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The emerging role of artificial intelligence in neuropathology: Where are we and where do we want to go?

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ABSTRACT

The field of neuropathology, a subspecialty of pathology which studies the diseases affecting the nervous system, is experiencing significant changes due to advancements in artificial intelligence (AI). Traditionally reliant on histological methods and clinical correlations, neuropathology is now experiencing a revolution due to the development of AI technologies like machine learning (ML) and deep learning (DL). These technologies enhance diagnostic accuracy, optimize workflows, and enable personalized treatment strategies. AI algorithms excel at analyzing histopathological images, often revealing subtle morphological changes missed by conventional methods. For example, deep learning models applied to digital pathology can effectively differentiate tumor grades and detect rare pathologies, leading to earlier and more precise diagnoses. Progress in neuroimaging is another helpful tool of AI, as enhanced analysis of MRI and CT scans supports early detection of neurodegenerative diseases. By identifying biomarkers and progression patterns, AI aids in timely therapeutic interventions, potentially slowing disease progression. In molecular pathology, AI's ability to analyze complex genomic data helps uncover the genetic and molecular basis of neuropathological conditions, facilitating personalized treatment plans. AI-driven automation streamlines routine diagnostic tasks, allowing pathologists to focus on complex cases, especially in settings with limited resources. This review explores AI's integration into neuropathology, highlighting its current applications, benefits, challenges, and future directions.

1. Introduction

Neuropathology, the branch of pathology focused on the study of diseases of the nervous system tissue, is pivotal for the diagnosis and understanding of various neurological disorders. Traditionally reliant on histological examination and clinical correlation, neuropathology is undergoing a significant change due to advancements in molecular pathology and artificial intelligence (AI) [1]. AI encompasses a range of technologies, including machine learning (ML) and deep learning (DL), which enable computers to perform tasks typically requiring human intelligence [2] (Table 1).

The integration of artificial intelligence (AI) into neuropathology represents a significant advancement, promising to enhance diagnostic accuracy, streamline workflows, and personalize treatment strategies [3]. AI algorithms have demonstrated remarkable capabilities in analyzing histopathological images with high precision [4]. This ability leads to significant improvement of traditional methods, enabling pathologists to identify subtle morphological changes that might be missed during routine examinations [5]. For instance, DL models applied to digital pathology can help distinguish between various tumor grades and identify rare pathologies, ensuring early and accurate diagnoses [6]. In the field of neuroimaging, AI-enhanced analysis of MRI and CT scans facilitates the early detection of neurodegenerative diseases [7] and the pre-operative prediction of tumor biology of meningiomas [8]. In this regard, some authors validated the development of a ML classifier to predict the Integrated Risk Score (IRS) pertaining to tumor biology in

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Table 1
Overview of AI Integration in Neuropathology.

Area	Details
Histopathological Analysis	AI algorithms improve precision in analyzing histopathological images, identify tumor grades, and rare pathologies.
Neuroimaging	AI aids in early detection of neurodegenerative diseases by analyzing MRI and CT scans for biomarkers and patterns.
Molecular Pathology	AI analyzes genomic data, identifies mutations, and helps in personalized treatment planning.
Automation	AI-driven automation enhances efficiency, especially in resource-limited settings, by reducing diagnostic workloads.

WHO grade 2/3 meningiomas using pre-operative MRI data, showing that radiomic features, such as tumor shape, can noninvasively predict the molecular IRS of meningiomas with high accuracy, especially for low-risk patients [8]. Similarly, in neurosurgery, new tools such as confocal laser technology have been employed in recent decades to obtain intraoperative histological data, particularly regarding tumor type and the presence of neoplastic cells at the resection margins during surgical procedures [9].

By identifying biomarkers and patterns indicative of disease progression, AI aids in the timely initiation of therapeutic interventions, potentially slowing disease progression and improving patient outcomes [10]. AI's role in molecular pathology is of increasing importance: it enables the analysis of complex genomic data, providing insights into the genetic and molecular basis of neuropathological conditions [11]. This facilitates the development of personalized treatment plans, as AI can identify mutations in brain tumors, guiding the selection of targeted therapies and improving treatment response [12]. Moreover, AI-driven automation in routine diagnostics allows pathologists to focus on more complex and critical cases. This is particularly advantageous in resource-limited settings, where there is a shortage of skilled professionals [13]. By enhancing efficiency and reducing diagnostic workloads, AI contributes to a better use of healthcare resources and to improve patient care [14].

This literature review delves into the integration of AI in neuropathology, exploring key applications, benefits, challenges, and future directions.

2. Historical overview of central nervous system tumor diagnosis: from histology to molecular profiling

Traditionally, brain tumors diagnosis and grading have relied on the visual examination of hematoxylin and eosin (H&E)-stained slides. This approach usually establishes a differential diagnosis, guiding further diagnostic steps like special stains and immunohistochemistry (IHC), which help the neuropathologist in rendering a better-defined diagnosis [15]. However, this approach has notable limitations due to interobserver variability and inconsistent correlations between histopathologic features and patient outcomes [16].

Advances in understanding the molecular mechanisms of brain tumors led to the inclusion of molecular diagnostic criteria in the 2016 WHO Classification of Central Nervous System (CNS) Tumors [17]. For instance, research by Parsons et al. and Yan et al. showed that diffuse gliomas with IDH1 and/or IDH2 (IDH1/2) mutations tend to have a less aggressive clinical course compared to IDH-wildtype tumors [18,19]. Consequently, tumors with IDH1/2 mutations were classified as either IDH-mutant astrocytoma or IDH-mutant secondary glioblastoma multiforme, depending on their morphological features. Furthermore, the presence of an IDH1/2 mutation along with a 1p/19q co-deletion is diagnostic of oligodendroglioma, regardless of whether the tumor exhibits astrocytic or oligodendroglial morphology [20].

The 2016 classification also brought significant changes to the categorization of embryonal tumors. Medulloblastomas were divided into four molecular subtypes based on WNT, SHH, and TP53 status [21]. SMARCB1/SMARCA4 loss became a crucial criterion for diagnosing atypical teratoid/rhabdoid tumors, and embryonal tumors with multilayered rosettes and C19MC amplifications were recognized as a distinct diagnostic category [22].

The concept of an integrated "histomolecular" diagnosis was further expanded in the 2021 WHO update to cover several tumor entities [23]. A major revision distinguished pediatric-type diffuse gliomas from adult-type diffuse gliomas due to their unique molecular signatures [24]. In the classification of adult-type diffuse gliomas, the significance of an IDH mutation evolved from the 2016 classification. Nowadays, tumors with an IDH mutation are designated as either IDH-mutant astrocytoma or IDH-mutant oligodendroglioma, depending on the 1p/19q status, thus making the term "IDH-mutant glioblastoma" obsolete [25]. The updated grading scheme for IDH-mutant astrocytomas also reflects the importance of CDKN2A/B homozygous deletion as a marker for poor prognosis [26].

Numerous molecular alterations, including those used in classification criteria, have shown prognostic relevance, such as IDH-mutation status or the WNT molecular subgroup of medulloblastoma [27]. Others, like O6-methylguanine-DNA methyltransferase (MGMT) promoter hypermethylation, predict therapeutic response [28]. Recently, DNA methylation profiling has emerged as an additional tool for diagnosing and subclassifying brain tumors beyond histopathologic and genomic characteristics [29]. For some CNS tumors, DNA methylation profiling serves as a supplementary diagnostic tool, while for others, such as high-grade astrocytoma with piloid features (HGAP), it is crucial for confirming the diagnosis [30].

Neoplastic cells undergo significant changes in DNA methylation patterns, which can be used to classify tumor types with high specificity through epigenome-wide methylation assays [31]. Capper et al. made significant contributions by developing a ML algorithm that classifies CNS tumors based on DNA methylation profiles [23]. They trained the algorithm using methylation data from 2801 pre-classified samples of nearly every type of CNS tumor. This algorithm employed supervised ML to recognize methylation patterns from known classifications, and unsupervised learning to identify patterns that could independently classify samples into computer-generated categories. As a result, the algorithm classified tumors into 82 distinct groups – about one-third corresponded to known WHO tumor types, another third represented sub-classes of WHO tumor types, and the rest were new tumor types that did not match WHO groupings, including previously unrecognized tumor types and those with histologic overlap but distinct methylation profiles.

When tested prospectively on 1104 new samples, the algorithm's classification matched the pathologist's diagnosis in 60.4 % of cases. In 15.5 % of the cases, the classifications matched, but the algorithm identified subgroups which were not recognizable through histopathology alone. In 12.6 % of cases, the pathologist and the algorithm made a different diagnosis, and further analysis, including gene sequencing, led to a reclassification in 92.8 % of these cases, often assigning a new tumor grade. The algorithm could not classify 11.5 % of the samples [23,32]. Since then, numerous studies have validated the algorithm's accuracy, and it has been adopted into clinical workflows at different centers worldwide [23,33–35]. This approach has proven particularly useful for classifying tumors with heterogeneous or difficult-to-distinguish morphology, such as ependymomas, medulloblastomas, and diffuse glioneuronal tumors [23,35]. Its role in guiding diagnoses for these tumors has been incorporated into the 2021 WHO guidelines for CNS tumor classification [19,36–38].

3. Artificial intelligence application in neuropathology

Histopathologic analysis has long been essential in oncology diagnosis, yet it is prone to interobserver variability that can hinder accurate

diagnosis and optimal management [39–41]. In neuro-oncology, grading gliomas based on atypia, mitosis, microvascular proliferation, and necrosis involves a degree of subjectivity [42–45]. The incorporation of molecular features such as IDH mutation and 1p/19q co-deletion status into the WHO grading of gliomas, along with the growing availability of individualized tumor genetic data, makes AI a helpful tool for pathologists in interpreting large, multiparametric data sets to establish diagnoses [42–44,46].

The emergence of high-quality digitized whole slide images (WSIs) has enabled the use of DL in histopathologic diagnosis [42–44,46]. In oncology, DL algorithms have been applied to detect metastatic breast cancer in lymph node biopsies [39], assess Gleason score in prostate cancer biopsies [40], and differentiate lung adenocarcinoma and squamous cell carcinoma from normal lung tissue [41], among other applications, with high accuracy.

In neuro-oncology, convolutional neural networks (CNNs) trained on WSIs of gliomas have been used to provide unbiased diagnoses of gliomas [47,48]. Ertosun et al. trained two CNNs on publicly H&E-stained images of gliomas from The Cancer Genome Atlas (TCGA) [42]. One CNN aimed to differentiate glioblastoma (GBM) from low-grade glioma (LGG), while the other aimed to distinguish between grade 2 and grade 3 gliomas. The CNNs showed a 96 % accuracy for GBM vs. LGG distinction, and 71 % accuracy for differentiating between a grade 2 and a grade 3 glioma [42]. Pei et al. developed a deep learning-based model that fused molecular and histopathologic features to predict glioma grade, with an accuracy of 93.8 % in distinguishing high-grade glioma (HGG) from LGG, and 74 % in distinguishing grade 2 vs. grade 3 gliomas. They used digital WSIs from 549 patients in TCGA with molecular information on IDH, 1p/19q, ATRX, and MGMT promoter alterations [47,48]. Another study by Truong et al. trained multiple CNNs using TCGA WSIs, with the best models achieving a 73 % mean accuracy in distinguishing GBM from LGG, and 53 % accuracy in distinguishing grade 2 from grade 3 gliomas [43]. All the above-mentioned studies, except for the one by Pei et al. [47], are limited by the absence of IDH-mutation and 1p/19q co-deletion status of the tumors.

Hollon et al. developed a rapid (<90 seconds), AI-based diagnostic screening system to streamline the molecular diagnosis of diffuse gliomas. In a cohort of 153 patients with diffuse glioma, the authors showed that this system was able to predict the molecular alterations used by the WHO to define adult-type diffuse gliomas (IDH mutation, 1p/19q co-deletion and ATRX mutation), achieving a mean molecular classification accuracy of 93.3 % [49].

Jin et al. developed a platform named “AI Neuropathologist”, which trained a CNN on over 79,000 H&E-stained WSIs from 267 patients to distinguish GBM, anaplastic astrocytoma, anaplastic oligodendroglioma, astrocytoma, oligodendroglioma, and background glia [44]. The CNN derived histopathologic features and classified gliomas from 59 unique patients with 83 % accuracy. The authors concluded that “AI Neuropathologist” may represent a useful tool for glioma grading, emphasizing that it should be used in conjunction with clinical information and molecular data.

In the field of molecular neuropathology, ML models are increasingly used to predict prognosis, therapy responses, and patient outcomes [46]. For example, in medulloblastoma, DL models trained on DNA methylation profiles have improved tumor classification accuracy and provided insights into underlying biological mechanisms [46]. Similarly, AI has been employed to analyze genomic and transcriptomic data to identify potential therapeutic targets in gliomas [46].

A recent approach, which has been used by Ravi et al., aimed at characterizing GBMs by spatially resolved transcriptomics, metabolomics and proteomics [50]. They inferred that GBM is organized by spatial segregation of lineage states. In their study, they used a two-step approach to explore transcriptional diversity in a spatial context: i) a machine-learning-based segmentation technique, and ii) an artificial neural network model trained to predict the number of tumor cells per spot [46]. Some researchers tested rapid nanopore sequencing combined with ML to enhance intraoperative diagnosis of CNS tumors, developing “Sturgeon”, a neural network trained to subclassify CNS tumors during surgery using sparse methylation profiles obtained via nanopore sequencing [51]. They found that 45 out of 50 retrospectively sequenced samples could be diagnosed accurately within 40 minutes [51]. During real-time application in 25 surgeries, the tool achieved a 72 % overall accuracy rate [51]. Similarly, Hoang et al. validated “Deploy”, a DL model designed to enhance the diagnosis and classification of brain tumors, using histopathology images by leveraging deep learning, thereby overcoming the limitations of DNA methylation profiling, which is time-consuming and not widely available [52]. An accurate prediction (95 % overall accuracy; 91 % balanced accuracy) of DNA methylation beta values from histopathology images was achieved for 10 major tumor categories [52].Integrating these AI models with traditional histopathologic data could further enhance diagnostic precision and patient-specific treatment strategies [53–55].

AI technologies have made considerable progress in neuropathology, enhancing diagnostic accuracy, streamlining workflows, and paving the way for personalized treatment strategies (Table 2). As AI continues to evolve, its integration with traditional neuropathologic methods promises to further improve patient outcomes and lead to a revolution in the field.

4. Challenges to overcome

The success of AI models is highly dependent on the availability of high-quality, annotated datasets. In the field of neuropathology, achieving standardized and representative data is difficult due to variations in how samples are prepared, stained, and interpreted by different observers [53,54]. Creating large, diverse, and well-annotated datasets is essential for developing robust AI models. To improve the possibility of generalization of these models, it is important to establish uniform protocols for data collection and annotation and to promote collaboration among institutions to create centralized data repositories [53,54].

Table 2
Main AI Applications in Neuropathology.

Study	Details	Accuracy
Ertosun et al. [42]	Trained CNNs to distinguish glioblastoma from low-grade glioma and grade 2 vs. grade 3 gliomas.	96 % for GBM vs. LGG; 71 % for grade 2 vs. 3
Truong et al. [43]	Trained CNNs on TCGA WSIs to differentiate GBM from LGG and grade 2 from grade 3 LGGs.	73 % mean accuracy for GBM vs. LGG; 53 % for grade 2 vs. 3
Jin et al. [44]	Developed “AI Neuropathologist” CNN to classify gliomas into several categories with high accuracy.	86.5 % patch-level; 87.5 % patient-level
Pei et al. [47]	Developed model integrating molecular and histopathologic features for glioma grading.	93.8 % for high vs. low-grade gliomas; 74 % for grade 2 vs. 3
Faust et al. [48]	Developed a workflow coupling different computer vision tools including SIFT and deep learning to integrate histopathological information.	91 % overall accuracy
Hollon et al. [49]	Developed DL-based method for rapid molecular classification of diffuse gliomas from intraoperative samples.	93.3 % overall accuracy
Vermeulen et al. [51]	Developed “Sturgeon”, neural network to subclassify brain tumors during surgery using methylation profiles obtained via nanopore sequencing.	72 % overall accuracy
Hoang et al. [52]	Developed “Deploy”, a DL model designed to predict DNA methylation beta values from histopathologic images.	95 % overall accuracy

Another critical aspect is represented by the fact that WSIs are commonly divided into patches, and each patch is analyzed separately, such as for ROI detection. The methodology used for integrating the results of all patches still has room for improvement [55]. Artifacts affecting tissue structure and color variation of standard stains can be introduced at various stages of the WSI creation process. Because these artifacts may impair interpretation, specific algorithms for detecting artifacts such as blur and tissue folds have been proposed that can be used during WSI preprocessing [55].

A significant challenge to the clinical adoption of AI models is their "black box" nature. Pathologists and clinicians need to understand the reasoning behind AI-generated outcomes to trust and effectively integrate these tools into clinical practice. It is crucial to develop AI models that are interpretable and provide clear and understandable results. Techniques like attention mechanisms, saliency maps, and explainable AI frameworks can clarify how AI models make decisions. Engaging clinicians in the development and validation processes can ensure that AI tools meet clinical needs and gain easier acceptance.

Furthermore, deploying AI in clinical settings brings up important regulatory and ethical concerns. Protecting data privacy and security is critical, particularly with sensitive patient information. Regulatory frameworks must adapt to address the specific challenges of AI, including the validation, approval, and continuous monitoring of AI systems. Ethical issues, such as potential biases in AI algorithms and their effects on patient care, need to be carefully considered. Transparent reporting on AI model performance, including their limitations and biases, is essential. Additionally, informed consent procedures should be updated to account for the use of AI in diagnosis and treatment planning.

5. Future perspectives

Future research should aim to integrate various data types, including imaging, genomic, and clinical information, to develop comprehensive AI models. These multimodal approaches may offer a more complete understanding of neuropathological conditions, improving diagnostic precision and guiding treatment decisions. It is crucial for researchers, clinicians, and data scientists to work together to create and validate these integrated models. The formation of interdisciplinary teams will help to reach an effective combination of various data types and ensure that AI tools remain relevant in clinical settings.

Improving the interpretability of AI models is essential for their acceptance in clinical practice. Research should focus on methods that make AI decisions clearer and more understandable for clinicians. Techniques such as explainable AI (which aim to clarify how AI models make their decisions) need further exploration and refinement. Involving clinicians in the development process can provide crucial feedback on interpretability requirements and practical applications of AI tools. This collaborative approach will help design AI models with user-friendly interfaces and straightforward explanations of their results.

Rapid progress in AI research with relevance to microscopy can be anticipated in the coming years. However, rather than seeing it as a threat to morphological diagnostics, we agree that, in the appropriate setting and by providing more quantitative evidence and appropriate decision support, ML and DL can improve medical decisions and ultimately patient care [55].

Ongoing collaboration between AI researchers, neuropathologists, and clinicians is vital for effectively incorporating AI into neuropathology. Cooperative efforts can help identify clinical needs, develop appropriate AI tools, and ensure smooth integration into existing workflows. Creating collaborative research networks and consortia can promote knowledge sharing, standardize best practices, and speed up the development and validation of AI models. Funding agencies and academic institutions should support interdisciplinary research to advance AI applications in neuropathology.

6. Conclusions

Incorporating AI into neuropathology presents significant advantages, such as improved diagnostic precision, customized treatment plans, and more efficient use of resources. Nevertheless, challenges related to data quality, model transparency, and ethical issues need to be addressed to unlock the full potential of AI in this field. Continuous research, collaboration, and the establishment of strong regulatory frameworks are crucial for overcoming these obstacles and ensuring that AI-driven innovations benefit both patients and healthcare providers. As the field evolves, the collaboration between AI and neuropathology is set to transform the diagnosis and management of neurological disorders, leading to better patient outcomes and advancing the field of medical science.

Ethics

Not applicable.

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CRediT authorship contribution statement

Francesco Certo: Resources. **Giuseppe Maria Vincenzo Barbagallo:** Resources. **Andrea Palicelli:** Methodology. **Magda Zanelli:** Methodology. **Serena Salzano:** Conceptualization. **Manuel Mazzucchelli:** Conceptualization. **Giuseppe Broggi:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Nektarios Koufopoulos:** Methodology. **Maurizio Zizzo:** Methodology. **Rosario Caltabiano:** Writing – review & editing, Validation. **Gaetano Magro:** Validation.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4° mini in the writing process to improve the readability and language of the manuscript. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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