



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/163905/>

Version: Accepted Version

Article:

Myszczyńska, M.A., Ojamies, P.N., Lacoste, A.M.B. et al. (2020) Applications of machine learning to diagnosis and treatment of neurodegenerative diseases. *Nature Reviews Neurology*, 16. pp. 440-456. ISSN: 1759-4758

<https://doi.org/10.1038/s41582-020-0377-8>

This is a post-peer-review, pre-copyedit version of an article published in *Nature Reviews Neurology*. The final authenticated version is available online at:
<http://dx.doi.org/10.1038/s41582-020-0377-8>

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



Applications of machine learning to diagnosis and treatment of neurodegenerative diseases

Monika A. Myszczyńska¹, Poojitha N. Ojamies², Alix M. B. Lacoste³, Daniel Neil², Amir Saffari², Richard Mead¹, Guillaume M. Hautbergue¹, Joanna D. Holbrook² and Laura Ferraiuolo¹ ✉

Abstract | Globally, there is a huge unmet medical need for effective treatments for neurodegenerative diseases. The complexity of the molecular mechanisms underlying neuronal degeneration and the heterogeneity of the patient population present massive challenges to the development of early diagnostic tools and effective treatments for these diseases. Machine learning, a subfield of artificial intelligence, is enabling scientists, clinicians and patients to address some of these challenges. In this Review, we discuss how machine learning can aid early diagnosis and interpretation of medical images as well as the discovery and development of new therapies. A unifying theme of the different applications of machine learning is the integration of multiple high-dimensional sources of data, which all provide a different view on disease, and the automated derivation of actionable insights.

Omics

A collective term for a field within biological research concerned with the study of 'omes'; for example, the genome, transcriptome or proteome.

First described in 1955 by John McCarthy as “the science and engineering of making intelligent machines”¹, artificial intelligence (AI) is a field of computer science research devoted to designing software capable of performing computations with a sophistication similar to that of human intelligence. AI encompasses a wide range of computational systems and tools that mimic actions that the human brain performs on a daily basis: problem solving, reasoning, pattern spotting and knowledge acquisition². Machine learning and natural language processing are the forms of AI most commonly used in health-care settings as they enable a robust interrogation of datasets in order to identify previously undiscovered patterns and relationships between different features in the data³. These two forms of AI are distinct, but share common features, as natural language processing largely uses machine learning to derive meaning from language. The functions of machine learning could aid diagnosis, development of novel therapies, and help improve our understanding of the disease course.

The application of machine learning algorithms to medicine and scientific research has been widely discussed in recent years^{4–9}. In the last decade, new technologies have enabled rapid accumulation of patient data such as ultrasonography and MRI readouts; omics profiles of biological samples; electronically captured clinical, behavioural and activity data; and social media-derived information^{10–13}. These big health datasets are high-dimensional, meaning the number of features

(or variables) recorded per observation can sometimes exceed the total number of observations. For example, gene expression datasets can contain the expression levels of ~20,000 genes, whereas obtaining data from 20,000 individuals with a given disease would be extremely challenging. These high-dimensional datasets are often sparse, noisy, cross-sectional and lack statistical power, making it extremely difficult to gain biological insights from these data using traditional data analytical approaches, which look for changes in single variables or perform simple correlations¹⁴. These problems with data analysis are further compounded by the integration of diverse data types (for example, imaging, genomics and clinical data) that is necessary to gain an understanding of disease mechanisms. In response to these challenges, advanced machine learning models are increasingly applied to biomedical and health-care data. Traditional computer science derives results from input data through the application of predefined rules, whereas machine learning learns rules and insights from input data directly, thus allowing the application of those rules to make predictions from data in new situations. Machine learning approaches can help overcome the challenge of high-dimensional data by reducing the number of features analysed in favour of the least variable¹⁵. Different machine learning algorithms can also be used to integrate data from different sources to increase statistical power.

By the year 2050, an estimated 22% of the global population will be over 60 years of age¹⁶. As age is the main



¹Sheffield Institute of Translational Neuroscience, University of Sheffield, Sheffield, UK.

²BenevolentAI, London, UK.

³BenevolentAI, Brooklyn, NY, USA.

✉e-mail: l.ferraiuolo@sheffield.ac.uk

<https://doi.org/10.1038/s41582-020-0377-8>

Key points

- Machine learning and natural language processing are forms of artificial intelligence that enable robust interrogation of multiple datasets to identify previously undiscovered patterns and relationships in the data.
- Machine learning approaches have been applied to the study of neurodegenerative diseases and show promise in the areas of early diagnosis, prognosis and development of new therapies.
- A substantial number of machine learning algorithms exist, and choosing the correct algorithm to apply to different types of data is crucial to obtain reliable results.
- Neuroimaging was the first area of neurology to benefit from the application of machine learning approaches to improve diagnosis; more recently, application of machine learning methods to motor function and language feature analysis has shown promise in decreasing the time taken to perform clinical assessments.
- The application of machine learning to longitudinal patient data collection and electronic health records has the potential to inform prognosis prediction and patient stratification.
- Large collections of curated datasets and robust assessment of machine learning methods will be needed to achieve full integration of machine learning into diagnostic and prognostic neurology practice and the design of future therapeutics.

risk factor for most neurodegenerative disorders, including Alzheimer disease (AD), Parkinson disease (PD) and motor neuron disease (MND), countries across the world are facing an unprecedented economic challenge¹⁷. In 2016 the global cost of caring for individuals with AD reached an estimated US\$946 billion, which was triple the estimated expenditure in the year 2000 (REF.¹⁶). These costs are expected to rise, as the number of individuals with AD is likely to reach 115 million worldwide by 2050 (REF.¹⁶). These estimates call for changes in the way that individuals are diagnosed and treated, and highlight the urgent need for effective therapeutic interventions. In this context, machine learning could enable data to be used more efficiently to provide insights into disease mechanisms, and to help with earlier diagnosis, prognosis, patient stratification and development of new therapies. With these goals in mind, many researchers have gathered rich, high-dimensional datasets from healthy individuals and individuals with neurodegenerative diseases; for example, the [Alzheimer's Disease Neuroimaging Initiative](#) (ADNI), the [Allen Brain Atlas](#) and the [UK Biobank](#). In this Review, we highlight the latest developments in the use of machine learning to interrogate neurodegenerative disease-related datasets, including the applications of machine learning to diagnosis, prognosis and development of new therapies.

Machine learning models

Machine learning methods are broadly categorized into supervised, unsupervised and reinforcement learning approaches¹⁸ (FIG. 1). Supervised machine learning algorithms are currently the methods most commonly applied to neurodegenerative disease-related data and require a labelled dataset from which to learn. Often, these labels require manual curation or expert assessment; for example, a radiologist is needed to label a set of MRI scan images and a neuropathologist is required to categorize a set of images obtained from post-mortem patient samples. Once this 'benchmark' dataset has been labelled, the machine learning algorithm builds a model of the relationship between the input features

(for example, the size of a brain region on an MRI scan) and the label (for example, a diagnostic category). The algorithm can then apply this model to new, unlabelled datasets to predict the label on the basis of the new input features. Gathering sufficiently large volumes of accurate labels for supervised machine learning can be a challenge¹⁹.

Supervised machine learning is divided into classification and regression algorithms¹⁸. Classification algorithms, such as the example above, predict the categorical output (diagnostic category) for each data sample (patient). In contrast, regression algorithms predict a real-valued variable (for example, degree of functional impairment measured on a continuous scale) for each data sample. When applied to health-care data, both classification and regression algorithms can define patient endotypes by identifying patterns within the data and clustering areas of similarity together. A practical example of regression approaches would be the subtyping of patients into progression endotypes on the basis of algorithms that model motor function decline, disease duration, or slope of progression to form nuanced representations of the progression time series. This regression approach contrasts with endotyping on the basis of categories, which might include specific genetic mutations or the site of disease onset. Most machine learning algorithms have variants to support both classification and regression.

In contrast to supervised machine learning, unsupervised machine learning algorithms do not require labelled data and are useful for tasks such as clustering data samples into groups, or reducing the dimensionality of datasets by generating a simpler representation of highly complex data^{20,21}. For example, unsupervised clustering algorithms can be used to analyse gene expression datasets and identify clusters of patients with shared molecular signatures²². Furthermore, unsupervised clustering approaches, such as latent variable models, can help identify co-expression modules of genes, which are sets of genes that are likely to be co-regulated or correspond to common biological mechanisms or pathways. In addition to analysing existing data, unsupervised clustering algorithms can also be used to make predictions; for example, a model can be trained on a set of historical clinical data to then predict survival from the cluster that a patient is placed in.

Supervised and unsupervised learning approaches can be combined, for example, to form semi-supervised learning methods²³. Semi-supervised methods enrich a small set of labelled data with additional unlabelled data, which allows clustering (unsupervised) methods to improve the performance of classification (supervised) methods, as well as regularising the predictive model with additional data. Similarly, transductive learning methods use the test data as unlabelled data to improve a standard supervised classification approach^{24,25}; these methods do not result in data leakage as the labels are not shared, and can increase performance in problems where low volumes of data are available.

Finally, in reinforcement learning approaches²⁶ a reward or punishment is given to achieve a desired output. For example, an algorithm might be used to explore

Endotypes

Clusters of individuals within a disease population that share functional and pathological traits.

Molecular signatures

A collection of proteins, genes and their variants that can be used as hallmarks for a given phenotype.

Regularizing

The technique of adding constraints or knowledge within the training process in order to prevent overfitting.

Data leakage

An undesirable process whereby information is accidentally shared between the training data and the test data, resulting in test evaluation scores that are not representative of real-world unseen data.

Q4

Q5

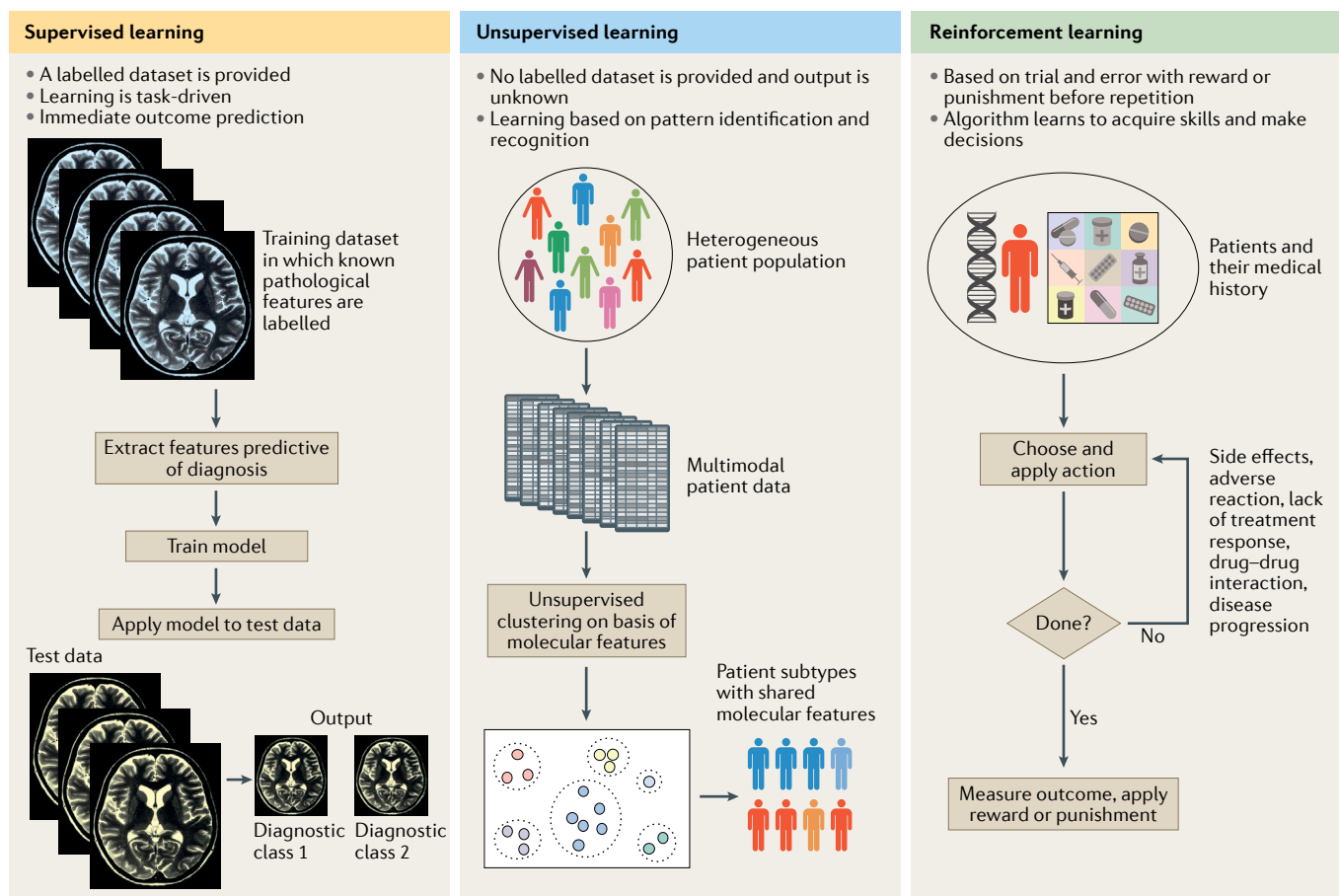


Fig. 1 | Categories of machine learning. Machine learning methods can be divided into three main categories: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning relies on a set of data labelled by a professional to train an algorithm to extract specific disease features. Once trained, the model identifies features of interest in unlabelled datasets to aid diagnosis. Unsupervised learning learns to determine patterns and classes within the dataset without labels, and can be particularly useful in identifying molecular signatures that categorize heterogeneous patient disease groups into molecular subtypes. Reinforcement learning models the process of decision making and the output is a result of knowledge gained from previous experiences. The algorithm is trained on a trial and error basis, with a reward or punishment driving the learning process and skills acquisition. Such an approach is ideal for automation and robotics, though use in medicine is increasing. Brain scan image credit: M. Andritoiu/Alamy Stock Photos.

a new medication regimen for a patient based on the patient's medical history. During training, in the event of a negative reaction to a new drug or adverse drug–drug interactions, a punishment would be given to the algorithm, whereas a reward would be given for a drug improving the disease course, which is the desired output. These approaches are being rapidly explored^{27,28}, but are not yet as widely used as supervised and unsupervised learning in the field of neurodegenerative diseases

Model selection

A substantial number of machine learning algorithms exist and choosing the correct algorithm to apply to a particular type of data is important. With a particular focus on supervised learning, two factors are particularly relevant for selecting the right algorithm: modality (the form that the data is in) and volume (the number of data samples). In terms of volume, for datasets with a low sample-to-feature ratio²⁹ (SFR <10:1), an algorithm will struggle to learn a useful 'featurization' in addition to classification (FIG. 2). Data featurization requires the

algorithm to identify and extract characteristics or 'features' in the data that enable the subsequent separation of data points into classes. The higher the SFR, the easier it will be for the algorithm to identify features that separate the data points. For example, given the limited availability of post-mortem tissue samples for certain neurodegenerative conditions, a model that needs a high SFR to make meaningful predictions about the data, such as a deep neural network, is unlikely to be able to learn from tens of samples and identify features that can accurately classify patients into different pathological subtypes. For such limited datasets, highly constrained or 'regularized' models, such as hierarchical Bayesian models, simplify the task and guide the algorithm by learning only a few parameters for that data.

For larger datasets, support vector machines (SVM)³⁰ or random forests^{31,32} (TABLE 1) are typically used. These approaches are more flexible than hierarchical Bayesian models, but require a greater volume of data and are more complex. SVMs map datasets into a space such that two categories (for example, healthy and diseased)

Sample-to-feature ratio (SFR). The number of data points divided by the number of features; for example, gene expression data comprising tens of patients with thousands of gene expression levels would have an SFR of <1.

Overfitting

When an algorithm learns the patterns within the training dataset as opposed to the rules representative of the whole class of problems.

Classifier

A type of model used to identify the correct category for a data point.

are separated as widely as possible. In the 1990s, pioneer work demonstrated that the mathematical theory behind SVM, initially used for two-group classification problems, could be applied to more complex and multiclass datasets³³. Random forests use a different approach to SVM. A random forest algorithm constructs numerous different, independent decision trees, which each require a series of binary choices to be made about the data. In this way, each decision tree provides a classification for the input data, and the algorithm then selects the most common output prediction from the different trees. This approach corrects for the overfitting that can occur when using a single decision tree. SVM and random forests were dominant until the more recent development of neural networks.

Artificial neural networks, which include the popular deep neural networks, are widely used to analyse many modalities of data, but particularly image, video and sound data^{19,34} (TABLE 1). These networks are designed to simulate the highly connected neural system found in the brain, and are based on the pioneering work of McCulloch and Pitts³⁵ who developed a mathematical model to help bridge the gap between statistics and neuropsychiatry. Similar to a neuron receiving electrical stimuli from other neurons, a node in an artificial neural network receives inputs from other nodes. Just

as a neuron needs to reach a certain threshold to fire an action potential, the nodes of an artificial neural network sum up the inputs from other nodes and calculate the likelihood that a potential output is true. Artificial neural networks are typically arranged into one or more layers of parallel ‘neurons’ that transform their inputs into outputs; networks that contain two or more layers are known as deep neural networks. In each successive layer, the neural network is able to manipulate more abstract representations of the data. Artificial neural networks require even fewer manual data manipulation steps during preprocessing than SVM or random forests and in some cases subsume the choice of classifier into the architecture of the network¹⁹. These networks are mostly supervised, but can also be unsupervised.

The use of a particular type of deep neural network, known as a convolutional neural network (CNN)^{36–38} (TABLE 1), has led to significant improvements in machine learning performance for medical image interpretation. CNN, which draws inspiration from the human visual system, extracts features at higher and higher levels of abstraction, initially combining local information and eventually integrating large-scale information across the image. This approach enables complex processing, such as distinguishing cats from dogs or the identification of cancerous cells³⁹. Many of the problems involved in

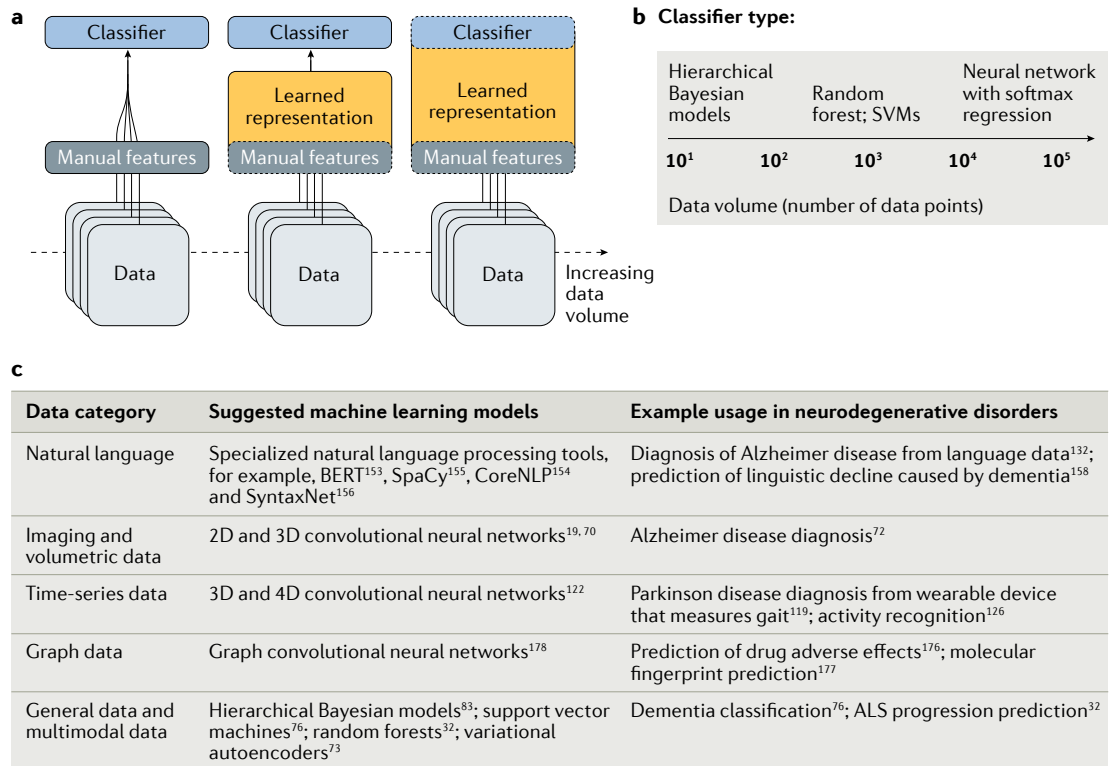


Fig. 2 | Determining the best machine learning model for a given problem. Two factors are particularly relevant to the choice of machine learning model: the data modality (for example, time series or imaging) and the data volume (number of data points). **a,b** | At small data volumes, manual features and well-regularized classifiers are needed. As data volume increases, a learned representation that discovers features from data automatically can be used, and eventually a separate, custom classifier on the learned representation is no longer needed. **c** | Choosing the right model to match the data type enables machine learning to extract a meaningful representation from the data, which can be paired with a variety of classifiers. ALS, amyotrophic lateral sclerosis; BERT, Bidirectional Encoder Representations from Transformers; SVMs, support vector machines.

Table 1 | Descriptions of key machine learning methods and examples of their application

Method	Supervised or unsupervised?	Classification, regression or clustering?	Definition	Examples of application
Deep neural networks	Supervised and unsupervised	Classification, regression, and clustering	A category of algorithms that are composed of multiple layers of transformation, and use artificial neural networks as each layer of processing	Disease diagnosis from neuroimages, speech recognition, natural language processing and pattern recognition ^{19,71}
Convolutional neural network	Supervised and unsupervised	Classification, regression and clustering	Form of a deep neural network designed to mimic neuronal connections and reduce dimensionality of the data	Image analysis and classification, video analysis, natural language processing and acoustic input ^{55,92,93,158}
Recurrent neural networks	Supervised and unsupervised	Classification, regression and clustering	A type of artificial neural network capable of forming internal memory, which makes it optimal for analyses of sequential data	Speech classification, handwriting classification and disease progression classification ^{92,140}
Network diffusion algorithm	Unsupervised	NA	A class of methods that model the spread of information through networks	Gene regulator analysis and network inference for gene prioritization ¹⁴⁹
Random forest	Primarily supervised	Primarily classification and regression	An algorithm that averages a large number of weak classifiers (trees) to form a strong classifier using random subsets of data	Disease progress prediction ³²
Support vector machines	Primarily supervised	Classification, regression and clustering	A method of separating distinct classes within a dataset by applying an optimal hyperplane	Disease classification ^{54,58–60,82,210}

NA, not applicable.

image classification can be solved by these kinds of algorithms. Another type of deep neural network, known as a recurrent neural network (RNN)⁴⁰ (TABLE 1), can extract information from sequences of data and is particularly useful for analysing clinical records. RNN models such as long short-term memory (LSTM)⁴¹ and gated recurrent units⁴² form building blocks used in most sequence tasks. These models contain a memory cell that allows the algorithms to learn long-term dependencies and gates that control the exposure of the memory content and the extent of the changes made to the memory content depending on the input.

Some of the key technical risks to mitigate when choosing a machine learning model include insufficient data volume, improper data representations, overfitting, incorrect hyperparameter selection and missing data^{43,44}. Although subject matter expertise can help address issues regarding data volume and data representation, overfitting is a fundamental issue. For example, when a model is trained on a dataset with low bias and high variance, and the model selected has the best performance on the training data, the model is likely to try to ‘memorize’ the training data. This memorization results in overfitting of the model on the training data, leading to poor predictive performance on test data as the model is no longer able to make generalizations to the additional datasets. Overfitting could, for example, lead to some pathological features in neuroimages not being identified. Methods such as cross-validation and regularization can help minimize this problem⁴⁵. All machine learning methods and data sources have caveats; therefore, a combination of multiple data sources and methods followed by confirmatory post-processing steps that use a variety of metadata is the best approach.

Diagnosis and prognosis

In many neurodegenerative diseases, including AD, PD and MND, symptoms do not manifest until a substantial loss of neurons has already occurred^{46–48}, which makes early diagnosis very challenging. Therefore, research into the application of machine learning models to early diagnosis is growing (TABLE 2). The aim of this research is to use machine learning to detect prognostic signals in data that can be collected relatively easily (for example, electronic health records (EHRs) or MRI data), thus enabling the prospective screening of ageing populations. The machine learning-driven automated diagnosis could then flag individuals for further clinical investigation. Such an approach would require machine learning models that are sensitive enough to detect early disease signals and specific enough not to over-burden health systems with unnecessary follow-up tests. Currently, test results need to be analysed and interpreted by trained staff, which can lead to delays in diagnosis. These delays could be reduced by applying machine learning approaches to the data as they are gathered in the clinic. These same data could be used to predict patient prognosis by comparing disease progression at any given time with historical data from patients sharing the same endotype or phenotype. Historical health records provide a helpful training dataset for prognosis algorithms, as they can cover the entire disease span.

Neuroimaging. Neuroimaging techniques such as CT and MRI are often used in the diagnosis of neurodegenerative diseases, and radiology was one of the first fields to benefit from the computerization of medicine and the introduction of ‘intelligent machines’⁴⁹ (FIG. 3). The early 1990s saw the introduction of supervised

Hyperparameter

A parameter the value of which is set before training; for example, the attributes of the model architecture.

Cross-validation

A training and evaluation procedure that consist of splitting the data into subsets and alternately holding out one subset for evaluation until all subsets have been evaluated.

Metadata

Data about other data; for example, information about an experimental protocol or the time and date of sample collection.

Table 2 | Key neurodegenerative disease-related data types used by machine learning algorithms

Neurodegenerative disease	Key data types used	
	For diagnosis	For monitoring disease progression
Dementias, including AD and MCI	Neuroimaging ^{30,55,72,75-77,79,82} ; cognitive performance tests ^{131,132,135,136} ; EEG data ¹⁰⁴ ; transcriptomic data ^{97,140} ; biomarker data ^{143,144,146}	Neuroimaging ^{77,83,211} ; cognitive performance tests ^{131,132,156} ; IADL records ^{125,126}
PD	Motor performance tests ^{114,115,119} ; neuroimaging ⁸⁶	Electronic health records ¹⁶⁵
MS	Metabolomic data ¹⁴⁵ ; neuroimaging ⁸⁵	Genomic data ¹⁴²

AD, Alzheimer disease; EEG, electroencephalogram; IADL, instrumental activities of daily living; MCI, mild cognitive impairment; MS, multiple sclerosis; PD, Parkinson disease.

knowledge-based expert systems⁵⁰⁻⁵⁵, which were capable of recognizing pathological events in the brain on the basis of a large amount of data and knowledge collected by the neuroradiological community⁵⁶. Initial studies used clinically relevant diagnostic features, such as cortical thickness or morphology of particular brain regions, to classify patients and help radiologists make a diagnosis⁵⁷⁻⁶³. This approach is known as computer-aided diagnosis, and continued to be developed and improved throughout the early 2000s⁶⁴⁻⁶⁸. Because machine learning is purely evidence-based and can analyse problems in an unbiased manner, the approach is helpful for making objective diagnoses from medical images and often surpasses the performance of trained professionals in terms of speed, precision and accuracy^{30,69}.

Computer-aided diagnosis systems can be supplemented with and powered by supervised learning techniques to further improve the interpretation of neuroimaging data and help identify subtle abnormalities in the images that are not detected by radiologists. For example, CNNs can categorize images by identifying and mapping a high number of features⁷⁰ (TABLE 1). Some studies have used CNNs to predict a diagnosis of AD^{71,72} and to study cognitive ageing⁷³ from MRI and PET images, sometimes alongside other clinical readouts (for example, biomarker information and assessments of motor or cognitive performance), to increase specificity.

SVMs have been used to analyse MRI data, sometimes combining structural and functional MRI, and cognitive assessment data to improve disease diagnosis⁷⁴ (TABLE 1). For example, one study used an SVM to differentiate between structural MR scans from individuals with different severities of AD and cognitively normal elderly individuals, as well as to differentiate between individuals with AD and individuals with frontotemporal lobar dementia (FTLD)⁷⁵. In another study of structural MRI data, an SVM was able to predict conversion from mild cognitive impairment (MCI) to AD, as well as separate healthy controls, individuals with MCI and individuals with AD better than a combination of statistical approaches and expert knowledge⁷⁶. In the same year, a study used a combination of linear dynamic system and SVM algorithms to integrate MRI data and cognitive test data to distinguish individuals with AD from healthy controls⁷⁷. This study is particularly interesting because of the use of two approaches to integrate data. SVMs have also been applied to whole-brain anatomical MRI images to identify new regions of interest that can differentiate between individuals with AD and

healthy controls⁷⁸, and to images of the hippocampus to classify its shape features⁷⁹. The latter method has been described as more accurate than traditional hippocampal volumetry^{80,81}. An SVM was also used to compare the utility of different combinations of neuroimaging data (functional MRI or structural MRI) and cognitive performance data for identifying individuals with MCI⁸². Analysis of MRI data with SVM has also been used in studies of cognitive function⁸³, stroke⁸⁴, multiple sclerosis (MS)⁸⁵ and parkinsonism⁸⁶.

MRI produces images of higher resolution than CT; however, the diagnostic performance of CT can be improved with the use of machine learning algorithms. For example, in one study, a random forest algorithm for automated white matter lesion detection was applied to a set of CT images from individuals with acute ischaemic stroke and performed similarly to the labelling of MR images by radiologists⁸⁷. The algorithm had a failure rate of 4% and an average processing time of less than 2 minutes, thus offering a possibility of similar approaches being extended to diagnosis of neurodegenerative diseases. Machine learning can assess images quickly, so it could be used to flag findings from CT images that need urgent review by a radiologist in life-threatening scenarios⁸⁸⁻⁹⁰. Quick image analysis could also be extended to MRI, which could prove particularly useful for individuals with MCI⁹¹⁻⁹³, as early prediction of possible conversion of MCI to AD could enable a swifter start of treatment.

In a global effort to improve our understanding of neurodegenerative diseases and their progression, databases of neuroimaging data from patients are being assembled with the aim of creating a comprehensive picture of the disease course from diagnosis onwards. Resources such as the [Parkinson's Progression Markers Initiative](#), [ADNI](#), [The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability \(FINGER\)](#)⁹⁴ or [European Alzheimer's Disease Consortium Impact of Cholinergic Treatment Use \(EADC-ICTUS\)](#) give researchers working with machine learning algorithms access to verified material to be used for algorithm training and validation. Although the training data are becoming widely available, applying algorithms to it can be challenging. Some pieces of software are not, or were not for a long time, capable of reading and processing the DICOM file format that is used for medical imaging. However, open source software and libraries with a strong user community, such as [Google TensorFlow](#) have now addressed this issue by extending support to additional file formats, including DICOM⁹⁵.

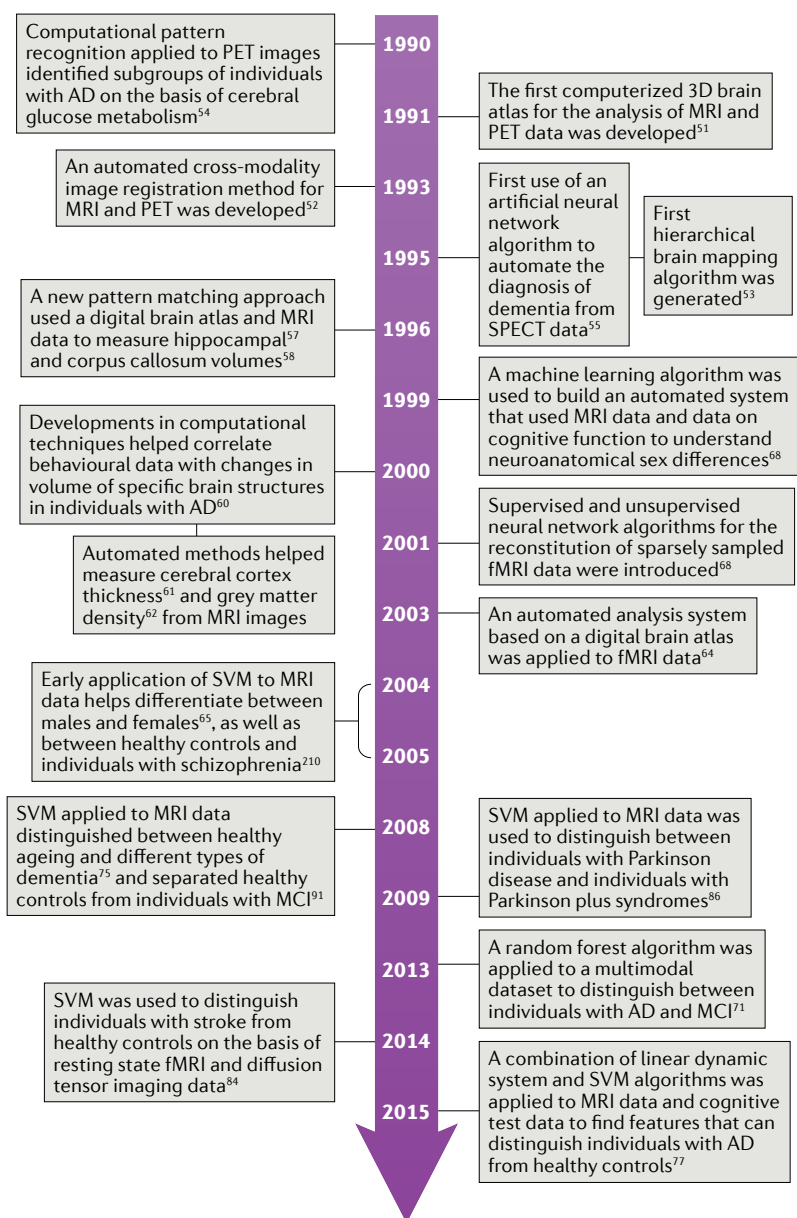


Fig. 3 | Key developments and novel applications of computational and machine learning techniques to neuroimaging since the 1990s. Interest in machine learning and its use for medical purposes towards the end of the 20th century led to the automation of previously time-consuming manual analysis and measurement of neuroimaging data. The low variance and high reproducibility of these AI-driven methods made them an attractive tool for use in clinical settings. Moreover, three-dimensional, high-resolution overview of deep brain structures, previously considered to be beyond analysis without surgical interventions, became within reach. AD, Alzheimer disease; fMRI, functional MRI; MCI, mild cognitive impairment; SPECT, single-photon emission computerized tomography; SVM, support vector machine.

Genome-wide association study (GWAS). An observational method of studying genetic variants across a population in search for associations between genetic changes and traits such as diseases.

Efforts to investigate the interaction between genetics and brain structure have led to the rise of a new field called neuroimaging genomics⁹⁶. The very first attempts to draw a correlation between genetics and brain function were initiated in the early 2000s and focused on single gene variants^{97,98}. These pioneer studies made several novel observations, including the association of the epsilon 4 allele of the apolipoprotein E gene (*APOE* ϵ 4) with abnormalities in brain activation assessed with

functional MRI during memory-activation tasks⁹⁹. Since these initial studies, the field has generated breakthroughs owing to large multicentre collaborations such as the **Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) Consortium**, which has analysed genome-wide association study (GWAS) and MRI data from 30,717 individuals across 50 cohorts¹⁰⁰. The ENIGMA Consortium has now identified common genetic variants that influence the volume of several brain structures, thus shedding light on potential complex genetic drivers of development and disease. As ENIGMA expands, specialized working groups dedicated to the study of several disorders, including PD, ataxia and FTLT, have been formed to help elucidate the pathogenesis of these diseases using imaging genomics.

Neuroimaging is one way of investigating brain activity. Other methods of monitoring brain activity, such as electroencephalography (EEG), can also benefit from machine learning-driven data analyses. EEG data have been used to distinguish individuals with AD from healthy controls¹⁰¹ or patients affected by other forms of dementia¹⁰², as well as to detect functional changes in dopaminergic neurons to diagnose PD¹⁰³. In order to do this, changes in electrical activity frequency over time in different areas of the brain are analysed. Algorithms based on artificial neural networks have been generated to differentiate between individuals with AD and individuals with MCI using only unprocessed EEG data, with the aim of speeding up diagnosis and simplifying the monitoring of dementia progression¹⁰⁴.

Motor function. Many neurodegenerative disorders, such as MND, Huntington disease (HD) and PD, are characterized by motor dysfunction, often culminating in loss of movement^{105,106}. An understanding of the progression and chronology of motor degeneration is essential for supporting patients appropriately at each stage of the disease. Motor performance is measured during routine clinical assessments, which often assess both fine and gross muscle functions (for example, muscle tone when picking up small objects and gait when walking), although the precise battery of tests varies depending on the disorder^{107–109}.

Machine learning can be used to assess the performance of individuals in complex tasks, such as drawing, in a time-efficient manner¹¹⁰. Simple drawing tasks and handwriting analysis are being increasingly used in the early diagnosis of PD^{111,112}, as handwriting is no longer an automated function in individuals with the disease and is performed in a more segmented and sequential manner, with numerous pauses¹¹³. Introduction of machine learning techniques into writing task analysis can help classify individuals with PD and serve as a diagnostic tool. In one study, classifier-based supervised machine learning algorithms were applied to data from a horizontal line drawing task in order to differentiate between normal and abnormal hand movements and identify irregularities characteristic of PD¹¹⁴. A set of metrics related to the velocity and spatiotemporal trace of the pen combined with naive Bayes classification helped to accurately distinguish between individuals with PD and healthy controls. Similarly, in another study, a supervised model was

used to automatically analyse Archimedean spiral tracing performed by individuals with PD¹¹⁵. Drawings were independently assessed and scored by trained experts, and the algorithm-scored drawings showed comparable results. The drawing tests were performed on patients' personal computers and the software support for such tests can be extended to commercially available smartphone or tablet set-ups, making it an easily obtainable and cost-effective approach to motor function analysis.

Machine learning-based hardware such as the Parkinson's KinetiGraph¹¹⁶ and the Kinesia system¹¹⁷ are designed to score motor function, dyskinesia and bradykinesia in individuals with PD, and are widely available. The Parkinson's KinetiGraph can be worn on a wrist and measures wrist acceleration. The Kinesia system is worn on either a finger or a wrist and detects motion with an in-built accelerometer and gyroscope. Both systems provide automatic scoring of an individual's motor symptoms, but the output data can also be analysed further using machine learning algorithms, such as SVM. For example, a recent study classified PD tremor severity using the Kinesia system's recordings¹¹⁸. Gait analysis algorithms also show a lot of promise in early diagnosis of motor disorders. For example, an RNN and LSTM were used to classify a database of gait analysis recordings, such as measures of stride-to-stride footfall times, and distinguished healthy controls from individuals with PD, HD or MND with an accuracy of 95–100%¹¹⁹. Moreover, the two algorithms in combination performed better than an SVM alone¹²⁰, suggesting that existing algorithms could be further improved to optimize performance.

Data on movement can also be useful in the study of AD. Film footage of patients performing instrumental activities of daily living (IADL) (for example, bathing, dressing and eating) can be watched and manually scored by clinicians¹²¹. However, this approach can be time-consuming and automating this process would be of major benefit to neurologists investigating IADL. Deep learning and CNN-based machine learning algorithms are capable of recognizing action from video footage¹²² and this technology has been applied to action recognition in IADL recordings¹²³. However, the use of cameras to monitor IADL has implications for patient privacy¹²⁴. New technologies such as the random forest algorithm-powered SmartFABER solve privacy issues by collecting data from motion and contact sensors placed around the home, feeding this data back to software installed on the individual's local personal computer, and analysing user movement and interactions with objects¹²⁵. Data from wearable sensors has also been used for machine learning-based activity recognition. For example, one study found that LSTM algorithms performed better than standard CNN approaches in activity identification and classification from this kind of data¹²⁶. In contrast to the Kinesia system or Parkinson's KinetiGraph, the sensors used to generate the data used in this analysis were worn on multiple parts of the body, which enabled the study of complex movements, such as using a toggle switch, cleaning a table, opening and closing doors and drawers. Although individuals with PD currently stand to benefit the most from wearable

technology, smartwatch-based wearable sensors that use SVM for recognition of agitated behaviour in individuals with dementia show promise¹²⁷.

Language features. Language features are important indicators of cognitive state, as communication skills and interpersonal behaviour deteriorate in many neurodegenerative diseases^{128–130}. Machine learning approaches have been used to extract language features from audio recording transcripts in order to distinguish between individuals with AD and healthy individuals. For example, the authors of one study analysed the way patients compose verbal utterances and used the resulting lexical features to differentiate between individuals with AD, MCI or vascular dementia and healthy controls¹³¹. Several different algorithms were tested, out of which the SVM performed most consistently. In another study, an n-gram language model was used to analyse the vocabulary of participants and the frequencies with which they used specific words together in a sequence¹³². The algorithm assigned a perplexity score to the utterances, meaning that the higher the perplexity score, the more unforeseen and convoluted the utterance, and the more likely the individual was to have an AD diagnosis. In individuals with AD, the perplexity scores were found to correlate with mini-mental state examination scores, thus showing the potential of this approach as a diagnostic tool.

In addition to the machine learning-based analysis of transcripts, AI-driven interactive avatars have been used to capture more complex language data. Inspired by early interactive computers¹³³, avatars are animated humans that ask the patient pre-programmed questions and record the resulting conversation¹³⁴. Avatars most often take the form of software installed on the patient's personal computer or tablet and no time limit is applied to patients' responses, which is a scenario that is difficult to re-create in face-to-face clinical visits. In one example of the use of an avatar¹³⁵, a set of questions based on clinical examination tools (mini-mental state examination, objective structural mental examination and the Wechsler memory scale-revise test) was used to assess participants for symptoms of dementia. In this study, SVM and logistic regression were used to assign a diagnostic category to patients on the basis of speech features and audiovisual cues extracted from the video recordings (for example, smiling, eye contact and consistent delays in answering the questions). This approach was able to distinguish between healthy individuals and individuals with dementia with an accuracy of 93%¹³⁵. This study highlights a key benefit of using avatars over the traditional analysis of transcripts, as allowing patients to speak freely and naturally enables the recognition of new speech features, such as pitch and tone changes or breathiness. Transcripts of conversation would not take such features into account and are limited by patient-doctor contact time constraints. A similar AI system was used as a conversation analysis aid in a memory clinic and identified four out of six participants with neurodegenerative dementia and six out of seven participants with functional memory disorders¹³⁶, which are important in the differential diagnosis of prodromal

dementia¹³⁷. As the number of individuals with suspected dementia is rising¹⁷, installation of avatar software on an individual's personal computer could enable the evaluation of speech features at home, which would help speed up diagnosis, save medical personnel time, and reduce the fatigue and potential distress caused by the need to travel to a memory clinic¹³⁶. Speech data are complex and contain a large number of different features. Therefore, deep neural networks¹⁹ (TABLE 1) are frequently used to perform pattern recognition in this kind of multilayered data.

Molecular and genetic data. Improving our understanding of the molecular foundations of neurodegenerative disorders is key for the development of new therapies and for diagnosis and prognosis. Next-generation sequencing techniques have increased the speed of DNA sequencing, enabling large volumes of data to be acquired relatively quickly. The volume of genomic data produced, especially in GWAS and other large cohort studies, requires a well-refined analysis approach and machine learning techniques are proving useful in this area. Multiple AD-associated genes have been identified¹³⁸, but the idiopathic nature of the disease, along with its high heritability, suggests that further genetic risk factors or complex genetic interactions might play important roles in disease onset or progression¹³⁹. GWAS aim to unravel some of these complex relationships. For example, in one study a supervised SVM-based algorithm was used to interrogate brain-specific gene expression data with the aim of identifying novel AD-associated genes¹⁴⁰. The authors used a training dataset of 335 AD-associated genes identified through previous GWAS and other genetic studies and 335 non-AD-associated genes, and integrated brain-specific gene expression data to train the classifier to identify AD-associated pathways. The authors then used the trained algorithm to identify genes that interacted closely with the known AD-associated genes in the brain-specific network and ranked these new candidate genes by AD association probability. The top candidates corresponded to genes previously identified as AD-associated by GWAS, but the authors also identified a number of genes involved in cellular processes, such as enzyme binding, that had not been identified before.

A different approach was taken in another study, in which gene expression profiles were predicted from ADNI GWAS data and a range of different machine learning algorithms used to identify associations between AD diagnosis and gene expression profiles across different tissues¹⁴¹. In this study, the RNN was the most accurate algorithm for distinguishing individuals with AD from healthy individuals. The authors also tested the performance of the algorithm in predicting disease phenotype, but the results were inconclusive, probably owing to the complexity of the interaction between genetics and environment. Using machine learning to cluster patients based on their genomic similarity is also helping to develop stratification tools for MS¹⁴², the hope is that this stratification will help triage patients after diagnosis and predict their individual disease trajectory.

Applying machine learning to study protein signatures in samples from patients can aid biomarker discovery, which in turn is likely to improve disease diagnosis. In a study by Ray et al.¹⁴³, published in 2007, a classification algorithm called predictive analysis of microarrays was used to identify plasma proteins that could discriminate between individuals with AD and healthy individuals when given a cohort of blinded samples. Starting from a pool of 120 proteins assessed using an enzyme-linked immunosorbent assay, the authors identified 18 signalling proteins, the blood expression level of which was used to distinguish between samples from individuals with AD and healthy controls with close to 90% accuracy. These 18 proteins were also used to identify patients who had MCI that progressed to AD within 2–6 years of sample collection. Several years later, in a study by Agarwal et al.¹⁴⁴, an unsupervised artificial neural network algorithm for both feature selection and classification was applied to the same dataset as used by Ray et al.¹⁴³. The artificial neural network identified a smaller set of nine proteins, as opposed to 18, that distinguished individuals with AD from healthy controls with accuracy similar to that found by Ray et al., resulting in significant economic savings. Of these nine proteins, seven were common between the two studies, whereas two were new findings. In addition, Agarwal et al.¹⁴⁴ identified a cluster of 29 proteins that identified individuals with MCI that would progress to AD, individuals with MCI that would progress towards other dementias, and individuals with AD. This prediction accuracy could not be achieved with either the nine-protein or the 18-protein clusters identified in the two studies. Comparative studies of this kind highlight how advances in machine learning approaches can refine and improve disease classification and prediction accuracy to benefit patient health, as well as reduce economic costs.

Similarly, in recent studies machine learning has been applied to metabolomics data from individuals with MS¹⁴⁵ or AD¹⁴⁶ to identify new biomarkers for these diseases. In the first study¹⁴⁵, 400 plasma metabolites were assessed in a small cohort of 12 individuals with MS and 13 healthy controls. Supervised random forests, with 5,000 trees and 100 randomly selected metabolites to determine classification at each node in a tree, were applied to identify six metabolites, an increase in the expression of which predicted a diagnosis of MS with a probability of 80%. In another study¹⁴⁶, a similar random forests approach was used to analyse the prediction power of a combination of clinical and biochemical data, including data on metabolomic, genetic, functional health, lifestyle, cognitive and bio-demographic risk markers. The analysis showed that different combinations of the six risk markers resulted in statistically significant discrimination between individuals with AD, individuals with MCI and healthy controls.

Clinical records. In addition to the applications discussed above, machine learning can be used to mine routinely collected health-care data for new insights. EHRs are compiled by health-care providers and contain the medical history of individuals under their care, which can include information on immunizations, prescribed

Next-generation sequencing

High-throughput, deep sequencing of DNA and RNA; this technique utilizes sequencing technologies that are capable of processing multiple DNA or RNA sequences in parallel.

Metabolomics

A study of metabolites, that is the small molecule substrates, intermediates and products of cellular metabolism, and their interactions within living organisms.

medications, test results and vital signs. EHRs are being increasingly implemented worldwide^{147,148} and the collection of data in this way requires no additional input from patients¹⁴⁹. However, EHR data were intended to be read by humans and often consist of unstructured notes written by health professionals. Therefore, EHRs need to be converted into computer-readable formats before being analysed with machine learning techniques. Machine learning-enabled natural language processing techniques focus on methods to process and interpret human language^{150–156} (TABLE 1), and can be used to access the information contained within EHRs^{157,158}. The current state-of-the-art approach¹⁵³ for natural language processing uses deep neural networks pre-trained on billions of words to perform tasks such as predicting missing words in sentences or identifying whether two sentences follow each other. After training, these deep neural networks can be fine-tuned for a variety of tasks, including question answering or inference, in an example of transfer learning. One example of the application of natural language processing to health-care data is the *Comprehend Medical initiative* by Amazon, which is a service that helps extract meaningful information, such as the presence of a gene mutation, date of symptom onset or identification of pathologies, from unstructured data such as EHRs.

Machine learning can be used to perform time series analyses on longitudinal EHR data. In these analyses, an algorithm learns prognostic signatures from historical data and looks for these signatures in new datasets to create personalized health forecasts for patients. For example, in one study, data from cognitive tests performed regularly at a memory clinic were used to plot the pattern of change associated with cognitive decline. This information, in combination with other clinical information, was applied to data from individuals who were in the early stages of the disease to identify early signs of worsening of dementia¹⁵⁹. Such an approach might prove particularly useful in diseases characterized by aggressive decline and poor survival such as MND, for which the average survival after diagnosis is 3–5 years¹⁶⁰. Existing statistical models of MND use data from routine clinical assessments to predict patient prognosis for up to one year¹⁶¹, and recent improvements to this approach can make personalized predictions for up to 120 months depending on the disease severity¹⁶². These models, however, do not take into consideration an individual's previous medical history, which could be informative, and missing data can result in biases.

In a study of PD progression, a Bayesian multivariate predictive inference platform was applied to clinical information, including analysis of motor progression assessments as well as complete genetic and molecular data, collected over a 2 year period from a cohort of 117 healthy controls and 312 individuals with PD¹⁶³. A total of 17,499 features were included in the model with the aim of identifying novel predictors of motor progression in the early stages of PD. The progression modelling confirmed some known factors for faster motor decline, such as higher baseline motor score, male sex and older age, but it also identified new predictors, such as genetic variation and cerebrospinal fluid biomarkers.

Deep learning methods rely on the input of large quantities of data and are suited to the analysis of EHRs, which, in some cases, contain information on the majority of a national population. RNN models have been effectively applied to EHRs to predict clinical events and improve diagnosis. For example, one study applied LSTM RNNs to data provided by the US National Alzheimer's Coordinating Center, which includes 12 years of heterogeneous medical information on 5,432 individuals with probable AD. The study aimed to predict the AD progression stage of the next hospital visit by a patient only on the basis of the information of the patient's historical visits. By integrating clinical data, including global staging Clinical Dementia Rating scores and the Functional Activities Questionnaire results, the algorithm could predict a patient's AD progression on the next visit with over 99% accuracy, significantly outperforming classic time series forecasting methods¹⁶⁴. Similarly, an RNN-based method was used to compare longitudinal health records from different individuals with PD and group these records according to similarity¹⁶⁵. This kind of approach could be used to identify disease subtypes within a patient population. In another study LSTM was applied to EHR data to predict the length of time that patients affected by different pathologies would stay in hospital¹⁶⁶. The algorithm performed better than traditional clinical predictive methods across different hospital wards, including neurological units, which is indicative of the versatility of machine learning approaches and shows promise for the application of this method to neurodegeneration.

Ensuring that the private data of individual patients is protected while allowing access to health records for research purposes is an ongoing challenge. In an attempt to address this challenge, machine learning was used to anonymize EHRs from a mental health-care provider and was able to mask 98.8–100% of patient identifiers that appeared in the text — the only errors resulted from misspelling of words in the original record¹⁶⁷.

Therapy development

Effective treatments for many neurodegenerative diseases are lacking, but the high failure rate of clinical trials for these diseases has led to the withdrawal of investment by large pharmaceutical companies^{168–171}. For example, over 400 clinical trials of potential treatments for AD were performed between 2002 and 2012, but only one drug, memantine, was approved¹⁷². Similarly, in the last 20 years, 50 clinical trials of drugs for MND have failed to show positive results. Riluzole and edaravone are the only drugs approved to treat MND and both have demonstrated only a modest improvement in patient survival and functional ability¹⁷³. These unfortunate failures highlight the complexity of developing therapies for brain conditions and create opportunities for new approaches to drug development.

Target identification. Neurodegenerative disorders involve a vast array of mechanisms that all contribute to disease pathology. For example, in MND, multiple processes, such as RNA metabolism, axonal transport, mitochondrial function and autophagy, are implicated

in the degeneration and death of motor neurons¹⁷⁴. The ability to explore the data related to these pathways in a thorough, holistic and efficient manner is key to understanding disease, but can be challenging for individual scientists. Machine learning can help make sense of this complexity and even predict drug targets.

One machine learning approach to drug target identification is relational inference on a knowledge graph, which links entities such as genes, diseases and drugs. Knowledge graphs are typically built from the integration of multiple data types; for example, data extracted from full text articles on PubMed, and from databases such as KEGG, OmniPath, Ensembl and ChEMBL^{175–178}. Knowledge graph approaches can learn non-obvious links between diseases and biological drug targets (for example, identifying a new therapeutic protein target on the basis of its interaction with a protein known to be mutated in a particular disease), and are attractive because a single algorithm can be used to make predictions for multiple diseases. One downside of using these approaches on their own is that they can lack granularity in their biological relationships (for example, context of different brain regions), which can lead to predictions with low specificity. This can be a particular problem in neuroscience, where differences in gene interaction networks between different brain regions might be important to understanding the disease pathophysiology and treatment potential¹⁷⁹. Several relational inference methods have been published that performed well on a benchmark dataset for a wide range of disorders, including neurodegenerative diseases¹⁸⁰. However, to date new hypotheses generated using these approaches have not been scientifically validated.

Machine learning can also be used to perform large-scale text mining to suggest proteins that might be related to a disease of interest. In contrast to knowledge graphs, which only take into account relationships between entities, this approach uses the entire text as substrate, thus enabling a more detailed specification of biological context. In one study, an automatic method was used to extract text features from the published literature and create a model of the RNA-binding proteins (RBPs) previously associated with MND¹⁸¹. This model was then applied to a candidate list of other RBPs and used a network diffusion algorithm to identify those most similar to the known MND-associated RBPs. Of the ten best candidate RBPs identified by the machine learning analysis, five showed significantly altered levels in individuals with MND when compared with controls, indicating that the model's predictions were accurate.

Machine learning-based analysis of biological samples (for example, post-mortem CNS tissue) might also provide useful information for target identification. Gene expression data from individuals with disease and healthy controls can be used to build molecular networks that visualize the biological processes that are altered in the disease state. For example, a combination of co-regulation, clustering and Bayesian inference was used to analyse transcriptomic data from brain tissue samples from individuals with late-onset AD and controls, and identified groups of genes that were altered in the diseased tissue¹⁸². A group of immune-related and

microglial-specific genes were more highly expressed in individuals with late-onset AD than in control individuals, and the microglial protein TYROBP was identified as a key regulator of this group. Deficiency of this protein was subsequently found to be neuroprotective in a mouse model of AD^{183,184}, suggesting TYROBP as a new therapeutic target.

Patient stratification. Heterogeneity in clinical manifestation, disease progression and genetic predisposition often exists within groups of individuals diagnosed with the same neurodegenerative disease¹⁸⁵. This heterogeneity makes it difficult to understand disease mechanisms from studying the diagnostic group as a whole, as different mechanisms could be responsible for the disease in different individuals and makes identifying effective therapies more challenging. Therefore, stratifying study participants according to more detailed criteria than a diagnostic class is becoming more common. The use of machine learning techniques for this purpose is becoming increasingly popular, as the entirety of an individual's clinical history and additional data, including, transcriptomic, neuroimaging or biomarker expression data, can be fed into the algorithm¹⁸⁶. One approach to patient stratification using deep data might be to use unsupervised machine learning methods to reduce dimensionality in high-dimensional labelled data and derive classifiers of patient outcomes. This approach can identify patients with different subtypes or endotypes of the disease, which would otherwise not have been obvious¹⁸⁷, for further study of disease mechanisms or development of endotype-specific therapeutic strategies (FIG. 4).

Heterogeneity in patient populations is also a problem for clinical trial design. Natural heterogeneity in the outcome variable is an unhelpful source of noise that can mask the effects of a therapeutic intervention. A lack of biomarkers means that clinicians often rely on subjective self-reported clinical measurements for diagnosis and detecting a response to therapeutic intervention¹⁸⁸. Therefore, using machine learning models to stratify patients and identify biomarkers of treatment response from clinical and molecular data could improve the efficacy of clinical trials. Indeed, patient stratification and biomarker identification are major objectives of large publicly funded databases such as the ADNI. For example, an approach was developed to combine multiple machine learning models that used clinical, cognitive and genetic data collected in an international, multicentre effort, to predict survival in patients with MND¹⁶². The aim of this model was to provide information that could be used to stratify patients for clinical trials. Another study used a random forest algorithm to predict disease progression in individuals with MND on the basis of 3 months of clinical examination data³². Although this model has not yet been used to stratify patients in a clinical trial, seeing patient data-driven models that are predictive of disease outcomes is encouraging.

Conclusions and future challenges

Machine learning algorithms can recognize patterns and make novel inferences from large amounts of multidimensional data in a way that humans cannot. However,

Bayesian inference

A method of statistical inference that uses Bayes' theorem to calculate the probability of a hypothesis being true on the basis of observed data and prior information.

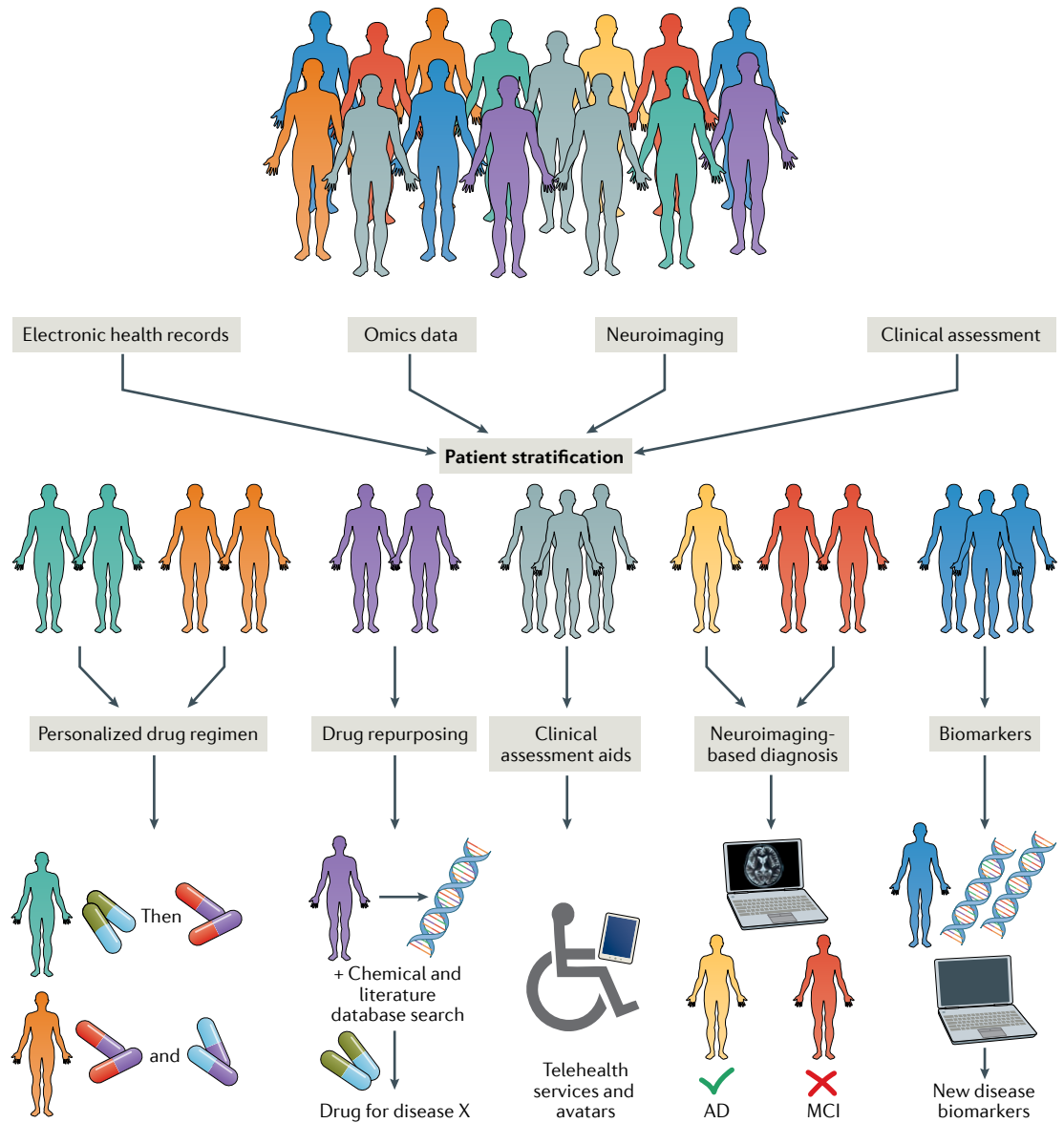


Fig. 4 | Application of machine learning approaches to development and implementation of treatments for neurodegeneration. Patient stratification, a process through which a heterogeneous patient population is separated into specific endotypes, helps identify different aetiologies of disease and targets or hallmarks that characterize them. Unsupervised machine learning algorithms can be fed all existing patient information at the point of diagnosis, as well as new information that is gathered as the disease progresses, in order to better understand the underlying disease aetiology. During the course of therapy, any significant event such as adverse reactions, lack of response or cross-reactivity with other medication, can be fed into machine learning algorithms to help build a better understanding of both the disease and the drug, as well as the best therapeutic course of action in each patient. As machine learning algorithms continue to harness the knowledge contained within relevant literature and databases (including chemical and genetic databases), they can help build a comprehensive picture of molecular changes happening in the disease, which can consequently aid identification of new disease targets. This in turn can initiate a new drug discovery cascade, if the target is not yet druggable. Outside the realm of pharmacological treatments, machine learning algorithms could provide therapeutic avatars, for individuals with dementias or could be an indirect point of contact for patients with decreased mobility. Moreover, the field of neurochemical artificial intelligence is focusing on development of novel drugs as well as modifying and/or repurposing existing ones. AD, Alzheimer disease; MCI, mild cognitive impairment. Brain scan image credit: M. Andritoiu/Alamy Stock Photos.

the use of machine learning to aid diagnosis, prognosis and therapeutic development is still in its infancy. In the future, machine learning technologies might enable more precise, earlier diagnosis of neurodegenerative diseases on the basis of medical history, molecular profiles and

imaging information, and through the identification of more specific diagnostic biomarkers. More precise diagnosis could be followed by a personalized treatment regimen that will take into consideration the patient's endotype. Machine learning could also reduce the time

and cost involved in performing clinical trials, and increase the likelihood of success, by enabling efficient patient stratification and identifying accurate biomarkers of treatment response. Recent advances in machine learning technology have been made possible by the increased availability of large, multidimensional datasets that are curated by multicentre initiatives, the democratization of machine learning algorithms through open-source code and libraries, and the increased affordability of high-performance computing infrastructures.

Despite the potential of machine learning, creating and applying machine learning algorithms to neurodegenerative disease data remains difficult. One challenge relates to the data itself — machine learning models are only as powerful as the data they rely on. The lack of large datasets, especially multidimensional patient data, for many diseases is a barrier to the application of machine learning. Patient datasets typically consist of only tens or hundreds of patients and tend to be noisy because of measurement inconsistency, error or participant drop-out; these factors all make statistical analyses more prone to errors. Metadata analyses are often necessary because the overlap between results from different datasets can be small. Conducting metadata analyses helps detect, analyse and understand inconsistencies across datasets and increases the statistical power of the data, as the combined dataset now includes more individual cases¹⁸⁹. Additionally, data are often biased towards certain demographic populations, which limits the generalization of the learning and results in disparity in health care¹⁹⁰.

Data limitations mean that, in practice, most machine learning pipelines start with careful curation of the data, which requires time and expert input. However, new machine learning approaches are being developed to address the problem of small datasets. For example, active learning strategies enable quality inferences from fewer samples than other machine learning methods and remove the need to label large datasets, which can be costly¹⁹¹. Active learning methods evaluate and provide feedback on the data as the model is being built, simultaneously making predictions for current datasets and identifying shortcomings in the model by suggesting additional data points to be included. Although active learning has been used in drug design and optimization¹⁹², and could be applied to medical image classification or even patient response profiling, the approach remains largely unexplored with regard to neurodegenerative disease research. In addition, transfer learning is a new method that uses data from one learning task to help in learning another task¹⁹³. For example, a transfer learning algorithm trained to diagnose AD from MRI images, was applied to T2-weighted FLAIR MRI images without a drop in performance¹⁹⁴. Transfer learning relies on the analysis of a selected subset of data features to reduce data dimensionality, thus avoiding overfitting and making the approach suitable for use on small datasets. Transfer learning has also been used to transfer information on biomarker expression across different neurodegenerative diseases¹⁹⁵, as well as for biomarker discovery from genomic data¹⁹⁶ and diagnosis and classification of individuals with AD

from neuroimaging data^{197–199}. Special types of generative models, called general adversarial neural networks²⁰⁰, have been used to generate more training data for learning on biomedical images, for example, by generating MRI images of the brain from images obtained via different imaging platforms such as PET⁷³. General adversarial neural networks enable such image manipulation and creation by learning the useful features of the training dataset and generating a new dataset based on the learnt features^{201,202}.

Robust assessment of machine learning model performance needs to be carried out to select the best model for the task, and to ensure that clinicians can have confidence in the model's output. For well-defined tasks, supervised models can be trained on labelled benchmark data (that is, sources of truth), and the performance of these models can be evaluated by comparing the model output with the benchmark data. However, many other tasks in neurology, such as patient stratification, require unsupervised models that involve no benchmark data, which means that assessing the performance of the model presents a significant challenge. Therefore, evaluation of the performance of unsupervised models uses feedback from experts to establish whether the model output is rational²⁰³, or correlation of the output with other known features such as clinical markers²⁰⁴. Even for well-defined tasks, benchmark data are often sparse, meaning that the performance of the model on benchmark data does not necessarily represent the performance of the model on new datasets. This sparsity of benchmark data is especially concerning because some machine learning models are known to be prone to overfitting, which means they become specific to the benchmark data and do not perform well on new datasets. If a machine learning model cannot reliably generalize to new, unseen scenarios, the practical applications are limited. Poor methods of performance evaluation can also lead to over-interpretation of findings and incorrect assumptions about causality.

Another limitation of many machine learning algorithms is that they are 'black boxes', that is, they cannot be used to understand the problem they address or the outputs they produce. Although algorithms are trained using medical knowledge and expertise, explaining exactly why the algorithm performed in a given way is not possible^{205,206}. For example, understanding why a deep learning algorithm labelled certain retinal images as showing hallmarks of retinopathy is impossible, even though the predictions might later prove accurate on review by experts²⁰⁷. This lack of transparency can severely limit the usefulness of machine learning outputs and therefore the willingness of researchers to adopt these approaches. Fortunately, explainable AI, which aims to build models that can be interpreted and explained, is a growing field²⁰⁸. In explainable AI, algorithms trace or rationalize their decision-making in a way that can be understood by humans.

Resolving the challenges involved in applying machine learning to neurodegenerative disease data will require collaboration between experts in biomedicine and machine learning. For example, selecting the right datasets for training and validation, and knowing how

Q8

to deal with missing data require a deep understanding of data collection procedures. In order to respond to the pressing demands of developing machine learning systems in a highly complex and often ambiguous space, more cross-disciplinary training programmes are needed. In addition, given the caveats of using and evaluating machine learning technologies, it would be wise to create industry-wide AI assessment and certification tests to ensure that only robust, well-validated technology can impact research or patient care. The widespread integration of machine learning into health-care settings would also pose several practical challenges. For example, implementation of new systems into clinics needs to take into account concerns around job security and career progression of existing health-care personnel, and training needs to be conducted in a way that allows personnel to adapt to the new technology. In a survey of physician perspectives on AI implementation in clinical

practice, the commercialization of medical AI systems and the legal, as well as ethical, responsibility of vendors of these systems were amongst the main concerns raised, which highlights the need for appropriate regulatory bodies to be introduced²⁰⁹.

In conclusion, the integration of machine learning into diagnostic and prognostic neurology practice, as well as the design of future therapeutics, is likely to be achieved with national and international efforts to establish multidisciplinary groups of experts to tackle some of the main challenges discussed in this Review article. The potential of these collaborative efforts is immense when we consider the health challenges our society will have to face in the next 50 years as a result of an increasing ageing population, and the benefits that would result from a faster and more accurate health service.

Q11

1. McCarthy, J. Basic questions: *What is Artificial Intelligence?* <http://www-formal.stanford.edu/jmc/whatsai/node1.html> (2007).
2. Agatonovic-Kustrin, S. & Beresford, R. Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research. *J. Pharm. Biomed. Anal.* **22**, 717–727 (2000).
3. Yu, K. H., Beam, A. L. & Kohane, I. S. Artificial intelligence in healthcare. *Nat. Biomed. Eng.* **2**, 719–731 (2018).
4. McDougall, R. J. Computer knows best? The need for value-flexibility in medical AI. *J. Med. Ethics* **45**, 156–160 (2019).
5. McDougall, R. J. No we shouldn't be afraid of medical AI; it involves risks and opportunities. *J. Med. Ethics* **45**, 559 (2019).
6. Vellido, A. Societal issues concerning the application of artificial intelligence in medicine. *Kidney Dis.* **5**, 11–17 (2019).
7. Di Nucci, E. Should we be afraid of medical AI? *J. Med. Ethics* **45**, 556–558 (2019).
8. de Saint Laurent, C. In defence of machine learning: debunking the myths of artificial intelligence. *Eur. J. Psychol.* **14**, 734–747 (2018).
9. Buch, V. H., Ahmed, I. & Maruthappu, M. Artificial intelligence in medicine: current trends and future possibilities. *Br. J. Gen. Practice* **68**, 143–144 (2018).
10. Denaxas, S. C. & Morley, K. I. Big biomedical data and cardiovascular disease research: opportunities and challenges. *Eur. Heart. J. Qual. Care Clin. Outcomes* **1**, 9–16 (2015).
11. Weber, G., Mandl, K. & Kohane, I. Finding the missing link for big biomedical data. *JAMA* **311**, 2479–2480 (2014).
12. Van Horn, J. & Toga, A. Human neuroimaging as a "big data" science. *Brain Imaging Behav.* **8**, 323–331 (2014).
13. Zhou, L. & Verstreken, P. Reprogramming neurodegeneration in the big data era. *Curr. Opin. Neurobiol.* **48**, 167–173 (2018).
14. Vallejos, C. A., Richardson, S. & Marioni, J. C. Beyond comparisons of means: understanding changes in gene expression at the single-cell level. *Genome Biol.* **17**, 1–14 (2016).
15. Ritchie, M. D. et al. Multifactor-dimensionality reduction reveals high-order interactions among estrogen-metabolism genes in sporadic breast cancer. *Am. J. Hum. Genet.* **69**, 138–147 (2001).
16. Xu, J., Zhang, Y., Qiu, C. & Cheng, F. Global and regional economic costs of dementia: a systematic review [abstract]. *Lancet* **390**, S47 (2017).
17. Prince, M., Prina, M. & Guerchet, M. *World Alzheimer's Report 2013. The Journey of Caring: An Analysis of Long-Term Care for Dementia* (Alzheimer's Disease International, 2013).
18. Bishop, C. *Pattern Recognition and Machine Learning* (Springer, 2006).
19. LeCun, Y., Bengio, Y. & Hinton, G. Deep learning. *Nature* **521**, 436–444 (2015).
20. Van Der Maaten, L. & Hinton, G. Visualizing data using t-SNE. *J. Mach. Learn. Res.* **9**, 2579–2605 (2008).
21. McInnes, L., Healy, J. & Melville, J. UMAP: uniform manifold approximation and projection for dimension reduction. Preprint at *arXiv* <https://arxiv.org/abs/1802.03426> (2018).
22. Oyelade, J. et al. Clustering algorithms: their application to gene expression data. *Bioinform. Biol. Insights* **10**, 237–253 (2016).
23. Chapelle, O., Schölkopf, B. & Zien, A. (eds) *Semi-Supervised Learning* (MIT Press, 2006).
24. Vapnik, V. *Statistical Learning Theory* (Wiley-Interscience, 1998).
25. Joachims, T. in *ICML '99: Proceedings of the Sixteenth International Conference on Machine Learning* (eds Bratko, I. & Dzeroski, S.) 200–209 (Morgan Kaufmann, 1999).
26. Watkins, C. J. C. H. *Learning with Delayed Rewards*. Thesis, King's College, Cambridge (1989).
27. Mnih, V. et al. Human-level control through deep reinforcement learning. *Nature* **518**, 529–533 (2015).
28. Popova, M., Isayev, O. & Tropsha, A. Deep reinforcement learning for de-novo drug design. *Sci. Adv.* **4**, 1–14 (2017).
29. Raudys, S. *Statistical and Neural Classifiers: An Integrated Approach to Design* (Springer, 2001).
30. Summers, M. J. et al. Deep machine learning application to the detection of preclinical neurodegenerative diseases of aging. *Sci. J. Digit. Cult.* **2**, 9–24 (2017).
31. Ho, T. K. Random decision forests perceptron training. in *ICDAR '95: Proceedings of the Third International Conference on Document Analysis and Recognition* 278–282 (IEEE Computer Society, 1995).
32. Hothorn, T. & Jung, H. H. RandomForest4Life: a random forest for predicting ALS disease progression. *Amyotroph. Lateral Scler. Front. Degener.* **15**, 444–452 (2014).
33. Cortes, C. & Vapnik, V. Support-vector networks. *Mach. Learn.* **297**, 273–297 (1995).
34. Rosenblatt, K. *The Perceptron – A Perceiving and Recognizing Automation* (Cornell Aeronautical Laboratory, 1957).
35. McCulloch, W. S. & Pitts, W. A logical calculus of the idea immanent in nervous activity. *Bull. Math. Biophys.* **5**, 115–133 (1943).
36. Fukushima, K. Neocognitron: a self-organizing neural network model for a mechanism of pattern recognition unaffected by shift in position. *Biol. Cybern.* **36**, 193–202 (1980).
37. LeCun, Y., Bottou, L., Bengio, Y. & Haffner, P. Gradient-based learning applied to document recognition. *Proc. IEEE* **86**, 2278–2324 (1998).
38. LeCun, Y., Hafner, P., Bottou, L. & Bengio, Y. in *Shape, Contour and Grouping in Computer Vision. Lecture Notes in Computer Science* Vol 1681 (eds Forsyth, D. A., Mundy, J. L., di Gesù, V. & Cipolla, R.) 319–345 (Springer, 1999).
39. Burt, J. R. et al. Deep learning beyond cats and dogs: recent advances in diagnosing breast cancer with deep neural networks. *Br. J. Radiol.* **91**, 2–11 (2018).
40. Hopfield, J. J. Neural networks and physical systems with emergent collective computational abilities. *Proc. Natl Acad. Sci. USA* **79**, 2554–2558 (1982).
41. Hochreiter, S. & Schmidhuber, J. Long short-term memory. *Neural Comput.* **9**, 1735–1780 (1997).
42. Cho, K. et al. in *Proceedings of the 2014 Conference on Empirical Methods in Natural Language Processing (EMNLP)* 1724–1734 (Association for Computational Linguistics, 2014).
43. Cawley, G. C. & Talbot, N. L. C. On over-fitting in model selection and subsequent selection bias in performance evaluation. *J. Mach. Learn. Res.* **11**, 2079–2107 (2010).
44. Chicco, D. Ten quick tips for machine learning in computational biology. *BioData Min.* **10**, 1–17 (2017).
45. Neumaier, A. Solving ill-conditioned and singular linear systems: a tutorial on regularization. *SIAM Rev.* **40**, 636–666 (1998).
46. Michel, P. P., Hirsch, E. C. & Hunot, S. Understanding dopaminergic cell death pathways in Parkinson disease. *Neuron* **90**, 675–691 (2016).
47. Donev, R., Kolev, M., Millet, B. & Thome, J. Neuronal death in Alzheimer's disease and therapeutic opportunities. *J. Cell. Mol. Med.* **13**, 4329–4348 (2009).
48. Fischer, L. R. et al. Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. *Exp. Neurol.* **182**, 232–240 (2004).
49. Hainc, N. et al. The bright, artificial intelligence-augmented future of neuroimaging reading. *Front. Neurol.* **8**, 10–12 (2017).
50. Grenander, U., Chow, Y. & Keenan, D. *HANDS: a Pattern Theoretic Study of Biological Shapes* (Springer, 1990).
51. Evans, A. C., Marrett, S., Torrescorzo, J., Ku, S. & Collins, L. MRI-PET correlation in three dimensions using a volume-of-interest (VOI) atlas. *J. Cereb. Blood Flow. Metab.* **11**, A69–A78 (1991).
52. Woods, R. P., Mazziotta, J. C. & Cherry, S. R. MRI-PET registration with automated algorithm. *J. Comput. Assist. Tomogr.* **17**, 536–546 (1993).
53. Joshi, S. C. et al. Hierarchical brain mapping via a generalized dirichlet solution for mapping brain manifolds. in *Proceedings of the SPIE's 1995 international symposium on optical science, engineering, and instrumentation. Vision geometry IV* Vol. 2573 (eds Melter, R. A., Wu, A. Y., Bookstein, F. L. & Green, W. D. K.) 278–289 (SPIE, 1995).
54. Grady, C. L. et al. Subgroups in dementia of the Alzheimer type identified using positron emission tomography. *J. Neuropsychiatry Clin. Neurosci.* **2**, 373–384 (1990).
55. DeFigueiredo, R. J. P. et al. Neural-network-based classification of cognitively normal, demented, Alzheimer disease and vascular dementia from single photon emission with computed tomography image data from brain. *Proc. Natl Acad. Sci. USA* **92**, 5530–5534 (1995).

This extensive review provides an elegant summary of deep learning methods and their application to images, video footage, speech recordings and written text.

This study is one of the first to have used an artificial neural network algorithm to automate the

- identification of normal ageing, AD, and vascular dementia from SPECT data.**
56. Wang, S. et al. Pathological brain detection by artificial intelligence in magnetic resonance imaging scanning. *Prog. Electromagn. Res.* **156**, 105–133 (2016).
57. Haller, J. W. et al. Hippocampal MR imaging morphometry by means of general pattern matching. *Radiology* **199**, 787–791 (1996).
58. Davatzikos, C. et al. A computerized approach for morphological analysis of the corpus callosum. *J. Comput. Assist. Tomogr.* **20**, 88–97 (1996).
59. Gur, R. C. et al. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J. Neurosci.* **19**, 4065–4072 (1999).
60. Mega, M. S. et al. Cerebral correlates of psychotic symptoms in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **69**, 167–171 (2000).
61. Fischl, B. & Dale, A. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl Acad. Sci. USA* **97**, 11050–11055 (2000).
62. Ashburner, J. & Friston, K. Voxel-based morphometry—the methods. *Neuroimage* **11**, 805–821 (2000).
63. Haller, J. W. et al. Three-dimensional hippocampal volumetry by high dimensional transformation of a neuroanatomical atlas. *Radiology* **202**, 504–510 (1997).
64. Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19**, 1233–1239 (2003). **The paper presents the first automated analysis system based on a digital brain atlas to show robust application to fMRI data, without the need for pre-defined region of interest masks.**
65. Lao, Z. et al. Morphological classification of brains via high-dimensional shape transformations and machine learning methods. *Neuroimage* **21**, 46–57 (2004). This paper presents an early application of SVM to MR image analysis and highlights the importance of analysing all voxels simultaneously, rather than focusing on a pre-defined region of interest.
66. Mourão-Miranda, J., Bokke, A. L. W., Born, C., Hampel, H. & Stetter, M. Classifying brain states and determining the discriminating activation patterns: support vector machine on functional MRI data. *Neuroimage* **28**, 980–995 (2005). **This study is an early demonstration of the superior performance of SVM over traditional statistical methods for MRI analysis and highlights the ability of SVM to select the brain regions from which the most accurate classification can be drawn.**
67. Mitchell, T. M. et al. Learning to decode cognitive states from brain images. *Mach. Learn.* **57**, 145–175 (2004). **In this study multiple machine learning algorithms, including SVM, are used on functional MR images to assess the feasibility of detecting patients' transient cognitive states at a single time interval.**
68. Reczko, M., Karras, D. A., Mertzios, B. G., Graveron-Demilly, D. & Van Ormondt, D. Improved MR image reconstruction from sparsely sampled scans based on neural networks. *Pattern Recognit. Lett.* **22**, 35–46 (2001).
69. Zhu, G. et al. Applications of deep learning to neuro-imaging techniques. *Front. Neurol.* **10**, 1–13 (2019).
70. He, K., Zhang, X., Ren, S. & Sun, J. in *Proceedings of the 29th IEEE Conference on Computer Vision and Pattern Recognition (CVPR 2016)* 770–778 (IEEE, 2016).
71. Gray, K. R. et al. Random forest-based similarity measures for multi-modal classification of Alzheimer's disease. *Neuroimage* **65**, 167–175 (2013).
72. Korolev, S., Safiullin, A., Belyaev, M. & Dodonova, Y. in *Proceedings of the 14th International Symposium on Biomedical Imaging* 835–838 (IEEE, 2017).
73. Choi, H., Kang, H. & Lee, D. S. Predicting aging of brain metabolic topography using variational autoencoder. *Front. Aging Neurosci.* **10**, 212 (2018).
74. Lundervold, A. S. & Lundervold, A. An overview of deep learning in medical imaging focusing on MRI. *Z. Med. Phys.* **29**, 102–127 (2019).
75. Klöppel, S. et al. Automatic classification of MR scans in Alzheimer's disease. *Brain* **131**, 681–689 (2008). **This study shows that an SVM can use MR scans to successfully distinguish between individuals with AD and individuals with FTD as well as between individuals with AD and healthy individuals.**
76. Bron, E. E., Smits, M., Niessen, W. J. & Klein, S. Feature selection based on the SVM weight vector for classification of dementia. *IEEE J. Biomed. Heal. Inform.* **19**, 1617–1626 (2015).
77. Moradi, E., Pepe, A., Gaser, C., Huttunen, H. & Tohka, J. Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. *Neuroimage* **104**, 398–412 (2015).
78. Magnin, B. et al. Support vector machine-based classification of Alzheimer's disease from whole-brain anatomical MRI. *Neuroradiology* **51**, 78–83 (2009).
79. Gerardin, E. et al. Multidimensional classification of hippocampal shape features discriminates Alzheimer's disease and mild cognitive impairment from normal aging. *Neuroimage* **47**, 1476–1486 (2009).
80. Li, S. et al. Hippocampal shape analysis of Alzheimer disease based on machine learning methods. *Am. J. Neuroradiol.* **28**, 1339–1345 (2007).
81. Amoroso, N. et al. Alzheimer's disease diagnosis based on the hippocampal unified multi-atlas network (HUMAN) algorithm. *Biomed. Eng. Online* **17**, 1–16 (2018).
82. De Marco, M., Beltrachini, L., Biancardi, A., Frangi, A. F. & Venneri, A. Machine-learning support to individual diagnosis of mild cognitive impairment using multimodal MRI and cognitive assessments. *Alzheimer Dis. Assoc. Disord.* **31**, 278–286 (2017).
83. Ahn, W., Krawitz, A. & Kim, W. A model-based fMRI analysis with hierarchical Bayesian parameter estimation. *J. Neurosci. Psychol. Econ.* **4**, 95–110 (2011).
84. Rehme, A. K. et al. Identifying neuroimaging markers of motor disability in acute stroke by machine learning techniques. *Cereb. Cortex* **25**, 3046–3056 (2014).
85. Weygandt, M. et al. MRI pattern recognition in multiple sclerosis normal-appearing brain areas. *PLoS ONE* **6**, e21138 (2011).
86. Duchesne, S., Rolland, Y. & Vêrin, M. Automated computer differential classification in Parkinsonian syndromes via pattern analysis on MRI. *Acad. Radiol.* **16**, 61–70 (2009).
87. Chen, L. et al. Rapid automated quantification of cerebral leukoaraiosis on CT images: a multicenter validation study. *Radiology* **288**, 573–581 (2018).
88. Prevedello, L. M., Little, K. J., Qian, S. & White, R. D. Automated critical test findings identification and online notification system using artificial intelligence in imaging. *Radiology* **285**, 923–931 (2017).
89. Titano, J. J. et al. Automated deep-neural-network surveillance of cranial images for acute neurologic events. *Nat. Med.* **24**, 1337–1341 (2018).
90. Chilamkurthy, S. et al. Deep learning algorithms for detection of critical findings in head CT scans: a retrospective study. *Lancet* **392**, 2388–2396 (2018).
91. Davatzikos, C., Fan, Y., Wu, X., Shen, D. & Resnick, S. M. Detection of prodromal Alzheimer's disease via pattern classification of magnetic resonance imaging. *Neurobiol. Aging* **29**, 514–523 (2008).
92. Fan, Y., Resnick, S. M., Wu, X. & Davatzikos, C. Structural and functional biomarkers of prodromal Alzheimer's disease. *Neuroimage* **41**, 277–285 (2008).
93. Fan, Y., Batmanghelich, N. K., Clark, C. M. & Davatzikos, C., Alzheimer's Disease Neuroimaging Initiative. Spatial patterns of brain atrophy in MCI patients, identified via high-dimensional pattern classification, predict subsequent cognitive decline. *Neuroimage* **39**, 1731–1743 (2008).
94. Kivipelto, M. et al. The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): study design and progress. *Alzheimer's Dement.* **9**, 657–665 (2013).
95. Zhang, Y. C. & Kagen, A. C. Machine learning interface for medical image analysis. *J. Digit. Imaging* **30**, 615–621 (2017).
96. Mufford, M. S. et al. Neuroimaging genomics in psychiatry—a translational approach. *Genome Med.* **9**, 1–12 (2017).
97. Bookheimer, S. Y. et al. Patterns of brain activation in people at risk for Alzheimer's disease. *N. Engl. J. Med.* **343**, 450–456 (2000).
98. Heinz, A. et al. Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology* **22**, 133–139 (2000).
99. Liang, Z. & Lauterbur, P. *Principles of Magnetic Resonance Imaging: A Signal Processing Approach* (IEEE, 2000).
100. Hibar, D. P. et al. Common genetic variants influence human subcortical brain structures. *Nature* **520**, 224–229 (2015).
101. Czigler, B. et al. Quantitative EEG in early Alzheimer's disease patients – power spectrum and complexity features. *Int. J. Psychophysiol.* **68**, 75–80 (2008).
102. Lee, H., Brekelmans, G. J. F. & Roks, G. The EEG as a diagnostic tool in distinguishing between dementia with Lewy bodies and Alzheimer's disease. *Clin. Neurophysiol.* **126**, 1735–1739 (2015).
103. Buscema, E. A. et al. Grand total EEG score can differentiate Parkinson's disease from Parkinson-related disorders. *Front. Neurol.* **10**, 1–11 (2019).
104. Buscema, M. et al. An improved I-FAST system for the diagnosis of Alzheimer's disease from unprocessed electroencephalograms by using robust invariant features. *Artif. Intell. Med.* **64**, 59–74 (2015).
105. Bosco, D. A., LaVoie, M. J., Petsko, G. A. & Ringe, D. Proteostasis and movement disorders: Parkinson's disease and amyotrophic lateral sclerosis. *Cold Spring Harb. Perspect. Biol.* **3**, 1–24 (2011).
106. Ross, C. A. & Tabrizi, S. J. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol.* **10**, 83–98 (2011).
107. [No authors listed]. The amyotrophic lateral sclerosis functional rating scale: assessment of activities of daily living in patients with amyotrophic lateral sclerosis. *Arch. Neurol.* **53**, 141–147 (1996).
108. [No authors listed]. Unified Huntington's disease rating scale: reliability and consistency. *Mov. Disord.* **11**, 136–142 (1996).
109. Fahn, S., Elton, R. & Members of the UPDRS Development Committee. in *Recent Developments in Parkinson's Disease* Vol. 2 (eds Fahn, S., Marsden, C. D., Calne, D. B. & Goldstein, M.) 153–163, 293–304 (Macmillan Health Care Information, 1987).
110. Davenport, T. & Kalakota, R. The potential for artificial intelligence in healthcare. *Futur. Healthc. J.* **6**, 94–98 (2019).
111. Rosenblum, S., Samuel, M., Zlotnik, S., Erikh, I. & Schlesinger, I. Handwriting as an objective tool for Parkinson's disease diagnosis. *J. Neurol.* **260**, 2357–2361 (2013).
112. Alty, J., Cosgrove, J., Thorpe, D. & Kempster, P. How to use pen and paper tasks to aid tremor diagnosis in the clinic. *Pract. Neurol.* **17**, 456–463 (2017).
113. McLennan, J., Nakano, K., Tyler, H. & Schwab, R. Micrographia in Parkinson's disease. *J. Neurol. Sci.* **15**, 141–152 (1972).
114. Kotsavasiloglou, C., Kostikis, N., Hristu-Varvakis, D. & Arnaoutoglou, M. Machine learning-based classification of simple drawing movements in Parkinson's disease. *Biomed. Signal. Process. Control.* **31**, 174–180 (2017). **This is the first study to have used a combination of simple line drawings and machine learning algorithms to aid PD diagnosis.**
115. Westin, J. et al. A new computer method for assessing drawing impairment in Parkinson's disease. *J. Neurosci. Methods* **190**, 143–148 (2010).
116. Griffiths, R. I., Kotschet, K., Arfon, S., Ming, Z. & Johnson, W. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *J. Parkinsons. Dis.* **2**, 47–55 (2012).
117. Giuffrida, J. P., Riley, D. E., Maddux, B. N. & Heldman, D. A. Clinically deployable Kinesia™ technology for automated tremor assessment. *Mov. Disord.* **24**, 723–730 (2009).
118. Jeon, H., Lee, W. & Park, H. High-accuracy automatic classification of parkinsonian tremor severity using machine learning method. *Physiol. Meas.* **38**, 1980–1999 (2017).
119. Zhao, A., Qi, L., Dong, J. & Yu, H. Dual channel LSTM based multi-feature extraction in gait for diagnosis of neurodegenerative diseases. *Knowl. Syst.* **145**, 91–97 (2018).
120. Pushparani, M. & Athisakthi, A. Detection of movement disorders using multi SVM. *Glob. J. Comput. Sci. Technol.* **13**, 23–25 (2013).
121. Sacco, G. et al. Detection of activities of daily living impairment in Alzheimer's disease and mild cognitive impairment using information and communication technology. *Clin. Interv. Ageing* **7**, 539–549 (2012).
122. Ji, S., Xu, W., Yang, M. & Yu, K. 3D convolutional neural networks for human action recognition. *IEEE Trans. Pattern Anal. Mach. Intell.* **35**, 221–231 (2013).
123. Raya, Z. et al. in *Proceedings of SPIE: Applications of Machine Learning* Vol. 11139 (eds Zelinski, M. E., Taha, T. M., Howe, J., Awwal, A. A. S. & Iftekharuddin, K. M.) 1113909 (SPIE, 2019).
124. Brand, D., DiGennaro Reed, F. D., Morley, M. D., Erath, T. G. & Novak, M. D. A survey assessing privacy concerns of smart-home services provided to individuals with disabilities. *Behav. Anal. Pract.* **13**, 11–21 (2020).

Q12

Q13

125. Riboni, D., Bettini, C., Civitaresse, G., Janjua, Z. H. & Helaoui, R. SmartFABER: Recognizing fine-grained abnormal behaviors for early detection of mild cognitive impairment. *Artif. Intell. Med.* **67**, 57–74 (2016).
126. Ordóñez, F. J. & Roggen, D. Deep convolutional and LSTM recurrent activity recognition. *Sensors* **16**, 115–140 (2016).
127. Alam, R., Homdee, N., Wolfe, S., Hayes, J. & Lach, J. In *IoTDI 2019: Proceedings of the International Conference on Internet of Things Design and Implementation* 281–282 (Association for Computing Machinery, 2019).
128. Rankin, K. P., Baldwin, E., Pace-Savitsky, C., Kramer, J. H. & BL, M. Self awareness and personality change in dementia. *J. Neurol. Neurosurg. Psychiatry* **76**, 632–639 (2005).
129. Solberger, M. et al. Neural basis of interpersonal traits in neurodegenerative diseases. *Neuropsychologia* **47**, 2812–2827 (2009).
130. Christidi, F., Migliaccio, R., Santamaria-Garcia, H., Santangelo, G. & Trojsi, F. Social cognition dysfunctions in neurodegenerative diseases: neuroanatomical correlates and clinical implications. *Behav. Neurol.* **2018**, 18 (2018).
131. Orimaye, S., Wong, J. & Golden, K. In *Proceedings of the Workshop on Computational Linguistics and Clinical Psychology: From Linguistic Signal to Clinical Reality* 78–87 (Association for Computational Linguistics, 2014).
132. Wankerl, S., Nöth, E. & Evert, S. In *Proceedings of the Annual Conference of the International Speech Communication Association, INTERSPEECH 2017* 3162–3166 (Association for Computational Linguistics, 2017).
133. Weizenbaum, J. ELIZA—a computer program for the study of natural language communication between man and machine. *Commun. ACM* **26**, 23–28 (1983). **This article describes the first question-and-answer computer program, which paved the way for AI-driven avatars as we know them today.**
134. Ireland, D. et al. Hello Harlie: enabling speech monitoring through chat-bot conversations. *Stud. Health Technol. Inform.* **227**, 55–60 (2016).
135. Tanaka, H. et al. Detecting dementia through interactive computer avatars. *IEEE J. Transl. Eng. Heal. Med.* **5**, 1–11 (2017).
136. Blackburn, D. et al. An avatar aid in memory clinic [abstract P0029]. *J. Neurol. Neurosurg. Psychiatry* **88**, A19–A20 (2017).
137. Schmidtke, K., Pohlmann, S. & Metternich, B. The syndrome of functional memory disorder: definition, etiology, and natural course. *Am. J. Geriatr. Psychiatry* **16**, 981–988 (2008).
138. Mahley, R. W., Weisgraber, K. H. & Huang, Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **103**, 5644–5651 (2006).
139. Van Cauwenbergh, C., Van Broeckhoven, C. & Sleegers, K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. *Genet. Med.* **18**, 421–430 (2016).
140. Huang, X. et al. Revealing Alzheimer's disease genes spectrum in the whole-genome by machine learning. *BMC Neurol.* **18**, 1–8 (2018).
141. Maj, C. et al. Integration of machine learning methods to dissect genetically imputed transcriptomic profiles in Alzheimer's disease. *Front. Genet.* **10**, 1–16 (2019).
142. Lopez, C., Tucker, S., Salameh, T. & Tucker, C. An unsupervised machine learning method for discovering patient clusters based on genetic signatures. *J. Biomed. Inform.* **85**, 30–39 (2018).
143. Ray, S. et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signalling proteins. *Nat. Med.* **13**, 1359–1362 (2007).
144. Agarwal, S., Ghanty, P. & Pal, N. R. Identification of a small set of plasma signalling proteins using neural network for prediction of Alzheimer's disease. *Bioinformatics* **31**, 2505–2513 (2015).
145. Andersen, S. L. et al. Metabolome-based signature of disease pathology in MS. *Mult. Scler. Relat. Disord.* **31**, 12–21 (2019).
146. Sapkota, S. et al. Alzheimer's biomarkers from multiple modalities selectively discriminate clinical status: relative importance of salivary metabolomics panels, genetic, lifestyle, cognitive, functional health and demographic risk markers. *Front. Aging Neurosci.* **10**, 1–13 (2018).
147. Tavares, J. & Oliveira, T. Electronic health record portal adoption: a cross country analysis. *BMC Med. Inform. Decis. Mak.* **17**, 1–17 (2017).
148. Stone, C. P. A glimpse at EHR implementation around the world: the lessons the US can learn. *e-healthpolicy.org* https://www.e-healthpolicy.org/sites/e-healthpolicy.org/files/A_Glimpse_at_EHR_Implementation_Around_the_World_1_ChrisStone.pdf (2014).
149. Chen, Y. et al. Applying active learning to high-throughput phenotyping algorithms for electronic health records data. *J. Am. Med. Inform. Assoc.* **20**, 253–259 (2013).
150. Schank, R. C. & Tesler, L. In *Proceedings of the 1969 Conference on Computational Linguistics* 1–3 (Association for Computational Linguistics, 1969).
151. Winograd, T. Procedures as a representation for data in a computer program for understanding natural language (Massachusetts Institute of Technology, 1971).
152. Schank, R. C. Computer understanding of natural language. *Behav. Res. Methods Instrum.* **10**, 132–138 (1978).
153. Devlin, J., Chang, M.-W., Lee, K. & Toutanova, K. BERT: pre-training of deep bidirectional transformers for language understanding. Preprint at arXiv <https://arxiv.org/abs/1810.04805> (2018).
154. Manning, C. et al. In *Proceedings of 52nd Annual Meeting of the Association for Computational Linguistics: System Demonstrations* 55–60 (Association for Computational Linguistics, 2014).
155. Honnibal, M. & Johnson, M. In *Proceedings of the 2015 Conference on Empirical Methods in Natural Language Processing* 1373–1378 (Association for Computational Linguistics, 2015).
156. Petrov, S. Announcing syntaxnet: the world's most accurate parser goes open source. *Google AI Blog* <https://ai.googleblog.com/2016/05/announcing-syntaxnet-worlds-most.html> (2016).
157. Ford, E., Carroll, J. A., Smith, H. E., Scott, D. & Cassell, J. Extracting information from the text of electronic medical records to improve case detection: a systematic review. *J. Am. Med. Inform. Assoc.* **23**, 1007–1015 (2016).
158. Weissenbacher, D. et al. In *Proceedings of the 2016 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies* 1198–1207 (Association for Computational Linguistics, 2016).
159. Grassi, M. et al. A novel ensemble-based machine learning algorithm to predict the conversion from mild cognitive impairment to Alzheimer's disease using socio-demographic characteristics, clinical information, and neuropsychological measures. *Front. Neurol.* **10**, 1–15 (2019).
160. Gordon, P. H. & Meininger, V. How can we improve clinical trials in amyotrophic lateral sclerosis? *Nat. Rev. Neurol.* **7**, 650–654 (2011).
161. Moura, M. C., Casulari, L. A., Rita, M. & Garbi, C. A predictive model for prognosis in motor neuron disease. *J. Neurol. Disord.* **4**, 4–10 (2016).
162. Westeneng, H.-J. et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *Lancet Neurol.* **17**, 423–433 (2018). **This study shows how the application of machine learning to large clinical datasets from various clinical centres enables the prediction of disease prognosis in individuals with amyotrophic lateral sclerosis.**
163. Latourelle, J. C. et al. Large-scale identification of clinical and genetic predictors of motor progression in patients with newly diagnosed Parkinson's disease: a longitudinal cohort study and validation. *Lancet Neurol.* **16**, 908–916 (2017). **This study exemplifies how integration of large clinical, molecular and genetic longitudinal datasets can be used to provide information on disease progression in PD.**
164. Wang, T., Qiu, R. G. & Yu, M. Predictive modeling of the progression of Alzheimer's disease with recurrent neural networks. *Sci. Rep.* **8**, 1–12 (2018).
165. Che, C. et al. In *Proceedings of the 2017 SIAM International Conference on Data Mining* 198–206 (SIAM, 2017).
166. Rajkomar, A. et al. Scalable and accurate deep learning for electronic health records. *NPJ Digit. Med.* **1**, 1–10 (2018).
167. Fernandes, A. C. et al. Development and evaluation of a de-identification procedure for a case register sourced from mental health electronic records. *BMC Med. Inform. Decis. Mak.* **13**, 1–14 (2013).
168. [No authors listed]. Stimulus package. *Nat. Med.* **24**, 247 (2018).
169. Zwierzyna, M., Davies, M., Hingorani, A. D. & Hunter, J. Clinical trial design and dissemination: comprehensive analysis of clinicaltrials.gov and PubMed data since 2005. *BMJ* **361**, 1–11 (2018).
170. Hay, M., Thomas, D. W., Craighead, J. L., Economides, C. & Rosenthal, J. Clinical development success rates for investigational drugs. *Nat. Biotechnol.* **32**, 40–51 (2014).
171. Cummings, J. Lessons learned from Alzheimer disease: clinical trials with negative outcomes. *Clin. Transl. Sci.* **11**, 147–152 (2018).
172. Cummings, J. L., Morstorf, T. & Zhong, K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers. Res. Ther.* **6**, 1–7 (2014).
173. Mitsumoto, H., Brooks, B. R. & Silani, V. Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved? *Lancet Neurol.* **13**, 1127–1138 (2014).
174. Ferraiuolo, L., Kirby, J., Grierson, A. J., Sendtner, M. & Shaw, P. J. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. *Nat. Rev. Neurol.* **7**, 616–630 (2011).
175. Neil, D. et al. Interpretable graph convolutional neural networks for inference on noisy knowledge graphs. Preprint at arXiv <https://arxiv.org/abs/1812.00279> (2018).
176. Zitnik, M., Agrawal, M. & Leskovec, J. Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics* **34**, i457–i466 (2018).
177. Duvenaud, D. et al. In *NIPS'15: Proceedings of the 28th International Conference on Neural Information Processing Systems* Vol. 2 2224–2232 (Neural Information Processing Systems Foundation, 2015).
178. Kipf, T. N. & Welling, M. Semi-supervised classification with graph convolutional networks. Preprint at arXiv <https://arxiv.org/abs/1609.02907> (2017).
179. Palop, J. J., Chin, J. & Mucke, L. A network dysfunction perspective on neurodegenerative diseases. *Nature* **443**, 768–773 (2006).
180. Zakeri, P., Simm, J., Arany, A., Elshal, S. & Moreau, Y. Gene prioritization using Bayesian matrix factorization with genomic and phenotypic side information. *Bioinformatics* **34**, i447–i456 (2018).
181. Bakkar, N. et al. Artificial intelligence in neurodegenerative disease research: use of IBM Watson to identify additional RNA-binding proteins altered in amyotrophic lateral sclerosis. *Acta Neuropathol.* **135**, 227–247 (2018).
182. Zhang, B. et al. Resource integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* **153**, 707–720 (2013). **This study exemplifies how machine learning approaches applied to omics data can lead to identification of new therapeutic targets.**
183. Haure-Mirande, J. V. et al. Deficiency of TYROBP, an adapter protein for TREM2 and CR3 receptors, is neuroprotective in a mouse model of early Alzheimer's pathology. *Acta Neuropathol.* **134**, 769–788 (2017).
184. Haure-Mirande, J. V. et al. Integrative approach to sporadic Alzheimer's disease: deficiency of TYROBP in cerebral A β amyloidosis mouse normalizes clinical phenotype and complement subnetwork molecular pathology without reducing A β burden. *Mol. Psychiatry* **24**, 431–446 (2019).
185. Wauters, E. et al. Neurobiology of aging clinical variability and onset age modifiers in an extended Belgian GRN founder family. *Neurobiol. Aging* **67**, 84–94 (2018).
186. Grollemond, V. et al. Machine learning in amyotrophic lateral sclerosis: achievements, pitfalls, and future directions. *Front. Neurosci.* **13**, 1–28 (2019).
187. Maudsley, S., Devanarayan, V., Martin, B. & Geerts, H. Intelligent and effective informatic deconvolution of 'big data' and its future impact on the quantitative nature of neurodegenerative disease therapy. *Alzheimer's Dement.* **14**, 961–975 (2018).
188. Meyer, S. et al. Optimizing ADAS-Cog worksheets: a survey of clinical trial raters' perceptions. *Curr. Alzheimer Res.* **14**, 1008–1016 (2017).
189. McDermott, J. E. et al. Challenges in biomarker discovery: combining expert insights with statistical analysis of complex omics data. *Expert. Opin. Med. Diagn.* **7**, 37–51 (2013).
190. Popejoy, A. & Fullerton, S. Genomics is failing on diversity. *Nature* **538**, 161–164 (2016).
191. Cohn, D. A., Ghahramani, Z. & Jordan, M. I. Active learning with statistical models. *J. Artif. Intell. Res.* **4**, 129–145 (1996).
192. Sellwood, M. A., Ahmed, M., Segler, M. H. S. & Brown, N. Artificial intelligence in drug discovery. *Future Med. Chem.* **10**, 2025–2028 (2018).
193. Gupta, A., Ayhan, M. S. & Maida, A. S. Natural image bases to represent neuroimaging data. *PLMR* **28**, 987–994 (2013).

Q14
Q15

Q16

194. Xu, Y., Raj, A. & Victor, J. D. Systematic differences between perceptually relevant image statistics of brain MRI and natural images. *Front. Neuroinform.* **13**, 1–15 (2019).
195. Marinescu, R. V. et al. in *Medical Image Computing and Computer Assisted Intervention – MICCAI 2019. Lecture Notes in Computer Science* Vol. 11765 (eds Shen, D. et al.) 860–868 (Springer, 2019).
196. Ganchev, P., Malehorn, D., Bigbee, W. L. & Gopalakrishnan, V. Transfer learning of classification rules for biomarker discovery and verification from molecular profiling studies. *J. Biomed. Inform.* **44**, S17–S23 (2011).
197. Young, J. et al. Accurate multimodal probabilistic prediction of conversion to Alzheimer's disease in patients with mild cognitive impairment. *NeuroImage Clin.* **19**, 735–745 (2013).
198. Cheng, B. et al. Multi-domain transfer learning for early diagnosis of Alzheimer's disease. *Neuroinformatics* **15**, 115–132 (2017).
199. Hon, M. & Khan, N. Towards Alzheimer's disease classification through transfer learning. Preprint at *arXiv* <https://arxiv.org/abs/1711.11117> (2017).
200. Goodfellow, I. J. et al. Generative adversarial nets. *Neural Inf. Process. Syst.* **27**, 1–9 (2014).
201. Huang, H., Yu, P. S. & Wang, C. An introduction to image synthesis with generative adversarial nets. Preprint at *arXiv* <https://arxiv.org/abs/1803.04469> (2018).
202. Kazuhiro, K. et al. Generative adversarial networks for the creation of realistic artificial brain magnetic resonance images. *Tomography* **4**, 159–163 (2018).
203. Palacio-Niño, J.-O. & Berzal, F. Evaluation metrics for unsupervised learning algorithms. Preprint at *arXiv* <https://arxiv.org/abs/1905.05667> (2019).
204. Löttsch, J., Lerch, F., Djaldetti, R., Tegder, I. & Ultsch, A. Identification of disease-distinct complex biomarker patterns by means of unsupervised machine-learning using an interactive R toolbox (Umatrix). *Big Data Anal.* **3**, 1–17 (2018).
205. Ravi, D. et al. Deep learning for health informatics. *IEEE J. Biomed. Heal. Inform.* **21**, 4–21 (2017).
206. Vial, A. et al. The role of deep learning and radiomic feature extraction in cancer-specific predictive modelling: a review. *Transl. Cancer Res.* **7**, 803–816 (2018).
207. Gulshan, V. et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA* **316**, 2402–2410 (2016).
208. Gilpin, L. H. et al. Explaining explanations: an overview of interpretability of machine learning. Preprint at *arXiv* <https://arxiv.org/abs/1806.00069> (2018).
209. Sarwar, S. et al. Physician perspectives on integration of artificial intelligence into diagnostic pathology. *NPJ Digit. Med.* **2**, 28 (2019).
- This article reports the perspective of pathologists towards the integration of artificial intelligence into diagnostic pathology.**
210. Fan, Y., Shen, D. & Davatzikos, C. in *Lecture Notes in Computer Science*, Vol. 3749 (eds Duncan, J. S. & Gerig, G.) 1–8 (Springer, 2005).
211. Shi, B., Chen, Y., Zhang, P., Smith, C. D. & Liu, J. Nonlinear feature transformation and deep fusion for Alzheimer's disease staging analysis. *Pattern Recognit.* **63**, 487–498 (2017).

Author contributions

L.F. researched data for the article, made a substantial contribution to the discussion of article content, wrote the article, and reviewed and edited the manuscript before submission. M.A.M. researched data for the article, made a substantial contribution to the discussion of article content and wrote the article. P.N.O. and J.D.H. made a substantial contribution to discussion of article content, and reviewed and edited the manuscript before submission. A.M.B.L. and D.N. researched data for the article, and reviewed and edited the manuscript before submission. A.S., R.M. and G.M.H. reviewed and edited the manuscript before submission.

Competing interests

M.A.M. is funded by BenevolentAI. P.N.O., A.M.B.L., D.N., A.S. and J.D.H. work for BenevolentAI. R.M. and L.F. have a project in collaboration with BenevolentAI.

Peer review information

Nature Reviews Neurology thanks S. Baranzini, D. Zhang and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Review criteria

A search for original articles published without date limitation was performed in PubMed. Search terms included: 'artificial intelligence' AND 'neuroscience' OR 'neurology' OR 'neurodegeneration' OR 'neuroimaging'; 'machine learning' AND 'neurodegeneration' OR 'Alzheimer disease' OR 'Parkinson disease' OR 'motor neuron disease' OR 'multiple sclerosis' OR 'dementia'; and 'machine learning' AND 'disease diagnosis' OR 'disease prognosis'.

RELATED LINKS

Allen Brain Atlas: <http://portal.brain-map.org/>
 Alzheimer's Disease Neuroimaging Initiative: <http://adni.loni.usc.edu/>
 Amazon Comprehend Medical initiative: <https://aws.amazon.com/comprehend/medical/>
 Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium: <http://enigma.ini.usc.edu/>
 European Alzheimer's Disease Consortium Impact of Cholinergic Treatment Use (EADC-ICTUS): http://www.eadc.info/sito/pagine/d_01.php?nav=d
 Google TensorFlow: <https://www.tensorflow.org/>
 Parkinson's Progression Markers Initiative: <http://www.ppmi-info.org/>
 The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): <http://www.alz.org/ww/fingers/overview.asp>
 UK Biobank: <http://www.ukbiobank.ac.uk/>

© Springer Nature Limited 2020

Q17

Q18

Q19

Q20

Q21

Q10

QUERY FORM

Nature Reviews Neurology	
Manuscript ID	377
Author	Monika A. Myszczyńska

AUTHOR:

The following queries have arisen during the editing of your manuscript. Please answer by making the requisite corrections directly in the e-proofing tool rather than marking them up on the PDF. This will ensure that your corrections are incorporated accurately and that your paper is published as quickly as possible.

Query No.	Nature of Query
Q1:	Please check your article carefully, coordinate with any co-authors and enter all final edits clearly in the eproof, remembering to save frequently. Once corrections are submitted, we cannot routinely make further changes to the article.
Q2:	Note that the eproof should be amended in only one browser window at any one time; otherwise changes will be overwritten.
Q3:	Author surnames have been highlighted. Please check these carefully and adjust if the first name or surname is marked up incorrectly. Note that changes here will affect indexing of your article in public repositories such as PubMed. Also, carefully check the spelling and numbering of all author names and affiliations, and the corresponding email address(es).
Q4:	Au: OK to move ref 18 to the sentence beginning “Machine learning methods are broadly”? In response to your answer to my previous query.
Q5:	Au: OK to move ref 18 to the sentence starting “Supervised machine learning is divided”? In response to your answer to my previous query.
Q6:	Au: Fig 2. Please confirm that the ref citations correctly relate to the ref list. And Fig 3
Q7:	Au: sentences starting “In the same year” and “This study is particularly” OK? In response to your answer to my previous query.
Q8:	Au: addition of “new” to sentence starting “In addition, transfer learning is a new method...” OK?
Q9:	Au: In the sentence beginning “The potential of these collaborative efforts is immense...”, the term ‘accurate health service’ does not seem clear. Is there a better wording?
Q10:	Au: ‘Amazon’ added to ‘Comprehend Medical initiative’ – according to the website. Is this OK? Please check
Q11:	AU: If ref. 21 (preprint) has now been published in final peer-reviewed form, please update the reference details.
Q12:	Au: Ref 67 annotation. ‘at a single time interval’. This does not seem clear (‘at an interval?’). ‘at a single time’ or ‘during a single time interval’
Q13:	Au: Ref 72. Please check amended ref, particularly ‘14th ...’ (not 4th)
Q14:	If ref. 153 (preprint) has now been published in final peer-reviewed form, please update the reference details if appropriate.

