

Deep learning for brain disorders: from data processing to disease treatment

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Abstract

In order to reach precision medicine and improve patients' quality of life, machine learning is increasingly used in medicine. Brain disorders are often complex and heterogeneous, and several modalities such as demographic, clinical, imaging, genetics and environmental data have been studied to improve their understanding. Deep learning, a subpart of machine learning, provides complex algorithms that can learn from such various data. It has become state of the art in numerous fields, including computer vision and natural language processing, and is also growingly applied in medicine. In this article, we review the use of deep learning for brain disorders. More specifically, we identify the main applications, the concerned disorders and the types of architectures and data used. Finally, we provide guidelines to bridge the gap between research studies and clinical routine.

Key words: deep learning; neurology; medical imaging; genomics

Introduction

Precision medicine, as a customization of healthcare, aims at providing specific care to each individual. Examples of precision medicine include providing the right diagnosis as early as possible, giving the most appropriate treatment and predicting the evolution of the disease for a specific patient. As disorders and patients are both highly heterogeneous, precision medicine requires gaining knowledge about the disorders that may be too complex to be feasible for a human being.

Machine learning allows computers to perform tasks (for instance, predicting patient survival) without having to explicitly provide rules. Instead, machine learning algorithms learn to perform a task by adjusting their parameters using training data. The trained model can then be applied on new unseen data to evaluate its performance. Standard machine learning, such as generalized linear models, support vector machines and tree-based algorithms, relies on pre-extracted features that are assumed to well characterize the samples. These features can

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be subjective, domain-specific and highly engineered. They are extracted using predefined procedures designed using expert knowledge (one often refers to them as ‘handcrafted’ features even though the feature extraction procedures are most often automatic). Deep learning (DL), a subpart of machine learning, consists of algorithms that can learn features themselves. In such approach, the algorithm is usually an artificial neural network where the different neurons are organized into layers. Specifically, DL refers to the use of networks with a large number of layers. For both theoretical and practical approaches on DL, we invite the readers to have a look at [1–3].

In order to achieve precision medicine and gain more knowledge about disorders, machine learning is increasingly used in medicine [4–8]. As it can deal with diverse data, such as imaging and genetic data, DL is growingly applied in fields such as cellular and medical imaging, genomics or drug discovery [9–15].

This review will enable readers to grasp the full potential of DL for brain disorders as it presents the main uses of DL all along the medical data analysis chain: from data acquisition to disease treatment. We first focus on data processing, covering image reconstruction, signal enhancement and cross-modality image synthesis (Data reconstruction and preprocessing section) and on the biomarkers that can be extracted from spatiotemporal neuroimaging data, such as the volume of normal structures or of lesions (Extraction of biomarkers section). We then describe how DL can be used to detect diseases (Disease detection and diagnosis section), predict their evolution (Disease prediction section), improve their understanding (Improving disease understanding section) and help develop treatments (Treating diseases section). For these applications, we emphasize the types of architectures and data used, as well as the concerned disorders. Finally, we highlight trending applications (Future trends section) and provide guidelines to bridge the gap between research studies and clinical routine (Bringing DL to the clinic section). Table 1 lists the acronyms and abbreviations used throughout the manuscript and Table 2 proposes a selection of the most frequently used and richer publicly available datasets. Summaries of the reviewed studies are available in Sections 2–8 are available in Supplementary Materials (see Tables S1–S7 available online at <https://academic.oup.com/bib>).

Data reconstruction and preprocessing

Image reconstruction

DL has been used for medical image reconstruction to enable shorter acquisitions [magnetic resonance imaging (MRI), positron emission tomography (PET)] and/or reduce radiation dose (PET). The idea of using artificial neural networks to reconstruct images is not recent [16–18] but is currently a very active field of research, see [19] for a review.

Raw MRI data are samples of the Fourier transform of the object being imaged. The image can thus be reconstructed by performing an inverse Fourier transform operation on the raw data. One of the main shortcomings of MRI is the long scanning time. MRI acquisition acceleration can be achieved by only partially filling the k-space (i.e. the frequency space). The information loss can then be compensated by using parallel imaging, and various techniques have been developed to enable the reconstruction from undersampled k-spaces and circumvent aliasing artifacts. As for the classic approaches, DL reconstruction approaches can operate at the k-space or at the image level, but they can also operate both at the k-space and image levels, or directly learn the transformation from k-space to image space

Table 1. Abbreviations in alphabetical order

Abbreviation	Full word
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
BraTS	Brain Tumor Segmentation challenge
CNN	Convolutional neural network
CT	Computed tomography
DL	Deep learning
EEG	Electroencephalography
FLAIR	Fluid-attenuated inversion recovery
GAN	Generative adversarial network
HC	Healthy control
LSTM	Long short-term memory
MCI	Mild cognitive impairment
pMCI	Progressive mild cognitive impairment
sMCI	Stable mild cognitive impairment
MR(I)	Magnetic resonance (imaging)
PD	Parkinson's disease
PET	Positron emission tomography
PPMI	Parkinson's Progression Markers Initiative
T1w/T2w	T1-weighted/T2-weighted

[20]. The majority of the DL methods operate at the image level [21–35] with the networks learning a mapping from aliased images, reconstructed from undersampled k-spaces using the inverse Fourier transform, to de-aliased images. The de-aliased image can be the final product [23–25, 27, 31, 32, 35], be used as input of classic approaches [21] or be combined with the initial undersampled k-space before a refinement step [26, 28, 34]. The network architecture can also be designed to mimic a classic iterative reconstruction where steps of reconstruction and DL-based regularization alternate [22, 29, 30, 33]. Several approaches aim to improve k-space interpolation [36, 37]. In [36], the network is trained on an autocalibrating signal specific to each scan, while in [37] it is trained offline using pre-acquired images. The method described in [38] operates at both the k-space and image levels by alternating between steps of k-space completion and image restoration. Finally, the approach proposed by Zhu *et al.* [39] learns the complete mapping from k-space data to the reconstructed image. Note that DL has also been used for MRI fingerprinting, to learn the mapping between the set of images acquired with different scan parameters (flip angle, repetition time, echo time) and parametric maps [40–42].

DL can also be used to recover high-quality PET images acquired with a reduced dose. As previously, the majority of the techniques operate at the image level, the network learning a mapping between low-dose and high-dose images [43–51]. While several methods rely only on the PET images to learn this mapping [43–46], others use MR images acquired simultaneously with the PET data on PET/MR scanners as input [47–49]. In the previous works, neural networks were applied post-reconstruction, but they can also be integrated within the iterative reconstruction [50, 51]. Alternatively, Sanaat *et al.* [44] proposed to predict a high-dose sinogram (the Radon transform of the image) from a low-dose sinogram, which appears to lead to higher quality images compared to the prediction in the image domain. More generally, several works aim at directly learning the mapping between sinograms and images [39, 52, 53], as neural networks are expected to enable the automatic optimization of the image reconstruction algorithms and be computationally more efficient than the classic techniques.

Table 2. Selection of publicly available datasets for brain disorders

Dataset	Disorder	Number of samples	Modalities	Longitudinal follow-up	Website
ADNI	AD	437 AD/1001 MCI/483 HC	Clinical data, MRI, PET, genotyping, whole genome sequencing	Yes	https://adni.loni.usc.edu/
AIBL	AD	211 AD/133 MCI/768 HC	Clinical data, MRI, PET	Yes	https://aibl.csiro.au/
OASIS	AD	OASIS-1: 416 subjects OASIS-2: 150 subjects OASIS-3: 1098 subjects	Clinical data, MRI, (OASIS-3: PET)	OASIS-1: No OASIS-2 & 3: Yes	https://www.oasis-brains.org/
CPAD	AD	6955 subjects	Clinical data	Yes	https://c-path.org/programs/cpad/
PPMI	PD	424 PD/196 HC	Clinical data, MRI, SPECT, genetic, genotyping, exome sequencing	Yes	https://www.ppmi-info.org/
TCGA	Cancer	+20k tumor and normal samples	Genomic, epigenomic, transcriptomic, proteomic	Yes	https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga
BraTS	Cancer	500+ subjects with high- or low-grade glioma	T1-weighted, post-contrast T1-weighted, T2-weighted, and Fluid Attenuated Inversion Recovery MRI	Partly	http://braintumorsegmentation.org/
SSC	ASD	2600 simplex families	Genomic	No	https://www.sfari.org/resource/simons-simplex-collection/
ABIDE	ASD	ABIDE I: 1112 subjects ABIDE II: +1k additional subjects	Clinical data, MRI	No*	http://fcon_1000.projects.nitrc.org/indi/abide/
Project MinE	ALS	15k ALS/7.5k HC	Genomic	No	https://www.projectmine.com/
Protein Data Bank	–	163 633 biological macromolecular structures	Protein	No	https://www.rcsb.org/
HCP	–	1200 healthy adults	Structural, functional and diffusion MRI	No	http://www.humanconnectomeproject.org/
IXI	–	600 healthy subjects	T1, T2 and proton density-weighted MRI, diffusion MRI, MRA	No	https://brain-development.org/ixi-dataset/

*Only 38 individuals were followed longitudinally at two time points in the ABIDE II dataset.

Notes: Datasets: ABIDE, Autism Brain Imaging Data Exchange; ADNI, AIBL, Australian Imaging, Biomarkers and Lifestyle; BraTS; CPAD, Critical Path for Alzheimer's Disease; HCP, Human Connectome Project; IXI, Information eXtraction from Images; OASIS, Open Access Series of Imaging Studies; PPMI; SSC, Simons Simplex Collection; TCGA, The Cancer Genome Atlas. Brain disorders: AD, ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; HC, MCI; PD, Modality: MRA, magnetic resonance angiography; MRI; PET; SPECT, single-photon emission computed tomography.

Signal enhancement

Many of the reconstruction techniques operating in the image domain could be considered as image denoising approaches as image translation is performed post-reconstruction. Denoising can be applied more generally on various modalities, for brain applications mainly MRI [54–56] and PET [57, 58]. Both images [55, 57] and spatiotemporal signals [54, 56, 58] can be denoised.

Another image enhancement technique is super-resolution. Most approaches rely on pairs of high- and low-resolution images of a single modality to learn the low- to high-resolution mapping [59–64]. Others do not use external training data. The self super-resolution method presented in [65] assumes that in-plane MRI slices have a high resolution and can therefore be used as high-resolution training data. By degrading the in-plane slices into low-resolution images, a neural network can be trained and then used to restore the images in the through-plane. Another self super-resolution strategy consists in combining multiple images of the same subject, one low resolution and the other high resolution, to improve the resolution of the former [66–68].

Cross-modality image synthesis

Image translation has also been used in a cross-modality context, such as to generate computed tomography (CT) from MR images [69–84] or to generate MR images of a certain sequence from MR images of another sequence [74, 85–90] or a set of other sequences [83, 91–97]. A large number of methods have been applied to improve attenuation correction on PET/MR scanners [73, 76, 78, 81, 98, 99] or to enable radiotherapy treatment planning from MRI only [71, 77, 80, 84]. Other studies aim to improve subsequent image processing steps such as segmentation or registration [90], improve classification in case of missing data [86, 91, 100, 101], improve detection and segmentation of tumors [90, 93] or white matter lesions [95, 102], correct distortions in diffusion MRI [88] or enable MR-less PET quantification [103].

As can be seen in Table S1, available online at <https://academic.oup.com/bib>, the most common networks used for image reconstruction, signal enhancement and cross-modality image synthesis are variations of convolutional neural networks (CNNs), the U-Net [104] and its variations, and conditional

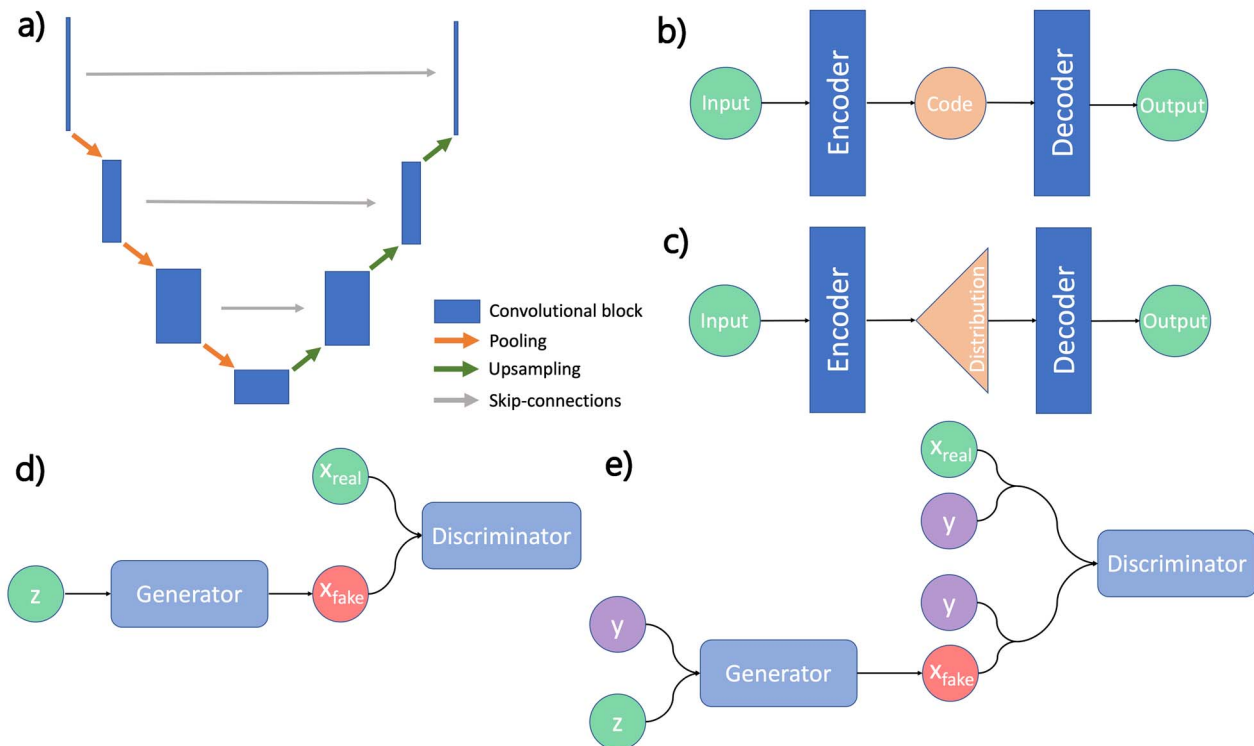


Figure 1. Common DL architectures for brain disorders. (A) U-Net [104] is the most popular architecture for biomedical image segmentation. It consists of a contraction (or encoder) path, where the size of the image gradually reduces while the depth gradually increases, and an expansion (or decoder) path, where the size of the image gradually increases and the depth gradually decreases. To obtain more precise locations, skip connections are used between the encoder and decoder blocks. U-Net architectures have also been used for image reconstruction and synthesis. (B) Autoencoder learns a latent representation (code) of the input data that minimizes the reconstruction error. Autoencoders have been used for disease detection, prediction of treatment and integration of multimodal data. (C) Variational autoencoder [242] is a variant of the autoencoder where the latent representation is a distribution. Variational autoencoders have been used for image segmentation, disease detection and disease subtyping. (D) Generative adversarial network [243] consists of a generator producing new samples and a discriminator classifying samples as original or generated. Generative adversarial networks can be used for data augmentation. (E) Conditional generative adversarial network [244, 245] is a variant of the generative adversarial network where the generator and the discriminator are conditioned by another feature. Conditional generative adversarial networks have been used for signal enhancement, image synthesis and disease prediction.

generative adversarial networks (GANs) (see Figure 1 for an illustration of several network architectures).

Extraction of biomarkers

DL can be used to extract different types of biomarkers, such as the volume of normal structures or of lesions, or age predicted from neuroimaging data.

Segmentation of anatomical structures

DL is widely used for the segmentation of normal structures from brain MR images. A general overview of the existing datasets, DL architectures and main results collected until 2017 is given in [105]. Two main segmentation strategies exist. In the sliding-window CNN framework, a network is trained to predict the class label of each pixel by providing a patch around that pixel as input. This approach was used in [106–108], where patches of different sizes were used as inputs to ensure spatial consistency, and in [109], where the CNN is combined with a Hough-voting strategy to perform anatomy localization. Other articles implement fully convolutional networks, with unimodal [110] or multimodal [111] data. Many adapt the U-Net architecture introduced by Ronneberger et al. [104], such as [112, 113]. More recently, adversarial learning strategies have been

used to force the automatic segmentations to resemble manual segmentations [114].

Segmentation of lesions

Beyond normal anatomical structures, segmentation of lesions, such as tumors, white matter hyperintensities and ischemic or hemorrhagic lesions, can provide key information for disease management. In particular, it allows tracking growth or reduction of lesions, which is essential to assess disease progression and treatment efficacy. As for the segmentation of anatomical structures, U-Net-like architectures are often employed. However, strategies aiming to particularly focus on lesions have been implemented. In the dual pathway CNN strategy, two image inputs first go through different convolutional blocks and are then merged in the fully connected layers. In the cascade CNN strategy, the output of a first CNN, trained to be more sensitive to potential voxels with lesions, is given as input to another CNN where the number of misclassified voxels is reduced.

Research on automatic segmentation and detection of brain tumors has been propelled by the availability of the Brain Tumor Segmentation (BraTS) challenge datasets [115, 116], which include multimodal MR images for subjects with glioblastoma and lower grade glioma. For this application, the dual pathway strategy is widely used [117–122]. DeepMedic is one of the most

common architectures [117]: it is a multiscale dual pathway network composed of two 3D CNN to take into account both local and global contextual information. It has also been adapted to segment traumatic brain injury lesions from multimodal MRI data [123]. Other works aiming to delineate brain tumors proposed cascade CNN architectures [124, 125], an adaptation of the U-Net architecture [126], an encoder-decoder architecture with a variational autoencoder branch reconstructing the input images jointly with segmentation to regularize the shared encoder [127] or a sliding-window CNN framework [128, 129]. Finally, segmentation of hyperspectral pictures (obtained with a visible and near-infrared push broom camera) was also used to help surgeons during tumor resection [130]. In this study, several DL methods (multilayer perceptron, CNN, U-Net) were assembled in one pipeline.

White matter lesion detection is often performed in the context of multiple sclerosis. Both the cascaded 3D CNN [131] and U-Net-like [132] approaches have been explored. Guerrero et al. [133] proposed a U-Net-like architecture for the segmentation and differentiation of white matter hyperintensities and stroke lesions from T1-weighted (T1w) and fluid-attenuated inversion recovery (FLAIR) MR images. Cerebral microbleeds, small hemorrhages near blood vessels, have been detected using a cascaded framework [134] and a 2D CNN [135].

Brain age

The 'brain age' approach can be used as a non-specific biomarker of different brain disorders. A model is optimized to predict the real (chronological) age of healthy controls (HCs) from neuroimaging data. Then, abnormalities can be detected in patients if their predicted brain age differs from their chronological age. This has been observed for many brain disorders such as Alzheimer's disease (AD) [136], epilepsy [137], multiple sclerosis [138], schizophrenia [139] or traumatic brain injury [140].

Many studies on that topic have been conducted by the same first author, James H. Cole. He proposed a DL system to predict age in healthy subjects [141], using a 3D CNN trained on gray matter, white matter or non-segmented T1w MRI. They compared their results to a standard machine learning method (Gaussian process regression) and observed that DL obtained comparable results for preprocessed data (gray matter and white matter) but significantly outperformed it for raw data. Their best mean absolute error was obtained with the CNN applied to gray matter. Jonsson et al. [142] proposed a similar framework with a 3D residual CNN and performed significantly better.

Identification of biomarkers in electroencephalography signals

DL is also used to identify biomarkers in electroencephalography (EEG) signals. In [143, 144], 2D CNN were applied to raw scalp EEG signals to perform a classification task. In [143], the goal was to detect P300 signals while spelling words, whereas in [144] the goal was to differentiate EEG signals containing or not an epileptic seizure. In either case, the input of the CNN is a matrix with rows corresponding to electrodes and columns to time points. In [143], weights of the convolutions were directly interpreted, while Hossain et al. [144] extracted correlation maps to find which channels are relevant. Finally, Schirrmeyer et al. [145] proposed different methods to train CNN for EEG decoding and visualization that could be used for biomarker discovery.

Disease detection and diagnosis

Most of the studies on disease detection have dealt with AD and Parkinson's diseases (PD) [146, 147]. This is partly due to the public availability of large datasets such as from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Parkinson's Progression Markers Initiative (PPMI) cohorts (more details in Table 2). The aim of disease detection and diagnosis can be to differentiate HCs from subjects with a disease or to distinguish between different diseases (disease recognition), but also, once a disease has been singled out, to quantify its severity or to differentiate between subtypes.

Disease recognition

Many studies focusing on AD aim to differentiate HCs from subjects with dementia, a relatively easy task useful when developing classification methods but clinically irrelevant [148]. The most commonly used approach is an end-to-end CNN for classification [146–148]. Wen et al. [148] provided a review on the use of CNN for AD classification, showing that results obtained with CNN are comparable to those obtained with traditional machine learning techniques. Nevertheless, other approaches exist. Silva et al. [149] used a CNN for feature extraction only and not classification. A variational autoencoder was used by Choi et al. [150] to detect anomalies in PET images, thereby providing a score of abnormality used to identify AD patients. The main imaging modalities used for AD classification are T1w MRI and ¹⁸F-fluorodeoxyglucose PET [147], but others, for example amyloid PET, have been used [151]. Other types of data, such as speech data [152], also bring meaningful information.

Several studies have dealt with the classification of PD patients versus controls. This can be achieved using single-photon emission computed tomography [153], neuromelanin-sensitive MRI [154], diffusion MRI [155] or handwriting images [156, 157].

Differentiating HCs from subjects with a psychiatric disease is also a research question widely addressed. Depression was studied using EEG as input [158, 159]. To overcome the lack of patient data, transfer learning was used in the work of Banerjee et al. [160], where they classified patients with post-traumatic stress disorder using a deep belief network model. Classification of schizophrenia versus HC is performed in several studies with a sparse multilayer perceptron [161], a deep discriminant autoencoder network [162] or a CNN combined with a pre-trained convolutional autoencoder [163], and classification of bipolar disorders versus HC is studied in [164] with a 3D CNN. The public availability of the Autism Brain Imaging Data Exchange dataset (Table 2) has propelled research on autism spectrum disorder. For example, functional MRI data were used in [165, 166] to distinguish patients with an autism spectrum disorder from controls using a CNN. Other works used genomic data with a neural network [167] or eye tracking data with a long short-term memory (LSTM) [168]. A multimodal approach for the integration of functional and structural MRI was proposed by Zou et al. [169] for the classification of attention deficit hyperactivity disorder versus healthy children using a 3D CNN. Finally, Zhang et al. [170] identified patients with conduct disorder using T1w MRI and a 3D variation of AlexNet.

The control versus disease task is not limited to neurodegenerative and psychiatric disorders. Classification of epileptic subjects versus HC has been addressed by Aoe et al. [171] who built a CNN called M-Net from magnetoencephalography signals. Fu et al. [172] performed natural language processing by using

a CNN to detect individuals with silent brain infarction using radiological reports, as early detection can be useful for stroke prevention. Using different features extracted from functional MRI data, Yang et al. [173] proposed to distinguish between migraine patients and HCs (but also between two subtypes of migraine) using an Inception CNN. Finally, MR angiography was used to detect cerebral aneurysms [174, 175] using a custom CNN [174] or a ResNet-18 [175].

Few studies have explored differential diagnosis with DL. Wada et al. [176] classified AD versus Lewy body dementia using a 2D CNN, while Huang et al. [177] classified bipolar disorder versus unipolar depression using a CNN followed by an LSTM, both with attention mechanisms.

Identification of known disease subtypes

Neurological disorders can be complex, and several works aim to identify known disease subtypes or quantify their severity. This is particularly the case in oncology. In the brain cancer domain, most of the studies [178–180] focused on low-grade gliomas. Low-grade gliomas are less aggressive tumors with better prognosis compared to high-grade gliomas. In low-grade gliomas, the genetics of the tumor can provide prognostic information, but this analysis requires biopsy, which is an invasive procedure. To rely only on non-invasive examinations, these studies proposed DL methods to distinguish between different genetic classes based on structural MRI. Ge et al. [179] performed two classification tasks: low-grade versus high-grade gliomas (tumor grading) and low-grade gliomas with or without 1p19q codeletion, a biomarker predictive of chances of survival (tumor subtyping). They used a 2D CNN on T1w, T2w and FLAIR MRI slices. Akkus et al. [178] also performed the same tumor subtyping task using 2D CNN on T2w and post-contrast T1w MRI, and Li et al. [180] predicted the mutation status of isocitrate dehydrogenase 1 in low-grade gliomas using a 2D CNN associated with a support vector machine applied to post-contrast T1w and FLAIR MRI. Additionally, Hollon et al. [181] classified images of biopsies (stimulated Raman histology) between 13 common subtypes covering 90% of the diversity of brain tumors with a 2D CNN. They compared their workflow with pathologists interpreting conventional histologic images and achieved a similar diagnostic accuracy for a large gain in diagnostic time (less than 2.5 versus 30 min). They also successfully identified rare phenotypes as they did not belong to any of their predefined classes, though they could not distinguish between them.

The distinction of disease subtypes has also been explored for other neurological disorders. Choi et al. [182] aimed to differentiate PD patients with dementia from those without dementia following a transfer learning strategy using a CNN initially trained to distinguish controls versus AD patients. In [183], the objective was to identify subtypes of PD progression using an LSTM with clinical and imaging data. Kiryu et al. [184] aimed to differentiate Parkinsonian syndromes. Different clinical profiles of patients with multiple sclerosis were identified in [185] using graphs extracted from diffusion MRI and graph CNN. Non-contrast head CT scanners were used by [186] for the detection of intracranial hemorrhage and its five subtypes. They used a CNN to identify the presence or absence of intracranial hemorrhage and a recurrent neural network for the classification of intracranial hemorrhage subtypes. In the context of epilepsy, Acharya et al. [187] used a CNN to distinguish three classes of EEG signal: normal, preictal and seizure. San-Segundo et al. [188] studied two different tasks using a CNN applied to EEG: classification

of epileptic versus non-epileptic brain areas and detection of epileptic seizures.

Disease prediction

This section focuses on the prediction of the future evolution of brain disorders. Three different protocols were implemented to perform such prediction: (i) binary classifications between participants who will develop or not the disease in a fixed time horizon, (ii) regression tasks estimating the time before disease development and finally (iii) the generation of future imaging modalities.

Fixed-time classification

Studies in this section aim at predicting the progression of patients in a pre-defined time frame. The length of this time frame depends on the disease studied: a few minutes for epilepsy [189] to several years for multiple sclerosis [190] or AD [191–195].

For epileptic patients who are drug-resistant, the short-term prediction of a seizure could improve their quality of life and independence. In [189], scalp and intracranial EEG 30-s windows processed by a short-time Fourier transform were used to distinguish preictal (before seizure onset) from interictal (between seizures) phases with a 2D CNN. With a seizure prediction horizon of 5 min and an occurrence prediction of 30 min, the system is significantly better than a random predictor for both modalities.

In multiple sclerosis, the disease course can be highly variable and predicting the evolution of the patients in early stages is difficult. Yoo et al. [190] studied patients who presented early symptoms of multiple sclerosis and aimed to classify those whose condition would worsen within 2 years and those who would stay stable. To that purpose, they used lesion masks extracted from T2- and proton density-weighted MRI, which were fed to a 3D CNN pre-trained in an unsupervised way.

In AD, a binary classification between stable mild cognitive impairment (sMCI) and progressive MCI (pMCI) allows the identification, as early as possible, of the patients who could benefit from a treatment. As most of these studies also tackled AD versus HC, their architectures were already described in Disease detection and diagnosis section. Therefore, in this section, we will only focus on transfer learning between these two tasks. Four possibilities were explored: (i) transferring weights from AD versus HC and then fine-tuning on pMCI versus sMCI [191, 192]; (ii) transferring from a classification with the first class mixing AD and pMCI labels and the second class HC and sMCI labels and then fine-tuning on pMCI versus sMCI [193]; (iii) directly testing the network on pMCI and sMCI patients without fine-tuning after learning the AD versus HC classification [195] and (iv) directly learning sMCI versus pMCI classification [194]. It is important to note that the definition of the labels may vary between studies. Most of them chose a prediction horizon (18, 36 or 60 months) and labeled as pMCI patients who converted within this prediction horizon and as sMCI patients who have a follow-up of at least the prediction horizon and did not convert at any time. However, some studies chose to remove patients with insufficient follow-up, thereby complicating the classification task. The absence of a common definition of the labels makes the comparison between studies difficult.

Time-to-disease regression

Several studies have estimated survival time after diagnosis of brain cancer. Two studies [196, 197] fused histological slices and genetic information from brain tumors. Patches of histological slices were processed by convolutional layers and genetic information was added at the level of the fully connected layers [197] or processed in its own branch [196]. Mobadersany et al. [197] only included 1p19q codeletion and isocitrate dehydrogenase mutation status, which were the target classes of studies in Disease detection and diagnosis section. Hao et al. [196] included more genetic data but allowed a restricted number of connections between the gene (first) layer and the pathway (second) layer, these restrictions being based on prior biological knowledge.

Longitudinal image prediction

Instead of predicting a diagnosis status relying on clinical assessments which may vary depending on the examiner and conditions of examination, one can predict future values of imaging modalities. In [198], a conditional GAN including two discriminators was used to predict the evolution of white matter hyperintensities from FLAIR images of stroke patients 1 year after their baseline, given the baseline FLAIR. Other studies aimed to predict the future T1w MR images of MCI and/or AD patients. Bowles et al. [199] used a Wasserstein GAN to learn a latent space of brain T1w MRI and identified the latent encoding of AD. This latent encoding was then added to the baseline AD images to predict their future values. Inspired by this study, Ravi et al. [200] proposed a conditional GAN that generates images for different age values. Thus, they can predict the images of patients for different time points depending on their diagnosis. Finally, Wegmayr et al. [201] predicted the future images of sMCI and pMCI patients with a conditional GAN trained on participants with other labels. These predicted images were then classified by a CNN trained for MCI versus AD. This protocol led to better results than directly training a CNN classifier on the sMCI versus pMCI task.

Most of the studies presented in this section performed fixed-time binary classifications as it is a common task in AD studies, which is a brain disease for which a large number of DL studies has been published. Although fixed-time classification is useful in a real-time setup (as it has been done in epilepsy), it might be misleading for predictions relying on modalities that are rarely acquired during the follow-up of the patient. In the context of AD, Ansart et al. [202] advise not to perform such long-term classification tasks that are not very useful in clinical practice, but instead to predict time to conversion.

Improving disease understanding

Complex diseases (such as AD and PD, or psychiatric disorders) are heterogeneous, with a large set of comorbidities and numerous risk factors. The known genetic risk factors usually explain a small part of the heritability estimated using family and twin studies. These diseases often consist of several subtypes that are important to identify at the early stage of the disease in order to improve patients' quality of life. Finding relevant clusters or associated genes may reveal new insight on diseases that are not yet well understood. Contrary to previous sections in which DL reproduced (and improved) tasks that were already performed by clinicians or other machine learning frameworks, the goal here is to find new ways to characterize brain diseases.

Identification of new disease subtypes

Only a few studies performed clustering using DL. Zhang et al. [183] used a recurrent neural network to learn representations of PD progression and showed that, using the k-means clustering algorithm, this representation yielded better clusters than dynamic time warping or the principal component analysis representation. They identified three subtypes with different baselines and disease progression patterns. de Jong et al. [203] used a recurrent layer followed by a variational autoencoder with a Gaussian mixture prior to performing clustering. They applied their network to the ADNI and PPMI datasets and found clusters with highly different disease trajectories for many variables.

Disease progression modeling

Many brain disorders, in particular neurodegenerative diseases, evolve over a long period of time, typically 10–20 years. Machine learning can be used to estimate models of disease progression. Such models provide a temporal ordering of alterations (which alterations appear first), characterize the variability of this ordering between patients and help identify the factors that influence disease evolution. Most models developed so far did not rely on DL. The main approaches include non-linear mixed-effects models using tools from Riemannian geometry [204], event-based models [205] and Gaussian processes [206]. More recently, DL techniques have been proposed for modeling disease progression. Louis et al. [207] proposed to use a recurrent neural network to model trajectories of the evolution of cognitive scores and anatomical MRI in patients with AD. Fisher et al. [208] used conditional restricted Boltzmann machines to generate trajectories of change for different clinical measures in AD.

Identification of genetic variants associated with a disease

Recently, several studies used DL to identify genetic variants associated with a brain disorder. Studies using sequencing data as input used a CNN to take into account the structure of the data, while studies using selected single-nucleotide polymorphisms applied a multilayer perceptron. Zhou et al. [209] trained a CNN using whole-genome sequences of 1790 autism spectrum disorder simplex families, identifying significant proband-specific signal in regulatory *de novo* noncoding space. Yin et al. [210] used a CNN to classify amyotrophic lateral sclerosis cases versus healthy subjects, finding known associated genes and potentially new associated genes by looking at the predictive performance of each gene. Khan et al. [211] trained two multilayer perceptrons to compute a genomic score for mental disorders and to prioritize susceptibility variants and genes, showing promising results in identifying new genes in autism spectrum disorder and schizophrenia.

Treating diseases

Prediction of treatment outcome

Predicting treatment outcome may allow for better, more personalized treatment choices and thus better care of patients. Some studies found an increased predictive performance using DL for such tasks, while others found a similar or decreased one. Chang et al. [212] used an ensemble of five CNN to predict drug response in 25 cancers including low-grade glioma and obtained higher performance compared to a support vector machine and a random forest. Hilbert et al. [213] trained a CNN to predict good

reperfusion after endovascular treatment and good functional outcome using CT angiography images in acute ischemic stroke patients, achieving higher performance than logistic regression and random forest models. Lin et al. [214] applied a multilayer perceptron to clinical and genetic data to distinguish between remitted and non-remitted major depressive disorder cases but obtained a predictive performance similar to a logistic regression model. Munsell et al. [215] used stacked autoencoders and a support vector machine to predict surgical outcome for temporal lobe epilepsy subjects. However, the predictive performance was lower than using a feature selection obtained with sparse canonical correlation analysis.

Drug development

DL is also increasingly used for drug discovery. Review papers have been published on that topic [216, 217]. Lavecchia [217] highlighted several specific uses of DL in this area. DL has been used to predict the molecular properties and activity of drugs, in particular their ability to bind to a target site on a receptor. One can go one step further and aim to synthesize molecules which potentially have the desired properties. The specific applications to neurological diseases seem to remain limited so far. Subramanian et al. [218] used DL, as well as other machine learning techniques, to predict the affinity of different β -secretase 1 inhibitors, a classic target for AD treatments. It can be expected that DL will be increasingly used for drug design in brain diseases in the future.

Future trends

Neuroimaging is the highly predominant modality used in the literature. This may be explained by the success of DL architectures for computer vision tasks in general and the availability of large public datasets targeting brain disorders for which neuroimaging provides important insight. Nonetheless, other modalities have been emerging and some studies integrate several modalities.

Smartphone/sensor data

Smartphones and sensors can generate a large amount of data, which is usually an advantage for training deep neural networks, and can be representative of the patient state in their daily life. Sensors can collect sound and movement data, while smartphones can gather a wider range of data types.

Sensor data can be particularly relevant for movement disorders. Kim et al. [219] used a CNN to measure tremor severity in PD, while Nancy Jane et al. [220] used a time delay neural network to diagnose gait severity. Similarly, Camps et al. [221] applied a 1D CNN to effectively detect freezing of gait in PD. The BEAT-PD DREAM challenge (synapse.org/beatpdchallenge) provided demographic, clinical and sensor data from smartphones and watches, with the objective of predicting an individual's medication state and symptom severity for dyskinesia and tremor. Other applications include diagnosis of late-life depression [222] and autism spectrum disorder [168] using recurrent neural networks.

Dedicated applications on smartphones allow for the collection of more specific data. Motor testing and speech data can distinguish PD cases from controls [223]. Park et al. [224] developed a mobile application to automatically evaluate the interlocking pentagon drawing test using a U-Net architecture.

Genetic and genomic data

Genetic and genomic data are increasingly used with DL architectures, either as a single modality or with other modalities. Zhou et al. [209] performed a whole-genome analysis using a CNN, identifying contribution of non-coding regions to autism risk. Yin et al. [210] developed a CNN taking into account the structure of genome data to improve the prediction of amyotrophic lateral sclerosis. Sun et al. [225] showed that a neural network taking as input genome data can identify 12 cancer subtypes.

Integration of multimodal data

Since most disorders are complex and heterogeneous, many studies aim to combine several modalities. Suk and Shen [226] used stacked autoencoders to extract features from MRI, PET and cerebrospinal fluid data and then multi-kernel learning to combine these with clinical data. More recent studies used a single neural network that can deal with multimodal data. Punjabi et al. [151] combined MRI and PET data for diagnosing AD and showed that using both modalities increases the diagnostic accuracy. Combining histopathological images, genomic data and clinical data can also improve survival prediction in cancers [196, 197].

There is no consensus on the best way to integrate multimodal data. Like preprocessing techniques, integration of several sources of data can be domain-specific. Nonetheless, a popular standard approach is to concatenate the features extracted from the different modalities at one of the fully connected layers, near the end of the network [151, 196, 197, 227].

Bringing DL to the clinic

Despite its tremendous success in many fields, including medical fields, DL faces several important challenges to be used in clinical routine:

- (i) It usually requires a large amount of data, which can be hard to collect for some medical applications.
- (ii) Research cohort specificities may prevent the application of models trained on such data to clinical cohorts.
- (iii) Algorithms are often black boxes, with poor interpretability of the decision-making process.
- (iv) Validating models accurately is crucial as the algorithms can very easily overfit the training data.

In this section, we provide an overview of what we observed in the literature and a list of guidelines to have in mind before using DL in clinical routine.

From research to clinical data

Around half of the reviewed studies (see Tables S1–S7 available online at [https://academic.oup.com/bib](https://academic.oup.com/bib/article/22/2/1560/6034041)) rely on publicly available datasets, the most frequently used being ADNI for studies on AD and BraTS for studies on brain tumors (Table 2). Such datasets are invaluable as they allow researchers to develop and evaluate methods, no matter whether their institution has access to local data, and they give the possibility to compare results obtained across laboratories using different approaches (even though other factors might prevent easy comparisons). Additionally, many of the publicly available studies gather data from several institutions (e.g. ADNI, PPMI, Human Connectome Project), leading to larger datasets than what could be achieved

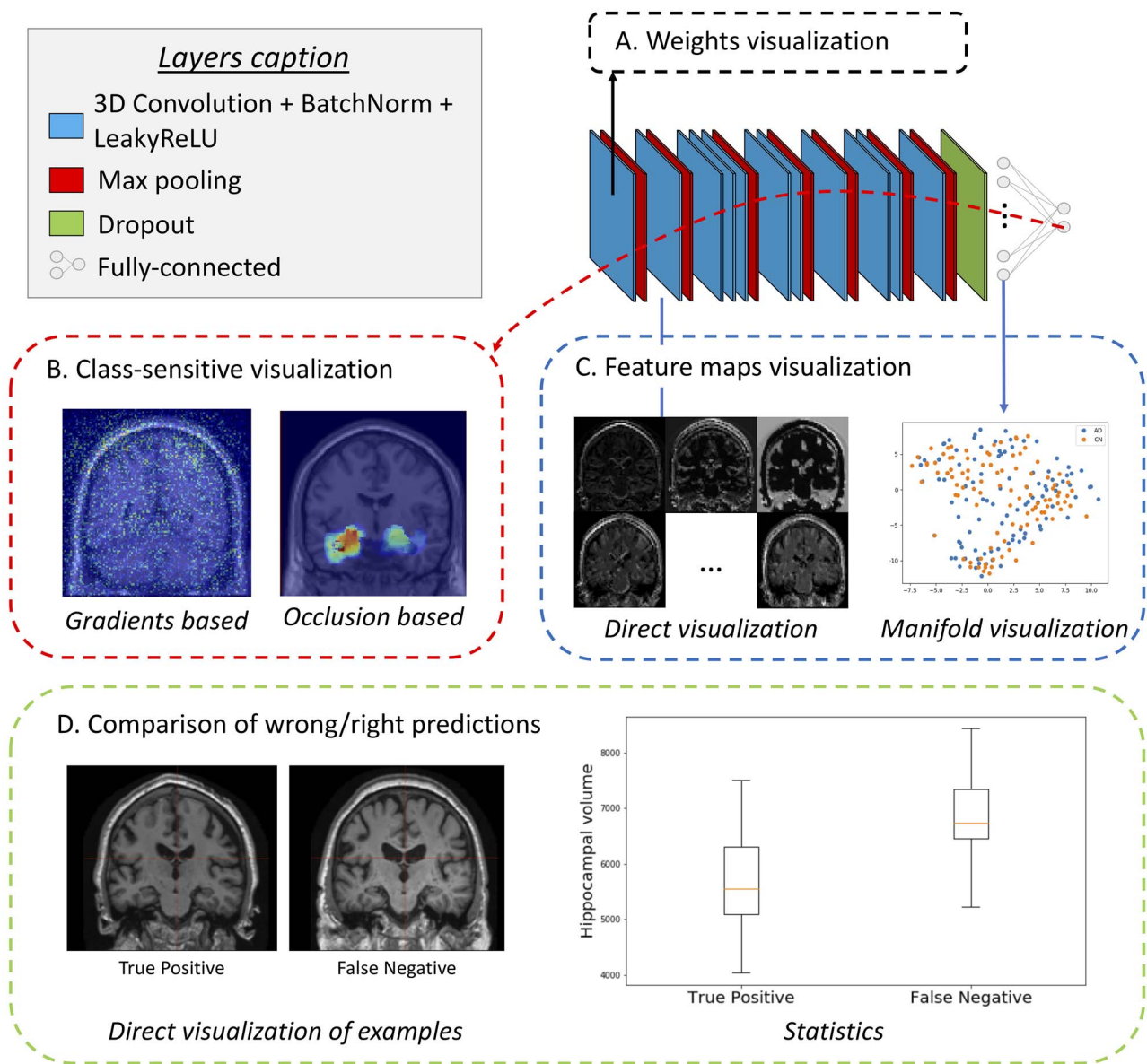


Figure 2. Main classes of interpretability for DL applied to imaging modalities. In this example, a convolutional neural network was trained to distinguish cognitively normal controls from patients with Alzheimer's disease. (A) Weight visualization is mainly used for large 2D kernels. (B) Class-sensitive methods belong to two categories, either gradient-based or occlusion-based methods [246]; they can be based on a single image or averaged across several images. (C) Feature maps visualization can be used to assess separation between classes. (D) Comparison of right/wrong predictions is useful to assess the limitations of the model and detect possible bias. These comparisons are part of interpretability methods that extract examples that maximize the activation of one node by sampling from the dataset or optimizing an input image.

by a single institution. However, depending on the application, these datasets may still not provide enough samples and several studies have generated synthetic data to train DL algorithms [228–231].

Focusing only on a small number of datasets can lead to biases. For example, selection bias, which is biasedly selecting an element of an algorithm, is common in AD literature [232]. Sequential analysis can also introduce important biases as studies tend to mainly report positive findings over negative findings [233]. To avoid these biases, several studies use publicly available datasets to develop their algorithms and subsequently apply them to data acquired locally (e.g. [39, 66, 182]). However, a limitation that comes with the use of local data is the impossibility to reproduce results as they often cannot be shared.

Finally, the vast majority of the reviewed studies rely on high-quality research data. An essential step to ensure translation to the clinic is the validation of the methods on clinical, imperfect data.

Interpretability

Many interpretability methods have been designed for DL [234]. This large amount of methods makes it difficult to choose the most appropriate one, as there is no real consensus in the field. It was also highlighted that some interpretability methods may not be reliable, even though they have been widely used [235]. Some studies in the scope of this review addressed this observation and assessed the robustness of their interpretability

method before using it to evaluate the robustness between CNN retrainings [236], or compared several interpretability methods to find the most appropriate [237].

Examples of interpretability methods applied to a classification task are illustrated in Figure 2. Different objectives may be pursued while using an interpretability method. The most common one is the validation of the model, thus some studies examined whether their heatmaps corresponded to previous knowledge on the disease they studied [163, 181, 186, 197, 213] or their differences with those of other machine learning methods [155, 170, 183]. They can also be used to establish the convergence of the model in the same way as the loss [124]. They were also used to assess the impact and choose the hyperparameters of the network [190]. Finally, the possible biases of classifiers were analyzed by studying the characteristics of false negatives [175].

Other objectives include biomarkers discovery, in which a general pattern for a disease or a particular condition is sought through the whole population [134, 154, 196]. Conversely, specific patterns can be identified for each patient to propose individual follow-up and treatment [144, 154]. Additionally, a study outside the scope of this review proposed to use saliency maps for clinical guidance, to improve inter-radiologist diagnosis variability [238]. Finally, some authors strove to provide a framework that is interpretable because of its architecture [143, 196] or constraints [200].

Why an interpretability method was applied to a network is not always clearly mentioned by the authors, and it is also not clear what the chosen method really highlights. Before its implementation, one should choose a clear motivation for interpretability: is the goal to convince clinicians that the model is reliable because it reproduces their way of thinking or is it to identify failure modes to reassure potential clients of an application? Once the good question is asked, the second challenge is to find an interpretability method that will give an appropriate answer. Readers willing to further think of these issues can refer to [239, 240].

Validation

Validating a model is a key component of any machine learning study and can take several forms depending on the extent of the validation. The objective can be to reproduce the same results using the same algorithm and data (reproducibility), to reproduce similar results on a different dataset (replicability) or to obtain a similar predictive performance on new data that can be in essence different from the training data, such as a clinical cohort versus a research cohort (generalizability).

Despite the extensive use of public datasets, reproducibility is difficult because of the lack of code sharing and the hardly detailed validation sections in the studies. Reproducibility is slowly becoming a standard, particularly in the AD field [148, 241], thanks to the development of open source software and community standards and guidelines. Another potential issue is the presence of biases in some cohorts that can heavily influence algorithms trained on them. For these reasons, it is extremely important to check for biases and methodological issues. A good starting point includes the points presented in the Machine Learning Reproducibility Checklist (<https://www.cs.mcgill.ca/~x007Ejpineau/ReproducibilityChecklist.pdf>).

Conclusion

In an era with increasing data and computational power, DL has revolutionized several computer science fields and is taking by

storm medicine. CNNs have been successfully applied to imaging and genetic data in numerous brain disorders, while recurrent neural networks showed encouraging results with longitudinal clinical data and sensor data. Many tasks, such as cross-modality image synthesis, image segmentation, disease diagnosis and outcome prediction, have been substantially improved thanks to DL.

Despite the promising results obtained with DL, several important limitations need to be addressed before an application in clinical routine becomes possible. Reproducibility is necessary to trust the results published in the literature and should be straightforward when public datasets are used. Assessing unbiasedly the performance of an algorithm, as well as evaluating it on diverse research and clinical cohorts, is crucial to estimate its generalizability. Interpretability is also required to trust the output of algorithms that are often considered black boxes, especially in medicine where the consequences of a decision can be extremely important. Nonetheless, we still believe that DL has had an important positive impact on brain disorder research. As the amount of data keeps increasing, good practices become more widespread and DL stays a hot research topic, we believe that DL will be a key component to achieve precision medicine and improve disease understanding for brain disorders and medicine in general.

Key Points

- Deep learning has been applied to various tasks related to brain disorders, such as image reconstruction, synthesis and segmentation, or disease diagnosis and outcome prediction.
- Convolutional neural networks have been successfully applied to imaging and genetic data in numerous brain disorders, while recurrent neural networks showed encouraging results with longitudinal clinical data and sensor data.
- Despite the promising results obtained with deep learning, several important limitations need addressing before an application in clinical routine becomes possible.
- Future research should especially focus on the generalizability and interpretability of deep learning models.

Data availability

No new data were generated or analyzed in support of this research.

Supplementary Data

Supplementary data are available online at *Briefings in Bioinformatics*.

Authors' contributions

Concepts and design: N.B. and O.C. Manuscript drafting or manuscript revision for important intellectual content: all authors. Approval of final version of submitted manuscript: all authors. Literature research: all authors. Study supervision: N.B. and O.C.

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None to disclose.

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