CHAPTER

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Application of artificial intelligence frameworks in the clinical practice of neurology: recent advances and future directions

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Introduction

The practice of clinical neurology requires the collection, integration, and modeling of relevant clinical information within the context of accumulated knowledge to guide decision-making about a single patient. These steps are often performed focally by a single or a handful of clinicians and are informed by static or slowly growing knowledge. The expanding era of open and large datasets, the increased use of computational technologies and data-driven methods for healthcare-related purposes, and the very nature of neurological disorders make the practice of clinical neurology poised for an artificial intelligence (AI)-driven transformation. In this chapter, we first highlight recent advances at the intersection of clinical neurology and computational neuroscience. We then list the major challenges that pose the deployment of AI frameworks into healthcare, and concomitantly describe an integrated model aimed at the successful implementation of AI-driven frameworks into the practice clinical neurology, the *ABC* cycle [1].

Current state of artificial intelligence in clinical neurology

The recent years have seen an exponential application of AI-related techniques to healthcare-related purposes. However, there are only a few instances where AI algorithms have either equated, surpassed, or improved expert-level performance in a rigorous and

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clinically meaningful manner. These examples are can be found in the disciplines of dermatology, cardiology, radiology and oncology and include classification of skin cancer types [2], prediction of all-cause mortality based on echocardiographic videos [3,4], analysis of electrocardiography recordings [5,6], fetal heart rate assessment [7], tumor segmentation [8], microscopy image analysis [9,10], and analysis of genomes [11].

In the field of neurology, AI algorithms have so far largely been used for research purposes and have yet to be implemented in clinical practice. We below review recent advances that exemplify how AI could eventually shape the practice of clinical neurology, with a particular emphasis on aging and dementia and epilepsy.

Brain imaging is essential to assess abnormalities in brain structure and function relevant to neurological disorders. Many recent advances using AI algorithms have been made in the field of aging and dementia. For instance, studies have leveraged unsupervised machine learning (ML) to delineate patterns of macro-scale anatomy associated with mental functions selectively degraded across a wide range of dementia syndromes. A recent study by Jones et al. [12] showed that up to 50% of covariance in fluorodeoxyglucose-positron emission tomography (FDG-PET) images from a large cohort of individuals standing along the biological spectrum of Alzheimer's disease (AD) could be explained by a small number of global spatial patterns that also describe functional brain networks. Importantly, these latent patterns could also index seven clinical dementia syndromes, highlighting the generalizability of such method. Other studies have used similar techniques to decipher the clinico-radiological heterogeneity within relatively circumscribed dementia syndromes [13,14]. For instance, Townley et al. [14] showed that eight latent factors could explain 50% of covariance in patterns of FDG-PET hypometabolism in a large cohort of patients with posterior cortical atrophy, and that these patterns related to differential clinical and cognitive symptomatology. Data-driven techniques including Subtype and Stage Inference (SuStaIn) [15], Bayesian clustering [16], and hierarchical clustering [17] algorithms have also been used to derive biological subtypes of AD in large cohorts of patients with available multimodal imaging and characterize their clinical presentation and trajectories. These studies have expanded the clinical and biological understanding of AD by quantifying the patterns associated with the well-known heterogeneity in AD associated with distinct clinical presentations and patterns of progression [18].

A different category of studies leveraging supervised ML and deep learning (DL) methods probed biological questions of direct relevance for clinical purposes. For instance, a few groups of researchers used biological, genetic and imaging data either alone or in combination to predict cross-sectional and future tau accumulation in AD [19,20]. One of these studies used a convolutional neural network architecture to generate tau-synthesized images based on FDG-PET images with impressive accuracy in large cohorts including individuals in the normal aging spectrum as well as patients with AD and non-AD dementia syndromes [20]. Others have used a variety of DL models based on MRI and FDG-PET to yield "brain age gap" metrics across aging and dementia syndromes [21–24], which have the potential to identify individuals at risk of pathology and future clinical decline. Overall, these studies not only provide a deeper understanding of the relationships and interactions between different biological processes across neurodegenerative diseases of the mind, but also have high clinical practicality. For example, such algorithms could be used to differentiate between various degenerative etiologies and diseases staging in clinical practice and clinical trials with minimal cost while keeping excellent accuracy.

Important advances have also been made in the field of epilepsy in recent years. A particular area of progress pertains to the development, deployment and utilization of systems based on implantable neurostimulators that allow the recording of long-term and continuous intracranial electroencephalography (iEEG) data in patients with refractory temporal lobe epilepsy while they live in their natural environments [25,26]. Using ML and DL models, these studies were able to develop a system for long-term monitoring of patients with epilepsy [25,26] tracking abnormal brain activity including seizures [27] and interictal epileptiform discharges [28] but also sleep [29,30]. These studies aim to provide a better understanding of the intricate associations between seizures, interictal epileptiform discharges, sleep, psychiatric comorbidities of epilepsy [31], their cycles [32,33] and how they can be modified by deep brain stimulation [34,35]. The longer-term aim would be to use such a system not only to track behavioral brain states but also to forecast seizures using brain signals and wearable devices [36,37]. This has potentially positive implications for patients with complex epilepsy disorders in terms of seizure monitoring and management (e.g., avoiding sensitive activities during high-risk periods) as well as the optimization of pharmacological and nonpharmacological therapies including deep brain stimulation. However, the implementation of such systems bears challenges to reach the desired aims. This is mainly due to the difficulty in patient enrollment, high within- and between-patient variability and consequently limited availability of training datasets to develop AI models [30]. Recent initiatives have been pursued to address these caveats, including the release of a publicly available multicenter iEEG dataset [38].

While these recent developments in the field of behavioral neurology and epilepsy highlight the potential of AI-related technologies to enhance healthcare-related decision-making, disease monitoring and advance our understanding of complex diseases, their incorporation into clinical practice remains minimal. We below describe the *ABC* cycle, an integrated framework aimed at addressing the challenges associated with the deployment of the integration of AI algorithms into healthcare systems.

Deployment of artificial intelligence frameworks in healthcare: the *ABC* cycle

Before taking a deep dive into the *ABC* cycle, it is important to define what is meant by "artificial intelligence" and the broader term "intelligence." While definitions of AI-related terms are notorious for varying, the field has generally referred to "AI" as machines being capable of generalizable and flexible human-like reasoning and rationalizing capacities, and other terms, such as augmented intelligence or augmented human intelligence, to describe how computational machines and/or algorithms can enhance human intelligence and decision-making. These definitions do not explicitly define intelligence, but only implicitly defines it as "human-like." The definition of intelligence currently used by the Mayo Clinic Department of Neurology Artificial Intelligence Program refers to "*the collection, processing, and modeling of data and information about environments that is needed by an agent to perform beneficial actions within those, or related, environments*" [1]. This definition emphasizes three core components: the agent, the product, and the process. When applied to healthcare systems, these components respectively refer to a given healthcare delivery organization, the services provided by this organization, and the elements of the *ABC* cycle (see Fig. 19.1). This implies that the tripartite components included in this definition are not intelligent in isolation but

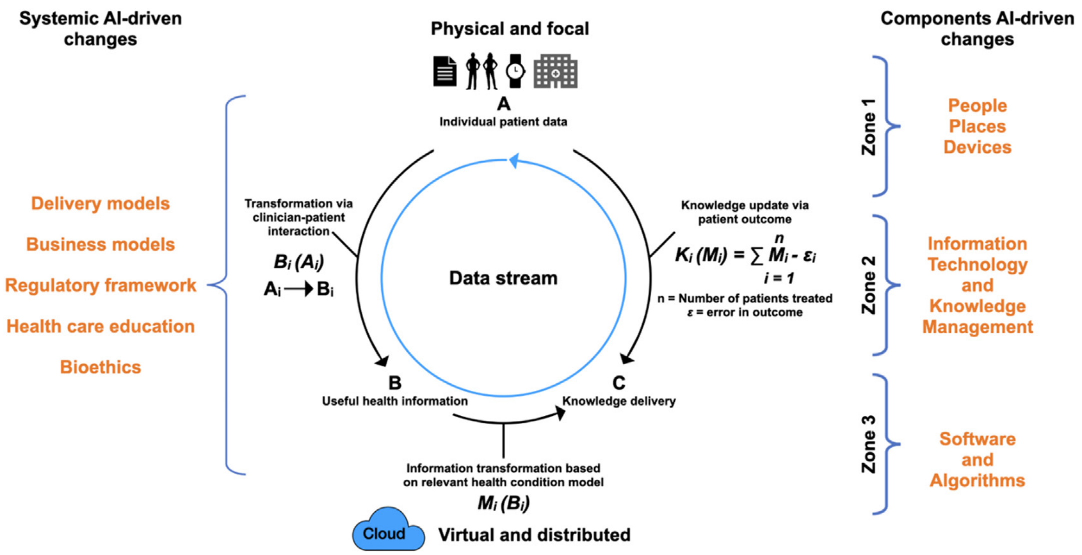

FIGURE 19.1 The ABC cycle model. This model positions at its core the data stream flow originating and ending with the individual patient (circular blue line) and the transformations applied to data and knowledge (black arrows). (A) Raw data are collected focally and physically from patients, places and/or devices and is then transformed into useful health information (B), which is most often done through the current clinician-patient interaction, that is, $B_i(A_i)$. This information is then contextualized within a model relevant to the patient's condition, that is, M. to update knowledge delivery in health care settings (C). Healthcare knowledge (C) can be updated in a feedback fashion through patient outcome (K) in real-world clinical settings. This whole data-centered process should organically drive systemic changes, such as delivery models and delivery models, regulatory framework, health care education and bioethics (left-hand side of the figure) and components of the ABC cycle spanning physical and focal components (zone 1) to virtual and distributed components (zone 3), which are tied by information and technology and knowledge management (zone 2).

can serve intelligence by fostering a dynamic synergy between high quality patient care, continuously informed disease models, and technological innovation.

The deployment of AI algorithms into healthcare delivery systems and clinical practice will require proper standards and integration. Such standards imply a fundamental transformation of how data streams flow within and even potential across healthcare institutions [1,39]. The actual model state in the vast majority of healthcare systems involves the focal acquisition of patient data that is transformed into relevant information mainly through patient-physician dyads ($Ai \rightarrow Bi$ in Fig. 19.1). The *ABC* cycle proposes the extension of this model for data streams to become virtually stored distributed in a systematic manner, with or without the implementation of federated learning infrastructure depending on the centralized or decentralized nature of the dataset [39]. This virtually distributed health information will allow for the development and implementation of AI algorithms that are naturally grounded in clinical purposes, leading to optimized physician-level knowledge in delivering high quality patient care. Importantly, these AI-driven models will be directly tested through clinical practice, allowing for their validation and refinement at every step of the way.

This data-centered transformation will inevitably rely on extensive information technology infrastructure that is scalable, robust, and adapted to every component of the *ABC* cycle. This will be critical for various purposes, which include but are not restricted to the automated processing of raw and heterogeneous data into curated information that is readily available to be modeled by AI algorithms, addressing data shifts and ensuring the storing, monitoring, labeling and securing of incoming and outgoing data. Ensuring success in the implementation of such infrastructure, especially at its early stages, will require the adoption of industry-wide standards, and even perhaps partnerships with big technology companies (or Big Tech) for cloud storage, computational infrastructure and expertise. It is however essential that offers made to healthcare institutions by such companies must be tailored to the *ABC* cycle core components (product, process, agent) to foster the development and growth of a dynamic data-centered system that begins and ends at the point of patient care. To put this another way, the healthcare sector must lead the technology sector and not the other way around.

The AI-driven extension of the practice of neurology and medicine in general will eventually and organically lead to the emergence of systemic changes surrounding the core components of the *ABC* cycle (left-hand side of Fig. 19.1). This includes regulatory frameworks concerning the use of computational software and patient data in the context of AI-related activities. Large-scale examples of this already exist, including the European Union's General Data Protection Regulation [40] or the US and the Food and Drug Administration's (FDA) AI/ML-Based Software as a Medical Device Action Plan (https://www.fda.gov/media/145022/download). Revamped bioethics guidelines and delivery models will also be needed to ensure that AI algorithms are in line with the rigorous tenets of research and clinical practice and respect patients' needs and rights. This includes, among other things, protecting patient privacy and safety, representativeness in terms of demographics and clinical diversity, and ensuring the accountability of AI algorithms (e.g., medical errors). Such a framework will also be essential to build public trust toward AI-enhanced health care delivery. Health education will also need to undergo changes to account for the upcoming AI-driven changes in clinical practice. This is tremendous to ensure physician-patient dyads, communication between healthcare providers and between the medical field and policy makers keep track with the technological advances aimed at the modernization of the practice of medicine [41].

Conclusions

The recent advances at the intersection of medicine and computational sciences have highlighted the potential of AI algorithms to aid decision-making in healthcare, improve patient outcomes, probe into biological questions and inform clinical trials. However, the successful integration of AI-driven technologies into the practice of clinical neurology is yet to come and is dependent on the implementation of integrated data-centered frameworks relying on extensive information technology infrastructure and industry-wide standards, as depicted by the *ABC cycle*.

Major takeaways

- The growing influence of AI on the practice of medicine is ubiquitous and has the potential to enhance high quality clinical care and inform disease models.
- Despite promising recent advances, AI algorithms have yet to be concretely implemented in the practice of clinical neurology.
- Integrated frameworks beginning and ending at the point of care centered on the needs of the patient and relying on extensive information technology infrastructure and industry-wide standards are required for the successful deployment of AI algorithms into health systems.
- Systemic changes should emerge from and track with the technological advances aimed at the modernization of the practice of medicine.

References

[1] Jones DT, Kerber KA. Artificial intelligence and the practice of neurology in 2035: the neurology future forecasting series. Neurology 2022;98(6):238–45. Available from: https://doi.org/10.1212/WNL.0000000000013200.
[2] Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017;542(7639):115–18.
[3] Ulloa Cerna AE, Jing L, Good CW, vanMaanen DP, Raghunath S, Suever JD, et al. Deep-learning-assisted analysis of echocardiographic videos improves predictions of all-cause mortality. Nat Biomed Eng 2021;5(6):546–54.
[4] di Ruffano LF, Takwoingi Y, Dinnes J, Chuchu N, Bayliss SE, Davenport C, et al. Computer-assisted diagnosis techniques (dermoscopy and spectroscopy-based) for diagnosing skin cancer in adults. Cochrane Database Syst Rev 2018;12.
[5] Ivora A, Viscor I, Nejedly P, Smisek R, Koscova Z, Bulkova V, et al. QRS detection and classification in Holter ECG data in one inference step. Sci Rep 2022;12(1):1–9.
[6] Nejedly P, Ivora A, Viscor I, Koscova Z, Smisek R, Jurak P, et al. Classification of ECG using ensemble of residual CNNs with or without attention mechanism. Physiol Meas 2022;43(4):044001.
[7] Lutomski JE, Meaney S, Greene RA, Ryan AC, Devane D. Expert systems for fetal assessment in labour. Cochrane Database Syst Rev 2015;4.
[8] Veiga-Canuto D, Cerdà-Alberich L, Sangüesa Nebot C, Martínez de las Heras B, Pötschger U, Gabelloni M, et al. Comparative multicentric evaluation of inter-observer variability in manual and automatic segmentation of neuroblastic tumors in magnetic resonance images. Cancers 2022;14(15):3648.
[9] Kromp F, Fischer L, Bozsaky E, Ambros IM, Dörr W, Beiske K, et al. Evaluation of Deep Learning architectures for complex immunofluorescence nuclear image segmentation. IEEE Trans Med Imaging 2021;40(7):1934–49.
[10] Lazic D, Kromp F, Rifatbegovic F, Repiscak P, Kirr M, Mivalt F, et al. Landscape of bone marrow metastasis in human neuroblastoma unraveled by transcriptomics and deep multiplex imaging. Cancers 2021;13(17):4311.
[11] Hess L, Moos V, Lauber AA, Reiter W, Schuster M, Hartl N, et al. A toolbox for class I HDACs reveals isoform specific roles in gene regulation and protein acetylation. PLoS Genet 2022;18(8):e1010376.
[12] Jones D, Lowe V, Graff-Radford J, Botha H, Barnard L, Wiepert D, et al. A computational model of neurodegeneration in Alzheimer's disease. Nat Commun 2022;13(1):1–13.
[13] Groot C, Yeo BT, Vogel JW, Zhang X, Sun N, Mormino EC, et al. Latent atrophy factors related to phenotypical variants of posterior cortical atrophy. Neurology 2020;95(12):e1672–85.
[14] Townley RA, Botha H, Graff-Radford J, Whitwell J, Boeve BF, Machulda MM, et al. Posterior cortical atrophy phenotypic heterogeneity revealed by decoding 18F-FDG-PET. Brain Commun 2021;3(4):fcab182.
[15] Vogel JW, Young AL, Oxtoby NP, Smith R, Ossenkoppele R, Strandberg OT, et al. Four distinct trajectories of tau deposition identified in Alzheimer's disease. Nat Med 2021;27(5):871–81.

[16] Poulakis K, Pereira JB, Muehlboeck J, Wahlund LO, Smedby Ö, Volpe G, et al. Multi-cohort and longitudinal Bayesian clustering study of stage and subtype in Alzheimer's disease. Nat Commun 2022;13(1):1−15.

[17] Levin F, Ferreira D, Lange C, Dyrba M, Westman E, Buchert R, et al. Data-driven FDG-PET subtypes of Alzheimer's disease-related neurodegeneration. Alzheimers Res Ther 2021;13(1):1−14.

[18] Graff-Radford J, Yong KX, Apostolova LG, Bouwman FH, Carrillo M, Dickerson BC, et al. New insights into atypical Alzheimer's disease in the era of biomarkers. Lancet Neurol 2021;20(3):222−34.

[19] Giorgio J, Jagust WJ, Baker S, Landau SM, Tino P, Kourtzi Z. A robust and interpretable machine learning approach using multimodal biological data to predict future pathological tau accumulation. Nat Commun 2022;13(1):1−14.

[20] Lee J, Burkett BJ, Min HK, Senjem ML, Lundt ES, Botha H, et al. Deep learning-based brain age prediction in normal aging and dementia. Nat Aging 2022;2(5):412−24.

[21] Abrol A, Fu Z, Salman M, Silva R, Du Y, Plis S, et al. Deep learning encodes robust discriminative neuroimaging representations to outperform standard machine learning. Nat Commun 2021;12(1):1−17.

[22] Jones D, Lee J, Topol E. Digitising brain age. Lancet 2022;400(10357):988.

[23] Lee J, Burkett BJ, Min HK, Senjem ML, Dicks E, Corriveau-Lecavalier N, et al. Synthesizing images of tau pathology from cross-model neuroimaging using deep learning. BioRxiv 2022.

[24] Bashyam VM, Erus G, Doshi J, Habes M, Nasrallah IM, Truelove-Hill M, et al. MRI signatures of brain age and disease over the lifespan based on a deep brain network and 14 468 individuals worldwide. Brain 2020;143(7):2312−24.

[25] Kremen V, Brinkmann BH, Kim I, Guragain H, Nasseri M, Magee AL, et al. Integrating brain implants with local and distributed computing devices: a next generation epilepsy management system. IEEE J Transl Eng Health Med 2018;6:1−12.

[26] Pal Attia T, Crepeau D, Kremen V, Nasseri M, Guragain H, Steele SW, et al. Epilepsy personal assistant device—a mobile platform for brain state, dense behavioral and physiology tracking and controlling adaptive stimulation. Front Neurol 2021;1195.

[27] Sladky V, Nejedly P, Mivalt F, Brinkmann BH, Kim I, St. Louis EK, et al. Distributed brain co-processor for tracking spikes, seizures and behaviour during electrical brain stimulation. Brain Commun 2022;4(3): fcac115.

[28] Janca R, Jezdik P, Cmejla R, Tomasek M, Worrell GA, Stead M, et al. Detection of interictal epileptiform discharges using signal envelope distribution modelling: application to epileptic and non-epileptic intracranial recordings. Brain Topogr 2015;28(1):172−83.

[29] Dell KL, Payne DE, Kremen V, Maturana MI, Gerla V, Nejedly P, et al. Seizure likelihood varies with day-to-day variations in sleep duration in patients with refractory focal epilepsy: a longitudinal electroencephalography investigation. EClinicalMedicine 2021;37:100934.

[30] Mivalt F, Kremen V, Sladky V, Balzekas I, Nejedly P, Gregg NM, et al. Electrical brain stimulation and continuous behavioral state tracking in ambulatory humans. J Neural Eng 2022;19(1):016019.

[31] Balzekas I, Sladky V, Nejedly P, Brinkmann BH, Crepeau D, Mivalt F, et al. Invasive electrophysiology for circuit discovery and study of comorbid psychiatric disorders in patients with epilepsy: Challenges, opportunities, and novel technologies. Front Hum Neurosci 2021;416.

[32] Karoly PJ, Rao VR, Gregg NM, Worrell GA, Bernard C, Cook MJ, et al. Cycles in epilepsy. Nat Rev Neurol 2021;17(5):267−84.

[33] Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun 2018;9(1):1−10.

[34] Gregg NM, Sladky V, Nejedly P, Mivalt F, Kim I, Balzekas I, et al. Thalamic deep brain stimulation modulates cycles of seizure risk in epilepsy. Sci Rep 2021;11(1):1−12.

[35] Marks VS, Richner TJ, Gregg NM, Sladky V, Dolezal J, Kremen V, et al. Deep brain stimulation of anterior nuclei of the thalamus and hippocampal seizure rate modulate verbal memory performance. 2022 IEEE international conference on electro information technology (eIT). IEEE; 2022. p. 1−4.

[36] Pal Attia T, Viana PF, Nasseri M, Duun-Henriksen J, Biondi A, Winston JS, et al. Seizure forecasting using minimally invasive, ultra-long-term subcutaneous EEG: generalizable cross-patient models. Epilepsia 2022.

[37] Baud MO, Proix T, Gregg NM, Brinkmann BH, Nurse ES, Cook MJ, et al. Seizure forecasting: bifurcations in the long and winding road. Epilepsia 2022.

[38] Nejedly P, Kremen V, Sladky V, Cimbalnik J, Klimes P, Plesinger F, et al. Multicenter intracranial EEG dataset for classification of graphoelements and artifactual signals. Sci Data 2020;7(1):1–7.
[39] Zhang A, Xing L, Zou J, Wu JC. Shifting machine learning for healthcare from development to deployment and from models to data. Nat Biomed Eng 2022;1–16.
[40] Das AK. European Union's general data protectionregulation, 2018: a brief overview. Ann Libr Inf Stud 2018;65(2):139–40.
[41] Kolyshkina I, Simoff S. Interpretability of machine learning solutions in public healthcare: the CRISP-ML approach. Front Big Data 2021;4:660206.