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Machine Learning Utility for Optical Coherence Tomography in Multiple Sclerosis: Is the Future Now?

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The research field of modern artificial intelligence (AI) was established at the Dartmouth Summer Research Project in 1956.[1] AI is an umbrella term encompassing a range of algorithmics that learn patterns and make predictions.[2] There is great interest in developing its utility in neurological disorders, including multiple sclerosis (MS). A few studies have applied AI techniques to optical coherence tomography (OCT), and a recent review described recommendations on how the existing OSCAR-IB criteria,[3] used for OCT quality control, could be adapted to incorporate AI.[4] Machine learning is a subfield of AI dealing with algorithms that can automatically learn relationships and patterns in large datasets. Different machine learning models (MLMs) have been tested recently (e.g. support vector machines (SVMs), decision trees) to distinguish MS from healthy controls with promising early results.[5,6] Two recent studies have used MLMs to evaluate prognostic markers in MS.[7,8] Hitherto, these studies have had relatively small sample sizes and have not investigated the value of MLMs at distinguishing eyes affected by previous optic neuritis (ON). This is of interest because the optic nerve is being debated as a potential location in future updates to the McDonald MS diagnostic criteria.[9]

In this issue of *Neurology*, Kenney et al[10] evaluate MLMs with OCT in MS in the largest cohort investigated to date (1,568 MS and 546 controls) as part of a multi-site collaboration with the IMSVISUAL (International Multiple Sclerosis Visual System) consortium. The study provides clinically valuable insights into the utility of MLMs to OCT in MS. Clinical, visual and OCT data were collected from 11 participating sites and included monocular, binocular and inter-eye differences (IEDs) for high and low contrast letter acuities, and monocular, inter-eye differences and inter-eye averages for macular ganglion cell-inner plexiform layer (GCIPL) and peripapillary retinal nerve fibre layer (pRNFL) thicknesses. Three clinical questions were addressed to distinguish: 1) Between MS and healthy controls, 2) Between the presence and absence of unilateral ON history by patient within the MS cohort, 3) Between the presence and absence of ON by eye.

Different feature selection procedures and classifiers were tested, giving accuracies of 0.65 to 0.77 for OCT measures to 0.89 when OCT was integrated with visual measures. Distinguishing between MS and controls, the optimal model comprised a composite of GCIPL IED, average GCIPL thickness across both eyes and binocular low contrast acuity at 2.5% derived from CART (classification and regression tree). The area under the curve (AUC) was 0.89 with sensitivity 81%, specificity 80%, and accuracy 81%. A comparative model, replacing low

with high contrast acuity, performed similarly (AUC 0.89, sensitivity 86%, specificity 76%, accuracy 84%). From this composite model, for a patient with the following three criteria, the MS diagnostic specificity would be 99.5%: 1) GCIPL IED ≥ 3 microns, 2) average GCIPL of both eyes ≤ 80 microns, 3) binocular low contrast 2.5% acuity ≤ 42 letters (20/40 Snellen). SVM analysis revealed comparable results on a subset (486 participants) of the whole dataset when using all variables with AUC 0.95, sensitivity 86%, specificity 79%, accuracy 84% and when using the variable subset from the composite model (AUC 0.93, sensitivity 83%, specificity 90%, accuracy 88%).

To distinguish a history of ON within MS patients, GCIPL IED was identified as the best predictor (AUC 0.77, sensitivity 68%, specificity 77%) and was comparable to a composite model combining GCIPL IED, average GCIPL of both eyes and pRNFL IED (AUC 0.77). A combination of GCIPL IED ≥ 4 microns, average GCIPL ≤ 75 microns and pRNFL IED ≥ 5 microns provided high specificity (97.9%) in distinguishing ON history within MS. SVM analysis produced comparable results without improving the logistic regression models.

Finally, for distinguishing ON history by eye, a composite model that included GCIPL IED, average GCIPL of both eyes, pRNFL by eye, average pRNFL of both eyes and age did not perform better than individual OCT measures, producing an AUC of 0.72 (sensitivity 58%, specificity 77%).

Overall, this study supports the potential of MLMs to address clinical questions for OCT in MS. A composite model using OCT and visual measures (GCIPL IED, average GCIPL of both eyes, binocular low contrast acuity 2.5%) was superior to monocular OCT measures at distinguishing MS from healthy controls. GCIPL IED identified unilateral ON within MS.

There are a few limitations with this study. The classification models relied upon binary outcomes (e.g. MS vs healthy controls); in the real world, other diagnoses that mimic MS are considered and excluded. The manuscript highlights that interpreting these models needs to be in the context of clinical presentation. Secondly, there is no gold standard for ON diagnosis, and this was determined, in the dataset, with historical record review. Consequently, the results rely on this process being highly accurate. Thirdly, it is not certain how GCIPL and pRNFL IED contribute to the model outcomes in patients with both eyes previously affected by ON, as the numbers of bilateral patients were relatively low (n=132). Multi-site statistical adjustment was not performed in the analyses, although the two OCT platforms used, were accounted for, by a validated conversion formula. Finally, it remains unclear how these models may generalize to new cohorts or prospective studies.

Future directions of study could include distinguishing MS mimics from MS. Other variables can be added to MLMs, such as electrophysiology and MRI, to increase the accuracy. Finally, longitudinal studies can evaluate composite models in identifying optic nerve involvement as an additional location for revisions of the McDonald MS diagnostic criteria. We look forward to future advances in this field with great anticipation.

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