Artificial intelligence and deep learning in ophthalmology - present and future (Review)

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Received May 29, 2020; Accepted June 30, 2020

DOI: 10.3892/etm.2020.9118

Abstract. Since its introduction in 1959, artificial intelligence technology has evolved rapidly and helped benefit research, industries and medicine. Deep learning, as a process of artificial intelligence (AI) is used in ophthalmology for data analysis, segmentation, automated diagnosis and possible outcome predictions. The association of deep learning and optical coherence tomography (OCT) technologies has proven reliable for the detection of retinal diseases and improving the diagnostic performance of the eye's posterior segment diseases. This review explored the possibility of implementing and using AI in establishing the diagnosis of retinal disorders. The benefits and limitations of AI in the field of retinal disease medical management were investigated by analyzing the most recent literature data. Furthermore, the future trends of AI involvement in ophthalmology were analyzed, as AI will be part of the decision-making regarding the scientific investigation, diagnosis and therapeutic management.

Contents

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Key words: artificial intelligence, deep learning, convolutional neural networks, machine learning, ophthalmology, OCT, image processing, image analysis

1. Introduction

In 1956 artificial intelligence (AI) was first described as a technology capable of thinking independently and reproducing human behavior after training (1). Machine learning (ML) was introduced in 1959 as an algorithm that, after exposure to multiple inputs can modify its behavior, automatically (2). Today, by developing computational power and neural networks, deep learning determines the perfection of automatic learning. Deep learning (DL), as a subset of machine learning, uses a programmable neural network that enables the machine to make its own decisions, without human aid. Convolutional neural networks (CNNs) play an important role in the development of these technologies (3). Convolutional layers, which are the basis of these networks, learn to extract the image features with the aid of convolutional filters (4).

Deep learning is used in ophthalmology for data analysis, segmentation, automated diagnosis and possible outcome predictions (5). The association of deep learning and optical coherence tomography (OCT) technologies has proven reliable for the detection of retinal diseases and improving the diagnostic performance of the eye's posterior segment diseases (6-8).

At present, some difficulties of translating these algorithms into the clinical practice may be encountered, such as inconsistency in the reporting metrics when analyzing data from multiple OCT devices, imaging protocols that are not standardized between devices, and limited capabilities in graphics processing.

The increase in the number of retinal disease cases has produced an ever-growing demand for retinal image readers. The development of artificial intelligence (AI) and deep learning analysis of retinal imaging can reduce the number of ophthalmologists needed for image interpretation and the time allocated for this procedure. At the same time, AI may increase the efficiency of healthcare providers by establishing the correct and rapid diagnosis of retinal diseases.

In this review, the possibility of implementing and using AI in establishing the diagnosis of retinal disorders was explored. Moreover, the benefits and limitations of AI in the field of retinal disease medical management were reviewed.

2. AI, ML, DL and computer programming

AI technologies entered the field of ophthalmology recently and have been in continue expansion ever since. In the near future AI will have an important impact on aiding research to achieve new discoveries and improving clinical practice.

Artificial intelligence. AI was defined by John McCarthy as the 'science of creating intelligent machines which replicate human behavior' (1).

Machine learning. ML is a subtype of AI. The computer software learns from large volumes, without explicit instructions, on how to derive the required output (through trial and error). It becomes better at making its own decisions but still needs human guidance.

Deep learning. DL is a subtype of ML. It uses multiple layers of CNNs. These are made of software-defined 'neurons' which together are processing data in order to get the required information. The neural networks are designed to be similar to the ones inside the human brain and reason in a similar manner. Thus the algorithm is able to determine on its own if the prediction made by the DL process is accurate or not.

Generative adversarial networks. GANs are paired neural networks used for unsupervised ML. This neural network generates images or other data and the discriminative neural network evaluates it and gives feedback to help in the learning process. GANs are used for fully supervised, semi-supervised and reinforcement learning.

Computer programming. The computer programming is very important. The software programmer has to know in advance how to process the data to produce the required information. When the ML software has finished learning, it will generate the required output (9).

3. OCT and AI/deep learning

OCT images are used for the diagnosis, monitoring and management of many retinal conditions such as diabetic macular edema (DME) and age-related macular degeneration (AMD). Investigative efforts have been directed at utilizing deep learning algorithms as tools for automated reading of OCT images, for diagnostic purposes. Numerous algorithms have been developed and various landmarks identified in order to recognize non-pathologic OCT images (10-12).

There are 10 relevant anatomic layers visible on spectral-domain OCT. Algorithms can identify anywhere from 4 to all 10 of these layers. Studies have shown wide variability in the identification of various landmarks. At the moment, the development of a consistently accurate algorithm is critically needed. The integration of these algorithms into a tele-retinal screening pathway will be one way of integrating automated OCT reading into clinical practice.

Automated OCT reading has shown promising results in DME and identifying exudative AMD (7,8,13). In a recent study, Kermany *et al* (8) found 97.8% sensitivity, 97.4% specificity, and 0.99 AUROC (area under the receiver operating characteristic) curve for detecting referable AMD. An AUROC curve score over 0.7 relates to good and outstanding results, while under 0.5 proves no discrimination was made. Thus, DL can accurately diagnose AMD in the early stages.

OCT demonstrates high accuracy in detecting small amounts of fluid and the need to commence treatment in neovascular AMD (14-17). Chakravarthy *et al* (16) recorded 91.0% accuracy for diagnosing exudative AMD and Prahs *et al* (15) showed 95.5% accuracy for predicting the need for intravitreal injections.

Automated OCT reading has also been proven useful in the diagnosis of diabetic retinopathy, central serous chorioretinopathy, polypoidal choroidal vasculopathy and macular holes (13,18,19). Obviously, physicians may benefit from OCT reading algorithms as a triaging mechanism and a guide in the therapy decision-making process.

4. AI and retinal diseases

Deep learning and the retinopathy of prematurity. ROP is a vasoproliferative disease that affects premature infants and it may lead to blindness (20). The initiation of ROP treatment is based on the International Classification Guide (ICROP), which is used to standardize the diagnosis and to determine treatment thresholds (21).

When examining a ROP eye, it is possible to visualize, at the level of the posterior pole, abnormal arterial tortuosity and venous dilatations, which define PLUS disease (22). The screening is performed by direct examination, by an ophthalmologist. For the same purpose, the images can be obtained with portable cameras examined afterward by a specialist.

Numerous clinical trials indicated that there are significant variability and inconsistency in the ROP diagnosis, which may lead to differences in treatment recommendations (23-25).

Some deep learning algorithms have been created to minimize the clinical reasoning variability and inconsistency in diagnosing ROP, many of them showing accuracy in detecting 'plus' or 'pre-plus' disease (lower degree of vascular tortuosity) (26-28). Brown *et al* (29) used deep learning for training a deep convolutional neural network on a set of 5,511 images. These images were previously rated by experts as 'plus', 'pre-plus' or 'normal'. The validation of a set of 100 retinal images showed: 93% sensitivity and 94% specificity for the detection of 'plus' disease and 100% sensitivity and 94% species in detecting 'pre-plus' disease. Similar studies showed that deep learning may be able to minimize inter-observer variability.

In order to generate reliable image analysis algorithms, it is very important to have a clinically accepted reference standard for diagnosis. The effectiveness of deep learning image analysis as a screening tool for ROP needs to be evaluated in clinical daily practice.

Deep learning and diabetic retinopathy (DR). The incidence of DR is on the rise as the prevalence of obesity increases and the population ages. Undiagnosed DR is one of the main causes of vision loss (30-32).

There are currently many studies aiming at the development of software programs that increase the efficiency of DR screening and management. Recent literature data showed that machine

learning classes (MLC, support vector machine, multiple layer perceptron classes and radial basis function neural network) can recognize and classify DR from images (30-35). The results obtained (MLCs, AI programs) are comparable to those obtained when the retinal images were analyzed by ophthalmologists. In these studies, Ting *et al* (37), Gulshan *et al* (36), and Gargeya and Leng (38) used large data sets to create MLCs.

The researchers used as training images normal images and DR images (separated into categories of mild, moderate, severe, proliferative DR; referable DME and referable DR were additional categories from the same data set, but separate from the others classifications) (36). The results obtained were remarkable. The data validated DR (sensitivity, 0.87-0.98; specificity, 0.90-0.98 and AUROC, 0.936-0.991) (36-38). The software is able to recognize hemorrhages, exudation, microaneurysms, cotton-wool spots and neovascularization, build a model and based on it, is able to classify DR in stages.

Further research into how deep learning fits in the screening pathway is warranted.

Deep learning and age-related macular degeneration. AMD is a frequent disease in the aging population, with the potential to cause important and irreversible visual function loss. AI has contributed significantly to the progress that has been made in screening AMD and may help both patients and health-providers benefit from implementing AI as support in ophthalmological decision making (39).

Lee *et al* (40) created an AMD screening system capable of differentiating between normal and AMD, OCT images. They obtained a peak sensitivity of 0.926, a specificity of 0.937 and an AUROC of 0.9746. Their studies analyzed smaller size samples.

In a larger study, Treder *et al* (17) used 1112 OCT images. They created an MLC software which differentiates a healthy macula of one showing exudative AMD and obtained a sensitivity of 1.00 and a specificity of 0.92.

Besides diagnosis, formulating a visual prognosis is a challenge for many researchers.

Some studies are focused on AMD grading and predicting the final visual acuity by using OCT images. The presumptive prognosis may influence the clinician's decision in establishing the treatment of the disease.

Schmidt-Erfurth *et al* (39) predicted best-corrected visual acuity at 1 year immediately after establishing the diagnosis of the disease with the help of AI. The registered error was 12.9 letters. They trained their MLC on data sets from 614 eyes (2456 OCT scans). Aslam *et al* (41), in a similar study, reported a mean error of 8.21 letters. They analyzed only 847 OCT scans.

Burlina *et al* (42,43) made imaging assessment more efficient through grading systems, which have the potential to function as a decision support system for clinicians. The study group developed software for different MLCs using more than 130,000 OCT images from 4,613 patients. Their conclusion was that deep CNN is the most precise. They obtained an accuracy of the analysis comprised between 0.884 and 0.916.

Some studies look at the role of AI as support to therapy decision-making in AMD (if and when the anti-vascular endothelial growth factor, anti-VEGF, treatment is necessary). AI and predictive treatment technology have been proven as a useful addition to clinical practice. This is possible by training MLCs using OCT imaging. Prahs *et al* (44), Chakravarthy *et al* (16), Schlegl *et al* (45) found that their deep learning CNN was able to correctly predict the need for anti-VEGF therapy (intravitreal injection) in 95% of the cases, similar to an average specialist. The researchers analyzed different features of the scan, particularly retinal fluid presence (46). Central retinal thickness and fluid localization are important biomarkers in OCT images.

Schmidt-Erfurth and Waldstein (47) performed an analysis able to predict the functional prognosis (best-corrected visual acuity outcomes) in neovascular AMD patients about to receive ranibizumab treatment. Bogunovic *et al* (48), applied an algorithm on 61 eyes with AMD. This algorithm used OCT biomarkers to reasonably predict drusen regression over the next 2 years. They obtained an AUROC curve of 0.75. Drusen regression has been shown to precede the progression of non-exudative AMD (49-52).

The above studies demonstrate that deep learning can be utilized to extract data that ophthalmologists cannot read. Deep learning results in image analysis are comparable to that of human performance (43). Many studies have already validated the potential of neural networks in diagnosing AMD.

5. Limitations

AI usage in clinical practice might present some potential risks. Some software programs are based on algorithms that lead to high false-negative rates of detection of retinal diseases. Improper interpretation of the false-positive results may lead to diagnostic errors and could be clinically disastrous for patients' vision.

Sometimes the ophthalmologist can not evaluate the metrics values used by the AI computer software to analyze the clinical data. The method by which a computer algorithm came to its conclusion, the reasoning process, is not always obvious.

It is possible that remote screening (patient's home screening) by automated AI systems, may become a problem due to a lack of patient confidence. Some studies show that many patients do not trust computer-aided diagnosis and prefer in-person ophthalmology visits (53).

Also, there is a risk for doctors to become addicted to technology and lose diagnostic abilities.

For some particular situations, when a physician disagrees with the results obtained by deep learning assessment, or when a patient does not receive counseling related to the required treatment it is necessary to introduce and apply medicolegal and ethical regulations.

All these potential shortcomings highlight the need for continuous improvement in AI technology.

6. The future

In the near future, AI will become more involved in the decision-making regarding the scientific investigation, diagnosis and therapeutic management. Tele-ophthalmology applications can transmit information to less developed regions that face a shortage of specialists (54). Already, a hybrid algorithm, with high sensitivity and specificity, named IDx-DR, approved by FDA as a low to moderate risk device, is used for diabetic

retinopathy screening, aiding the management of patients that need referral to an ophthalmologist.

AI can quickly analyze large databases. Based on these analyzes, AI can explore the associations between disease features that may not be easily obvious to humans.

The clinical analysis of the ophthalmologist supported by the DL analysis results will improve the individualization of the medical management, for the benefit of the patients (55).

AI also plays an important role in scientific research. With the help of AI, the features of newly discovered eye diseases can be identified (53). It is expected that AI algorithms will help in identifying new biomarkers, specific to each disease, as they are able to search for characteristics themselves and are not limited to only recognizing clinical features.

Ongoing research aims to develop autonomous software able to diagnose simultaneously AMD, diabetic retinopathy and glaucoma, predict progression and recommend personalized treatment.

7. Conclusions

AI/ DL (deep learning) algorithms using both OCT and fundus images will revolutionize techniques and methodologies of image analysis. Optimizing these (combined) technologies will accelerate the progress in this area. Currently, there are software programs that standardize OCT images from various devices and the results of these software packages are comparable when the appropriate metrics are used consistently. Nevertheless, large databases, using real patient data, are required to optimize the performance of this type of analysis. Thus, computer-assisted screening, diagnosis and prediction of the ophthalmic disease will reach new frontiers.

In ophthalmology AI has the potential to increase patient access to clinical screening/diagnosis and decrease health-care costs, especially when the risk of the disease occurrence is high or the communities confront with low financial resources. However, legal regulations and solving of the reproducibility issues are required before AI based screening is incorporated in clinical practice.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

ADM and DC contributed to the design of the study, participated in the entire review process and prepared the manuscript. DCB, ADM and RLM performed the literature research and contributed to the analysis and critical interpretation of the data. ADM, DCB and RLM conceived the review and revised the manuscript. DC gave the final approval of the version to be published. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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