Artificial Intelligence and Machine Learning in Stroke Care

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Stroke is an emergency for which delays in treatment can lead to significant loss of neurological function and be fatal. Technologies that increase the speed and accuracy of stroke diagnosis or assist in post-stroke rehabilitation can improve patient outcomes. No resource exists that comprehensively assesses artificial intelligence/machine learning (AI/ML)-enabled technologies indicated for the management of ischemic and hemorrhagic stroke.

machine learning | artificial intelligence | stroke

1. Introduction

Stroke is a neurological emergency and the fifth leading cause of death in the United States [1][2][3]. Established clinical interventions exist for many stroke subtypes such as large vessel occlusion (LVO) and intracranial hemorrhage (ICH). Prompt treatment is one of the more important factors in maximizing the preservation of neurological function. Notably, each minute of treatment delay results in significant neuronal death and the loss of 4.2 days of healthy life [4].

Tools to improve the speed and accuracy of stroke diagnosis and treatment could improve patient outcomes. Artificial intelligence/machine learning (AI/ML) will play a large role in developing such tools. AI/ML in healthcare is growing at 40% per year, and its adoption has the potential to cut USD 150 billion in healthcare costs by 2026 [5]. Recognizing the potential AI/ML has to improve healthcare, the United States Food and Drug Administration (FDA) has developed new protocols to assess the safety and efficacy of AI/ML-enabled health technologies [6]. AI/ML-enabled algorithms have been leveraged for various clinical applications such as detecting liver fibrosis [7], analyzing EKGs [8], monitoring Parkinson's [9], diagnosing glaucoma [10], and classifying lung cancer [11]. The FDA has approved 22 AI/ML-enabled technologies for indications specifically related to stroke diagnosis and rehabilitation. Existing literature reviews in this area have broadly evaluated AI/ML algorithms that have largely been developed for research purposes [12][13][14][15][16]. No study to date has comprehensively evaluated the real-world clinical performance of clinically available, FDA-approved devices indicated for the diagnosis and management of stroke.

2. Large Vessel Occlusion (LVO) Identification in Acute Ischemic Stroke

An important application of AI/ML is the automated detection of large vessel occlusions. Viz ContaCT, commercially known as Viz LVO, was the first FDA-approved, AI/ML-enabled technology indicated for stroke and uses a convolutional neural network (CNN) as the underlying algorithm to detect LVOs from CT angiography (CTA). In data submitted to the FDA, Viz LVO displayed an area under the receiver operating curve (AUC) of 0.91 and reduced time from scan reading to specialist notification from 58 to 7 min [17], indicating improvement of clinical workflow efficiency. Others found similar increases in efficiency when using Viz LVO, reporting decreased transfer and stroke team notification times [18][19], as well as lengths of stay in the neurological ICU [19]. Assessment of Viz LVO's performance has shown negative predictive values (NPV) ranging from 79 to 99% and sensitivities between 81 and 88%, with relatively fast run times (~3 min) and consistent performance across different vascular structures [20][21]. Notably, Viz LVO is an application within the broader Viz.ai platform, which includes tissue perfusion analysis on CTP and ICH identification on CT of the head.

RapidAI is a technology platform similar to Viz.ai. In addition to LVO identification on CTA (RAPID-CTA, RAPID-LVO), RapidAI includes software to analyze CT perfusion (RAPID-CTP) and MRI (RAPID-MRI) images for stroke triaging [22]. Though RAPID-LVO has a reported NPV range of 97–99% [23] and sensitivity ranging from 80–94%, there is a wide range of reported positive predictive values (PPV). Importantly, the PPV is 14% when identifying LVOs in the M2 segment of the MCA [23]. This is in contrast to Viz LVO's reported lower bound PPV of 65%, which did not vary significantly across ICA, M1-MCA, and M2-MCA [21]. Variations in and relatively low PPVs highlight the use of these platforms as initial screening tools (given their high sensitivities and negative predictive values) that require subsequent expert confirmation to determine the presence of LVO. Use of both RAPID and Viz LVO has improved clinical workflows/outcomes (e.g., reducing CT-to-groin puncture times) with similar run times of ~3 min per scan [18][19][24].

Newer technologies for LVO identification include CINA-LVO [25] and HALO [26], which have shown promising performance in the few studies that have assessed their functionality. CINA has demonstrated relatively strong performance (PPV of 86–99%, NPV of 64–99%) across LVO anatomy [27][28]. The limited data for HALO reports an NPV of 91% and a PPV of 47%; however, performance varied based on the anatomical location of the LVO, with the lowest performance in M2 LVOs [29].

3. CT Head (CTH) Analysis (ASPECTS Score) in Acute Ischemic Stroke

Assessing the extent of irreversible ischemic damage to guide treatment decisions is equally important as identifying suspected LVOs. The Alberta Stroke Program Early CT Score (ASPECTS) is one widely used method for accomplishing this task. While diffusion-weighted MR imaging provides the most accurate information regarding acute infarction, CTH is more readily available in the acute setting. FDA-approved Rapid ASPECTS determines ASPECTS from CTs in patients with known MCA or ICA occlusions, but not for primary interpretation of CT images. In addition, the technology is only intended for use on GE Lightspeed VCT Scanners [30]. Overall, many have shown a strong correlation between ASPECTS determined manually by experts (e.g., neuroradiologists), which is currently the gold standard, and those calculated by Rapid ASPECTS [31][32][33]. Some even report superior performance by Rapid ASPECTS in analyzing imaging obtained soon after symptom onset [34][35]. Rapid ASPECTS' individual impact on clinical efficiency and patient outcomes has not yet been studied. However, use of the broader RapidAI mobile app, which includes Rapid ASPECTS functionality, decreased door-to-groin puncture times and improved subsequent NIH stroke scale scores [36].

4. CT Perfusion (CTP) Analysis in Acute Ischemic Stroke

Another class of FDA-approved, AI/ML-enabled technologies for the management of stroke includes technologies that analyze CTP or MR perfusion images to assess the core and penumbra volumes and predict final infarct volumes. CTP can demonstrate ischemic tissue, which consists of non-salvageable tissue and at-risk tissue that could be rescued with successful reperfusion. CTP analysis provides specific parameters, including cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT). Rapid-CTP is a comprehensively studied tool for CTP analysis within the broader RAPID platform and performs well in estimating final infarct volumes, with high accuracy and relatively strong correlations to the gold standard (e.g., human estimates of volumes) [37][38][39][40][41][42]. Vitrea CT Brain Perfusion was approved by the FDA in November 2018 to quantify cerebral blood flow and predict final infarct volumes [43]. Many groups have found Vitrea outperforms Rapid-CTP with respect to final infarct volume predictions [44][45][46], with the gold standard determined by human interpretation of DWI/FLAIR imaging. FastStroke/CT Perfusion 4D is a similar technology that not only predicts ischemic core volume but also assesses the quantity and quality of collateral perfusion [47][48]. Similar to Vitrea CT, FastStroke/CT Perfusion 4D performed comparably to Rapid-CTP (intraclass correlation coefficient of 0.95) [49], and its additional capability to assess collateral circulation improved accuracy in predicting good outcomes [50]. Icobrain CTP uses a CNN to estimate penumbra volumes and cerebral blood flow, both of which have strong correlations to expert assessments by radiologists [51][52]. Viz CTP is a similar software that performed well in predicting final infarct volume (r = ~0.6) [53]. While the above software solutions are well-characterized, there are no studies demonstrating improved time-to-reperfusion. Solutions such as Augmented Vascular Analysis [54] and Neuro.AI Algorithm [55] are yet to be independently assessed in the literature.

5. Intracranial Hemorrhage (ICH) Identification

Technologies indicated for the detection of ICH generally performed better than those indicated for LVO detection. BriefCase was the first FDA-approved, AI/ML-enabled technology for the identification of ICH from non-contrast head CT [56]. BriefCase's CNN-based algorithm [57] has shown strong performance by reducing outpatient scan interpretation delays by 90% (604 min reduction) and inpatient delays by 10% (38 min reduction) [58]. Cases flagged by BriefCase as suspicious for ICH had an average turnaround time of 73 min, versus 132 min for non-flagged cases [59]. Recent studies assessing BriefCase have reported NPVs of 96–99% and PPVs of 72–96% [58][60][61]. A main driver of false negatives was ICH anatomy (e.g., under the calvaria), while false positives were driven by tumors and calcifications [62][63].

CINA-ICH has similar reported performance in ICH detection compared to BriefCase. NPVs ranged from 92–99%, PPVs from 80–97%, and the algorithm had a sensitivity of 72% when identifying relatively small-volume bleeds (volume less than 5 mL) [27][64]. CINA has additional subclassification functionality (e.g., differentiating between subarachnoid and intraventricular hemorrhage) with a sensitivity of at least 90% [27]. CuraRad-ICH, on the other hand, had subclassification sensitivities between 61 and 99% [65][66], though the software was studied on a larger sample of scans and has specificities roughly comparable to those of CINA.

Rapid-ICH [67], with PPV, NPV, accuracy, sensitivity, and specificity of at least 95% [68], and HealthICH [69], with an AUC of 0.96 [70], are two other technologies indicated for ICH detection. Some FDA-approved technologies for ICH detection have yet to be studied independently in the literature. These include Accipiolx [71], DeepCT [72], NinesAI [73], qER [74], and Viz ICH [75].

6. Rehabilitation

Tools for post-stroke rehabilitation require further development, especially given the poor natural recovery that is often seen with stroke [56]. There is a need for technologies that can extend the therapeutic window for patients and/or enable neurological recovery.

An Israeli-based company, BrainQ, is developing a non-invasive brain-computer interface (BCI) device that leverages extremely low frequency and low intensity electromagnetic fields (ELF-EMF) to promote post-stroke recovery [76][77]. After a stroke, patients often have abnormal neural oscillatory patterns, and exposure to tuned EMFs can influence these oscillations [78], thereby promoting periods of neuroplasticity [79][80]. BrainQ's technology uses ML to extract motor-related spectral features from electrophysiology measurements (EEG, MEG/EMG) [81] and then translates these into a specific ELF-EMF treatment for patients [82].

BrainQ received FDA breakthrough status in February 2021 based on results from a pilot trial of 25 patients with a history of sub-acute ischemic stroke. Patients who received 40 min of ELF-EMF treatment 5 days a week for 8 weeks had superior recovery compared to the sham group as assessed by multiple metrics (e.g., NIH stroke score) and did not report any adverse events [83]. BrainQ has planned a double-blind national clinical trial across up to 20 inpatient rehabilitation facilities in the United States [84]. A previous BrainQ clinical trial was terminated due to the COVID-19 pandemic [85].

IpsiHand Upper Extremity Rehabilitation System (IpsiHand), granted breakthrough status by the FDA in April 2021, is the first FDA-approved device to use BCI technology to facilitate motor rehabilitation in patients who are more than 6 months post-stroke. The device uses an EEG electrode headset to translate neural activity of movement intent from the uninjured brain hemisphere into physical movements of a robotic exoskeleton worn around the impaired hand, wrist, and forearm [86]. A study of ten chronic hemiparetic stroke survivors with upper-limb impairment showed significant improvement in arm functionality after 12 weeks of IpsiHand therapy, with only minor side effects (e.g., skin redness) [87]. A randomized clinical trial is needed to assess whether use of IpsiHand alone proves more beneficial for upper extremity function versus traditional physical therapy. IpsiHand has the potential to enhance functional recovery with convenient, in-home post-stroke rehabilitation.

References

1. Virani, S.S.; Alonso, A.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Delling, F.N.; et al. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. Circulation 2020, 141, e139–e596.
2. An, S.J.; Kim, T.J.; Yoon, B.-W. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J. Stroke 2017, 19, 3–10.
3. Mendelson, S.J.; Prabhakaran, S. Diagnosis and Management of Transient Ischemic Attack and Acute Ischemic Stroke: A Review. JAMA 2021, 325, 1088–1098.
4. Meretoja, A.; Keshtkaran, M.; Tatlisumak, T.; Donnan, G.A.; Churilov, L. Endovascular Therapy for Ischemic Stroke: Save a Minute-Save a Week. Neurology 2017, 88, 2123–2127.
5. Bohr, A.; Memarzadeh, K. The Rise of Artificial Intelligence in Healthcare Applications. Artif. Intell. Healthc. 2020, 25–60.
6. Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan. 2021. Available online: https://www.fda.gov/media/145022/download (accessed on 18 October 2021).
7. Sarvestany, S.S.; Kwong, J.C.; Azhie, A.; Dong, V.; Cerocchi, O.; Ali, A.F.; Karnam, R.S.; Kuriry, H.; Shengir, M.; Candido, E.; et al. Development and Validation of an Ensemble Machine Learning Framework for Detection of All-Cause Advanced Hepatic Fibrosis: A Retrospective Cohort Study. Lancet Digit. Health 2022, 4, e188–e199.
8. Bos, J.M.; Attia, Z.I.; Albert, D.E.; Noseworthy, P.A.; Friedman, P.A.; Ackerman, M.J. Use of Artificial Intelligence and Deep Neural Networks in Evaluation of Patients With Electrocardiographically Concealed Long QT Syndrome From the Surface 12-Lead Electrocardiogram. JAMA Cardiol. 2021, 6, 532–538.
9. Chandrabhatla, A.S.; Pomeraniec, I.J.; Ksendzovsky, A. Co-Evolution of Machine Learning and Digital Technologies to Improve Monitoring of Parkinson’s Disease Motor Symptoms. Npj Digit. Med. 2022, 5, 1–18.
10. Thompson, A.C.; Jammal, A.A.; Berchuck, S.I.; Mariottoni, E.B.; Medeiros, F.A. Assessment of a Segmentation-Free Deep Learning Algorithm for Diagnosing Glaucoma From Optical Coherence Tomography Scans. JAMA Ophthalmol. 2020, 138, 333–339.

11. Le Page, A.L.; Ballot, E.; Truntzer, C.; Derangère, V.; Ilie, A.; Rageot, D.; Bibeau, F.; Ghiringhelli, F. Using a Convolutional Neural Network for Classification of Squamous and Non-Squamous Non-Small Cell Lung Cancer Based on Diagnostic Histopathology HES Images. Sci. Rep. 2021, 11, 23912.
12. Sirsat, M.S.; Fermé, E.; Câmara, J. Machine Learning for Brain Stroke: A Review. J. Stroke Cereb. Dis. 2020, 29, 105162.
13. Mainali, S.; Darsie, M.E.; Smetana, K.S. Machine Learning in Action: Stroke Diagnosis and Outcome Prediction. Front. Neurol. 2021, 12, 734345.
14. Chavva, I.R.; Crawford, A.L.; Mazurek, M.H.; Yuen, M.M.; Prabhat, A.M.; Payabvash, S.; Sze, G.; Falcone, G.J.; Matouk, C.C.; de Havenon, A.; et al. Deep Learning Applications for Acute Stroke Management. Ann. Neurol. 2022, 92, 574–587.
15. Shlobin, N.A.; Baig, A.A.; Waqas, M.; Patel, T.R.; Dossani, R.H.; Wilson, M.; Cappuzzo, J.M.; Siddiqui, A.H.; Tutino, V.M.; Levy, E.I. Artificial Intelligence for Large-Vessel Occlusion Stroke: A Systematic Review. World Neurosurg. 2022, 159, 207–220.e1.
16. Campagnini, S.; Arienti, C.; Patrini, M.; Liuzzi, P.; Mannini, A.; Carrozza, M.C. Machine Learning Methods for Functional Recovery Prediction and Prognosis in Post-Stroke Rehabilitation: A Systematic Review. J. Neuroeng. Rehabil. 2022, 19, 54.
17. US Food and Drug Administration. Viz ContaCT/LVO 513(f)(2) de Novo Letter (DEN170073). Available online: https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170073.pdf (accessed on 25 December 2021).
18. Morey, J.R.; Zhang, X.; Yaeger, K.A.; Fiano, E.; Marayati, N.F.; Kellner, C.P.; De Leacy, R.A.; Doshi, A.; Tuhrim, S.; Fifi, J.T. Real-World Experience with Artificial Intelligence-Based Triage in Transferred Large Vessel Occlusion Stroke Patients. Cereb. Dis 2021, 50, 450–455.
19. Hassan, A.E.; Ringheanu, V.M.; Rabah, R.R.; Preston, L.; Tekle, W.G.; Qureshi, A.I. Early Experience Utilizing Artificial Intelligence Shows Significant Reduction in Transfer Times and Length of Stay in a Hub and Spoke Model. Interv. Neuroradiol. 2020, 26, 615–622.
20. Yahav-Dovrat, A.; Saban, M.; Merhav, G.; Lankri, I.; Abergel, E.; Eran, A.; Tanne, D.; Nogueira, R.G.; Sivan-Hoffmann, R. Evaluation of Artificial Intelligence-Powered Identification of Large-Vessel Occlusions in a Comprehensive Stroke Center. AJNR Am. J. Neuroradiol. 2021, 42, 247–254.
21. Rodrigues, G.; Barreira, C.M.; Bouslama, M.; Haussen, D.C.; Al-Bayati, A.; Pisani, L.; Liberato, B.; Bhatt, N.; Frankel, M.R.; Nogueira, R.G. Automated Large Artery Occlusion Detection in Stroke: A Single-Center Validation Study of an Artificial Intelligence Algorithm. Cereb. Dis. 2022, 51, 259–264.

22. Robert Ochs US Food and Drug Administration, Division of Radiological Health. ISchemaView RAPID 510(k) Premarket Notification Letter (K182130). 2018. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182130.pdf (accessed on 24 December 2021).

23. Amukotuwa, S.A.; Straka, M.; Smith, H.; Chandra, R.V.; Dehkharghani, S.; Fischbein, N.J.; Bammer, R. Automated Detection of Intracranial Large Vessel Occlusions on Computed Tomography Angiography. Stroke 2019, 50, 2790–2798.

24. Adhya, J.; Li, C.; Eisenmenger, L.; Cerejo, R.; Tayal, A.; Goldberg, M.; Chang, W. Positive Predictive Value and Stroke Workflow Outcomes Using Automated Vessel Density (RAPID-CTA) in Stroke Patients: One Year Experience. Neuroradiol. J. 2021, 34, 476–481.

25. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. CINA 510(k) Premarket Notification Letter (K200855). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200855.pdf (accessed on 21 December 2021).

26. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. HALO 510(k) Premarket Notification Letter (K200873). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200873.pdf (accessed on 27 December 2021).

27. McLouth, J.; Elstrott, S.; Chaibi, Y.; Quenet, S.; Chang, P.D.; Chow, D.S.; Soun, J.E. Validation of a Deep Learning Tool in the Detection of Intracranial Hemorrhage and Large Vessel Occlusion. Front. Neurol. 2021, 12, 655.

28. Rava, R.A.; Peterson, B.A.; Seymour, S.E.; Snyder, K.V.; Mokin, M.; Waqas, M.; Hoi, Y.; Davies, J.M.; Levy, E.I.; Siddiqui, A.H.; et al. Validation of an Artificial Intelligence-Driven Large Vessel Occlusion Detection Algorithm for Acute Ischemic Stroke Patients. Neuroradiol. J. 2021, 34, 408–417.

29. Luijten, S.P.R.; Wolff, L.; Duvekot, M.H.C.; van Doormaal, P.-J.; Moudrous, W.; Kerkhoff, H.; Lycklama A Nijeholt, G.J.; Bokkers, R.P.H.; Yo, L.S.F.; Hofmeijer, J.; et al. Diagnostic Performance of an Algorithm for Automated Large Vessel Occlusion Detection on CT Angiography. J. Neurointerv. Surg. 2022, 14, 794–798.

30. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. Rapid ASPECTS 510(k) Premarket Notification Letter (K200760). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200760.pdf (accessed on 27 December 2021).

31. Lasocha, B.; Pulyk, R.; Brzegowy, P.; Latacz, P.; Slowik, A.; Popiela, T.J. Real-World Comparison of Human and Software Image Assessment in Acute Ischemic Stroke Patients' Qualification for Reperfusion Treatment. J. Clin. Med. 2020, 9, 3383.

32. Hoelter, P.; Muehlen, I.; Goelitz, P.; Beuscher, V.; Schwab, S.; Doerfler, A. Automated ASPECT Scoring in Acute Ischemic Stroke: Comparison of Three Software Tools. Neuroradiology 2020, 62, 1231–1238.

33. Mansour, O.Y.; Ramadan, I.; Abdo, A.; Hamdi, M.; Eldeeb, H.; Marouf, H.; Elsalamawy, D.; Elfatatry, A.; Elnekidy, A.; Reda, M.I. Deciding Thrombolysis in AIS Based on Automated versus on WhatsApp Interpreted ASPECTS, a Reliability and Cost-Effectiveness Analysis in Developing System of Care. Front. Neurol. 2020, 11, 333.
34. Maegerlein, C.; Fischer, J.; Mönch, S.; Berndt, M.; Wunderlich, S.; Seifert, C.L.; Lehm, M.; Boeckh-Behrens, T.; Zimmer, C.; Friedrich, B. Automated Calculation of the Alberta Stroke Program Early CT Score: Feasibility and Reliability. Radiology 2019, 291, 141–148.
35. Albers, G.W.; Wald, M.J.; Mlynash, M.; Endres, J.; Bammer, R.; Straka, M.; Maier, A.; Hinson, H.E.; Sheth, K.N.; Taylor Kimberly, W.; et al. Automated Calculation of Alberta Stroke Program Early CT Score: Validation in Patients with Large Hemispheric Infarct. Stroke 2019, 50, 3277–3279.
36. Al-Kawaz, M.; Primiani, C.; Urrutia, V.; Hui, F. Impact of RapidAI Mobile Application on Treatment Times in Patients with Large Vessel Occlusion. J. NeuroInterventional Surg. 2021, 14, 233–236.
37. Hokkinen, L.; Mäkelä, T.; Savolainen, S.; Kangasniemi, M. Computed Tomography Angiography-Based Deep Learning Method for Treatment Selection and Infarct Volume Prediction in Anterior Cerebral Circulation Large Vessel Occlusion. Acta Radiol Open 2021, 10, 20584601211060348.
38. Hokkinen, L.; Mäkelä, T.; Savolainen, S.; Kangasniemi, M. Evaluation of a CTA-Based Convolutional Neural Network for Infarct Volume Prediction in Anterior Cerebral Circulation Ischaemic Stroke. Eur. Radiol. Exp. 2021, 5, 25.
39. Wouters, A.; Robben, D.; Christensen, S.; Marquering, H.A.; Roos, Y.B.W.E.M.; van Oostenbrugge, R.J.; van Zwam, W.H.; Dippel, D.W.J.; Majoie, C.B.L.M.; Schonewille, W.J.; et al. Prediction of Stroke Infarct Growth Rates by Baseline Perfusion Imaging. Stroke 2022, 53, 569–577.
40. Potreck, A.; Seker, F.; Mutke, M.A.; Weyland, C.S.; Herweh, C.; Heiland, S.; Bendszus, M.; Möhlenbruch, M. What Is the Impact of Head Movement on Automated CT Perfusion Mismatch Evaluation in Acute Ischemic Stroke? J. NeuroInterventional Surg. 2022, 14, 628–633.
41. Bouslama, M.; Ravindran, K.; Harston, G.; Rodrigues, G.M.; Pisani, L.; Haussen, D.C.; Frankel, M.R.; Nogueira, R.G. Noncontrast Computed Tomography E-Stroke Infarct Volume Is Similar to RAPID Computed Tomography Perfusion in Estimating Postreperfusion Infarct Volumes. Stroke 2021, 52, 634–641.
42. Kim, Y.-C.; Lee, J.-E.; Yu, I.; Song, H.-N.; Baek, I.-Y.; Seong, J.-K.; Jeong, H.-G.; Kim, B.J.; Nam, H.S.; Chung, J.-W.; et al. Evaluation of Diffusion Lesion Volume Measurements in Acute Ischemic Stroke Using Encoder-Decoder Convolutional Network. Stroke 2019, 50, 1444–1451.
43. Robert Ochs US Food and Drug Administration, Division of Radiological Health. VitreaCT Brain Perfusion 510(k) Premarket Notification Letter (K181247). 2018. Available online:

https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181247.pdf (accessed on 16 December 2021).

44. Rava, R.A.; Snyder, K.V.; Mokin, M.; Waqas, M.; Allman, A.B.; Senko, J.L.; Podgorsak, A.R.; Shiraz Bhurwani, M.M.; Hoi, Y.; Siddiqui, A.H.; et al. Assessment of a Bayesian Vitrea CT Perfusion Analysis to Predict Final Infarct and Penumbra Volumes in Patients with Acute Ischemic Stroke: A Comparison with RAPID. AJNR Am. J. Neuroradiol. 2020, 41, 206–212.
45. Rava, R.A.; Snyder, K.V.; Mokin, M.; Waqas, M.; Allman, A.B.; Senko, J.L.; Podgorsak, A.R.; Bhurwani, M.M.S.; Davies, J.M.; Levy, E.I.; et al. Effect of Computed Tomography Perfusion Post-Processing Algorithms on Optimal Threshold Selection for Final Infarct Volume Prediction. Neuroradiol. J. 2020, 33, 273–285.
46. Rava, R.A.; Podgorsak, A.R.; Waqas, M.; Snyder, K.V.; Mokin, M.; Levy, E.I.; Davies, J.M.; Siddiqui, A.H.; Ionita, C.N. Investigation of Convolutional Neural Networks Using Multiple Computed Tomography Perfusion Maps to Identify Infarct Core in Acute Ischemic Stroke Patients. J. Med. Imaging 2021, 8, 014505.
47. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. FastStroke, CT Perfusion 4D 510(k) Premarket Notification Letter (K193289). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K193289.pdf (accessed on 27 December 2021).
48. Verdolotti, T.; Pilato, F.; Cottonaro, S.; Monelli, E.; Giordano, C.; Guadalupi, P.; Benenati, M.; Ramaglia, A.; Costantini, A.M.; Alexandre, A.; et al. ColorViz, a New and Rapid Tool for Assessing Collateral Circulation during Stroke. Brain Sci. 2020, 10, E882.
49. Liu, Q.C.; Jia, Z.Y.; Zhao, L.B.; Cao, Y.Z.; Ma, G.; Shi, H.B.; Liu, S. Agreement and Accuracy of Ischemic Core Volume Evaluated by Three CT Perfusion Software Packages in Acute Ischemic Stroke. J. Stroke Cereb. Dis. 2021, 30, 105872.
50. Ospel, J.M.; Cimflova, P.; Volny, O.; Qiu, W.; Hafeez, M.; Mayank, A.; Najm, M.; Chung, K.; Kashani, N.; Almekhlafi, M.A.; et al. Utility of Time-Variant Multiphase CTA Color Maps in Outcome Prediction for Acute Ischemic Stroke Due to Anterior Circulation Large Vessel Occlusion. Clin. Neuroradiol. 2021, 31, 783–790.
51. de la Rosa, E.; Sima, D.M.; Menze, B.; Kirschke, J.S.; Robben, D. AIFNet: Automatic Vascular Function Estimation for Perfusion Analysis Using Deep Learning. Med. Image Anal. 2021, 74, 102211.
52. de la Rosa, E.; Robben, D.; Sima, D.M.; Kirschke, J.S.; Menze, B. Differentiable Deconvolution for Improved Stroke Perfusion Analysis. In Proceedings of the Medical Image Computing and Computer Assisted Intervention—MICCAI 2020; Martel, A.L., Abolmaesumi, P., Stoyanov, D., Mateus, D., Zuluaga, M.A., Zhou, S.K., Racoceanu, D., Joskowicz, L., Eds.; Springer International Publishing: Cham, Switzerland, 2020; pp. 593–602.

53. Pisani, L.; Mohammaden, M.; Bouslama, M.; Al-bayati, A.R.; Haussen, D.C.; Frankel, M.R.; Nogueira, R.G. Abstract P466: Comparison of Three Automated Ct Perfusion Software Packages for Thrombectomy Eligibility and Final Infarct Volume Prediction. Stroke 2021, 52, AP466.
54. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. Augmented Vascular Analysis 510(k) Premarket Notification Letter (K201369). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201369.pdf (accessed on 27 December 2021).
55. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. Neuro.AI Algorithm 510(k) Premarket Notification Letter (K200750). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200750.pdf (accessed on 27 December 2021).
56. Robert Ochs US Food and Drug Administration. BriefCase 510(k) Letter Premarket Notification Letter (K180647). 2018. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180647.pdf (accessed on 15 December 2021).
57. Ojeda, P.; Zawaideh, M.; Mossa-Basha, M.; Haynor, D. The Utility of Deep Learning: Evaluation of a Convolutional Neural Network for Detection of Intracranial Bleeds on Non-Contrast Head Computed Tomography Studies. In Medical Imaging 2019: Image Processing; SPIE: Bellingham, WA, USA, 2019; Volume 10949, pp. 899–906.
58. Ginat, D. Implementation of Machine Learning Software on the Radiology Worklist Decreases Scan View Delay for the Detection of Intracranial Hemorrhage on CT. Brain Sci. 2021, 11, 832.
59. Wismüller, A.; Stockmaster, L. A Prospective Randomized Clinical Trial for Measuring Radiology Study Reporting Time on Artificial Intelligence-Based Detection of Intracranial Hemorrhage in Emergent Care Head CT. In Medical Imaging 2020: Biomedical Applications in Molecular, Structural, and Functional Imaging; SPIE: Bellingham, WA, USA, 2020; Volume 11317, pp. 144–150.
60. Ginat, D.T. Analysis of Head CT Scans Flagged by Deep Learning Software for Acute Intracranial Hemorrhage. Neuroradiology 2020, 62, 335–340.
61. Voter, A.F.; Meram, E.; Garrett, J.W.; Yu, J.-P.J. Diagnostic Accuracy and Failure Mode Analysis of a Deep Learning Algorithm for the Detection of Intracranial Hemorrhage. J. Am. Coll. Radiol. 2021, 18, 1143–1152.
62. Kundisch, A.; Hönning, A.; Mutze, S.; Kreissl, L.; Spohn, F.; Lemcke, J.; Sitz, M.; Sparenberg, P.; Goelz, L. Deep Learning Algorithm in Detecting Intracranial Hemorrhages on Emergency Computed Tomographies. PLoS ONE 2021, 16, e0260560.
63. Rao, B.; Zohrabian, V.; Cedeno, P.; Saha, A.; Pahade, J.; Davis, M.A. Utility of Artificial Intelligence Tool as a Prospective Radiology Peer Reviewer—Detection of Unreported Intracranial Hemorrhage. Acad. Radiol. 2021, 28, 85–93.

64. Rava, R.A.; Seymour, S.E.; LaQue, M.E.; Peterson, B.A.; Snyder, K.V.; Mokin, M.; Waqas, M.; Hoi, Y.; Davies, J.M.; Levy, E.I.; et al. Assessment of an Artificial Intelligence Algorithm for Detection of Intracranial Hemorrhage. World Neurosurg. 2021, 150, e209–e217.
65. Ye, H.; Gao, F.; Yin, Y.; Guo, D.; Zhao, P.; Lu, Y.; Wang, X.; Bai, J.; Cao, K.; Song, Q.; et al. Precise Diagnosis of Intracranial Hemorrhage and Subtypes Using a Three-Dimensional Joint Convolutional and Recurrent Neural Network. Eur. Radiol. 2019, 29, 6191–6201.
66. Guo, D.; Wei, H.; Zhao, P.; Pan, Y.; Yang, H.-Y.; Wang, X.; Bai, J.; Cao, K.; Song, Q.; Xia, J.; et al. Simultaneous Classification and Segmentation of Intracranial Hemorrhage Using a Fully Convolutional Neural Network. In Proceedings of the 2020 IEEE 17th International Symposium on Biomedical Imaging (ISBI), Iowa City, IA, USA, 3–7 April 2020; pp. 118–121.
67. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. Rapid ICH 510(k) Premarket Notification Letter (K193087). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K193087.pdf (accessed on 27 December 2021).
68. Heit, J.J.; Coelho, H.; Lima, F.O.; Granja, M.; Aghaebrahim, A.; Hanel, R.; Kwok, K.; Haerian, H.; Cereda, C.W.; Venkatasubramanian, C.; et al. Automated Cerebral Hemorrhage Detection Using RAPID. Am. J. Neuroradiol. 2021, 42, 273–278.
69. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. HealthICH 510(k) Premarket Notification Letter (K190424). 2019. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K190424.pdf (accessed on 16 December 2021).
70. Bar, A.; Havakuk, M.M.; Turner, Y.; Safadi, M.; Elnekave, E. Improved ICH Classification Using Task-Dependent Learning. In Proceedings of the 2019 IEEE 16th International Symposium on Biomedical Imaging (ISBI 2019), Venice, Italy, 8–11 April 2019; pp. 1567–1571.
71. Robert Ochs US Food and Drug Administration, Division of Radiological Health. Accipiolx 510(k) Premarket Notification Letter (K182177). 2018. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182177.pdf (accessed on 26 December 2021).
72. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. DeepCT 510(k) Premarket Notification Letter (K182875). 2019. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182875.pdf (accessed on 16 December 2021).
73. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. NinesAI 510(k) Premarket Notification Letter (K193351). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K193351.pdf (accessed on 27 December 2021).
74. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. QER 510(k) Premarket Notification Letter (K200921). 2020. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200921.pdf (accessed on 27 December 2021).

75. Mills, T.T. US Food and Drug Administration, Division of Radiological Health. Viz ICH 510(k) Premarket Notification Letter (K210209). 2021. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210209.pdf (accessed on 27 December 2021).
76. BrainQ. BrainQ Gets FDA Breakthrough Status for Its Device for Reducing Disability Following Stroke. Available online: https://www.prnewswire.com/news-releases/brainq-gets-fda-breakthrough-status-for-its-device-for-reducing-disability-following-stroke-301226735.html (accessed on 27 December 2021).
77. BrainQ Gets FDA Breakthrough for Device to Reduce Disability Following. NS Medical Devices. 2021. Available online: https://www.nsmedicaldevices.com/news/brainq-ai-device/# (accessed on 27 December 2021).
78. Wang, C.X.; Hilburn, I.A.; Wu, D.-A.; Mizuhara, Y.; Cousté, C.P.; Abrahams, J.N.H.; Bernstein, S.E.; Matani, A.; Shimojo, S.; Kirschvink, J.L. Transduction of the Geomagnetic Field as Evidenced from Alpha-Band Activity in the Human Brain. eNeuro 2019, 6, ENEURO.0483-18.2019.
79. Adaikkan, C.; Tsai, L.-H. Gamma Entrainment: Impact on Neurocircuits, Glia, and Therapeutic Opportunities. Trends Neurosci 2020, 43, 24–41.
80. Iaccarino, H.F.; Singer, A.C.; Martorell, A.J.; Rudenko, A.; Gao, F.; Gillingham, T.Z.; Mathys, H.; Seo, J.; Kritskiy, O.; Abdurrob, F.; et al. Gamma Frequency Entrainment Attenuates Amyloid Load and Modifies Microglia. Nature 2016, 540, 230–235.
81. He, Q.; Pursiainen, S. An Extended Application 'Brain Q' Processing EEG and MEG Data of Finger Stimulation Extended from 'Zeffiro' Based on Machine Learning and Signal Processing. Cogn. Syst. Res. 2021, 69, 50–66.
82. Our Technology. Available online: https://brainqtech.com/our-technology (accessed on 15 December 2021).
83. Weisinger, B.S.; Bornstein, N.M.; Shohami, E.; Segal, Y.; Alter, A.; Lifshitz, A.; Prasad, A.; Pandey, D. Abstract P194: Artificial Intelligence-Powered Non-Invasive and Frequency-Tuned Electromagnetic Field Therapy Improves Upper Extremity Motor Function in Sub-Acute Stroke Patients: A Pilot Randomized Controlled Trial. Stroke 2021, 52.
84. BrainQ Technologies Ltd. The Efficacy of a Frequency-Tuned Electromagnetic Field Treatment in Facilitating the Recovery of Subacute Ischemic Stroke Patients—A Pivotal Study; Clinicaltrials.gov: Bethesda, MD, USA, 2021.
85. Efficacy of EMF BCI Based Device on Acute Stroke—Full Text View—ClinicalTrials.Gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04039178 (accessed on 22 December 2021).
86. Device. Available online: https://www.neurolutions.com/device (accessed on 16 December 2021).

87. Bundy, D.T.; Souders, L.; Baranyai, K.; Leonard, L.; Schalk, G.; Coker, R.; Moran, D.W.; Huskey, T.; Leuthardt, E.C. Contralesional Brain–Computer Interface Control of a Powered Exoskeleton for Motor Recovery in Chronic Stroke Survivors. Stroke 2017, 48, 1908–1915.