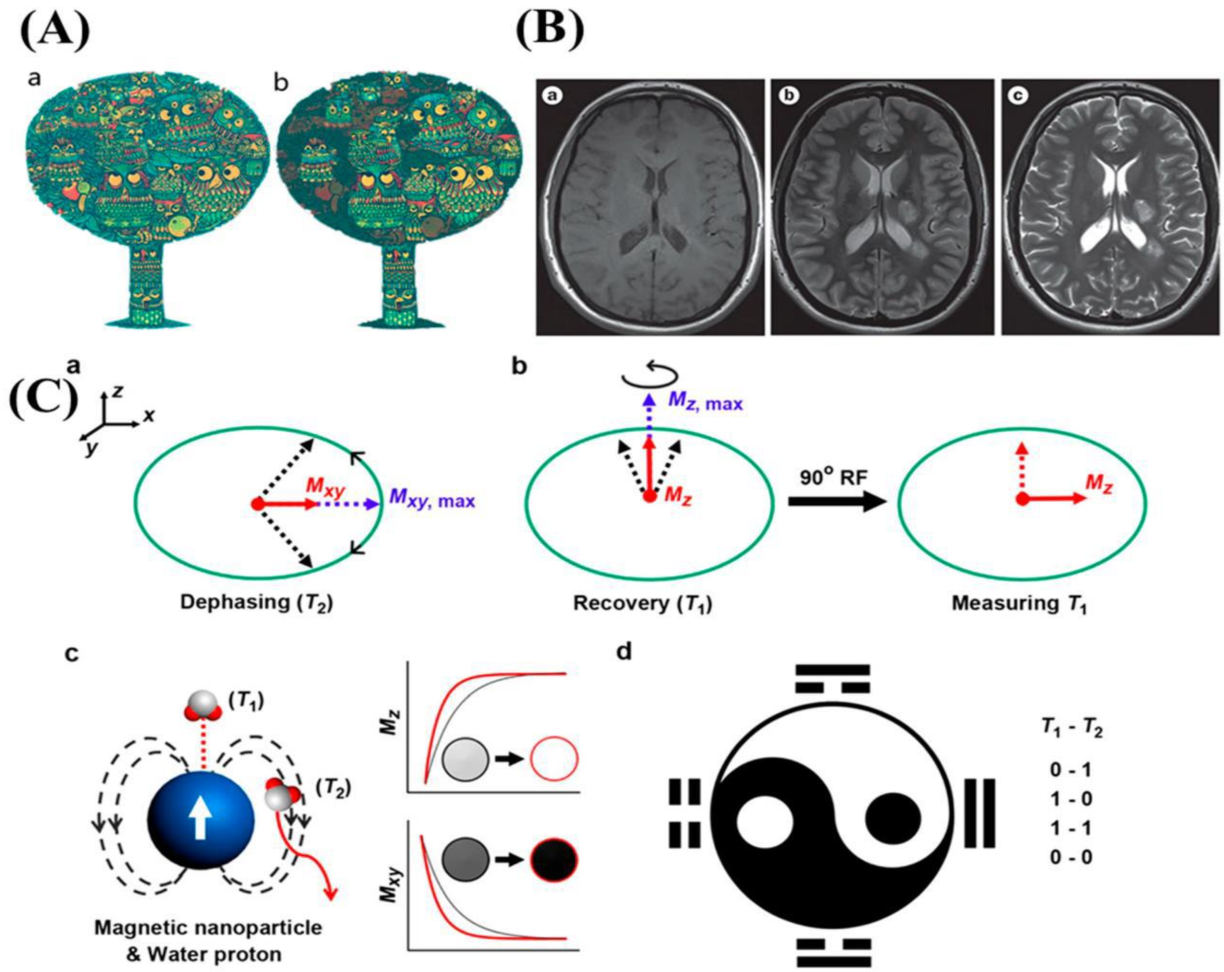

Figure 2. (A) Nature enjoys imitation, and radiologists, in a similar spirit, like to emphasize lesions while doing medical diagnoses. While a typical MRI (a) may disclose some information about the topic of study, it often lacks defined limits. However, using an external contrast agent (b) may help to emphasize certain disorders, allowing for easier diagnosis. (B) (a) Before giving the contrast agent, acquire axial T1-weighted and dual-echo T2-weighted sequences. (C) (a) T2 relaxation is accompanied with a loss of magnetization in the xy plane (Mxy) after a 90° radiofrequency (RF) pulse. Mxy,max represents the maximal Mxy immediately after nuclear magnetic resonance. (b) T1 relaxation is defined as the recovery of magnetization in the z direction (Mz) from zero to maximum value (Mz,max) while the nuclei are spinning. To measure Mz, another RF pulse is used to switch the magnetization from the z to the xy plane. The T2 decay effect, caused by this second pulse, may reduce the T1 impact. (c) The T1 relaxation enhancement is directly connected to the coordination with a magnetic nanoparticle, but the T2 relaxation enhancement is linked to the diffusion surrounding the nanoparticle. When it comes to water protons, thisresults in higher contrast in T1 imaging and a darker contrast in T2. (d) T1-T2 dual-modal imaging follows a logic of four states: OFF-ON (0-1), ON-OFF (1-0), ON-ON (1-1), and OFF-OFF (0-0). These states provide up new options for exhibiting various parameter characteristics in magnetic resonance imaging (MRI) (Foster & Larsen, 2023).

2. Targeting diseases with MRI CAs.

In the realm of contemporary science, various aptamers are added to certain manganese-coated nanoparticles to enhance their ability to target and contrast. Li et al., for instance, used hydrophilic MnO nanoparticles with PEG-bis (carboxymethyl) ether 600 as an solvent to create T1 MRI nano-CA within a single container. Additionally, they functionalized AS1411 aptamer with a covalently attached amine group towards the diagnosis of neurological conditions. At 3.0 T, good stability in the glutathione environment was found together with a low r2/r1 ratio (4.66) and a strong T1 relaxivity (12.942 mM^{-1} s^{-1}). Renal malignancy was assessed using AS1411-PEG-MnO nanoprobe target-specific MRI. The mice having cancer of the renal system showed increased contrast in their heart, muscle, kidney, and liver; this contrast peaked forty-five minutes after injection, primarily at the tumor site. 24 hours following injection, the signals totally vanished, indicating the fact that the nanoprobe was successfully removed, mainly through the kidneys and bladder (Khalilnejad et al., 2021).

In order to enhance T1-weighted MRI, target-specific cargo discharge, and colloidal stability, dispersion, the ability to dissolve, and biocompatibility, it is frequently used to modify Mn nanoparticles alongside different chemical moieties or polymers (such as PVP polyglycerol adipate, or polyethyleneimine). PEG-phospholipid is one of the most preferred ligands for stabilizing MnO nanoparticles (Xu et al., 2021). The Mn nanoparticles are shielded from water by the strong hydrophobic coating of the phospholipid micelles, which lowers the r1 relaxivity or water exchange efficiency. On the other hand, the water exchange effectiveness and the T1 relaxation time will both benefit from hydrophilic coating material. In addition, if the terminal reactive groups regarding PEG moieties, Mn nanoparticle binding with biological receptors may be controlled. Wang et al., for example, altered MnO nanoparticles by including L-cysteine and PEG for T1-weighted MRI. L-cysteine prolonged the circulation of blood and decreased macrophage cellular absorption, whereas PEG improved stability (Wang et al.)

Furthermore, MRI-guided theranostics is being used by practitioners more and more. The foundation of chemodynamic treatment (CDT) is the theory that an acidic tumor microenvironment (high levels of GSH and H_2O_2) leads to oxidative stress, which in turn sets off the Fenton or Haber-Weiss reaction and produces reactive species such •OH, $^1O_2$, or $•O_2^-$. Ultimately, this results in the tumor cells dying off or necrotizing, which suppresses the tumor (Meng et al., 2021).

Through Fenton or Fenton-like reactions, the abundance of Mn^{2+} may start the process that produces the •OH radical from the endogenous H_2O_2. MRI-guided treatments, apart from chemodynamic therapy, have sparked other studies. Zhang et al. presented a new concept: MnO_2/DOX-loaded albumin nanoparticles (BMDN) for MDR tumor treatment reversal. MDR reversal is accomplished by coming into touch with cancer cells' excessively expressed albumin receptors, which reduces the hypoxic microenvironment of the tumor and promotes on-demand release of drugs and drug outflow. High-quality T1-weighted imaging may be obtained both in vitro and in vivo by amplifying the contrasting effect by the stimulation of Mn2+ release in an acidic microenvironment. But recently, there has been a lot of interest in MRI-guided surgery. The application of laser interstitial thermal therapy was proven by Del Bene et al. The process targets and destroys certain tissues or tumors employing heat from a laser with an MRI as a guide. LITT is a nonsurgical treatment that is considered less invasive than surgical procedures for people who are not able to tolerate surgery (Del Bene et al., 2022).

This clearly indicates that such new-generation MRI CAs' tumor-targeted techniques, this microenvironment-based targeting, could be effective in achieving higher imaging quality and specificity. Furthermore, using these targeted strategies could be necessary to localize the CAs in order to reduce their dosage and consequently subsequent toxicities. The new age therapeutic regimens for improved vision and treatment are also made possible by these targeted modalities.

3. Future of MRI Imaging

AI relies on two major pillars: machine learning and deep learning. While machine learning use pre-existing data to build a logical problem solver, deep learning leverages neural networks that resemble the human brain to do the same task. Although the outcomes produced by these two terminologies are comparable, their fundamental ideas vary significantly. MRI-mediated diagnostics has recently made extensive use of deep learning and machine learning (ML) methods (Amin et al., 2021). These contemporary methods may improve picture quality or might be helpful in determining how the illness is spreading.

- **Machine Learning (ML) in MRI**

Molecular imaging analysis has made major advancements in the last several years, which ML discusses. In the meantime, a number of organizations have done effective studies to identify diseases and estimate their spread. Beatriu Reig and colleagues, for example, presented a number of machine-learning models for detecting breast cancer. They describe how the area of machine learning in breast MRI is rapidly expanding due to advancements in radiogenomics, lesion identification, lesion categorization, and neoadjuvant chemotherapy response prediction. Since supervised and unsupervised machine learning algorithms have not yet been used in therapeutic contexts, more study is necessary. This study compares the capabilities of many machine learning classifiers in diagnosing breast cancer (Reig et al., 2020).

Similarly, brain tumor diagnosis has been accomplished with success using ML. David and Arun made the diagnosis of whether the tumors were primary gliomas or metastases based on the sizes and textures of the tumors in the MRI pictures. The glioma is then graded utilizing a pattern classification algorithm in this investigation. A number of procedures are included in the suggested strategy, including locating the region of interest, choosing pertinent characteristics, extracting features, and categorizing the tumors of the brain. The tumor's form, intensity, and rotation-invariant texture features will all be included in the retrieved features. To lower the amount of features, the use of a support vector machine using recursive feature elimination might be implemented. A set of 102 brain tumors with various cancer diagnoses, such as glioblastoma, meningiomas, and metastases, were used to evaluate the method. Applying the support vector machine technique of classification with leave-one-out cross-validation, the researchers managed to attain an accuracy of 88 percent in differentiating high-grade tumors against low-grade tumor and eighty-five percent in differentiating metastasis from gliomas. For detecting metastases, the degree of sensitivity was eighty-seven percent and the specificity was seventy-nine percent The degree of specificity and sensitivity for discriminating high-grade tumors against low-grade malignancies were eighty-five percent and ninety-six percent respectively, according to David and Arun (2020).

Moreover, Alzheimer's disease, another serious neurodegenerative disorder, may have its prognosis predicted using machine learning approaches. As a unique way to detect the shift from mild cognitive impairment to Alzheimer's disease, Moradi and colleagues recommended using MRI scans. Using supervised as well as semi-supervised learning approaches, an aggregate biomarker for MRI was developed. In order to completely remove the impacts of aging identified in the MRI scans, the MRI biomarker was developed using a semi-supervised method. Features were selected from MRI information gathered from participants with Alzheimer's disease along with normal controls with no using of data from individuals with moderate cognitive impairment. The MRI biomarker has then merged with additional data, including the MCI individuals' age and cognitive assessments, to form the aggregate biomarker. These are a few of the special qualities of the method. The effectiveness of the method was shown using data from the Alzheimer's Disease Neuroimaging Initiative database. The MRI biomarker was demonstrated to discriminate between patients with stable and growing moderate cognitive impairment, having an area under the receiver operating characteristic curve (10-fold cross-validation) of 0.7661 (Zhou et al., 2021).

There are four primary phenotypic categories for Multiple Sclerosis, and ML has been effectively used to diagnose MS. Machine learning may be used to use multidimensional data to identify groups with similar properties. In this work, brain MRI images from previously published research are subjected to unsupervised machine learning to categorize MS subtypes according to pathological characteristics. An independent cohort of 3068 patients is utilized for validation, while a training dataset of 6322 multiple sclerosis patients is used to create MRI-based subgroups. Based on the early anomalies seen, three subgroups of MS are identified: lesion-led, cortex-led, and white matter-led with normal appearance. The greatest incidence of recurrence and verified disability progression (CDP) are linked to the lesion-led subtype. In several clinical studies, patients with the lesion-led multiple sclerosis subtype show positive response to therapy. Our results imply that MRI-based subtypes may be used to identify patient groups in interventional trials and to predict the course of MS disability and treatment response (Zhou et al., 2021).

In addition to these studies, researchers have focused on a variety of other illnesses, including cardiovascular disorders and prostate cancer (Comelli et al., 2021). If properly developed, machine learning (ML) has the potential to become an excellent tool for diagnosing chronic illnesses in the near future due to its activity in several disease detection fields. More study on this approach is required, and scientists and physicians should work together on it.

- **Deep Learning (DL) in MRI**

As new deep learning architectures advance, earlier state-of-the-art conventional AI methods are falling behind. DL has been used to various fields, including as image processing and medical diagnostics. Akkus et al. released a review paper which seeks to summarize the most recent deep learning-based segmentation algorithms using quantitative brain MRI. Initially an overview of the deep learning architectures presently used for segmenting brain lesions and anatomical brain areas was provided. Following that, the characteristics, speed, and accuracy of deep learning algorithms were shown and discussed. Finally, a critical evaluation of the existing situation was performed, and prospective future advancements and patterns were identified. In the area of brain tumor MRI imaging, this review presents many viewpoints. According to their research, the brain's intricate structure and variability within appearance, non-standardized MR scales resulting from variations in imaging protocols, problems with image acquisition, and the existence of pathology have all made the analysis of images of the brain exceedingly challenging for computer-aided approaches. Thus, more generic approaches like deep learning are required to effectively handle these variabilities. In the context of medical imaging datasets, deep learning's potential is limited, regardless of a notable progress. Relative to the techniques' performance on large-scale datasets (millions of pictures) such as ImageNet, these datasets' relatively small size restricts the methods' ability to reach their full potential (Magadza & Viriri, 2021).

Liu and his colleagues also addressed a variety of deep learning designs, including artificial neural networks, stacking autoencoders, deep feedforward networks, deep belief networks, and so on, to illustrate the DL's utility in decoding an MRI picture. Researchers additionally presented a range of deep learning applications in this area, which include image recognition, registration, segmentation, and classification (Dong et al., 2021).

Deep learning was previously used to diagnose a range of ailments, much like machine learning. In order to develop a deep neural network to differentiate among patients with schizophrenia and healthy controls, Masoudi et al. employed MRI data. The network used a deep belief network and a softmax layer to collect high-level latent features. The network was trained in two stages: first, utilizing a deep belief network to pre-train it, followed by using a softmax layer for supervised fine-tuning. The pre-trained network has been used to extract high-level latent features from MRI data. The softmax layer simplified the final classification process by improving the pre-trained network via supervised fine-tuning (Masoudi et al., 2021). Suk et al. presented a similar technique to identify moderate cognitive impairment, the prodromal stage of Alzheimer's disease, using deep learning. High-level latent and common features were extracted from two imaging modalities: MRI and Positron Emission Tomography (PET) images. To identify discriminative patches between classes, a statistical significance test was employed. These paired patches were used to build a multimodal deep Boltzmann machine, which extracted high-level latent and shared information. The matched patches within the multimodal deep Boltzmann device have been trained to produce binary vectors applying the Gaussian Restricted Boltzmann Model. Such binary vectors acted as inputs to the multimodal deep Boltzmann model. Using paired patches and an improved multimodal deep Boltzmann machine, high-level latent and common properties were found, resulting in the development of an image-level classifier for final classification. Tu et al. (2022) identified three main steps in the process of generating a classifier: learning the classifier at the patch-level; building mega-patches; and collective learning. Such deep learning methods are essential to the analysis of current MR images. But before clinical translation, DL has to be thoroughly investigated for accuracy.

CONCLUSION

This review begins by examining the fundamentals of MRI CAs, their reasonable design, and their drawbacks. The authors then went on to describe the targeted techniques for MRI CAs in order to achieve higher contrast and better picture quality. New researchers and physicians in this field will undoubtedly get a better knowledge from such targeting techniques and creating approaches. The case studies and examples in these sections, which are recent publications, call for a greater emphasis on the mainstream MRI CAs. In an attempt to support the usage of multimodal MRI probes and theranostic MRI CAs in clinics soon, this paper addresses a few of them.

A special emphasis has also been placed on different image processing methods. AI approaches, which are based on machine learning and deep learning, have lately received a lot of attention, demonstrated by the many examples and case studies that have been published. Their restrictions were additionally demonstrated to support their clinical translation potential in the near future.

Nonetheless, rationally designed biocompatible CAs and other image-processing AI approaches, together with classical MRI, will influence the future of MRI and other molecular imaging modalities. These improvements may undoubtedly result in a cutting-edge imaging regimen that is simple to apply from the bench to the patient's bedside.

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