

# Artificial Intelligence for Brain Diseases: a Systematic Review

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**INTRODUCTION:** Artificial intelligence (AI) is a major branch of computer science that is fruitfully used for analysing complex medical data and extracting meaningful relationship in data sets, for several clinical aims. Especially in the brain care domain, several innovative approaches have achieved remarkable results and open new perspectives in terms of diagnosis, planning and outcome prediction. In this work, we present an overview of different artificial intelligent techniques used in the brain care domain, along with a review of important clinical applications.

**METHOD:** A systematic and careful literature search in major databases such as Pubmed, Scopus and Web of Science was carried out using “artificial intelligence” and “brain” as main keywords. Further references were integrated by cross-referencing from key articles. **RESULTS:** 155 studies out of 2696 were identified which actually made use of AI algorithms for different purposes (diagnosis, surgical treatment, intra-operative assistance and post-operative assessment). Artificial neural networks (ANNs) have risen to prominent positions among the most widely used analytical tools. Classic Machine Learning (ML) approaches such as Support Vector Machine (SVM) and Random Forest (RF) are still widely used. Task-specific algorithm are designed for solving specific problems. Brain images are one of the most used data type. **CONCLUSION:** AI has the possibility to improve clinicians’ decision-making ability in neuroscience applications. However, major issues still need to be addressed for a better practical use of AI in brain. To this aim, it is important to both gather comprehensive data and build explainable AI algorithms.

## I. INTRODUCTION

Over the last three decades hospitals and healthcare systems produced a vast quantity of unstructured data such as Medical Imaging (MI) data, genomic information, free text and data streams from monitoring devices<sup>1</sup>. The analysis of such data significantly changed the approaches used by medical experts and practitioners for identifying, understanding and treating brain pathologies, as well as identifying risks and reactions to therapies<sup>2</sup>. In particular, MI and MI processing started a revolution in the field; indeed, they paved the way to quick and non-invasive ways to study, treat, manage, and predict diseases. Furthermore, advances in image and image processing technologies led to more and more cost-effective and low-risk analysis<sup>3</sup>. Computed Tomography (CT), Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), for instance, have revolutionized the study of the brain by allowing doctors to perform noninvasive evaluations of the brain structure, and to infer causes of abnormal function due to different diseases<sup>4,5</sup>.

However, “manually” processing medical data, and brain images in particular, is often time consuming, and chances of errors in the interpretation are not irrelevant. For example, it has been estimated that day-to-day error rates and discrepancies in radiology are greater than 3-5%<sup>6</sup>. This called for novel methods to help physicians at efficiently and effectively analyzing data. As more computational power has been available and the medical data quality increased, the interest in employing advanced algorithms has increased<sup>7</sup>. However, despite the significant results obtained during years, given the raise in complexity and volume of data many traditional

computer-based techniques and algorithms are not feasible in real world scenarios. For instance, objects like lesions and organs in MI may be too complex to be accurately represented simply by traditional equations or models. Furthermore, it is not always easy for experts to define precise rules to apply, for example, for disease analysis and control. Hence, the use of Artificial Intelligence (AI) techniques has received a growing interest in the field of brain imaging and computational neurosciences over the last decade, as demonstrated in the exponential grow of scientific publications reported in Figure 1. Among these approaches, Machine Learning (ML) techniques are now renowned and widely used for addressing brain-related problems.

ML is a subset of AI algorithms that automatically “learn” to identify categories or forecast future or unknown conditions starting from data. Several solutions have been developed during years, and many of them still provide successful results in the analysis and processing of brain data.

Quantitative and qualitative characterization of normal and pathological structures are often part of clinical tasks in which ML has achieved the most promising results<sup>8-10</sup>. In this context, brain data processing using ML methods has been widely used to identify brain conditions such as Alzheimer’s disease, dementia, schizophrenia, multiple sclerosis, cancer, and infectious and degenerative diseases. Furthermore, approaches for segmentation and detection brain structures, as well as pathological tissues, are also widely studied<sup>11</sup>. Detection and precise localization of the abnormal tissue and surrounding healthy structures, indeed, are crucial for diagnosis, surgical planning, postoperative analysis, and chemo/radiotherapy treatment.

Nevertheless, it is worth to note that, because of the complexity and the amount of brain data, ML methodologies usually comprise several steps in order to actually perform a task. For example, image pre-processing, feature selection and ranking, as well as dimensionality reduction, are often re-

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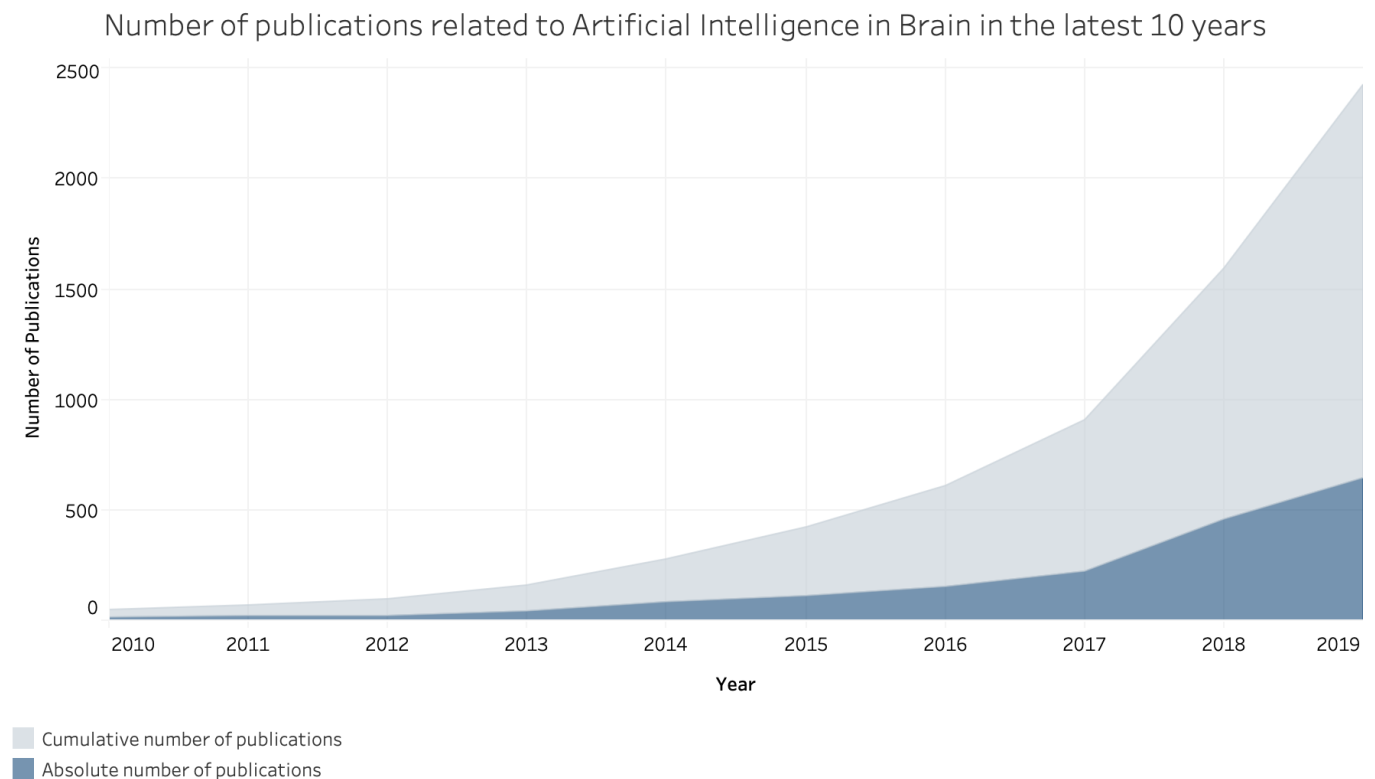


Figure 1. Cumulative and absolute number of papers on artificial intelligence in brain published in the latest ten years (as reported in the considered databases).

quired as initial stages to boost algorithm performances up to adequate levels<sup>12</sup>.

In recent years, a subfield of AI, Deep Learning (DL), has revolutionized a variety of neurosurgical tasks<sup>10,13,14</sup> (Figure 2). In particular, DL algorithms rose a prominent position in computer vision, outperforming other methods on several high-profile image analysis benchmarks<sup>15</sup>. Differently from traditional ML models, in DL useful representations and features are learnt automatically, directly from raw data, overcoming the issue of manually compute and select potentially relevant attributes. Thanks to critical advancement in computing power, including the use of Graphic Processing Unit (GPU), such algorithms started to be effectively used for learning from the 3-D and 2-D images typical of the medical domain<sup>12</sup>.

This work primarily focuses on providing an overview of the recent literature on AI techniques directly supporting brain care. We provide a brief analysis of key ideas and areas of application of AI as well as the principal modalities and knowledge used in neuroscience. First, we present a summary of the key clinical uses of AI in brain, including classification, segmentation, organizational preparation, postoperative analysis and predictive methods; furthermore, we provide a thorough description of recent classification methods based on brain connectivity; eventually, taking into account recent developments and the rapidly growing potential of the field, we discuss how AI might transform brain care in the near and long

term, identifying open issues and promising directions for future work.

The remainder of the paper is organized as follows. We briefly introduce the main type of data used for brain analysis, as well as the main AI techniques adopted for solving brain-related tasks. The methodology used for evaluating the state-of-the-art is explained in section V and analysed more in detail in Section VII. We discuss our findings in Section VIII and draw our conclusions in Section IX.

## II. Type of Data

Many different technologies have been developed with the aim of understanding brain structure without the need for invasive neurosurgery. CT and MRI are the two primary innovations that improved diagnostic and management efficiency across the spectrum of neurological disorders<sup>8,12</sup>. CT uses computer-processed adaptations of several X-ray measurements taken from various angles to produce cross-section (tomographic) images. PET is used to observe metabolic processes at cellular levels. MRI uses a strong magnetic field and radio waves to render high-quality imagery of biological structures<sup>5</sup>.

By controlling the radio frequency pulses and the oscillations of the gradient, specific pulse sequences determine how the image is obtained (weighed) and how the different tissues

appear. T1- and T2- weighted imagery is useful for demonstrating the anatomy and pathology of the brain, respectively. A third commonly used sequence is the Fluid Attenuated Inversion Recovery (FLAIR).

Advanced imaging is playing an increasingly more important role in the management of patients with neuro-oncologic disease. In this way, advances in Diffusion Tensor Imaging (DTI) and Functional Magnetic Resonance Imaging (fMRI) provide noninvasive means of brain mapping<sup>16</sup>. More in detail, DTI provides *in vivo* visualization of white matter tracts in the brain, helping to analyze pathological alterations outside visible lesions on MRI<sup>17</sup>. This is achieved through the creation of a map of the axonal network in the brain by measuring the diffusivity of water molecules. fMRI is a technique to detect eloquent cortex by identifying increased blood oxygen levels in areas of the brain that are activated by task-based paradigms. During the last two decades, an explosion of fMRI studies took place mapping neural functions to distinct parts of the brain at rest or during task performance. However, more attention has been directed towards Resting State Functional Magnetic Resonance Imaging (rs-fMRI) data<sup>18</sup>.

Hyperspectral Imaging (HSI) is an emerging imaging modality for medical applications, especially in disease diagnosis and image-guided surgery. It provides diagnostic information about the tissue physiology, morphology, and composition. HSI acquires a three-dimensional dataset called hypercube, with two spatial dimensions and one spectral dimension<sup>19</sup>. Another technique which gained interest because of the capabilities of obtaining real-time visualizations is Intra-operative Ultrasound (IUS), a diagnostic imaging tool that uses high-frequency sound waves to create images of structures in the body<sup>20</sup>. Ultrasound images are captured in real time using an external probe and ultrasound gel placed directly on the skin.

A fundamental concept in modern neuroscience is that anatomical and functional links between brain regions are arranged in such a way that information processing is close to optimal. Recently applied in neurosciences, graph-based models opened up new perspectives for the study of brain structural and functional integration through graph-derived metrics<sup>21,22</sup>. In this context, brain connectivity analysis rests upon three different but related forms of connectivity: Structural Connectivity (SC) consists of nodes, corresponding to segmented cortical regions, and links, e constructed by tractography from white matter fibers-tracts<sup>23,24</sup>. Functional Connectivity (FC), instead, is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions. Other brain connectivity forms exist, which, however, are not treated in this review.

Other type involved in the brain care are gene sequence, Electronic Health Record (EHR), Electroencephalography (EEG), Microelectrode Recording (MER) data. EHR are digitizing valuable medical data on a massive scale. Electronic health records (EHR) capture “real-world” disease and care processes and hence offer richer and more generalizable data for comparative effectiveness research than traditional randomized clinical trial studies. EEG measure the weak electromagnetic signals generated by in-brain neuronal activities. It

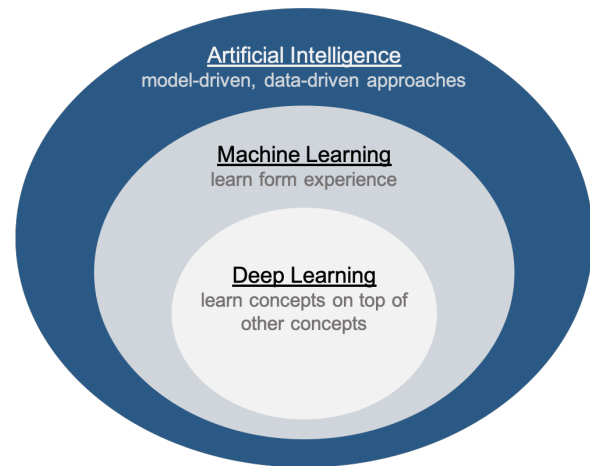


Figure 2. Relations among artificial intelligence, machine learning and deep learning.

captures both slowly and rapidly changing dynamics of brain activations with a time resolution of milliseconds. This enables the investigation of neuronal activity over a wide range of frequencies that can offer potentially complementary insights regarding how the brain works as a large system<sup>25</sup>. MER technique further enhance the ability of the surgeon subcortical area; MER data are used as an adjunct approach to ensure that the Deep Brain Stimulation (DBS) electrode is correctly placed within the target structure<sup>26</sup>.

All input data of the reviewed article are reported in Table XI.

### III. Artificial Intelligence, Machine Learning and Deep Learning

One of the main AI goals is the development of software for computers or computer-controlled machines able to perform tasks commonly associated with intelligent beings<sup>1</sup>. Its use in healthcare commonly attempts to emulate and even overcome human cognition in the analysis of complicated medical data.

As schematized in Figure 2) among the various AI branches, ML has a prominent role in brain data analysis. ML is an adaptive process that enables computers to learn from experience, learn by example, and learn by analogy<sup>27</sup>. The goal is to define generic algorithms able to automatically improve their performance over time on the basis of previous results, and is achieved by *training* the algorithms via proper optimization approaches. One of the most valuable properties of such models is the capability of achieving accurate results on several tasks, such as classification or prediction, over unseen data, thus generalizing their learned expertise. In general, every ML algorithm falls into one of two main categories: supervised learning and unsupervised learning. Supervised learning is generally used when the answer to the problem is known. In this scenario, a set of samples with known labels (*training set*), is provided to the ML algorithm. Thus, a model is prepared through a training process where its param-

eters are tuned to produce accurate predictions for the labeled data. Classification methods fall in this category. With unsupervised learning, differently from supervised learning, input data are not labelled and no known result is provided to the model. In this case, the algorithm is generally trained at deducing structures and common patterns present in the input data. Clustering is a prime example.

In this review we mainly focus on supervised approach, as widely adopted in brain image processing tasks. In this context, several ML solutions provide promising and reliable solutions. According to the function used to process the input, they can be classified in many categories. Among the most common we find Decision Tree (DT), that predict the output  $Y$  based on a sequence of splits in the input feature space  $X$ . Ensembles of DT, such as Random Forest (RF) or boosted trees (e.g. AdaBoost), are thus a more popular choice in most applications since they yield much better prediction performance. Support Vector Machines (SVM) search for an optimal separating hyperplane between classes that maximizes the margin, i.e., the distance from hyperplane to points closest to it on either side.

Among the various ML solutions, Deep Neural Network (DNN) are nowadays considered as the state-of-the-art solution for many problems, including tasks on brain images. Such human brain-inspired algorithms have been proven capable of extracting highly meaningful statistical patterns from large-scale and high-dimensional datasets. A DNN is a DL algorithm aiming to approximate some function  $f^*$ . For example, a classifier can be seen as a function  $y = f^*(x, \theta)$  mapping a given input  $x$  to a category labelled as  $y$ .  $\theta$  is the vector of parameters that the model learns in order to make the best approximation of  $f^*$ . Artificial Neural Networks (ANN) are built out of a densely interconnected set of simple units, where each unit takes a number of real-valued inputs (possibly the outputs of other units) and produces a single real-valued output (which may become the input to many other units). DNN are called networks because they are typically represented by composing together many functions. The overall length of the chain gives the depth of the model; from this terminology the name “deep learning” arises. Recently, more advanced neural networks models with local receptive fields, like Convolutional Neural Network (CNN), have proven promising classification accuracy in image processing tasks such as classification or segmentation. CNNs replace the fully-connected operations by convolutions with a set of “learnable” filters. Success of this approach stems from its ability to exploit the full-resolution of 2-D and 3-D spatial structures (e.g., MRI) without the need for learning too many model parameters, thanks to the weight sharing. Many other DL architectures have been presented during years; here, it is worth mentioning Recurrent Neural Network (RNN), widely used where longitudinal data are available, and Graph Neural Network (GNN), which extend neural networks with the purpose of processing graph structures data.

#### IV. Clinical Aims

AI is a major branch of computer science; it counts many methods for building effective tools for analysing complex domains, including medical data. Its potential to exploit meaningful relationship within a data set can be used in diagnosis, surgical treatment, intra-operative assistance and post-operative predicting outcome in many clinical scenarios. Indeed, modern medicine is faced with the challenge of acquiring, analysing and applying the large amount of knowledge necessary to solve complex clinical problems. The development of medical AI has naturally been related to the development of AI techniques; in the brain care these are intended to support healthcare workers in their duties, especially with tasks that rely on the manipulation of data and knowledge. More specifically, in the context of brain care, one of the main purpose is to help clinicians in the formulation of diagnosis “classification” problems, using anatomical, morphological and connectivity information<sup>7,8,12,18</sup>. Usually, automatic classification helps clinical decision making on a pathology of the brain or multiple classes of it, by discerning patterns corresponding to classes. For example, classification methods, using anatomical information, are widely used for the detection of Alzheimer’s Disease (AD) and other cognitive impairments<sup>8</sup>, as well as the characterization of various brain tissues including brain tumors<sup>14</sup>. Moreover, a classification using morphological information is performed, the task is known as “image segmentation”<sup>11</sup>. The goal is to partition an image into multiple regions that share similar attributes, enabling localization and quantification. Segmentation is commonly used for detecting, measuring and analyzing the main morphological structures of the brain and eventually identifying pathological regions. This accurate structural classification is particularly important in patients with tumors, edema, and necrotic tissues. Brain image segmentation is also useful in clinical diagnosis of neurodegenerative and psychiatric disorders, treatment evaluation, and surgical planning.

To help the formulation of the surgical treatment, similarly, classification is used for surgical candidate selection and segmentation is used for finding and categorizing the surgical target. In brain images, ML detection techniques are performed to identify the areas where the patient’s lesions are located as box coordinates and localization of stimulation zones within the brain for DBS treatment used for brain lesion and Parkinson patients. Moreover, AI systems are used for assisting a surgeon during the definition of an optimal trajectory.

Prognosis is extremely important in planning appropriate post-operative treatment. Accurate identification of high-risk patients may facilitate targeted aggressive adjuvant therapy which may help cure the disease and prolong survival<sup>28</sup>. The implementation of EHR in hospitals is increasing rapidly; the generated data can be fed to an AI algorithm in its raw form, and the algorithm can try to learn which features are associated with the outcome of interest<sup>29</sup>. This way, the algorithm can be able to predict mortality, postoperative hospitalization, transphenoidal surgery response, DBS outcome, reperfusion, disease recurrency in a variety of disease conditions including Cushing’s disease, Parkinson’s disease, brain tumor, brain

injury, brain lesion and neurological disorders, easing the burden of clinicians who have to come up with meaningful structured data.

## V. METHODS

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In particular, Pubmed, Scopus and Web of Science databases were searched to identify all potentially relevant studies back to January 1, 2008. The search queries were carefully built with the guidance of a professional librarian using search terms related to ‘artificial intelligence’ and ‘brain’. A comprehensive list of the keywords used for the search is reported in Table XII. All biomedical studies that evaluated AI models assisting in brain care were included; duplicates are discarded by using the EndNote reference management software. Following the elimination of duplicates, a careful screening of titles and abstracts was made in order to identify paper that were relevant to our research topic. Any work that matched at least one of the following exclusion criteria was crossed out:

- (i) no full-text available
- (ii) no AI application
- (iii) conference abstracts
- (iv) animal models
- (v) conference papers
- (vi) books
- (vii) book chapters
- (viii) non-English language

After a proper check of full-texts and references, a total of 154 articles/reviews were identified as eligible, and hence included into this systematic review. Any article appearing to help our research was included and classified; nevertheless, we decided to not cover, papers already covered by previous reviews. Data considered from each study were:

1. application
2. name of first author
3. year of publication
4. clinical aim
5. pathology
6. type of data
7. data
8. AI method
9. benchmark measure
10. results.

On this basis, we computed the distribution of all published articles within the domains of clinical aim, pathology, ML algorithm and type of data used as input feature.

We considered a quantitative synthesis to be inappropriate, due to the heterogeneity in the applications. A qualitative synthesis of results is hence provided next by means of a narrative approach. Concerning classification tasks, given the large amount of publications in literature and the recent results sublimely analysed, both quantitatively and qualitatively, by previous surveys, we limited the detailed overview to the 50 most cited papers of 2019. Finally, we made a strong dis-

inction between image-based and connectivity-based classification tasks. In fact, given the promising results obtained by these techniques, we find the latter to be an evolving challenge that deserves a thorough analysis.

## VI. Evaluation Metrics

For all AI applications, and ML is no exception, performance measurement is an essential task. Benchmark measures used for the evaluation of the reviewed studies are explained in in Table IX. Accuracy, precision, sensitivity, and specificity are metrics widely used to evaluate performance in ML classification tasks. Accuracy and precision reveal a test’s basic reliability, while specificity and sensitivity reveal the likelihood of false negatives and false positives. Those parameters are largely used, but, as reported by other reviews<sup>30</sup>, in some cases these evaluation metrics might not constitute a realistic measure. For these reasons, several works are starting to extend their evaluations by also reporting Positive Predictive Value (PPV) and Negative Predictive Value (NPV)<sup>31–35</sup>. Area Under the Curve (AUC) Receiver Operating Characteristic (ROC) curve is one of the most important evaluation metrics to check or visualize the performance of a ML classification problem. It tells how much model is capable of distinguishing between classes: the higher the AUC, the better the model is at predicting. To make a quantitative evaluation of automatic segmentation results the frequently used procedure is to determine the overlap with the gold standard that in this field is the manual segmentation by and expert radiologist. Generally, Jaccard Coefficient (JC) or Dice Similarity Index (DSI) is used. It ranges from 0 to 1, ranging from no overlap to perfect overlap. For probabilistic segmentation, the validation metric is AUC. Other validation metrics include Mean Square Error (MSE), Peak Signal-to-Noise Ratio (PSNR), Mean Absolute Distance (MAD) and Hausdorff Distance (HDD) values. Regarding path planning problem, the most important evaluation metric reported are Center of Mass Distance (CMD), Mean Square Distance (MSD), min Square Distance (mSD) and risk score for the trajectories evaluation and time complexity to evaluate the total time of execution for time-constrained applications. For predictive model the metric reported are error rate, Mean Absolute Error (MAE) and Root Mean Square Error (RMSE) that can be interpreted as a measure of the ratio between the true and predicted values.

As a final remark, it is worth mentioning the efforts spent by researchers to validate their methods, in order to reduce the possibility of human error and handle variations in brain data. To this aim, a crucial role is played by validation methods. Cross-validation methods (k-fold, leave-one-out, leave-one-group out) are still the most valuable approach in this sense. Such methods allow to better validate ML and DL algorithms, avoiding biases which might be present in a single dataset.

PRISMA Flow Diagram of Systematic Review

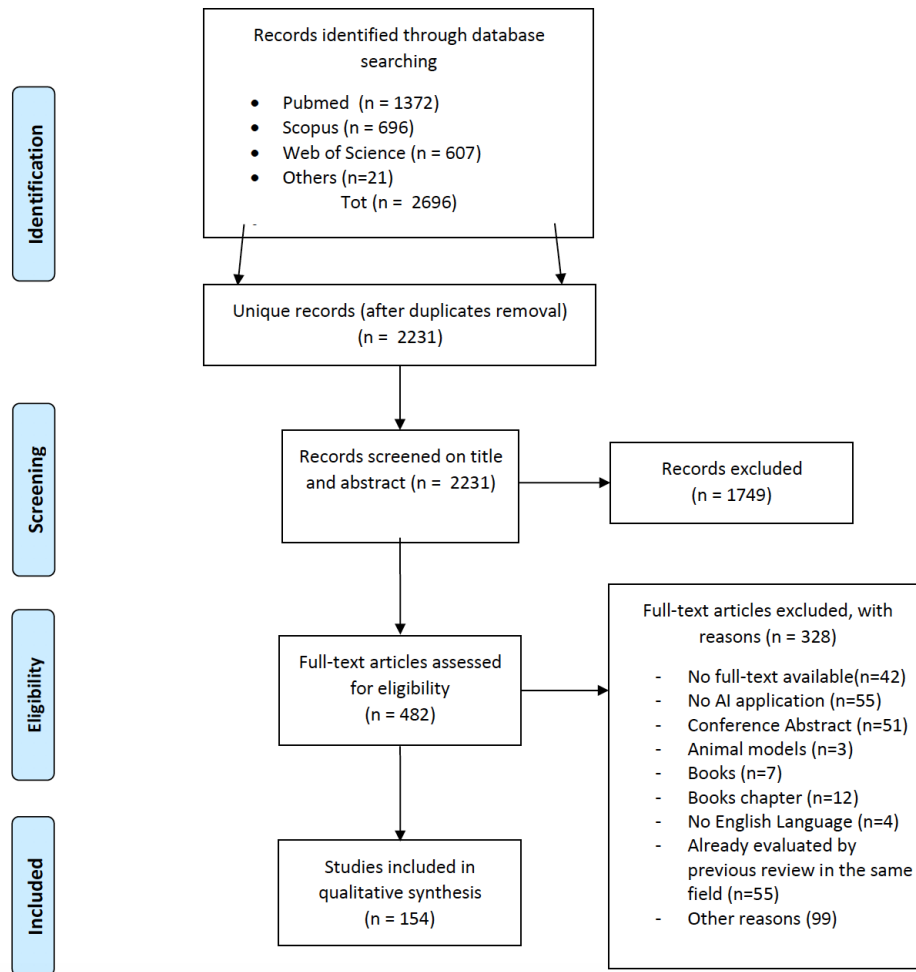


Figure 3. PRISMA flow diagram of systematic identification, screening, eligibility and inclusion. 154 studies were included in the final analysis out of the 2696 screened.

## VII. RESULTS

Out of the 2696 citations initially identified in the selected databases, 2231 were selected by title/abstract and full-text screening (Figure 3). We witnessed an exponential growth, in the latest ten years, of the number of studies evaluating AI models as an assisting tool across multiple paradigms of brain care; such paradigms include diagnosis with anatomical information, diagnosis with morphological information, diagnosis with connectivity information, candidate selection for surgical treatment, target definition for surgical treatment, trajectory definition for surgical treatment, modelling of tissue deformation for intra-operative assistance and prediction of patient outcome for post-operative assessment, as outlined in Figure 4; AI-enhanced brain care in patients with a wide variety of brain disorders, including, epilepsy, brain tumors, brain lesion, Parkinson’s diseases, brain injury, and cerebrovascular abnormalities. Algorithms used were Natural Language Processing (NLP) algorithms, Genetic Algorithm (GA), ANN, SVM, fuzzy C-means, RF, logistic regression, linear regres-

sion, K-nearest Neighbors (KNN), DT, Gradient Boosting Machine (GBM), Sparse Autoencoder (SAE) and k-means all described in Table X. A trend in adopting *custom* solutions, as well as less widely used ML algorithm, was also observed. Commonly used Type of data were MRI, CT, IUS, DTI, HSI, EHR, MER, EEG and Functional Near-Infrared Spectroscopy (fNIRS). MRI data were the most frequently used input features. Radiological brain tumor segmentation and classification were the most frequently evaluated applications.

### A. Diagnosis

121 studies considered AI for diagnosis. This includes classification using anatomical information, morphological information and connectivity information for neurological disorders, brain tumors, brain lesion, brain injury, Parkinson’s disease, epilepsy and cerebral artery, schizophrenia, Alzheimer’s disease, autism disorder and multiple sclerosis. CT, MRI, PET, SC and FC data were used as input features for the de-

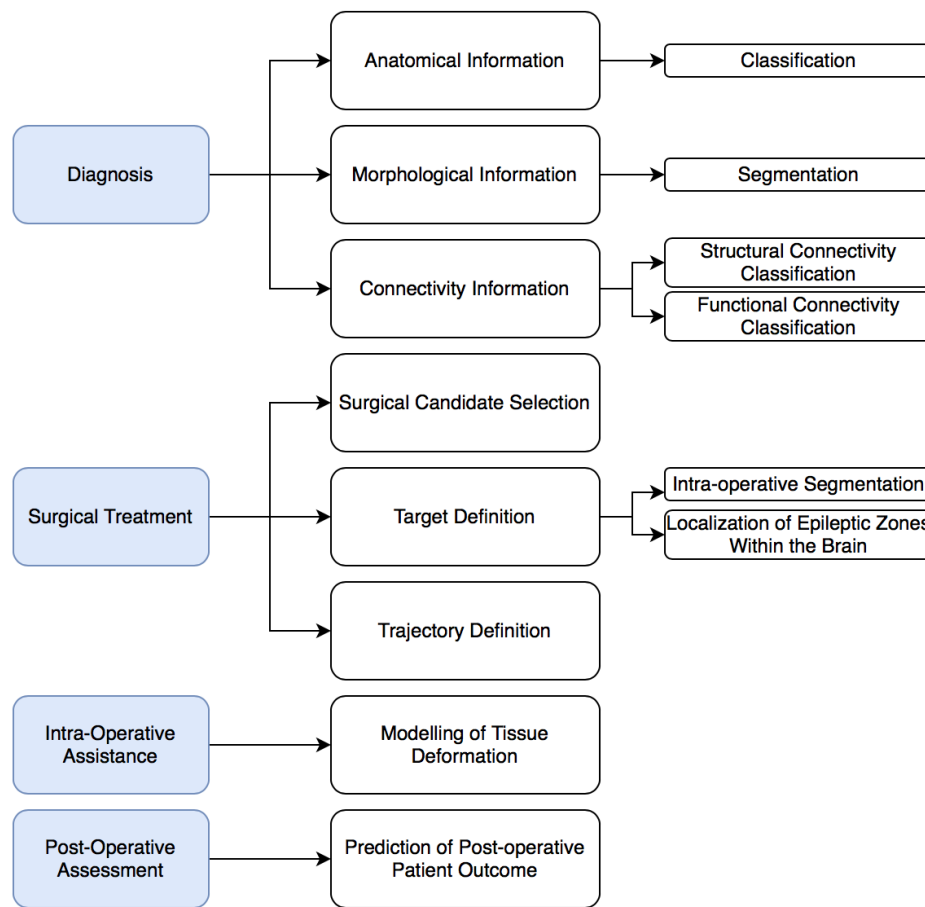


Figure 4. Diagram of multiple paradigms using AI in brain care identified in this review including diagnosis with anatomical information, diagnosis with morphological information, diagnosis with connectivity information, candidate selection for surgical treatment, target definition for surgical treatment, trajectory definition for surgical treatment, modelling of tissue deformation for intra-operative assistance and prediction of patient outcome for post-operative assessment

velopment of classification algorithm. Results of the distributions for pathology, AI methods and type of data for diagnosis are reported in Figure 5. Notice that, due to the vast heterogeneity of sub-tasks found concerning classification using anatomical information, a qualitative rather than a quantitative research design was chosen.

Computer Assisted Diagnostic (CAD) reflects a large portion of the various facets of AI for medical imaging<sup>12</sup>. Such tools constitute a valuable resource for the assistance of medical doctors in diagnosis, prognosis and pre-and post-surgical processes. One key task is to automatically determine the presence or absence of a disease or a particular type of malignancy. This classification stage is focused on making clinical decisions on a pathology of the brain or multiple classes of it, by discerning patterns corresponding to classes.

Several ML based algorithms have been proposed in recent years for automatically discovering and exploiting visual characteristics statistically associated with clinical outcomes<sup>5</sup>. Specifically, as previously observed by related studies<sup>5,7,12,36</sup> a variety of suitable solutions, mainly based on supervised learning techniques, have been developed for addressing classification tasks in brain imaging. As observable from Table I,

different works still exploit classic ML algorithms such as SVM and its variants<sup>37–41</sup> and RF<sup>42–44</sup>. Such algorithms, indeed, provide desirable characteristics, especially for the clinical domain. Other than achieving accurate solutions, indeed, their capability to quantify feature importance measures form the basis for their explainability.

However, it is evident that a lot of work relies on DL solutions. Independently from the clinical aim, several papers have been proposed exploiting CNN for classification purposes<sup>7,36</sup>. Thanks to their capability of extracting latent complex patterns, such algorithms still caught the interest of a wide community and constitute the state of the art for many classification tasks. Nevertheless, several novel architectures have been proposed, achieving significant performance with overall accuracy greater than 90% for many classification tasks. In<sup>45</sup>, an ensemble of 3D densely connected CNN for AD and Mild Cognitive Impairment (MCI) diagnosis was proposed, outperforming previous methods in all four classification tasks. Pang *et al.*<sup>46</sup>, introduced a novel fused CNN which combines shallow layer features and deep layer features. In the analysis, it was observed that the shallow layers provided more detailed local features, which could distinguish differ-



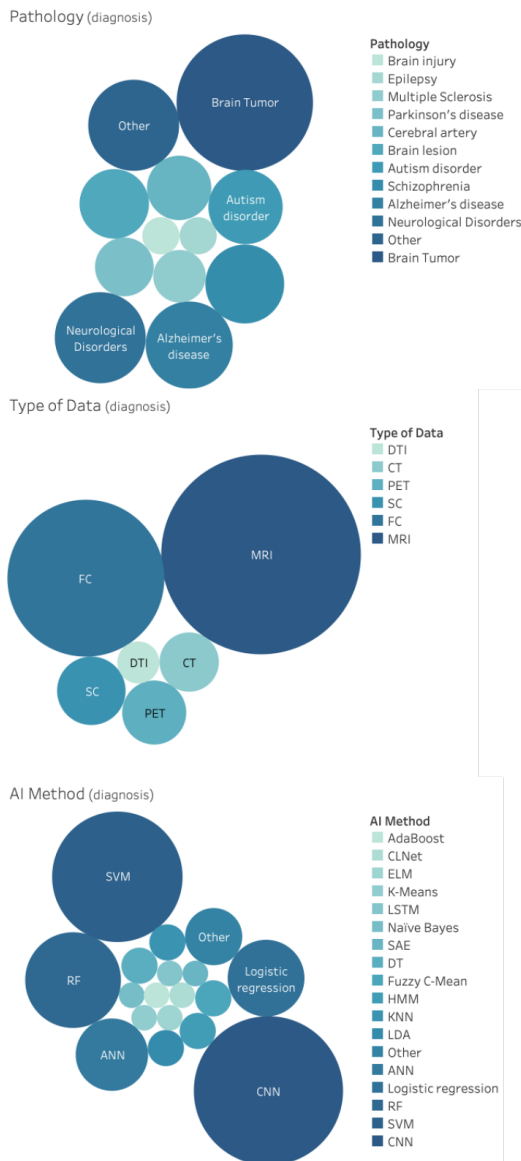


Figure 5. Distribution of general applications for diagnosis, in the brain care literature, related to classification using anatomical information, morphological information and connectivity information. From top: Pathology, AI method and type of data

ent diseases in the same category, while the deep layers could convey more high-level semantic information used to classify the diseases among the various categories. In<sup>47</sup>, the authors aim to maximally utilize multimodality neuroimaging and genetic data for identifying AD and its prodromal status, MCI from normal aging subjects. The proposed approach consists in stage-wise learning latent representations of each modality first independently and then jointly in order to finally learn diagnostic labels.

A widely used technique for enhancing results on limited dataset is transfer learning (also known as fine-tuning or pre-training) which consists in training the model on large banks of natural images, before actually training it over the small

(medical) dataset. This technique allows the model to learn general features like shapes, colors and patterns, which can be used to process the small dataset more effectively.

Several works applied this technique to enhance their results<sup>48–51</sup>. They show how fine tuned models achieved state-of-the-art results, and how the effect of reduction in training data did not impact the performance of the fine tuned CNN models.

Another possible way to overcome limited data availability, is to artificially create new data. As an example, new instance images can be obtained by applying linear transformations (i.e., rotation, reflection, scaling, etc.) to already available ones. One of the most interesting alternatives, when dealing with image data, consists of learning the latent manifold on which the input images lie, and then sample realistic pictures (and their labels) from this manifold. Researchers are investigating this approach in the biomedical domain, achieving promising results. For example, the recently proposed Wasserstein-Generative Adversarial Network (GAN) model was applied by Wegmayr *et al.*<sup>52</sup> to generate a synthetically aged brain image given a baseline image. The aged image is passed to an MCI or AD discriminator deciding the future disease status, achieving 73% accuracy on MCI-to-AD conversion prediction at a 48 months follow-up using only one coronal slice of a patient's baseline T1 image.

Another current DL limitation is related to the understanding of the model when performing the decision-making process. In this direction, Lee *et al.*<sup>53</sup> proposed a DL system to detect acute intracranial hemorrhages and classify Intracerebral Hemorrhage (ICH) sub types. The system was equipped with an *attention map* and a prediction basis retrieved from training data in order to enhance explainability. In Bohle *et al.*, Layerwise Relevance Propagation (LRP) was used to produce *heatmaps* to visualize the importance of each voxel. They showed how this method was very specific for individuals with high inter-patient variability. A similar approach was introduced in<sup>54</sup>, where LRP helped in explaining MS diagnosis by showing relevant brain areas beyond visible lesions. Wang *et al.*<sup>55</sup>, trained a CNN to distinguish six hepatic tumor entities. Interestingly, the presence of previously manually defined features was assessed by analyzing the CNN activation patterns. Lee *et al.*<sup>56</sup>, proposed a novel framework to better understand which parts of the brain were pathological and how different brain regions are related to symptomatic observations. To this aim *Regional Abnormality Representations* were extracted using complex linear relationships among voxels.

Also “hybrid” approaches are widely adopted. In a typical CNN architecture, the feature extraction part includes several convolution layers followed by max-pooling and an activation function. Output of these layers provide latent representation of the original input space, which could constitute an useful information. In hybrid approaches, features are extracted from the CNN layers and then used to feed a shallow classifier which performs the classification task. To this aim, a widely adopted pipeline, consists in encoding input features by means of Autoencoder architectures. In such models, a network is trained to reconstruct its input. This technique is



typically used for dimensionality reduction, since, in its simplest version, the input is projected in a smaller latent space before being reconstructed. In this scenario, the latent encoding is used as input for the shallow classifier, as it contains “compressed” informative content. Martinez-Murcia *et al.*<sup>57</sup>, for example, extracted high-level abstract features directly from MRI images and performed an exploratory data analysis of AD based on deep convolutional autoencoders. They observed how the imaging-derived markers could predict clinical variables with correlations above 0.6, achieving a classification accuracy over 80% for the diagnosis of AD. As reported in Table II AI methods were used preoperatively for radiologic segmentation, as previously reported by other reviews<sup>1,29</sup>. Segmentation of anatomical structure is important for the diagnosis and treatment of many neurological disorders. Yepes *et al.*<sup>58</sup> presented a segmentation strategy for cerebral ventricular volume, based on an algorithm that uses four features extracted from the medical images to create a statistical estimator capable of determining ventricular volume. When compared with manual segmentation, the correlation was 94% and holds promise for even better accuracy by incorporating the unlimited data available. Cherukuri *et al.*<sup>59</sup> used a learning approach that treats segmentation as supervised classification at the pixel level. The proposed algorithm is computationally less burdensome and exhibits a graceful degradation against a number of training samples.

Tumor segmentation is used for neurosurgical planning to extract the 3-dimensional shape from an MRI scan and its relationship with the surrounding anatomy. Thillaikarasi *et al.*<sup>60</sup> presented a novel DL algorithm (kernel based CNN) with M-SVM to segment the tumor automatically and efficiently. Experimental results of proposed method can show that this presented technique can executes brain tumor segmentation accurately reaching almost 84% in evaluation with existing algorithms. Sharma *et al.*<sup>61</sup> proposed a method of segmentation based on a statistical model called Hidden Markov Model (HMM). The results obtained from parametric analysis show that this algorithm has performed better than the technique of Support Vector Regression (SVR) for brain cancer segmentation, in terms of PSNR, MSE, Fault Rate Dust Detection (FRDD) and accuracy. Pushpa *et al.*<sup>62</sup> presented a SVM algorithm to segment the tumor. The proposed method obtained a better accuracy in classifying the malignant tumor (accuracy of 99%) comparing to the other existing systems. Laukamp *et al.*<sup>63</sup> used a multiparametric DL model on routine MRI data in automated detection and segmentation of meningiomas in comparison to manual segmentation. The DL model yielded accurate automated detection and segmentation of meningioma tissue. Chen *et al.*<sup>64</sup> adopted a Random Forest-based feature selection methods to select the most significant features. They developed a reliable MRI-based radiomics approach to perform pathological and molecular diagnosis. Soltaninejad *et al.*<sup>65</sup> suggested a novel 3D supervoxel based learning method for segmentation of the tumor. The method provides a close match to expert delineation across all tumour grades, leading to a faster and more reproducible method of brain tumour detection and delineation to aid patient management images. Sengupta *et al.*<sup>66</sup> presented a semi-

automatic method for segmentation between non-enhancing tumor and vasogenic edema, based on an SVM classifier trained on an alternative ground truth to a radiologist’s manual delineation of a tumor. The proposed methodology may prove to be a useful tool for pre- and post-operative evaluation of glioma patients. Rundo *et al.*<sup>67</sup> implemented a novel fully automatic method for necrosis extraction, using the Fuzzy C-Means algorithm, after the gross tumor volume segmentation. This unsupervised ML technique detects and delineates the necrotic regions also in heterogeneous cancers. Perkuhn *et al.*<sup>68</sup> evaluate a DL-based, automatic glioblastoma tumor segmentation. The proposed approach for automatic segmentation of this kind of tumor proved to be robust on routine clinical data and showed on all tumor compartments an high automatic detection rate and a high accuracy, comparable to interrelated variability. Liu *et al.*<sup>69</sup> combined CNN features and SVM classifier for the segmentation task. Experiments demonstrate that the cascaded CNN method achieves good tumor segmentation result with a high DSI of 77.03%. Fabelo *et al.*<sup>70</sup> obtained the segmentation map via unsupervised clustering employing a Hierarchical K-Means algorithm. It demonstrated that the use of this method can improve the outcomes of the undergoing patient, assisting neurosurgeons in the resection of the brain tumor. Binaghi *et al.*<sup>71</sup> suggested a fully automatic procedure based on the allied use of Graph Cut and SVM. Experimental results, obtained by processing in-house collected data, prove that the method is robust and oriented to the use in clinical practice.

Regarding brain lesion segmentation is used for the diagnosis and follow-up treatment. Sundaresan *et al.*<sup>72</sup> used LOcally Adaptive Threshold Estimation (LOCATE), a supervised method for determining optimal local thresholds to apply to the estimated lesion probability map, as an alternative option to global thresholding. It allowed to detect more deep lesions and provided better segmentation of periventricular lesion boundaries. Praveen *et al.*<sup>73</sup> designed a deep architecture is using SAE layers. The experimental results showed that the proposed approach significantly outperforms the state-of-the-art methods in terms of precision, DC, and recall.

Segmentation is also used for diagnosis and follow-up treatment of brain injury. Remedios *et al.*<sup>74</sup> used three neural networks to convergence on a CT brain hematoma segmentation task. Resultant lesion masks with the multi-site model attain an average DSI of 0.64 and the automatically segmented hematoma volumes correlate to those done manually with a Pearson Correlated Coefficient (PCC) of 0.87, corresponding to an 8% and 5% improvement, respectively, over the single-site model counterparts.

Segmentation is also used to evaluate deep surgical planning targets for DBS. Park *et al.*<sup>75</sup> developed DL semantic segmentation-based DBS targeting. A Fully Convolutional Neural Network (FCNN) (VGG-16) was used to ensure margin identification by semantic segmentation. Proving that the accuracy of DL-based semantic segmentation may surpass that of previous methods.

Segmentation is used to evaluate deep surgical planning targets for epilepsy treatment. Hadar *et al.*<sup>76</sup> implemented automated segmentation through the Corrective Learning Network

(CLNet) method. It demonstrate the clinical utility of automated segmentation in the Temporal Lobe Epilepsy (TLE) MR imaging pipeline prior to surgical resection, and suggest that further investigation into CLNet-assisted MRI reading could improve clinical outcomes.

Segmentation is used to assess cerebrovascular reconstruction. Li *et al.*<sup>77</sup> implemented a novel intensity and shape-based Markov statistical modeling for complete cerebrovascular segmentation. To regularize the individual data processes, Markov regularization parameter is automatically estimated by using a ML algorithm. This methods obtained satisfying results in visual and quantitative evaluation. The proposed method is capable of accurate cerebrovascular segmentation. Lee *et al.*<sup>78</sup> suggested a fully automated segmentation via unsupervised classification with fuzzy c-means clustering to analyze the Arteriovenous Malformation (AVM) nidus on T2-weighted. The automated segmentation algorithm was able to achieve classification of the AVM nidus components with relative accuracy.

Human connectome research has attained growing interest in neuroscience<sup>18,79</sup>. Computational methods, particularly graph theory-based methods, have recently played an important role in understanding the architecture of brain connectivity because of their notable ability to describe complex brain systems<sup>22</sup>. Although graph theoretical approach can generally be applied to either functional or structural connectivity patterns, to date, most articles have concentrated on resting-state functional connectivity. In this context, there has been an increasing trend to identify biological markers for the characterization of various brain disorders, including either cognitive impairments and pathological alterations<sup>30</sup>. Connectivity features alone offer promising diagnostic biomarkers, even if several studies apply feature selection and ranking techniques in order to reduce their complexity. Graph-theory derived metrics and high-level network organization have also been considered as valuable biomarkers and widely used in several studies<sup>79</sup>.

Concerning the classification of brain disorders, during the last decade, several conventional studies focus on binary classification tasks. They primarily seek to discriminate between patients and Healthy Control (HC), as well as separating patients into different sub-groups according to the different stages of brain disorder progression. However, recent studies have also drawn their attention to multi-class classification problems.

Table III present a summary of recent studies concerning brain network based classification tasks. Among various brain disease and disorders Alzheimer, Autism, Schizophrenia are the most studied in recent years. However, several studies are also focused on Parkinson's disease, Multiple Sclerosis, Tourette Syndrome, among others.

Among ML approaches based on *classical* ML algorithms, a wide range of classifiers has been applied in the classification of brain disorders. SVM is so far the most popular method, as also observed in earlier reviews<sup>18,30</sup>.

Many studies are related to schizophrenia, bipolar disorder, autism spectrum disorder, attention, AD and MCI. Kazeminejad *et al.*<sup>80</sup>, for example, used graph theoretical metrics of

fMRI-based functional connectivity of patients with Autism and HC, to inform a SVM. They achieved state-of-the-art results (accuracy 96%), also observing that measures of centrality provide the highest contribution. Lei *et al.*<sup>81</sup>, analysed topological properties of patients with Schizophrenia, comparing them with HC. Connectome-wide connectivity allowed single subject classification of patients and HC (average accuracy 81%) better than both whole-brain images and graph-based metrics. However, SVM is also widely used also in other brain connectivity analysis applications. Saccà *et al.*<sup>32</sup> used functional connectivity to train SVM, along with various ML algorithms, to distinguish MS patients and HC. Feature selection was performed to identify the most important variables. SVM and RF achieved the best results (85.7 %). In<sup>82</sup>, SVM was used to classify patients with Tourette syndrome. They observed successful performance in children and adults separately, which however, did not generalize across age groups, suggesting that connectivity characteristics are age specific. Weis *et al.*<sup>83</sup>, employed SVM to assess how accurately participant's sex can be classified based on spatially specific resting state brain connectivity.

Ensembles methods, such as RF or boosted trees, are also a more popular choice in most applications since they yield much better prediction performance. In<sup>31</sup>, authors used tract-based connectivity metrics from structural connectome to classify children with Autistic Spectrum Disorder (ASD). High level of accuracy was achieved (75%), also observing reduced density of connection edges in the posterior white matter tracts of children with ASD. In<sup>84</sup>, functional connectivity, along with regional activities over a wide range of different parcellation schemes, was used as input for an ensemble ML algorithm. They outperformed earlier ML models built for diagnosing Schizophrenia using rs-fMRI.

DL methods have attracted increasing interest in various areas and also have been applied in the classification of brain disorders. Ju *et al.*<sup>85</sup> used DL with functional brain network and clinical relevant text information to make early diagnosis of AD. Specifically, a targeted autoencoder is built to distinguish HC from MCI. The study revealed discriminative brain network features and provided a reliable classifier for AD detection (Accuracy 86%, AUC 0.91). In<sup>86</sup>, a six layer CNN was trained using structural connectivity to classify among patients with AD, Dementia and HC. A 3D-CNN architecture was used in<sup>87</sup> for the automated discrimination of Schizophrenia based on 3D-ICA based functional connectivity networks, achieving promising results (Accuracy 98%, AUC 0.99). A similar approach was proposed in<sup>88</sup> for AD detection.

A 3D-CNN approach was also used in Khosla *et al.*<sup>89</sup> for Autism classification. An ensemble learning strategy to combine the predictions from models trained on connectivity data extracted using different parcellation schemas was proposed. They observed how ensemble learning with stochastic parcellations outperform atlas-based models (Accuracy: 72%, AUC: 0.77).

## B. Surgical Treatment

18 studies considered AI in surgical treatment. This includes surgical candidate selection, trajectory planning and target definition with intra-operative segmentation of anatomical structures and localization of stimulation zones for Parkinson's disease, epilepsy, and general neurosurgery. CT, MRI, EHR, IUS and HSI data were used as input features for the development of prediction algorithm. Results of the distributions for pathology, AI methods and type of data for surgical treatment are reported in Figure 6.

As reported in Table. IV, AI were also useful to identify patients who are potentially eligible for surgery as reported in Senders *et al.*<sup>1</sup> review. Wissel *et al.*<sup>90</sup> validated a NLP application that uses provider notes to assign epilepsy surgery candidacy scores.

As reported in Table. V AI methods were used for target definition using intra-operative segmentation and localization of stimulation zones within the brain.

*a. Intra-operative Segmentation* . In Intra-operative segmentation for general neurosurgery, Nitsch *et al.*<sup>91</sup> presented a robust and fully automatic neural-network-based segmentation of central structures of the brain on B-mode IUS.

In Intra-operative segmentation for DBS, Valsky *et al.*<sup>92,93</sup> showed the feasibility of real-time ML classification of striato-pallidal borders and Subthalamic Nucleus (STN) to assist neurosurgeons during DBS surgery. ML algorithms enable real-time Globus Pallidus (GP) and STN navigation systems to potentially shorten the duration of electrophysiological mapping of borders, while ensuring correct border detection.

*b. Localization of stimulation zones within the brain* . AI methods were also used for brain lesion and Parkinson patients to localize the stimulation zone and estimate the volume of activated tissue as previously reported by other reviews<sup>1, 94</sup>.

Regarding Brain lesion stimulation zones, Jeong *et al.*<sup>95</sup> presented a supervised ML method to obtain associations between EEG and fNIRS modalities to improve precision and localization in assessing neurovascular signals in the prefrontal cortex in opiate addiction patients.

Regarding Parkinson's disease stimulation zone, Wang *et al.*<sup>96</sup> described a functional localization method in the brain. Cubic SVM was used to train spike pattern recognition model for functional localization with accuracy of 10% in normal monkey, and the evaluation of trained model demonstrated reasonably excellent recognition accuracy of 99.5%. Weighted KNN showed a better performance of accuracy (94.5%) of spike pattern recognition for functional localization than cubic SVM. These two works<sup>97,98</sup> demonstrated that The 7T-ML method is highly consistent with microelectrode-recordings data. This method provides a reliable and accurate patient-specific prediction for targeting the STN. Khosravi *et al.*<sup>99</sup> suggested an unsupervised ML technique to localize the STN during DBS Surgery. Bermudez *et al.*<sup>100</sup> used a patch-based convolutional neural network to classify a stimulation coordinate as having a positive reduction in symptoms during surgery.

Regarding epilepsy stimulation zones, Cimbalnik *et al.*<sup>101</sup>

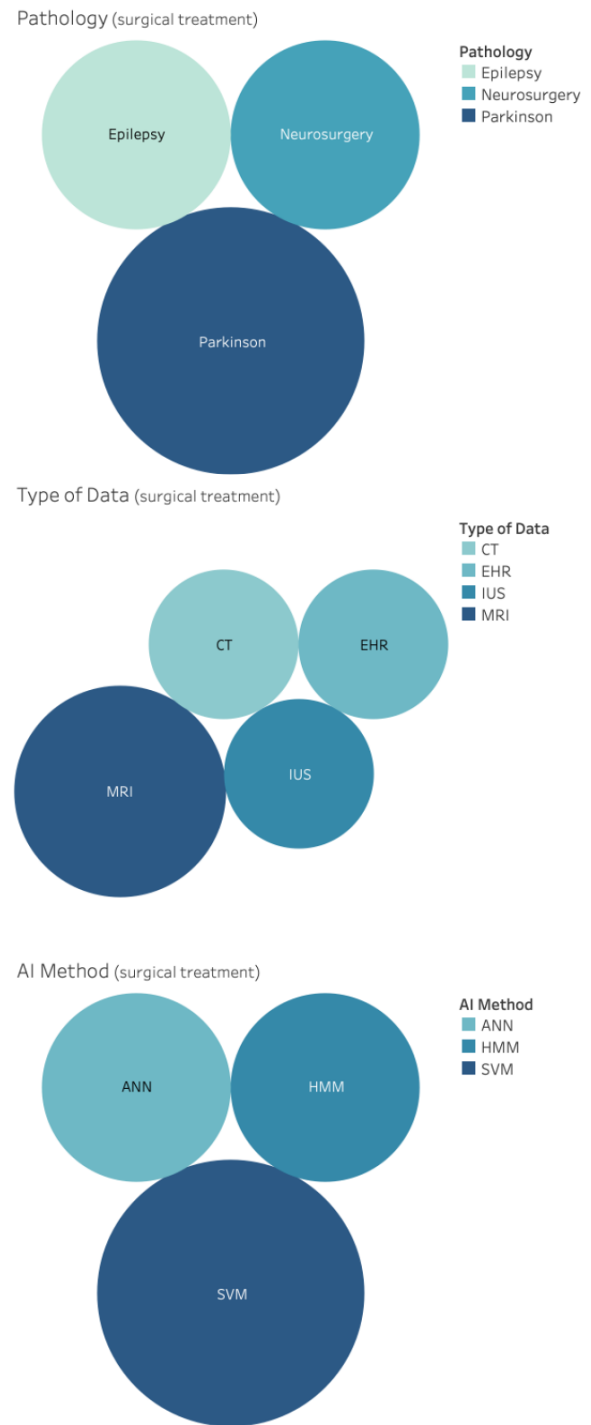


Figure 6. . Distribution of general applications for surgical treatment, in the brain care literature, related to target definition and trajectory definition. From top: Pathology, AI method and type of data

applied a support vector machine (SVM) model for accurate localization of the epileptogenic tissue. The tissue under the iEEG electrodes, classified as epileptogenic, was removed in 17/18 excellent outcome patients and was not entirely resected in 8/10 poor outcome patients. The overall best result was achieved in a subset of 9 excellent outcome patients with the

area under the ROC=0.95. Bharath *et al.*<sup>102</sup> proposed a SVM to identify and validate the possible existence of resting-state. This approach could classify individuals with epilepsy with 97.5% accuracy, 100% sensitivity and 94.4% specificity.

As reported in Table. VI, AI methods were used for preoperative trajectory definition as reported in Senders *et al.*<sup>29</sup> review. AI in general neurosurgery can be used to assist the surgeon preoperatively for the definition of an optimal trajectory. Briefly, usually the algorithm aims to minimize the intracerebral catheter length, drilling angle from orthogonal to skull, while maximizing distance from critical structures. Villanueva *et al.*<sup>103</sup> proposed the use of a GA that drastically reduces the computational cost.

Liu *et al.*<sup>104</sup> used a Vector-model-supported optimization for brain tumor surgery. With this approach there was a significant reduction in the median planning time, a 40% reduction from 3.7 to 2.2 hours.

Segato *et al.*<sup>105</sup> presented a GA that drastically reduces the number of trajectories to analyze, speeding up the preoperative planning procedure for DBS in parkinson patients.

In three works<sup>93,106,107</sup> two ML approaches, RF and linear regression, were investigated to predict composite ablation scores and determine entry and target point combinations that maximize ablation for Laser Interstitial Thermal Therapy (LITT). RF and linear regression predictions had a high correlation with the calculated values in the test set for both methods.

### C. Intra-operative assistance

As reported in Table. VII, 2 studies considered AI in intra-operative assistance. This includes modelling of tissue deformation for brain tumor. MRI data were used as input features for the development of prediction algorithm. Results of the distributions for pathology, AI methods and type of data for diagnosis are reported in Figure 7

In modelling the tissue deformation for brain tumor surgery, Sharma *et al.*<sup>61</sup> developed a ML approach to detect and model tissue deformation with classification of soft and hard tissues so that the tissues having risk of future problem can also be recognized. Tonutti *et al.*<sup>108</sup> presented a real-time soft tissue deformation computation method. A brain tumour was used as the subject of the deformation model. Once trained, the models can predict the deformation of the tumour in real-time with relative positional errors below 0.3mm.

### D. Post-operative assessment

As reported in Table. VIII, 9 studies considered AI in post-operative assessment. This includes prediction of post-operative patient outcome for brain lesion, brain injury, brain tumor, neurological disorder and general neurosurgery. CT, MRI, EHR data were used as input features for the development of prediction algorithm. Results of the distributions for pathology, AI methods and type of data for surgical treatment are reported in Figure 8 DL techniques can be used for test-

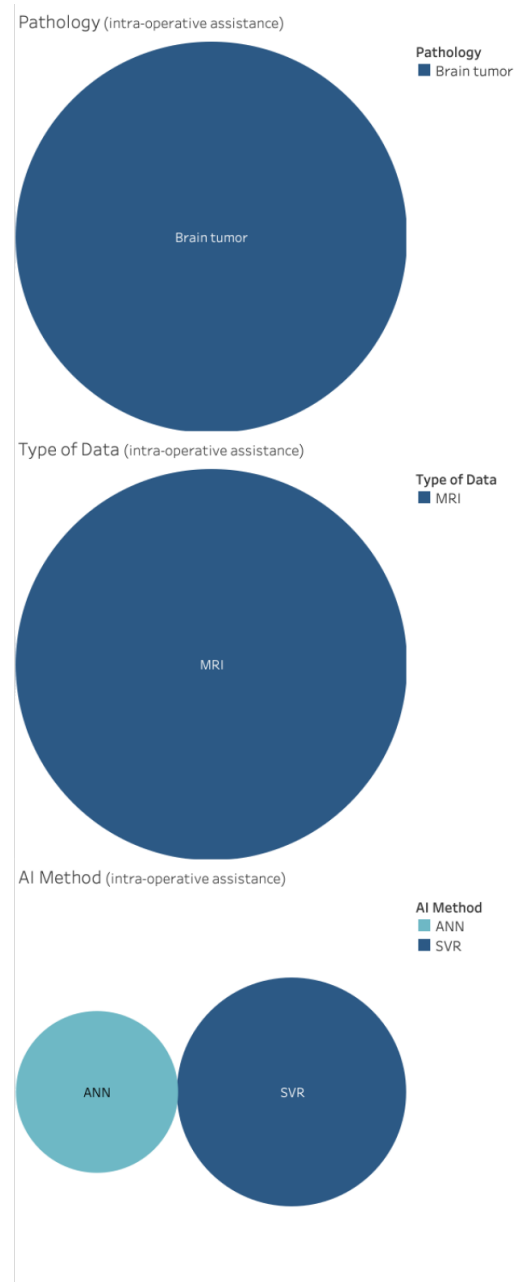


Figure 7. Distribution of general applications for intra-operative assistance, in the brain care literature, related to intra-operative modelling of tissue deformation. From top: Pathology, AI method and type of data

ing the informativeness of neurosurgical operative reports for predicting the duration of postoperative stay in a hospital<sup>29</sup>. Shabo *et al.*<sup>109</sup> applied a RNN to the word-embedded texts in EHR. Results prove the potential utility of narrative medical texts as a substrate for decision support technologies in neurosurgery. In two works<sup>110,111</sup> six and seven ML algorithms, respectively, were applied to construct Transsphenoidal Surgery (TSS) response prediction models. The ML models showed good discrimination ability and calibration, with the highest levels of accuracy and specificity. The presented models was

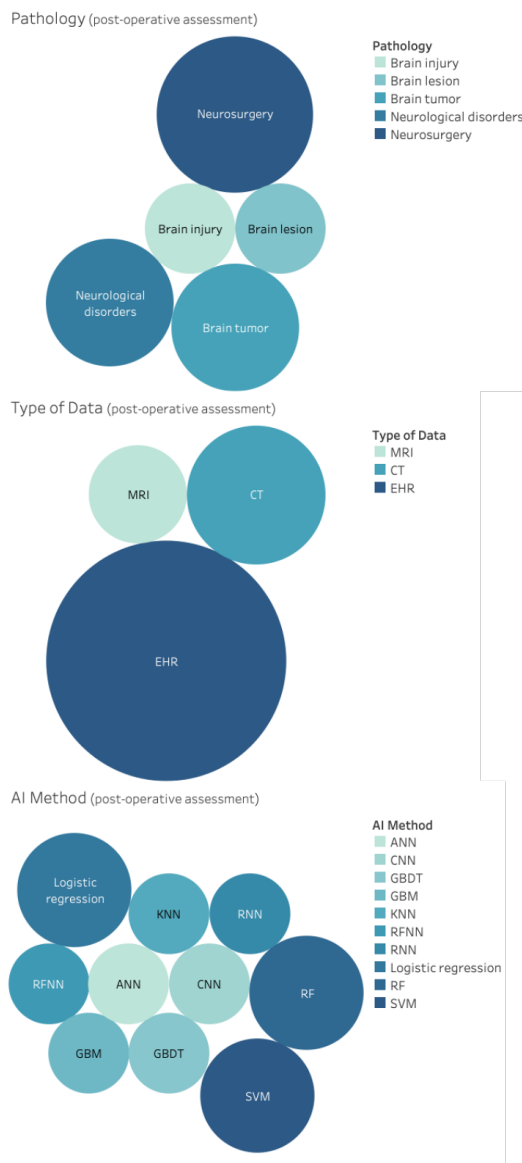


Figure 8. Distribution of general applications for post-operative assessment, in the brain care literature, related to prediction of post-operative patient outcome. From top: Pathology, AI method and type of data

significantly better than that of some conventional models.

AI can be applied to investigate risk factors and predicting complications in treatments used for the treatment of neurological disorders such as DBS and Dilated Cardiomyopathy (DCM). A work of Farrokhi *et al.*<sup>112</sup> reports results obtained via supervised learning algorithms achieving high discrimination performance when predicting any complication. Merali *et al.*<sup>113</sup> applied a supervised ML approach to develop a classification model to predict individual patient outcome after surgery for DCM. The best performing predictive model used a RF structure and had an average AUC of 0.70, classification accuracy of 77%, and sensitivity of 78% when evaluated on a testing cohort that was not used for model training.

AI methods can be used for predicting inpatient Length of Stay (LOS) after brain tumor surgery overall survival time. Muhlestein *et al.*<sup>114</sup> implemented an ML ensemble model to predict LOS with good performance on internal and external validation, and yields clinical insights that may potentially improve patient outcomes. Nie *et al.*<sup>115</sup> presented a multi-channel architecture of 3D CNN for DL and a SVM to generate the prediction of overall survival time. The experimental results demonstrate that this multi-model, multi-channel deep survival prediction framework achieves an accuracy of 90.66%, outperforming all the competing methods.

AI can be applied to investigate risk factors and predicting complications in treatments used for the treatment of brain lesion such as ischemic stroke. Hilbert *et al.*<sup>116</sup> proposed a DL approach for predicting outcomes of acute ischemic stroke patients using CT angiography images. The model outperformed the models using traditional radiological image biomarkers in three out of four cross-validation folds for functional outcome (average AUC of 0.71).

AI can also be applied to investigate mortality prediction after traumatic brain injury. Raj *et al.*<sup>117</sup> used ML-based logistic regression modeling to create two algorithms able to discriminate between survivors and non-survivors with accuracies up to 81% and 84%.

Table I: Anatomical information: Details on Clinical Aim, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
<b>Anatomical Information</b>							
Pang,2019 <sup>46</sup>	Classification of various brain disorders	Neurological disorders	CT MRI	-	CNN SVM RF	Acc	-
Talo,2019 <sup>118</sup>	Classification of various brain disorders	Neurological disorders	MRI-T2WI	-	CNN	Acc	-
Spiteri,2019 <sup>41</sup>	Cerebellar mutism syndrome identification	Neurological disorders	MRI	40	SVM	AUC ROC	-

Squarcina,2019 <sup>119</sup>	Bipolar disorders classification	Neurological disorders	MRI-T1WI	75	Graph Based semisupervision	Acc Sp Se AUC	-
Ramasubbu,2019 <sup>120</sup>	Depression disorder classification	Neurological disorders	MRI-T1WI clinical	44	SVM	Acc Sp Se	-
Zhou,2019 <sup>47</sup>	AD vs MCI classification	Alzheimer's disease	MRI PET Gene sequence	805	DNN	Acc	-
Basaia,2019 <sup>121</sup>	AD vs MCI classification	Alzheimer's disease	MRI-T1WI	1409	CNN	Acc	-
Spasov,2019 <sup>122</sup>	AD vs MCI classification	Alzheimer's disease	MRI-T1WI	785	CNN	Acc AUC	-
Wang,2019 <sup>45</sup>	AD vs MCI classification	Alzheimer's disease	MRI-T1WI	624	CNN	Acc Pr Rec DSI	-
Mehdipour,2019 <sup>123</sup>	AD progression modeling	Alzheimer's disease	MRI-T1WI	742	LSTM	AUC ROC	-
Bohle,2019 <sup>124</sup>	AD classification	Alzheimer's disease	MRI-T1WI	344	CNN	Acc	-
Martinez-Murcia,2020 <sup>57</sup>	AD diagnosis	Alzheimer's disease	MRI-MRI-T1WIWI	479	CNN SVM	Se Sp Acc DSI	-
Raza,2019 <sup>125</sup>	AD diagnosis	Alzheimer's disease	MRI	432	CNN SVM	Acc Rec Pr Se Sp	-
Wang,2019 <sup>126</sup>	MCI vs AD classification	Alzheimer's disease	MRI-T1WI	624	CNN	Acc Pr Rec DSI	-
Yamashita,2019 <sup>39</sup>	AD diagnosis	Alzheimer's disease	PET MRI	507	SVM	Acc Pr Rec Sp ROC	-
Benyoussef,2019 <sup>127</sup>	AD diagnosis	Alzheimer's disease	MRI	416	CNN KNN	-	-
Forouzaneshad,2019 <sup>128</sup>	MCI diagnosis	Alzheimer's disease	MRI PET clinical	-	CNN	Acc Sp Se	-
Jabason,2019 <sup>129</sup>	AD diagnosis	Alzheimer's disease	MRI-T1WI	-	CNN	Acc Se Sp	-
Khan,2019 <sup>49</sup>	AD diagnosis	Alzheimer's disease	MRI	-	CNN	Acc Pr Rec DSI	-
Punjabi,2019 <sup>130</sup>	AD classification	Alzheimer's disease	MRI-T1WI PET	723	CNN	Acc	-
Kim,2019 <sup>131</sup>	AD vs Dementia classification	Alzheimer's disease	MRI-T1WI	339	LDA	Acc Sp Se AUC	-
Sato,2019 <sup>132</sup>	AD classification	Alzheimer's disease	PET	379	CNN	AUC ROC	-
Eitel,2019 <sup>54</sup>	MS diagnosis	MS	MRI-T2WI	147	CNN	Acc AUC	-



Mato-Abad,2019 <sup>133</sup>	MS classification	MS	DWI	34	Naive Bayes DNN	AUC ROC	-
Ebdrup,2019 <sup>44</sup>	Diagnosis of Schizophrenia	Schizophrenia	MRI EHR	104	SVM RF DT	Acc	-
Talpalaru,2019 <sup>134</sup>	Schizophrenia identification	Schizophrenia	MRI-T1WI	167	Logistic Regression RF SVM	ROC AUC	-
Kniep,2019 <sup>42</sup>	Metastatic Tumor Type classification	Brain tumor	MRI-T1WI MRI-FLAIR	189	RF	Acc AUC	-
Kunimatsu,2019 <sup>37</sup>	Tumor type classification	Brain tumor	MRI-T1WI	76	SVM	Se Sp AUC	-
Wu,2019 <sup>43</sup>	Tumor type classification	Brain tumor	MRI	126	RF	Acc AUC	-
Kebir,2019 <sup>135</sup>	Tumor type classification	Brain tumor	MRI PET	39	SVM	ROC AUC	-
Swati,2019 <sup>48</sup>	Tumor type classification	Brain tumor	MRI	233	CNN	Acc Pr Rec Sp DSI	-
Jeong,2019 <sup>136</sup>	Tumor type classification	Brain tumor	MRI-T2WI MRI-FLAIR	25	RF	Acc AUC	-
Pan,2019 <sup>137</sup>	Tumor mutation prediction	Brain tumor	MRI-T1WI MRI-T2WI	151	RF	Acc AUC	-
Sultan,2019 <sup>138</sup>	Tumor type classification	Brain tumor	MRI-T1WI	233 + 73	CNN	Acc Pr Se Sp	-
Ozyurt,2020 <sup>139</sup>	Brain tumor detection	Brain tumor	MRI-T1WI	500	CNN	Acc AUC ROC	-
Ahammed,2019 <sup>140</sup>	Tumor grade identification	Brain tumor	MRI-T2WI	20	CNN	Acc Pr Rec DSI Se Sp	-
Wang,2019 <sup>55</sup>	Diagnosis of liver tumor	Brain tumor	MRI	334	CNN	PPV Se Pr Rec	-
Shrot,2019 <sup>40</sup>	Tumor type classification	Brain tumor	MRI DTI	141	SVM	Acc Sp Se	-
Rehman,2019 <sup>50</sup>	Tumor type classification	Brain tumor	MRI	233	CNN SVM	Acc Pr Se Sp	-
Tian,2019 <sup>141</sup>	Glioblastoma vs Anaplastic Astrocytoma classification	Brain tumor	MRI-T1WI	123	LDA	Se Sp AUC	-
Ortiz-Ramon,2019 <sup>142</sup>	Ischaemic Stroke lesions identification	Brain lesions	MRI-T1WI MRI-T2WI MRI-FLAIR	100	RF SVM	AUC	-
Lau,2019 <sup>143</sup>	WM hypertension detection	Brain lesions	MRI-T1WI MRI-T2WI MRI-FLAIR	180	DNN	Se Sp AUC	-

Kim,2019 <sup>144</sup>	Ischaemic Stroke lesions identification	Brain lesions	EHR	-	DT	Acc Pr Rec DSI	-
Shen,2019 <sup>145</sup>	Parkinson's disease diagnosis	Parkinson's disease	PET	350	Deep Belief Network	Acc Se Sp	-
Lee,2019 <sup>53</sup>	haemorrhage detection	Cerebral artery	CT	196	CNN	Se Sp AUC	-
Ker,2019 <sup>146</sup>	brain haemorrhage detection	Cerebral artery	CT	399	CNN	DSI	-
Dawud,2019 <sup>147</sup>	haemorrhage classification	Cerebral artery	CT	-	CNN SVM	Acc	-
Liu,2019 <sup>148</sup>	Cerebral microbleed detection	Cerebral artery	MRI	255	CNN	AUC ROC	-
Gunter,2019 <sup>38</sup>	DESH detection	Other	MRI-T1WI	1576	SVM	AUC ROC	-
Xin,2019 <sup>149</sup>	Gender identification	Other	diffusion MR	1065	CNN	Acc	-

Table II: Morphological information: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
<b>Morphological Information</b>							
Yepes,2018 <sup>58</sup>	Determine the quantity of CSF	Neurological disorders	MRI-T1WI	44	SVM	Acc	94%
Cherukuri,2018 <sup>59</sup>	Determine the quantity of CSF	Neurological disorders	CT	15	CNN	Time	0.003sec
Thillaikkarasi,2019 <sup>60</sup>	Early detection of brain tumor	Brain tumor	MRI	40	CNN SVM	Acc Error Time	98% 15% 15ms
Sharma,2019 <sup>61</sup>	Simulating tissue deformation and locating cancerous nodes	Brain tumor	MRI-T1WI	6	HMM	Acc PSNR MSE FRDD	88% 21 985mm 72%
Pushpa,2019 <sup>62</sup>	Detect and classify the tumor type	Brain tumor	MRI	60	SVM	Acc	99%
Rundo,2018 <sup>67</sup>	Necrosis extraction of brain tumor	Brain tumor	MRI	32	Fuzzy C-Means	DSI MAD	95.93% 0.22px
Laukamp,2019 <sup>63</sup>	Volumetric assessment of meningiomas	Brain tumor	MRI-T1WI MRI-T2WI	56	CNN FCNN	DSI	81%
Chen,2019 <sup>64</sup>	Detect mutations in craniopharyngioma patients	Brain tumor	MRI-T1WI	44	RF	AUC Acc Sp Se	89% 86% 85%
Soltanine,2018 <sup>65</sup>	Segmentation of brain tumor	Brain tumor	MRI MRI-DTI	30	RF	DSI Se Error	89% 96% 2%
Sengupta,2018 <sup>66</sup>	Segmentation of brain tumor	Brain tumor	MRI-T1WI MRI-T2WI	9	SVM	Error	8.2%

Perkuhn,2018 <sup>68</sup>	Segmentation of brain tumor	Brain tumor	MRI-T1WI MRI-T2WI MRI-FLAIR	64	CNN FCNN	DSI	86%
Liu,2018 <sup>69</sup>	Segmentation of brain tumor	Brain tumor	MRI	-	CNN SVM	DSI Acc	77.03% 94.85%
Fabelo,2018 <sup>70</sup>	Segmentation of brain tumor	Brain tumor	HSI	5	K-Means	Acc Se Se	99% 96% 96%
Binaghi,2019 <sup>71</sup>	Segmentation of meningiomas	Brain tumor	MRI-T1WI MRI-T2WI	15	SVM	JD DSI Error	81% 88.9% 21.74%
Sundaresan,2019 <sup>72</sup>	Lesion segmentation	Brain lesions	MRI-T1WI MRI-T2WI MRI-FLAIR	60	Supervised Learning LOCATE	DSI	70%
Praveen,2018 <sup>73</sup>	Segmentation of ischemic stroke lesion	Brain lesion	MRI	28	SAE SVM	DSI Sp Acc Se	94.3% 96.8% 90.4% 92.4%
Remedios,2019 <sup>74</sup>	Segmentation of brain injury	Brain injury	CT	-	3 ANN	DSI PCC	64% 87%
Park,2019 <sup>75</sup>	Segmentation for DBS	Parkinson's disease	MRI-T2WI	102	FCNN	DSI Acc JD	90.2% 90.4% 81.3%
Hadar,2018 <sup>76</sup>	Hippocampal segmentation in temporal lobe epilepsy	Epilepsy	MRI-T1WI	47	CLNet	DSI	85%
Li,2020 <sup>77</sup>	Cerebrovascular segmentation	Cerebral artery	MRI-T1WI	109	HMM	DSI	93%
Lee,2019 <sup>78</sup>	AVM identification and quantification	Cerebral artery	MRI-T2WI	39	Fuzzy C-Means	DSI Se Sp	79.5% 73.5% 85.5%

Table III: Connectivity information: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
Connectivity Information							
Nielsen,2020 <sup>82</sup>	Tourette syndome analysis	Neurological disease	FC	202	SVM	Acc	71%
Hirshfeld-Becker,2019 <sup>150</sup>	Depression diagnosis	Neurological disease	FC (longitudinal)	68	SVM	Acc Se Sp	92% 90% 93%
Liu,2019 <sup>151</sup>	Depression diagnosis	Neurological disease	FC	85	LR	Acc Se Sp AUC	77% 84% 72% 87%
Shao,2019 <sup>152</sup>	Bipolar disorders classification	Neurological disease	FC (longitudinal)	200	SVM	Acc Se Sp	78.13% 82% 75%
DSouza,2019 <sup>153</sup>	HiV-associated disorders analysis	Neurological disease	FC	29	AdaBoost	Acc AUC	79% 84%
Ju,2019 <sup>85</sup>	AD diagnosis	Alzheimer's disease	FC	170	DNN	Acc Se Sp AUC	86.47% 92% 81% 91%

Li,2019 <sup>154</sup>	AD diagnosis	Alzheimer's disease	FC	26 292	SVM	Acc Se Sp AUC	84.6% 92% 79% 0.80
Li,2019 <sup>155</sup>	MCI diagnosis	Alzheimer's disease	FC	73	DNN	Acc Se Sp	80.82% 81% 81%
Song,2019 <sup>156</sup>	AD diagnosis	Alzheimer's disease	FC	30	KNN	Acc Se Sp AUC	96% 94% 1% 98%
Wada,2019 <sup>86</sup>	AD vs Dementia classification	Alzheimer's disease	FC	48	CNN	Acc Pr Rec	73% 78% 73%
Qureshi,2019 <sup>88</sup>	AD progression analysis	Alzheimer's disease	FC	133	CNN	Acc Sp Se	92% 95% 70%
Nguyen,2019 <sup>34</sup>	Dementia diagnosis	Alzheimer's disease	FC	95	ELM	Acc Se Sp PPV NPV	89.92% 87% 84% 94% 87.40%
Peraza,2019 <sup>157</sup>	AD diagnosis	Alzheimer's disease	SC	78	SVM	Acc Se Sp AUC	89.07% 79% 99% 78%
Kam,2019 <sup>35</sup>	MCI diagnosis	Alzheimer's disease	FC	49	CNN	Acc Se Sp PPV NPV	73.85% 74% 74% 74.38% 73.79%
Wang,2019 <sup>158</sup>	AD diagnosis	Alzheimer's disease	SC (multimodal)	211	LR	Acc <sup>1</sup> Acc <sup>1</sup> Acc <sup>1</sup>	97% 83% 97%
Azarmi,2019 <sup>159</sup>	MS diagnosis	MS	FC	20	SVM	Acc Se Sp	95% 0.88% 100%
Sacca,2019 <sup>32</sup>	MS diagnosis	MS	FC	37	SVM RF	Acc Se Sp PPV NPV	85.7% 100% 67% 60% 100%
Lisowska,2019 <sup>160</sup>	Dementia diagnosis	Dementia	SC	84	SVM	Acc Se Sp AUC	76.88% 67% 78% 76%
Wang,2019 <sup>161</sup>	Autism diagnosis	Autism spectrum disorder	FC	1112	Sparse MVTC	Acc Se Sp AUC	73% 79% 64% 72%
Kazeminejad,2019 <sup>80</sup>	Autism classification	Autism spectrum disorder	FC	816	SVM	Acc Se Sp	95% 97% 95%
Payabvash,2019 <sup>31</sup>	Autism diagnosis	Autism spectrum disorder	SC	47	RF	Acc Sp PPV	75.3% 97% 81.5%
Yamagata,2019 <sup>162</sup>	Autism diagnosis	Autism spectrum disorder	FC	60	LR	Acc AUC	75% 78%

Khosla,2019 <sup>89</sup>	Autism diagnosis	Autism spectrum disorder	FC	387 389 213 163	CNN	Acc AUC	100% 77%
Song,2019 <sup>163</sup>	Autism diagnosis	Autism spectrum disorder	FC	39	LDA	Acc Pr Rec	82.08% 81% 81%
Dekhil,2019 <sup>164</sup>	Autism diagnosis	Autism spectrum disorder	FC	185	RF	Acc Se Sp AUC	81% 85% 79% 0.82
Wang,2019 <sup>165</sup>	Autism diagnosis	Autism spectrum disorder	FC	531	SVM	Acc Se Sp	90.60% 91% 91%
Kalmady,2019 <sup>84</sup>	Schizophrenia diagnosis	Schizophrenia	FC	174	Ensemble Learner	Acc Se Sp Pr	87% 80% 93% 92%
Lei,2019 <sup>81</sup>	Schizophrenia diagnosis	Schizophrenia	FC	747	SVM	Acc	81.74%
Li,2019 <sup>166</sup>	Schizophrenia diagnosis	Schizophrenia	FC	148	LDA	Acc	76.34%
Qureshi,2019 <sup>87</sup>	Schizophrenia diagnosis	Schizophrenia	FC	144	CNN	Acc AUC	98.09% 99%
Phang,2019 <sup>167</sup>	Schizophrenia diagnosis	Schizophrenia	FC (multimodal)	84	CNN	Acc Se Sp Pr	90.37% 91% 90% 92%
Deng,2019 <sup>168</sup>	Schizophrenia diagnosis	Schizophrenia	SC	125	RF	Acc Se Sp AUC	71% 67% 75% 79%
Zhao,2019 <sup>169</sup>	Schizophrenia diagnosis	Schizophrenia	FC SC	283	SVM	Acc Se Sp	91.75% 91% 93%
Rangaprakash,2019 <sup>170</sup>	Neurotrauma analysis	Brain injury	FC	87	SVM	Acc	81.4%
Rubbert,2019 <sup>171</sup>	Parkinson's disease diagnosis	Parkinson's disease	FC	89	LR	Acc Sp Se	76.2% 72% 81%
Baggio,2019 <sup>172</sup>	Parkinson's disease diagnosis	Parkinson's disease	FC	151	SVM	Acc Se Sp	77.17% 80% 77%
Pena-Nogales,2019 <sup>173</sup>	Parkinson's disease progression analysis	Parkinson's disease	SC	51	LR	Acc Se Sp AUC	84% 91% 77% 89%
Bharath,2019 <sup>174</sup>	Epilepsy diagnosis	Epilepsy	FC	132	SVM	Acc Se Sp	97.5% 100% 94%
Nielsen,2019 <sup>175</sup>	Brain maturity prediction	Other	FC	122	SVM Multivariate Analysis	IGV	57%
Zhigalov,2019 <sup>176</sup>	Attentional states classification	Other	FC	24	SVM	Acc <sup>1</sup> Acc <sup>2</sup> Acc <sup>3</sup>	62% 62% 55%
Brauchli,2019 <sup>177</sup>	Absolute pitch identification	Other	FC	100	SVM	Acc	71.75%
Fede,2019 <sup>178</sup>	Alcohol use severity classification	Other	SC FC	59 24	Linear Regression	IGV	-

Weis,2019 <sup>83</sup>	Gender classification	Other	FC	434 410 941	SVM	Acc	70.33%
Bidelman,2019 <sup>179</sup>	Age-related hearing loss prediction	Other	FC	32	SVM	Acc AUC DSC	85.7% 88% 86%
Wetherill,2019 <sup>180</sup>	Nicotine use disorder identification	Other	FC	216	SVM	Acc AUC	88.1% 93%
Chen,2019 <sup>33</sup>	Fatigue identification	Other	FC	16	SVM	Acc Pr Se FAR	94.4% 94% 95% 5.7%
Al-Zubaidi,2019 <sup>181</sup>	Metabolic state classification	Other	FC	24	SVM	Acc Se Sp	81% 89% 83%
Shen,2019 <sup>145</sup>	Chronic low back pain analysis	Other	FC	160 37	SVM	Acc <sup>1</sup> Se <sup>1</sup> Sp <sup>1</sup> Acc <sup>2</sup> Se <sup>2</sup> Sp <sup>2</sup>	79.3% 83% 74% 67% 72%
Chriskos,2020 <sup>182</sup>	Sleep state classification	Other	FC	23	CNN	Acc Rec	99.85% 100%
Feng,2019 <sup>183</sup>	Prediction of dispositional worry	Other	SC	59	LR	RMSE p	13.65% < 0.005

Table IV: Surgical candidate selection: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication.	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
Surgical Candidate Selection							
Wissel,2019 <sup>90</sup>	Candidate selection	Epilepsy	EHR	4211	NLP SVM	AUC Se Sp	80% 77%

Table V: Target definition: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
Intra-operative Segmentation							
Nitsch,2019 <sup>91</sup>	Segmentation of central ultrasound images	Neurosurgery	IUS MRI	18	ANN	DSI HDD	88% 5.21mm
Valsky,2019 <sup>92</sup>	Segmentation of striato borders	Parkinson's disease	MER	42	HMM	-	-
Valisky,2017 <sup>93</sup>	Discrimination between the STN and SN	Parkinson's disease	CT MRI	46	SVM	pFDR Time	<0.05% -98%
Localization of Epileptic Zones Within the Brain							
Ieong,2019 <sup>95</sup>	localization of lesion due to opiate	Brain lesion	EEG fNIRS	19	SVM GBM ANN	PCC	55%
Wang,2019 <sup>96</sup>	Functional localization	Parkinson's disease	MER	1	K-Means SVM KNN	Acc	96%



Shamir,2019 <sup>97</sup>	Visualize STN	Parkinson's disease	MRI	16	RF	Acc	93%
Kim,2019 <sup>98</sup>	Visualize STN	Parkinson's disease	MRI	80	RF	CMD MSD DSI Acc	1.25mm 0.57mm 64% 89%
Khosravi,2019 <sup>99</sup>	Visualize STN	Parkinson's disease	MER	50	K-Means	Acc	80%
Bermudez,2019 <sup>100</sup>	Localization of the optimal stimulation zone	Parkinson's disease	MRI	187	CNN	AUC	67%
Cimbalnik,2019 <sup>101</sup>	Localization of epileptic foci	Epilepsy	EEG	9	SVM	AUC	<95%
Bharath,2019 <sup>102</sup>	Localization epilepsy Network	Epilepsy	MRI-T1WI	42	SVM	Acc Sp Se	97.5% 94.4% 100%

Table VI: Trajectory definition: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
Trajectory Definition							
Villanueva,2018 <sup>103</sup>	Risk assessment for trajectory planning	Neurosurgery	CT MRI	1	GA	Risk Time	2347 -98%
Liu,2017 <sup>104</sup>	Planning stereotactic radiotherapy	Brain Tumor	CT MRI	46	SVM	pFDR Time	<0.05% -98%
Valisky,2017 <sup>93</sup>	Discrimination between the STN and SN	Parkinson's disease	CT MRI	46	SVM	pFDR Time	<0.05% -98%
Segato,2019 <sup>105</sup>	Curvilinear DBS	Parkinson's disease	MRI-T1WI DTI CT	10	GA	MSD mSD	+145% +25%
Li,2019 <sup>106</sup>	Computer assisted planning	Epilepsy	MRI-T1WI CT	10	RF Linear Regression	PCC	70%
Vakharia,2019 <sup>107</sup>	Trajectory planning for laser	Epilepsy	MRI-T1WI	95	RF Linear Regression	Risk Length Angle MSD	1.1% 93.5mm 28.8 ° 6.7mm

Table VII: Intra-operative assistance: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
Modelling of Tissue Deformation							
Sharma,2019 <sup>184</sup>	Modelling of tissue deformation	Brain tumor	MRI	4	SVR	PSNR MSE FRDD Acc	17.31% 1240mm 54% 80%
Tonutti,2019 <sup>108</sup>	Modelling of tissue deformation	Brain tumor	MRI	1	ANN SVR	MSE Error Time	0.11mm <sup>2</sup> 0.3mm 3.1sec

Table VIII: Prediction assessment: Details on Clinical Aim, Pathology/Anatomical area, Type of data, Dataset, AI Method, Benchmark measure and Results

First author, Year of publication	Clinical Aim	Pathology, Anatomical area	Type of data	Dataset	AI Method(s)	Benchmark measure	Results
Prediction of Post-operative Patient Outcome							
Shabo,2019 <sup>109</sup>	Postoperative ospitalization prediction	Neurosurgery	EHR	-	RNN	MAE	2.8 days
Fan,2019 <sup>110</sup>	TSS response prediction	Neurosurgery	EHR	-	GBDT	AUC	81%
Liu,2019 <sup>111</sup>	CD recurrency prediction	Neurosurgery	EHR	354	RF	AUC	0.78%
Farrokhi,2019 <sup>112</sup>	DBS outcome prediction	Neurological disorders	EHR	501	GBM	AUC Se Sp Acc	-
Merali,2019 <sup>113</sup>	Postoperative outcome prediction	Neurological disorders	EHR	757	KNN RF SVM Logistic regression ANN	AUC Acc Se	70% 77% 78%
Muhlestein,2019 <sup>114</sup>	Postoperative ospitalization prediction	Brain tumor	EHR	41222	29 ML Methods	RMSLE	55%
Nie ,2019 <sup>115</sup>	Survival prediction	Brain tumor	MRI-T1WI MRI-DTI	68	CNN SVM	Acc	90.66%
Hilbert,2019 <sup>116</sup>	reperfusion prediction	Brain lesion	CT	1301	RFNN	AUC <sup>1</sup> AUC <sup>2</sup>	71% 65%
Raj ,2019 <sup>117</sup>	Mortality prediction	Brain injury	CT	472	Logistic regression	AUC <sup>1</sup> AUC <sup>2</sup> Acc	67-81% 72-84% 81-84%

Table IX: Benchmark measures explained

Benchmark measures	definition
Acc (Accuracy)	is the proportion of correct predictions among the total no. of predictions (TP + TN)/total population.
Sp (Specificity)	is the proportion of negatively classified cases among the total no. of negative cases; TN/(TN + FP).
Se (Sensitivity)	is the proportion of positively classified cases among the total no. of positive cases; TP/(TP + FN);
TP (True Positive)	is an outcome where the model correctly predicts the positive class.
TN (True Negative)	is an outcome where the model correctly predicts the negative class.
FP (False Positive)	is where you receive a positive result for a test, when you should have received a negative results.
FN(False Negative)	is where you receive a negative result for a test, when you should have received a positive results.
Error (Error rate)	refer to the frequency of errors occurred, defined as “the ratio of total number of data units in error to the total number of data units transmitted.”
Risk (Risk Score)	is designed to represent an underlying probability of an adverse event denoted $Y = 1$ given a vector of $P$ explaining variables $X$ containing measurements of the relevant risk factors.
Time (Time complexity)	is the computational complexity that describes the amount of time it takes to run an algorithm.
JD (Jaccard Coefficient)	also known as Intersection over Union and the Jaccard similarity coefficient, is a statistic used for gauging the similarity and diversity of sample sets. The Jaccard coefficient measures similarity between finite sample sets, and is defined as the size of the intersection divided by the size of the union of the sample sets

DSI (Dice Similarity Index)	Statistic for similarity.
PSNR (Peak Signal-to-Noise Ratio)	represents the ratio between the maximum possible power of a signal and the power of corrupting noise that affects the fidelity of its representation.
MSE (Mean Square Error)	measures the average of the squares of the errors.
RMSE (Root Mean Square Error)	measures the standard deviation of the residual.
FRDD (Fault Rate Dust Detection)	is calculated as $FRDD = (TP + FN) / (TP + TN + FP + FN)$
PCC (Pearson Correlation Coefficient)	is a measure of the linear correlation between two variables X and Y.
HDD (Hausdorff distance)	measures how far two subsets of a metric space are from each other.
AUC (Area Under the Curve)	is a graphical plot illustrating the sensitivity as a function of “1 – specificity” in a binary classifier with a varying discrimination threshold. The area under the curve corresponds to the probability that a binary classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one; range 0 to 1.
MAD (Mean Absolute Distance)	is the average absolute distance between two surface points.
CMD (Center of mass distance)	is the distance between two center of mass of surface points.
MSD (Mean distance of surface point)	is the average distance between two surface points.
mSD (Min distance of surface point)	is the minimum distance between two surface points.
pFDR (Positive False Discovery Rate)	can be written as $pFDR = E[V / R   R > 0]$ . Where V is the number of false positives (Type I error), R is the number of rejected null hypotheses. The term “positive” describes the fact that we have conditioned on at least one positive finding having occurred.
MAE (Mean Absolute Error)	is an average of the absolute errors. $ e_i  =  y_i - x_i $ , where $y_i$ is the prediction and $x_i$ the true value.
RMSLE (Root Mean Square Logarithmic Error)	measures the ratio between actual and predicted. It is then $\sqrt{\text{mean}(\text{squared logarithmic errors})}$ .
Rec (Recall)	quantifies the number of positive class predictions made out of all positive examples in the dataset. It is calculated as the number of TP divided by the total number of TP and FN.
Pr (Precision)	quantifies the number of positive class predictions that actually belong to the positive class. It is calculated as the ratio of correctly predicted positive examples divided by the total number of positive examples that were predicted.
PPV (Positive Predictive Value)	is the probability that subjects with a positive screening test truly have the disease.
NPV (Negative Predictive Value)	is the probability that subjects with a negative screening test truly don't have the disease.
FAR (False Alarm Rate)	is the number of false alarms per the total number of warnings or alarms in a given study or situation.
ROC (Receiver operating characteristic)	is created by plotting the true positive rate against the false positive rate at various threshold settings.
IGV (Inter-group Variance)	refers to variations caused by differences within individual groups.

Table X: AI Algorithm explained

AI Algorithm	Mechanism
Regression Algorithms	Regression is concerned with modeling the relationship between variables that is iteratively refined using a measure of error in the predictions made by the model.
Linear Regression	Relationships between variables are modeled by fitting a linear equation to observed data.
Logistic Regression	Explains the relationship between one dependent binary variable and one or more independent variable regressing for the probability of a categorical outcome using a logistic function.
Instance-based Algorithms	Instance-based learning model is a decision problem with instances or examples of training data that are deemed important or required to the model. Such methods typically build up a database of example data and compare new data to the database using a similarity measure in order to find the best match and make a prediction.
KNN (k-Nearest Neighbor)	Categorize instances based on their similarity with the neighborhood, defined using a proper similarity function (e.g. Euclidean distance).
SVM (Support Vector Machines)	Search for an optimal separating hyperplane between classes that maximizes the margin, i.e., the distance from hyperplane to points closest to it on either side.
Bayesian Algorithms	Bayesian methods are those that explicitly apply Bayes' Theorem for problems such as classification and regression.
NB (Naive Bayes)	Apply Bayes' theorem with the naive assumption of conditional independence between the features.

<b>Clustering Algorithms</b>	Clustering, like regression, describes the class of problem and the class of methods.
K-Means	By following an iterative procedure, the algorithm create $K$ partitions and assign entry points to each partition using some heuristic (e.g. similarity with a representative point called centroid).
Fuzzy C-Means	Allows one piece of data to belong to two or more clusters. The procedure is carried out through an iterative optimization of an objective function, with the update of membership of each data point in each cluster.
HMM (Hidden Markov Model)	A Markov chain in which states are not directly observable.
SAE (Sparse Autoencoder)	DNN models trained at reproducing their inputs. Using proper loss function the model is forced to rely on a small number of neurons (sparsity).
<b>Artificial Neural Network Algorithms</b>	Artificial Neural Networks are models that are inspired by the structure and/or function of biological neural networks. They are a class of pattern matching that are commonly used for regression and classification problems but are really an enormous subfield comprised of hundreds of algorithms and variations for all manner of problem types.
ANN (Artificial Neural Network)	Network of highly interconnected processing units, which process information by their dynamic state response to external inputs
<b>Deep Learning Algorithms</b>	Modern update to Artificial Neural Networks that exploit abundant cheap computation. They are concerned with building much larger and more complex neural networks and, as commented on above, many methods are concerned with very large datasets of labelled analog data
FCNN (Fully Connected Neural Network)	ANN in which each unit in a layer is connected with all the units in the next layer.
CNN (Convolutional Neural Network)	ANN in which the fully-connected operations by convolutions with a set of learnable filters.
CLNet (Corrective Learning Network)	Explicitly learn a mapping from a new speech segment and the current predictions, to a correction
RNN (Recurrent Neural Networks)	Allows you to model a temporal dynamic behavior dependent on the information received at the previous instants of time by interconnecting higher levels with lower levels.
RFNN (Recurrent Fuzzy Neural Networks)	Finds the parameters of a fuzzy system (i.e., fuzzy sets, fuzzy rules) by exploiting approximation techniques from neural networks.
LSTM (Long Short-Term Memory Networks)	Special kind of RNN, capable of learning long-term dependencies.
DBN (Deep Belief Networks)	Stack of Restricted Boltzmann Machines, where the nodes in each layer are connected to all the nodes in the previous and subsequent layer.
ELM (Extreme Learning Machines)	Single hidden layer NN where the weights between inputs and hidden nodes are randomly assigned and remain constant during training and predicting phases.
<b>Dimensionality Reduction Algorithms</b>	Like clustering methods, dimensionality reduction seek and exploit the inherent structure in the data, but in this case in an unsupervised manner or order to summarize or describe data using less information. This can be useful to visualize dimensional data or to simplify data which can then be used in a supervised learning method. Many of these methods can be adapted for use in classification and regression.
LDA (Linear Discriminant Analysis)	Projects a dataset of $n$ -dimensional samples onto a latent subspace $k$ ( $k \leq n - 1$ ) while preserving class-discriminatory information.
<b>Ensemble Algorithms</b>	Ensemble methods are models composed of multiple weaker models that are independently trained and whose predictions are combined in some way to make the overall prediction.
AdaBoost	The algorithm generates $H$ hypotheses through an ensemble of learning algorithms. The output of the learning algorithms is combined into a weighted sum that represents the final output of the boosted classifier.
RF (Random Forest)	Consists of a large number of individual decision trees that operate as an ensemble. Each individual tree outputs a class prediction and the class with the most votes represents the model's prediction.
GBM (Gradient Boosting Machines)	ML technique providing a prediction model in the form of an ensemble of weak prediction models
GBRT (Gradient Boosted Regression Trees)	GBM with decision tree predictors.
Sparse MVTC (Sparse Multi-View Task-Centralize)	multi-view and multi-task ensemble classification method for image-based ASD diagnosis.
<b>Other Artificial Intelligence Algorithms</b>	
GA (Genetic Algorithm)	A number of candidate solutions (individuals) for a problem are created. The algorithm reflects the process of natural selection where the fittest individuals are selected for reproduction in order to produce offspring of the next generation. Fitness is evaluated by a proper optimization function.

NLP (Natural Language Processing)	Techniques to process and understand the natural language.
GBS (Graph Based Semisupervision)	Semisupervised learning method in which labeled and unlabeled data are jointly represented as a weighted graph; the resulting graph structure is then used as a constraint during the classification of unlabeled data points.
Multivariate Analysis	Involves observation and analysis of more than one statistical outcome variable at a time.
Supervised LOCATE (LOCally Adaptive Threshold Estimation)	Determines the optimal local thresholds to apply to the estimated lesion probability map, as an alternative option to global thresholding.

Table XI: Type of Data explained

Type of data	Definition
<b>Medical Imaging</b>	
MRI (Magnetic Resonance Imaging)	MRI uses a strong magnet and radiofrequency (RF) waves to provide clear and detailed pictures of internal organs and tissues.
MRI-T1WI (T1 Weighted Image)	T1 weighted image is one of the basic pulse sequences in MRI and demonstrates differences in the T1 relaxation times of tissues.
MRI-T2WI (T2 Weighted Imaging)	T2 weighted image is one of the basic pulse sequences in MRI. The sequence weighting highlights differences in the T2 relaxation time of tissues.
MRI-FLAIR (Fluid-attenuated Inversion Recovery)	FLAIR is an MRI sequence with an inversion recovery set to null fluids.
MRI-DWI (Diffusion Weighted Imaging)	DWI measures the strength of molecular motions of diffusion within a tissue structure or boundaries of white and gray matter brain tissues and brain lesions which have their own diffusion criteria and can be restricted by the diseases
MRI-DTI (Diffusion tensor imaging)	DTI is a magnetic resonance imaging technique that enables the measurement of the restricted diffusion of water in tissue in order to produce neural tract images instead of using this data solely for the purpose of assigning contrast or colors to pixels in a cross-sectional image
PET (Positron Emission Tomography))	PET offers superior soft-tissue contrast and a means of assessing cellular density with diffusion-weighted imaging
CT (Computed Tomography)	Uses computer-processed adaptations of several X-ray measurements taken from various angles to produce cross-section (tomographic) images.
IUS (Intra-operative Ultrasound)	IUS is a Dynamic imaging modality based on ultrasounds that provides interactive and timely information during surgical procedures.
fNIRS (Functional Near-Infrared Spectroscopy)	fNIRS is Noninvasive optical imaging technique used to monitor changes in hemoglobin (Hb) amounts within the brain by means of the characteristic absorption spectra of Hb in the near-infrared range.
HSI (Hyperspectral Imaging)	HSI is an imaging techniques based on capturing and processing of an image using information from all over the electromagnetic spectrum.
<b>Connectivity</b>	
FC (Functional Connectivity)	FC is a network representing temporal dependency of neuronal activation patterns of anatomically separated brain regions.
SC (Structural Connectivity)	SC is a network representing anatomical brain regions connected each other through fiber bundles.
<b>Other data</b>	
MER (Microelectrode Recording)	MER is a technique used to recording electrical patterns from surrounding brain structures.
EEG (Electroencephalography)	EEG ia a technique for recording and interpreting the electrical activity of the brain.
Gene sequence	Gene sequence are string of data representing the order of nucleotides in DNA.
EHR (Electronic Health Record)	EHR are digital version of a patient's paper chart.

## VIII. DISCUSSION

AI algorithms have increasingly caught, in recent years, the attention of many researchers in the neuroscience field. ML, in particular, have been used for finding ways to increase quality and precision of diagnosis and peri-operational decision-making, in order to improve neurosurgical treatments. In this work, a systematic review of the recent applications of AI in brain care was presented. Four main categories have

been found and analysed both quantitatively and qualitatively, namely diagnosis, surgical treatment, intra-operative assistance and post-operative assessment.

Concerning diagnosis, CNN models are widely adopted. However, despite DL architectures having been demonstrated to be able to achieve excellent results, they present several drawbacks which need to be taken into account. One of the most difficult issues to address, is the large amount of data to minimize overfitting and improve performances. How-

ever, obtaining them might not be trivial. Several works face this issue by designing proper frameworks which are able to achieve excellent results even using relatively limited amounts of data<sup>53,121</sup>, training from incomplete data<sup>123</sup> and by the adoption of semi-supervised and unsupervised techniques<sup>119</sup>. These algorithms, indeed, remain a *black box* in terms of the bases on top of which the predictions are generated from the input data. For this reason, “explainability” will be a crucial part of the development of new algorithms and many researches follow this direction. To this aim, an interesting alternative is represented by brain connectivity representation of the human brain. Such kind of data allow to represent the brain using mathematical models, opening a remarkable opportunities to study hidden pathological alterations outside visible objects in conventional images. High performance has been achieved using classical ML and DL models for the diagnosis and inter-class classification of several neurodegenerative diseases. An interesting perspective in this sense can be open by the use of novel graph-based DL approaches, including Graph Neural Networks<sup>185</sup>. Notwithstanding, as pointed out in related studies<sup>8</sup>, a major limitation is still the limited sample size, which, however, has started to be overcome by the availability of public datasets; it is worth to mention here The Alzheimer’s Disease Neuroimaging Initiative (ADNI)<sup>186</sup> and The Human Connectome Project<sup>187</sup>.

Concerning surgical treatment, EHR data can be used to select candidate potentially eligible for surgery. As previously mentioned, by Wissel *et al.*<sup>90</sup>, an electronic health record-integrated NLP application can accurately assign surgical candidacy scores to patients in a clinical setting. In surgical planning, brain structure demarcation may be inaccurate, consequently the exact detection of the target is difficult, leading to sub-optimal planning strategy and inadequate clinical outcomes. Interesting applications in surgical treatment concerning the target identification and involving AI approach is obtaining accurate, and automatic real-time target detection with intra-operative segmentation and localization of epileptic zones. This work provides neurosurgeons and neurologists with accurate means for automatic patient-specific targeting of the STN and its sub-regions, potentially reducing the need for other approaches that may lengthen the procedure and/or be associated with a higher risk of side effects<sup>36</sup>. To assist surgeons for a complete planning procedure AI techniques are exploring the definition of an optimal trajectory giving an alternative to standard approach such as graph-based or sampling-based method. In brief, usually the algorithm aims to minimize the intracerebral trajectory length, drilling angle from orthogonal to skull, while maximizing distance from critical structures. The use of ML in this context has allowed quantification of hitherto unidentified trajectory parameter combinations to be determined<sup>106</sup> and the decrease of the time complexity<sup>103</sup>.

Concerning intra-operative assistance, and in particular intra-operative modelling of tissue deformation, accurate reconstruction and visualisation of soft tissue deformation in real time is crucial in image-guided surgery, particularly in augmented reality applications<sup>108</sup>. The AI approach are able to address the needs of image-guided surgical systems.

In addition, we found that there is an emerging interest in the application of AI for post-operative assessment. The accurate prediction of an individual patient’s tumor response to treatment is a sort of Holy Grail of oncology<sup>188</sup>. Indeed, recent discoveries in molecular medicine and improvements in clinical treatments have made it now more important than ever to predict tumor behavior. They have shown that AI methods can predict tumor behavior with greater accuracy than traditional statistical methods<sup>104</sup>. Mining and advanced analysis of “big data” in brain care provide the potential not only to perform “in silico” research but also to provide predictive model for mortality prediction, post-operative outcome, post-operative hospitalization and DBS outcome. “On-demand” access to high-performance computing and large health care databases will support and sustain our ability to achieve personalized medicine. Unfortunately, these increased demands of health care providers create greater risk for diagnostic and therapeutic errors<sup>189</sup>. Developing large database of practice guidelines requires knowledge-based technologies to create and maintain them. Ultimately, what is required is also a way for practicing clinicians to access such guidelines quickly, incorporate them into their clinical practices, and then submit their own experiences back to the knowledge base to help improve it<sup>190</sup>.

Although the potential of AI in brain care is promising, in order to observe practical benefits in real-world systems, it is critical to delineate some challenges. Data quality, data inconsistency and instability, limitations of large size and diversity in support of new studies, are one of the major concerns. To this aim, the research community created and populated public repositories and leaderboards to make resources publicly available and submit new results, implicitly dealing with medical-related problems such as validation, and legal issues. Kaggle<sup>191</sup>, Grand Challenge<sup>192</sup> are concrete examples in this direction. Furthermore, an effort is spent to encourage synergy between AI researchers and non-tech users (as clinicians and medical experts). In this context, a crucial role is played by web platforms aimed at collaborative learning paradigm that enables research hospitals and institutions to collaborate and develop more robust AI algorithms and collect annotated data. The NVIDIA Clara medical imaging platform<sup>193</sup>, the Structured Planning and Implementation of New Explorations project (SPINE)<sup>194</sup>, the Artificial Intelligence On-Demand Platform and Ecosystem<sup>195</sup> are some examples.

As a final remark, we suggest here that, as DL techniques become more and more effective in solving brain related tasks, a considerable effort should be spent into developing new ways of interpreting such algorithms. Indeed, this study suggests that the primary role of AI in brain will be to **assist** experts and clinicians in their duties. For this reason, it is important that researchers do not focus only on algorithm performances, but rather also at increasing their trustworthiness.



**IX. CONCLUSION**

In this study, a general overview of the current literature on AI methods directly assisting brain care was presented. The use of artificial intelligence techniques is gradually bringing efficient theoretical solutions to a large number of real-world clinical problems related to brain. Especially in recent years, thanks to the accumulation of relevant data and the development of increasingly effective algorithms, it has been possible to significantly increase the understanding of complex brain mechanisms. The researchers’ efforts are leading to the creation of increasingly sophisticated and interpretable algorithms, which could favor a more intensive use of “intelligent” technologies in practical clinical contexts.

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**Data Availability**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Appendix**

Table XII: Keywords for Systematic Review

Database	Query
SCOPUS	TITLE-ABS-KEY ( "Machine Learning" AND "Deep Learning" AND ( "Classification" OR "Detection" OR "Identification" OR "Diagnosis" ) AND ( "brain disease" OR "neuro" OR "MRI" OR "medical imaging" ) ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) OR LIMIT-TO ( DOCTYPE , "cp" ) ) AND ( LIMIT-TO ( LANGUAGE , "English" ) ) AND ( LIMIT-TO ( EXACTKEYWORD , "Brain" ) OR EXCLUDE ( EXACTKEYWORD , "Image Segmentation" ) OR EXCLUDE ( EXACTKEYWORD , "Image Reconstruction" ) OR EXCLUDE ( EXACTKEYWORD , "Connectivity" ) OR EXCLUDE ( EXACTKEYWORD , "Functional" ) )
WEB OF SCIENCE	(("Machine Learning" AND "Deep Learning") AND ("Classification" OR "Detection" OR "Identification" OR "Diagnosis") AND ("brain disease" OR "brain disorders" OR "MRI" OR "medical imaging" OR "neuro") NOT "segmentation" NOT "functional" NOT "connectivity") AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Proceedings Paper)

PUBMED	("Machine Learning"[Title/Abstract/MeSH] OR "Deep Learning"[Title/Abstract/MeSH]) AND ("classification"[Title/Abstract] OR "diagnosis"[Title/Abstract] OR "identification"[Title/Abstract] OR "detection"[Title/Abstract]) AND ("Brain"[All Fields] AND "MRI"[All Fields]) NOT "Connectivity"[Title/Abstract/MeSH] NOT "Segmentation"[Title/Abstract/MeSH] NOT "Functional"[Title/Abstract/MeSH] NOT Review[ptyp] AND English[lang]
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**Acronyms**

- AD:** Alzheimer’s Disease. 4, 7, 8, 9, 10
- AI:** Artificial Intelligence. 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 25, 26, 27
- ANN:** Artificial Neural Networks. 4, 6
- ASD:** Autistic Spectrum Disorder. 10
- AUC:** Area Under the Curve. 5, 10, 13
- AVM:** Arteriovenous Malformation. 10
- CAD:** Computer Assisted Diagnostic. 7
- CLNet:** Corrective Learning Network. 9, 10
- CMD:** Center of Mass Distance. 5
- CNN:** Convolutional Neural Network. 4, 7, 8, 9, 10, 13, 25
- CT:** Computed Tomography. 1, 2, 6, 9, 11, 12, 13
- DBS:** Deep Brain Stimulation. 3, 4, 9, 11, 12, 13, 17, 21, 26
- DCM:** Dilated Cardiomyopathy. 13
- DL:** Deep Learning. 2, 4, 5, 7, 8, 9, 10, 12, 13, 25, 26
- DNN:** Deep Neural Network. 4
- DSI:** Dice Similarity Index. 5, 9
- DT:** Decision Tree. 4, 6
- DTI:** Diffusion Tensor Imaging. 3, 6
- EEG:** Electroencephalography. 3, 6, 11
- EHR:** Electronic Health Record. 3, 4, 6, 11, 12, 26
- FC:** Functional Connectivity. 3, 6
- FCNN:** Fully Convolutional Neural Network. 9
- FLAIR:** Fluid Attenuated Inversion Recovery. 3
- fMRI:** Functional Magnetic Resonance Imaging. 3
- fNIRS:** Functional Near-Infrared Spectroscopy. 6, 11

- FRDD:** Fault Rate Dust Detection. 9
- GA:** Genetic Algorithm. 6
- GAN:** Generative Adversarial Network. 8
- GBM:** Gradient Boosting Machine. 6
- GNN:** Graph Neural Network. 4
- GP:** Globus Pallidus. 11
- GPU:** Graphic Processing Unit. 2
- HC:** Healthy Control. 10
- HDD:** Housdorff Distance. 5
- HMM:** Hidden Markov Model. 9
- HSI:** Hyperspectral Imaging. 3, 6, 11
- ICH:** Intracerebral Hemorrhage. 8
- IUS:** Intra-operative Ultrasound. 3, 6, 11
- JC:** Jaccard Coefficient. 5
- KNN:** K-nearest Neighbors. 6, 11
- LITT:** Laser Interstitial Thermal Therapy. 12
- LOCATE:** LOcally Adaptive Threshold Estimation. 9
- LOS:** Length of Stay. 13
- LRP:** Layerwise Relevance Propagation. 8
- MAD:** Mean Absolute Distance. 5
- MAE:** Mean Absolute Error. 5
- MCI:** Mild Cognitive Impairment. 7, 8, 10
- MER:** Microelectrode Recording. 3, 6
- MI:** Medical Imaging. 1
- ML:** Machine Learning. 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 25, 26
- MRI:** Magnetic Resonance Imaging. 1, 2, 3, 4, 6, 9, 10, 11, 12
- mSD:** min Square Distance. 5
- MSD:** Mean Square Distance. 5
- MSE:** Mean Square Error. 5, 9
- NLP:** Natural Language Processing. 6, 11, 26
- NPV:** Negative Predictive Value. 5
- PCC:** Pearson Correlated Coefficient. 9
- PET:** Positron Emission Tomography. 1, 2, 6
- PPV:** Positive Predictive Value. 5
- PSNR:** Peak Signal-to-Noise Ratio. 5, 9
- RF:** Random Forest. 4, 6, 7, 10, 12, 13
- RMSE:** Root Mean Square Error. 5
- RNN:** Recurrent Neural Network. 4, 12
- ROC:** Receiver Operating Characteristic. 5, 12
- rs-fMRI:** Resting State Functional Magnetic Resonance Imaging. 3
- SAE:** Sparse Autoencoder. 6, 9
- SC:** Structural Connectivity. 3, 6
- STN:** Subthalamic Nucleus. 11
- SVM:** Support Vector Machines. 4, 6, 7, 9, 10, 11, 12, 13
- SVR:** Support Vector Regression. 9
- TLE:** Temporal Lobe Epilepsy. 10
- TSS:** Transsphenoidal Surgery. 12

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