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REVIEW

Use of artificial intelligence in magnetic resonance imaging for the diagnosis of Alzheimer's disease: a review

Uso da inteligência artificial na ressonância magnética para o diagnóstico da doença de Alzheimer: um artigo de revisão

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ABSTRACT

Objective: Alzheimer's Disease (AD) is a neurodegenerative disease which has been the main cause of dementia worldwide. New therapeutic approaches have been developed for the correct diagnosis, such as the use of Artificial Intelligence techniques. Therefore, the goal of this article is to product a literature review about using it for Alzheimer's diagnosis. **Data Sources:** Research using Portuguese and English articles, with publication between 2003 and 2020, which were found in data bases like Scielo, Lilacs, Google Scholar and Pubmed. The criteria considered agreement between authors, observation of title and references, through reading, and selection of data of interest for this work. **Data Synthesis:** Radiologic exams can be inconclusive and need techniques that optimize the precision of results. Techniques of Artificial Intelligence have the objective of using computational methods that analyze faster innumerable imagens of data bases helping to identify and classify alterations. Besides improving the detection capacity over time it also has application in other diseases. **Conclusion:** The use of Artificial Intelligence in Alzheimer's Disease is promising and should be implemented into the diagnosis routine of health, in a way that guarantees an early patient diagnosis and an adequate multidisciplinary follow-up.

RESUMO

Objetivo: A Doença de Alzheimer (DA) é uma doença neurodegenerativa que tem sido a principal responsável pelos casos de demência no mundo. Novas abordagens terapêuticas têm sido desenvolvidas para o diagnóstico correto, como o uso de técnicas de inteligência artificial. Sendo assim, este artigo teve como objetivo a produção de uma revisão bibliográfica sobre seu uso no diagnóstico do Alzheimer. **Fontes dos dados:** Foram realizadas buscas de artigos em português e em inglês e com data de publicação entre 2003 e 2020, os quais foram encontrados em bases de dados como Scielo, Lilacs, Google Scholar e Pubmed. Os critérios de escolha levaram em consideração concordância entre autores, observação do título e referências, leitura minuciosa e seleção dos de interesse para o trabalho. **Síntese dos dados:** Exames radiológicos podem ser inconclusivos, necessitando de técnicas que otimizem a precisão dos resultados. As técnicas de inteligência artificial possuem o objetivo de utilizar métodos computacionais que analisam, de forma rápida, inúmeras imagens de bancos de dados, ajudando a identificar e classificar alterações, além de aprimorar sua capacidade de detecção ao longo do tempo de uso e possuir aplicação em outras doenças. **Conclusões:** O uso da Inteligência Artificial na Doença de Alzheimer se mostra promissor e deve ser implementado na rotina diagnóstica de saúde, de forma que se garanta um diagnóstico precoce dos pacientes e um acompanhamento multidisciplinar adequado.

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Introduction

Along with population aging and increased life expectancy of the elderly, there are pathologies related to senescence, including Alzheimer's disease (AD). Alzheimer's disease is a neurodegenerative and progressive disease that encompasses several signs and symptoms associated with memory decline and deficits in cognitive domains, such as language, perception and motor activities, causing an inability to perform basic and routine activities and loss of autonomy.[1, 2, 3]

Studies show that the earlier the person is diagnosed, the better their prognosis, as treatments and intervention methods to delay the progress of the disease are applied before the patient presents characteristic signs of Alzheimer's in an advanced stage, increasing their quality of life.[1,4,5,6] The brain of Alzheimer's patients has diffusely atrophied regions, mainly in the temporal, frontal and parietal lobes, together with loss of neurons, cortical synaptic degenerations, senile plaques extracellularly and neurofibrillary tangles intracellularly. Many patients, despite having all these lesions, often still do not present the characteristic signs and symptoms of Alzheimer clinically, making the diagnosis difficult for neurologists.[3,2]

With Structural Magnetic Resonance (MRI) and Functional MRI at rest, it is possible to detect these lesions, which may lead to a pre-diagnosis.[7, 6]. Even so, the specialist may not be able to diagnose accurately, mainly because the lesions presented also appear in other types of dementia and because the patient may be in the so-called prodromal or preclinical phase, in which signs and symptoms are still very unspecific for an accurate diagnosis. Thus, it is extremely important to use Computational Intelligence (AI) techniques to avoid diagnostic errors and provide the patient with intervention methods as early as possible. Among the AIs, there are the MultilayerPerceptron Neural Networks, Deep Learning Neural Networks, Deep Learning, Learning Machine, among others.[8,7,9,6]

These systems are fed into computer neural networks, which store, retrieve and analyze data from different people with the same disorder and follow algorithms defined by experts, being able to analyze similarities in MRI scans and help in the correct diagnosis of the disease.[7,9] In this review article, the uses of Artificial Intelligence in Magnetic Resonance Imaging for the diagnosis of AD will be reported in detail, considering its importance and its methods in tracking the disease and addressing abnormal brain areas such as atrophy, damage, or loss.[1,6]

Objective

This work aimed to produce a literature review of artificial intelligence techniques for the diagnosis of Alzheimer's. Artificial intelligence allows for the correct diagnosis, in addition to making it more efficient and consequently allowing treatment, to improve the well-being of people affected by the disease.

Methods

To find the studies that deal with the subject in question in this article, searches were carried out in the electronic databases Scielo, Lilacs, Google Scholar and Pubmed with the keywords Artificial Intelligence, Alzheimer Disease, Diagnostic, Magnetic Resonance, Deep Learning, Machine Learning and their correspondents in Portuguese, with language filters (Portuguese and English) and year of publication (2003 to 2020). After applying the exclusion criteria (equal articles, correlation between the title and the abstract with the objective of the work and agreement between authors), 38 articles remained.

For the selection of articles, the four authors were analyzed, ensuring that there was no divergence between ideas. After a consensus, it was then defined which of the selected ones would serve as the basis for the work. Initially, the verification was done through the titles, followed by the proper reading, observation of the references to assess the quality of the information and discarding those that would not reach the desired purpose. Finally, those who had only the information of interest for the work were approved.

Development

The need for an early and definitive diagnosis of Alzheimer's Disease makes magnetic resonance imaging using artificial intelligence (AI) an extremely important tool, especially considering that even today, the diagnosis of AD is made by excluding other dementias and it is confirmed only with an autopsy of the brain tissue, after the death of the individual.[10] There is currently no cure for Alzheimer's. However, if diagnosed early, it is possible to identify patients who are at high risk of developing it completely, reducing the incidence of the disease.[11,12,13]

Early diagnosis is also performed by other procedures such as neuropsychological testing and studies with the cerebrospinal fluid assay, but studies argue that neuroimaging is much more promising, mainly because it is less invasive, because of the use of biomarkers and the possibility of differentiating different dementias.[14,15] Furthermore, a high-resolution structural MR scan requires only 5 to 10 minutes of acquisition time, and it is a widely available technique and its methods of analysis have been established since the early 1990s.[16]

Neuroimaging is extremely important in the diagnosis of brain diseases, however, even with all the existing collection, there is still no method or biomarkers that can confirm the diagnosis of brain disorders with 100% certainty, although the existing analyzes have several advantages. The challenge results in numerous studies with the primary objective of preventing or halting the progression of Alzheimer's disease.[17]

The hippocampus is one of the first areas affected in AD and, for this reason, it is essential that the exams initially focus on this region so that it is possible to detect the disease early. Therefore, some neurobiological changes can happen years before the real symptoms of Alzheimer's appear, such as mild cognitive impairment (MCI).[2,18] One of the first symptoms of AD is the loss of part of the memory, especially when it comes to episodic memory, that is, the memory of recent events and changes in language.[19]

Some changes occur even before the onset of symptoms, mainly observed in the medial temporal lobe, including the entorhinal cortex and hippocampus, followed by progressive neocortical damage. Atrophy is accompanied by microstructural loss (dendritic, myelin, and axonal) and metabolite changes, and the simplest way to assess medial temporal lobe atrophy is by visual inspection of coronal T1-weighted magnetic resonance imaging.[20,21,18]

Two abnormalities are considered frequent and diagnosable by MRI in the patient with Alzheimer's disease: dense layers of protein deposited intra and extracellularly to nerve cells and areas of damaged and tangled nerve fibers within neurons. In addition, the cerebral cortex is smaller than normal and the ventricles are expanded. These last two characteristics are used to outline the prognosis of the disease.[22]

The most observed changes in MRI scans of patients with AD were in the hippocampus and medial temporal lobe region, where it was possible to observe that the activation of the region was decreased. Other areas, such as the ventrolateral prefrontal cortex, showed increased activation that may have a compensatory effect on others that are not being activated correctly. This increase in activation may be the result of cognitive deterioration. In addition, to aid the diagnosis, the use of MR spectroscopy is also considered, which provides chemical and physiological information on the samples in question.[20,23]

We can also observe biomarkers. Biological markers that indicate neuronal integrity in Alzheimer's patients include a decrease in the concentration of N-acetyl aspartate in several brain regions and an increase in myoinositol, creatinine, importance in energy metabolism, atrophy with a marked reduction in brain volume, failure to remove of Aβ peptides with consequent accumulation and formation of amyloid plaques, causing changes in synaptic plasticity and neuronal integrity, in addition to adulteration of proteins such as τ protein, destabilizing microtubules and forming neurofibrillary tangles.[20,24,23]

Among all AD markers, MRI-detected hippocampal atrophy is the most recognized and can be correlated with cognitive deficits that appear to be inevitable and progressive. The main MRI-based sites of tau deposition are usually along the polysynaptic hippocampal pathway. Atrophies in the parietal and frontal lobes are related to neuronal loss that leads to disorders in speech, behavior and visuospatial functions.[21,18]

In addition to detecting these changes and structures, medical evaluation including previous patient records, and neurobiological and mental status exams are extremely important to confirm the diagnosis. Structural and functional magnetic resonance imaging at rest is essential, mainly because they can analyze the different activities of the brain and changes that can be considered attention.[4,7,22]

Functional MRI is extremely important mainly because of its BOLD effect. Through it, there is the possibility of detecting neuronal activity while the patient performs some routine tasks. The effect is based on observation of the increase in local oxygen consumption and analysis of changes in signal intensity on MRI caused by brain activation. In the resting state, it analyzes synchronous BOLD fluctuations that include the Default Mode Network, which is active during periods of rest and is found to be altered in AD patients in the anterior medial frontal cortex and cingulate cortex regions.[23]

Among the various possibilities of MRI, there are ultra-high field 3D T1-weighted MRI acquisitions with an isotropic resolution of approximately 1 mm, through which it is possible to detect and evaluate brain atrophies; image segmentation can provide reproducible measurements of hippocampal volume, detecting subtle changes not visible in global volumetric measurements; it can be combined with biomarkers to make the diagnosis more accurate.[25,4,26,27]

Resonance has provided a great advance in imaging, mainly encephalic, as it has high contrast for soft tissues and possibilities of cuts in different planes, in addition to the fact that, when combined with artificial intelligence, a leap was obtained in the diagnosis of neurological diseases, as AD.[28,29] According to Kehoe et al. 2014, AI systems in MRI for the diagnosis of AD have sufficient competencies to distinguish healthy control groups from patients with the disease, from milder degrees (such as MCI) to more critical degrees of the disease, in addition to being able to differentiate from other neurodegenerations. For these functions, the use of biomarkers is considered, which are highly effective in the early diagnosis of Alzheimer's disease, indicating its progression, and can be recognized and quantified, alone or in clusters, in AD patients, by AI algorithms.[30,9]

As much as there are all these characteristics found in studies of years following the progression and which changes occur, there is still a risk of false-positive and the goal of an accurate diagnosis ends up not being reached. It is in this aspect that artificial intelligence comes in as a complement to imaging tests and the knowledge of specialist physicians since the technology can compare different results look for patterns quickly and help to conclude the diagnosis.[18]

Computational techniques are applied to obtain linguistic variations that are compared to traditional clinical variables, including the patient's relevant history, such as medical history and genetic information, measuring the value of the extracted prognosis. Non-linguistic variables such as age and sex are also taken into account when making the prognosis.[13]

Tests include an assessment of reasoning such as object naming, memory, attention and language skills. This prediction is based on data collected on patients without AD traits and on computers capable of handling multivariate linguistic performance data. These tests demonstrated that the future onset of AD is associated with an insistence on speech repetition, spelling errors and reduced speech, where words are omitted.[13]

Use of artificial intelligence in the diagnosis of AD

Artificial intelligence is a recent technology, whose main objective is the development and application of computational methods that reproduce human actions, that is, they end up making decisions on a certain subject autonomously, without human interference, given that the IA's actions are based on databases.[31]

Compared to the main imaging equipment, tomography and magnetic resonance are the ones that stand out the most for the diagnosis in question.[32] Machine learning methods are being much sought after lately, because radiological exams such as Magnetic Resonance may have ambiguities. Over the years, the range of tests performed has increased considerably, as has their accuracy. This ended up creating difficulties for the radiology professionals, however, experienced they may be. For this reason, computer systems to support the diagnosis are being extensively studied and elaborated, to optimize radiological exams, leading to greater precision.[8]

To facilitate the analysis of the images obtained in the exam by professionals in the area, numerous computational intelligence techniques were used to help identify features that are not entirely explicit in the image, and classify and diagnose AD. Artificial intelligence (AI) has been used in the medical field to assist in various functions, from obtaining patient data to improving image acquisitions. Improvements such as noise elimination, faster scanning of MRI images, improvement in spatial resolution and even a reduction in the level of radiation emitted by diagnostic imaging equipment were feasible.[33]

Several studies, as demonstrated in the review by Zamrini, Santi, Tolar, 2004, have concluded that cognitive tests, without any other complementary imaging tests, are inadequate and inconclusive to accurately diagnose Alzheimer's disease. Reliability ranges from fair or moderately reliable to good, leaving a significant margin of error.[5]

The AI used in diagnostic imaging is not yet capable of interpreting exam images and generating reports alone. Its mechanism is based on classifiers that rely on data provided by other imaging exams, being able to assist the radiologist in interpreting the images more quickly and accurately, and identifying possible abnormalities. For example, if the AI system is trained to identify neoplastic cells, it will generate faster responses in exams that appear to be neoplasms, optimizing time and increasing the radiologist's performance.[33]

When we use this system to analyze MRI images of undiagnosed people likely to have AD, the images stored on these computers are analyzed by the system itself, which generates possible diagnostic probabilities based on established algorithms and standard characteristics. In addition, it can also self-modify as a result of results obtained with other patients over time (self-improvement), improving diagnostic accuracy and increasingly reducing medical errors.[34]

There are numerous computational intelligence techniques, such as Deep Learning Networks, Machine Learning, Convolutional Neural Network, among others.[8] We will address some of them below:

Computational Intelligence Techniques

One of the methods of greatest interest within artificial intelligence has been Machine Learning, which is based on pattern recognition based on later occurrences or experiences. This method can be applied to categorize images from different radiological exams, using different characteristics to detect different diseases.[8]

This technique can be classified into supervised and unsupervised learning.35,8 In this review, we will only address supervised learning algorithms, as they are more commonly used in neurodegenerative disease data. Therefore, in supervised learning, from true information provided by human experts, the algorithm can develop based on already expected responses.8 This technique requires a set of labeled data to learn. However, it is necessary to label, for example, a compilation of MRI images, so that the machine learning algorithm associates the input image and the label. Therefore, this system will recognize patterns and allow the prediction of new labels.[35]

Another area of AI that has been gaining interest is Deep Learning, used in the interpretation of images. It contains algorithms that integrate attribute extraction and image classification processes within the neural network itself, reducing the need for pre-processing or segmentation.[8]

Deep Learning (DL) systems allow the characterization of AD in magnetic resonance images from computational models, these models are composed of several processing layers. DL can extract its information, avoiding the subjectivity of the specialist, as in the classic model of Machine Learning.[36]

In the area of deep learning, the field that most stood out in medicine was the Convolutional Neural Network (CNN)[8], important for capturing and classifying images. This network was developed to demand the least amount of pre-processing possible when compared with other algorithms, this being performed in a hidden way in the convolutional layers.[11]

Unlike traditional networks (example: MLP — Multi-Layer Perceptron), CNNs have a process for extracting image characteristics, which occurs due to the application of a kernel filter on the input image. For this, these networks have mainly three types of layers: convolutional layer, pooling layer and fully connected (fully connected).[11]

Diagnostic systems, specifically MRI in this article, when aided by artificial intelligence technologies such as the Learning Machine, can obtain much more accurate results, helping the radiologist to interpret neuroimaging data, in addition to detecting important imperceptible details. Among the learning algorithms of techniques for classification, purposes are the Support Vector Machines (SVMs), which have been used to aid in the analysis of MRI images, improving the results of disease examinations.[35]

According to the study cited by Myszczynska 2020, SVM was used to differentiate between MRI scans in patients with different degrees of Alzheimer's to be able to differentiate it from other degenerative diseases and healthy control groups. Furthermore, with this technique, it was also possible to predict the evolution from MCI to AD more accurately than traditional approaches. Among several different algorithms to test the ability to differentiate between AD, MCI and other dementias, the one that stood out the most was SMV. This difference, which is also capable of differentiating between healthy individuals, is based on audiovisual and language resources, analyzing the patient's ability to answer questions, and checking for delays and changes in tone, by analyzing eye contact and facial features.[35]

In another study, presented by Signaevsky et. al, 2019, methods based on machine learning were addressed, to obtain evaluative and quantitative information about neuropathological images, especially AD. Using Deep Learning, the neurofibrillary tangles of postmortem brain tissue were evaluated using deep learning classifiers, other computing platforms and data provided by human experts. With this, it was discovered that deep learning neural networks can identify and quantify deep neurofibrillary tangles. therefore, the use of machine learning is an efficient tool to aid in the diagnosis of AD.[37]

Another AI method used would be MCADNNet, this deep learning algorithm is based on a convolutional neural network that recognizes mild cognitive impairment, characteristic of early stages of AD, and patients who already have the disease in more advanced stages, using structural and functional MR images. Thus, the system works, together with a decision-making algorithm, following a programmed and optimized classification.[38]

Voxel-based morphometry (VBM) is another technique used. According to Savio et al., 2009, the procedure includes spatial normalization of patients' images in a standard space; tissue class segmentation using a priori probability maps; smoothing to reduce noise and small variations and voxel statistical tests. After image acquisition, pre-processing is performed to compare voxel values in normal and morphologically different brains, in sequence the images are recorded.[10,24]

Finally, a statistical analysis is performed using the General Linear Model to verify and prove brain alterations. After the procedure, MR images can be used to classify the disorder, either by morphometric methods in regions of interest or by brain gray matter voxels in automated segmentation images.[10,24]

Artificial neural network classifiers use these images to classify the brain volume of AD patients. The extraction of features is performed using VBM analysis, which detects changes between AD patients and control patients with accuracy, in the case of the Savio et al., 2009 study, of 83%. Improvements still need to be made, as those misclassified in the study are considered the most critical: controls classified as having AD (false positives) and patients with very early or mild dementia classified as negative (false negatives).[10]

Conclusion

The longer it takes to confirm the diagnosis of Alzheimer's Disease, the less there is a guarantee for the patient that he will have a good prognosis and effectiveness about treatments, compared to a scenario in which the diagnosis and treatment were carried out previously. The attempt to correct this flaw came through MRI scans combined with artificial intelligence techniques.

The big difference between artificial intelligence concerning other exams is the possibility of analyzing large banks of images simultaneously and quickly, learning from each image analyzed and improving its learning ability. Furthermore, another interesting point is the fact that the system is based on the functioning of the human brain. These benefits are promising, and differential and call attention to the need to include these methods in the diagnostic routine in the health area.

Importantly, these AI systems can be used to diagnose other dementias and even other non-brain-related diseases. As much as they are techniques that require government and private investment, in addition to skilled labor for handling, maintenance and understanding of processes and results, the long-term consequences are striking. At the same time that they guarantee a better quality of life for the elderly who can remain active in their routine for a longer time, it also reduces, on the other hand, government and family costs with the entry and support of these elderly people in nursing homes.

Therefore, with this review article, we hope to reinforce the idea that these methods are included in the diagnostic routine, both to help doctors and the health system, as well as to guarantee an early treatment and diagnosis of affected patients, so that multidisciplinary follow-up should be applied to this patient and ensure a better quality of life for him and his family.

Conflict of interests

The authors declare that there is no potential conflict of interest.

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