SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Review of MR spectroscopy analysis and artificial intelligence applications for the detection of cerebral inflammation and neurotoxicity in Alzheimer's disease

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ABSTRACT

Introduction: Magnetic resonance spectroscopy (MRS) has an emerging role as a neuroimaging tool for the detection of biomarkers of Alzheimer's disease (AD). To date, MRS has been established as one of the diagnostic tools for various diseases such as breast cancer and fatty liver, as well as brain tumours. However, its utility in neurodegenerative diseases is still in the experimental stages. The potential role of the modality has not been fully explored, as there is diverse information regarding the aberrations in the brain metabolites caused by normal ageing versus neurodegenerative disorders.

Materials and Methods: A literature search was carried out to gather eligible studies from the following widely sourced electronic databases such as Scopus, PubMed and Google Scholar using the combination of the following keywords: AD, MRS, brain metabolites, deep learning (DL), machine learning (ML) and artificial intelligence (AI); having the aim of taking the readers through the advancements in the usage of MRS analysis and related AI applications for the detection of AD.

Results: We elaborate on the MRS data acquisition, processing, analysis, and interpretation techniques. Recommendation is made for MRS parameters that can obtain the best quality spectrum for fingerprinting the brain metabolomics composition in AD. Furthermore, we summarise ML and DL techniques that have been utilised to estimate the uncertainty in the machine-predicted metabolite content, as well as streamline the process of displaying results of metabolites derangement that occurs as part of ageing.

Conclusion: MRS has a role as a non-invasive tool for the detection of brain metabolite biomarkers that indicate brain metabolic health, which can be integral in the management of AD.

KEYWORDS:
Alzheimer's disease; magnetic resonance spectroscopy; brain metabolites; deep learning; machine learning; artificial intelligence

INTRODUCTION

Alzheimer's disease (AD) is a major neurodegenerative disorder and has been cited as the most common type of dementia in the Western population.[1] A study by Ibrahim, et al.[2] reported that vascular dementia and mixed dementia were more prevalent in Malaysia and Asian countries based on their survey at a tertiary public hospital in Kuala Lumpur, Malaysia. In view of mixed clinical findings, there is a need for advanced diagnostic imaging to provide further information to help characterise the type of dementia.

Conventionally, structural magnetic resonance imaging (MRI) is used to help diagnose AD with the support of clinical assessment and neuropsychological testing. A common finding in conventional MRI is the detection of accelerated brain atrophy in AD.[3] Furthermore, brain morphometry and seed-based analysis of resting-state fMRI (functional MRI) functional connectivity revealed that there were abnormalities in the default mode network of AD patients compared to healthy control subjects.[4]

Typical MRI findings in AD patients is a decline in both white matter (WM) volume and grey matter (GM) volume specifically beginning in the hippocampus, which becomes accelerated in this condition.[5] One of the limitations of structural MRI is that the detection of anatomical changes of neurodegeneration as evidenced by brain atrophy occurs later in the disease.[6] Thus, newer biomarkers using hybrid functional imaging such as positron emission tomography/computed tomography (PET/CT) are utilized to aid in the early detection and better characterization of AD.

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Radiopharmaceuticals utilized for PET/CT imaging in patients suspected of AD consist of two main categories, i.e., glucose-analogue tracers and amyloid protein tracers. Initially, 2-Deoxy-2-[^{18}F] fluorodeoxyglucose ([^{18}F]-FDG), a glucose analogue was utilised for PET/CT brain imaging, then followed by amyloid and tau protein PET/CT imaging, for the management of AD.[7] Although the role of [^{18}F]-FDG has been established for making the diagnosis of AD, the accuracy of the scan interpretations can decline markedly when it involves younger patients or when there are overlapping features with other types of dementia.

Consequently, this limitation was the catalyst for the development of more specific biomarkers, namely amyloid precursors. The detection of amyloid precursors is said to be able to predict the conversion of at-risk subjects to full-blown AD 10 years earlier than the onset of AD symptoms.[8] Further review of amyloid PET/CT imaging concluded that this diagnostic tool holds promise for a beneficial role in diagnosing AD in cases of inconclusive clinical findings; however, there is an inherent limitation to this modality.[8]

These limitations include its cost-effectiveness, involving ionising radiation, and practical concerns for its execution due to many variations in protocols and cut-off values for the interpretation of results.[9] Among the recent advances in MRI technology and applications, the utility of magnetic resonance spectroscopy (MRS) has been gaining momentum for improved diagnostic accuracy.

In vivo, MRS is a non-invasive tool for characterising alterations in metabolite concentration and, by extension, bioenergetic and metabolic dysfunction associated with neurodegenerative disease progression.[10] There is a need to standardise the application of MRS techniques for the diagnosis of AD to help detect the alterations in brain metabolite levels in AD patients.

Additionally, artificial intelligence (AI) has spiked in popularity in recent years including its usage in the medical imaging field. AI has led to the development of automated image classification, segmentation, super-resolution, and image reconstruction.[11] Several classes of AI have been studied extensively, including machine learning (ML) and deep learning (DL), which utilise artificial neural networks (NN) inspired by neuronal architectures.[12]

This review aims to report on the advancement in the usage of MRS analysis and MRS-related AI applications for the detection of AD. Our specific aim is to probe into the patterns of metabolite changes in the brain that represent neural inflammation and degeneration related to AD, as well as to explore the automated analysis of MRS data using AI. A literature search was carried out to gather eligible studies from the following widely sourced electronic databases such as Scopus, PubMed, and Google Scholar. The search was conducted to gather all relevant publications till August 2023.

Besides, to achieve a wider search, all relevant studies were further cross-referenced for potentially eligible studies through their bibliography. Using Boolean operators, i.e., "AND" and "OR," the following search terms were entered in the search engines of the above listed electronic databases. The keywords used were AD, MRS, brain metabolites, DL, ML, and AI.

MRS Data Acquisition

MRS utilises magnetic resonant signals obtained from a volume of interest (VOI) and performs a fast Fourier transform (FFT) to identify the types and concentrations of each metabolite within the frequency domain, i.e., the MR spectrum. Based on whether the signal is captured from a single voxel or multiple voxels, it is technically categorised as single voxel spectroscopy (SVS) or MR spectroscopic imaging (MRSI). The MR spectrum generally consists of metabolites, water, lipids, and mobile and immobile proteins within the tissue.

Each component demonstrates unique chemical shift (ppm) and J-coupling (Hz) properties based on their respective MR characteristics. This occurs via the Zeeman effect, shielding effects, and Fermi contact of the molecular structure, and can thus be distinguished within the MR spectrum.[13] In MRS, a specific VOI is selected from the anatomical image and a spectrum is collected. The spectrum has different peaks or signals from many different metabolites in brain tissue.

Each of the peaks is highly reproducible and unique. Hence, it helps to identify the specific metabolites that correspond to specific signals. The difference in frequencies occurs due to electron shielding.

There are two main sequences in MRS, namely the STEAM and PRESS sequences. In the "STEAM" sequence, three identical 90° excitation pulses are used to form a "stimulated echo" while the "PRESS" sequence uses one 90° excitation and two identical 180° refocusing pulses to create a "spin echo", which is also known as double spin echo. A comparison of these two techniques has been done, and the most obvious difference is that the spin echo-based PRESS sequence acquires double the signal-to-noise ratio (SNR) compared to STEAM, hence, it is often preferred in clinical field strength.

As the repetition time (TR) increases, the scan time required for MRS data acquisition also significantly increases, leading to unwanted additional data artefacts such as patient movement.[14] Hence, a compromise is made by performing approximately 2 – 3 pre-scans prior to the main MRS data acquisition to make the magnetisation of the metabolites to a steady state, and then data is repeatedly collected.[15] The TR commonly used at 3T is 2000 ms.

Time to echo (TE) is the duration from RF excitation for spatial localization to the resonance signal produced in the target voxel and is one of the important parameters that characterize the MRS signal. In the clinical use of MRS, the shortest TE (~30 ms at 3T, for PRESS) is commonly used.[16] This allows for the anticipation of high signal yields of all metabolites in the brain while minimising the T2-effects and J-evolution of each metabolite.

Table I: Technical features of MRS data analysis softwares

Software	Language	Fitting domain	Baseline approach	Basis set preparation
LCModel[32]	Fortran	Frequency Domain	Spline baseline	Pre-prepared basis set utilization Cannot be custom-built within the program
Tarquin[28]	C++	Time Domain	Smooth baseline	Pre-prepared basis set utilization Cannot be custom-built within the program
Osprey[29]	MATLAB	Frequency Domain	Spline baseline	Pre-prepared basis set utilization Cannot be custom-built within the program
Vespa[30]	Python	Frequency Domain	Wavelet baseline	Can be built within the program (Simulation)
INSPECTOR[31]	MATLAB	Frequency Domain	Polynomial baseline	Can be built within the program
jMRUI-QUEST[32]	Java	Time Domain	Truncated points	Can be built within the program and has user-friendly graphical interface

LCModel: Linear Combination Model, MATLAB: MATrix LABoratory by MathWorks, Inc., jMRUI-QUEST: Java-based graphical user interface magnetic resonance spectroscopy user interface quantification simultor algorithm, VESPA: Versatile Simulation Pulses Analysis

Table II: MRS-based AI classification models for Alzheimer's disease and MCI

No	Author (Year)	ML/DL	Subjects, (N)	Objective	Outcome
1	Munteanu et al., 2015[42]	ML	HC (79), AD (56)	To test and evaluate the effectiveness of machine-learning schemes for single-subject level classification of individuals affected by different stages of dementia (HC, MCI, and AD) based on ^{1}H-MRS data.	Composition of WM, GM, and CSF of the spectroscopic voxel is essential in a ^{1}H-MRS study to improve the accuracy of the quantifications and classifications, e.g., metabolite derangements were matched to regions of decreased GM in the hippocampus of AD subjects.
2	Ahmed et al., 2020[43]	DL	HC (79), AD (56)	To propose an end-to-end deep learning network for early AD and HC classification using ^{1}H-MRS raw data from the PCC area	Classification of metabolite features in PCC of patients with early AD compared to HC using Deep MRS algorithm, achieved AUC of approx. 94% for AD, with a sensitivity of 100% and a specificity of approx. 89%.
3	Kherchouche et al., 2022[44]	DL	HC (33), MCI (49), AD (29)	To propose an explainable classification framework for early AD detection using ^{1}H-MRS	Accuracy of 82% for the most challenging classification task (MCI vs. AD classification).
4	Wang, et al., 2022[45]	DL	AD (27), HC (15)	To improve the diagnosis and classification of AD using a model combining MRI and MRS metabolite levels at the frontal and parietal regions.	GABA levels in the parietal region correlated with MMSE scores of AD, and resulted in the most significant improvement in model performance, the AUC increased from 0.97 to 0.99, specificity increased from 90 to 95%.

AD: Alzheimer's disease, AUC: area under the curve, DL: deep learning, GABA: gamma-aminobutyric acid, GM: gray matter, HC: healthy control, 1H-MRS: proton magnetic resonance spectroscopy, MCI: mild cognitive impairment, ML: machine learning, MMSE: mini mental state examination

These factors work together to increase the overall SNR of the MRS signal, enabling complex metabolite profiling.[17] This is an advantage when compared to spectral-edited MRS methods using a longer TE. In AD, the commonly targeted VOI is the posterior cingulate cortex (PCC) and the precuneus because these two regions have been found to exhibit cortical thinning on structural MRI,[18] reduced glucose metabolism on PET/CT imaging and histopathological changes on brain autopsy.[19]

Even though SVS can be performed quickly and easily in most parts of the human brain, it only captures metabolite information in a specific brain region and does not provide spatial variations of metabolites in other parts of the brain. Information is generally only limited to one or two brain regions in most clinical settings. Conversely, MRSI is usually more time-consuming, but can be used to measure multiple-voxel locations simultaneously. It has a larger total coverage, hence, higher spatial information.

Advantageously, ^{1}H MRS has a high sensitivity, however, it also has the drawback of having a large water signal. This has to be suppressed to allow for the observation of tissue metabolites that are relatively smaller in representation.[20] Commonly in ^{1}H MRS, brain metabolites are observed in the millimolar concentration range, while cerebral water makes up 65-75% of the brain composition.

MRS Data Processing and Analysis

Generally, the post-acquisition workflow of SVS MRS involves a sequence of steps: 1) pre-processing for data correction, 2) performing metabolite quantification, and 3) data screening for error estimation to quantify the results. The main reason for pre-processing in MRS is due to the inevitable degradation caused by experimental imperfections such as RF slice profile imperfections, eddy currents, frequency drift, and subject motion.

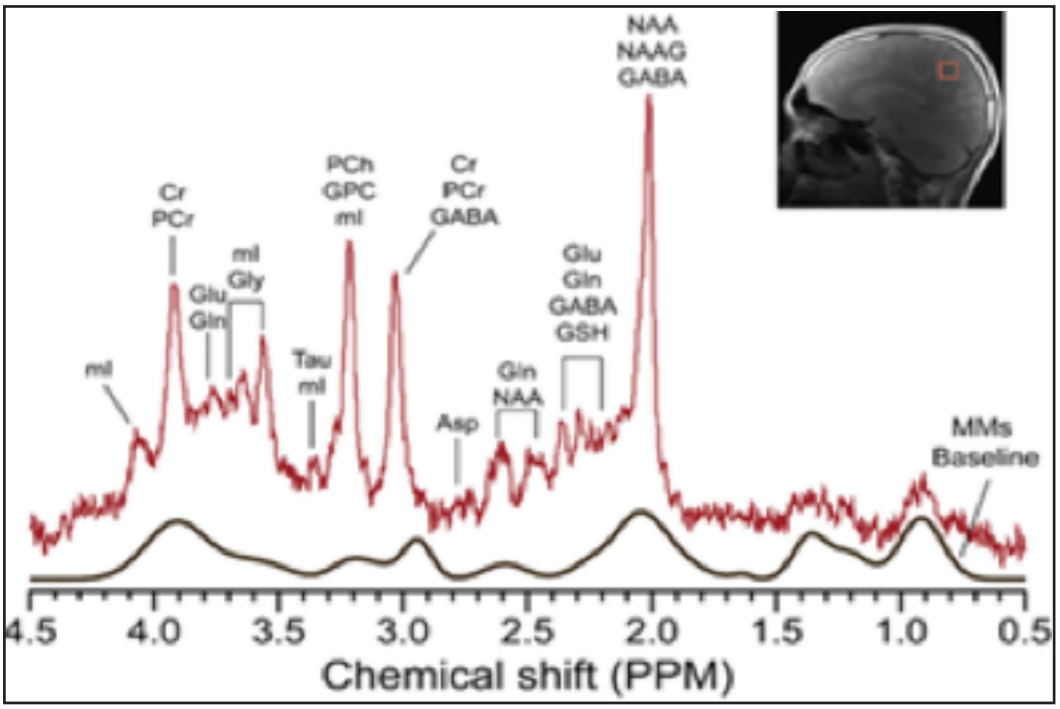

Fig. 1: Proton MR spectrum acquired at 3.0 T (TE=30 ms) of healthy older adult subject. Reproduced, with permission, from Lee.[26]

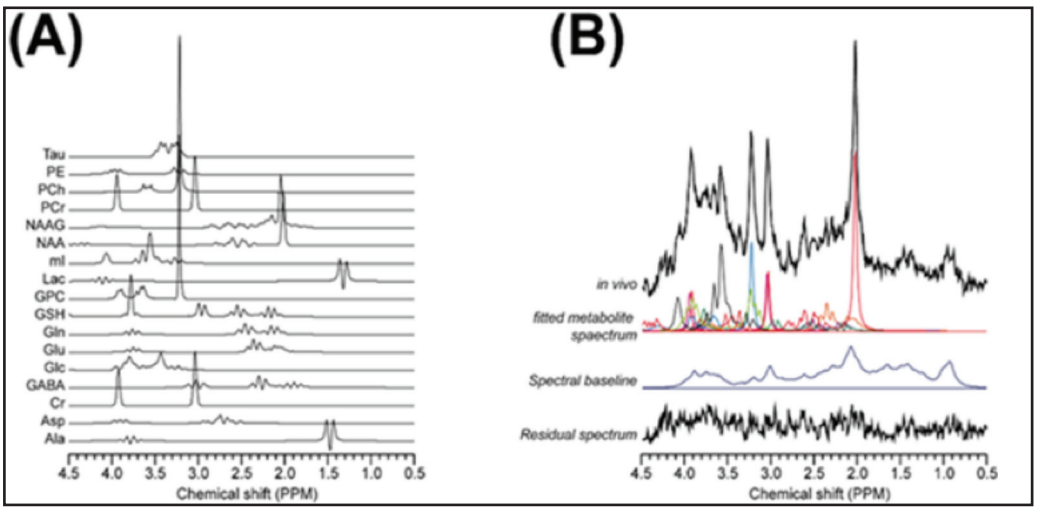

Fig. 2: Representative spectra of a metabolite basis set and quantification process. A metabolite basis set (A) incorporates chemical shifts, J-coupling, and line shapes of expected metabolites. The basis set is used for metabolite quantification from in vivo MR spectrum with spectral baseline (B). Reproduced, with permission, from Lee.[26]

Secondly, raw data are usually multi-dimensional, with multiple signal averages acquired by multiple coil channels from parallel receive array coils. Therefore, these signals must be combined to reduce the data into one dimensional single complex-valued data to be analysed. Before conducting quantitative analysis, MRS data, once merged, may undergo several pre-processing steps depending on the quality of the data.

For example, spectral distortions due to eddy currents are typically corrected using water-unsuppressed data.[21] Additional data correction may be necessary if there are severe frequency shifts or zeroth or first-order phase shifts.[22]

SNR or spectral resolution of the MR spectrum can be artificially enhanced using post-processing methods, such as apodisation and zero-filling techniques, respectively. However, the former may fail to reflect the line shape characteristics of each metabolite signal due to their respective T2 characteristics and can ultimately influence the results of metabolite quantification.[16]

The zero-filling technique remains controversial in terms of improvements in data quantification.[23] Therefore, these two functions for improving the SNR are generally used to assist in improving visual interpretation.[24] A range of software is available to perform quantitative analysis, which provides

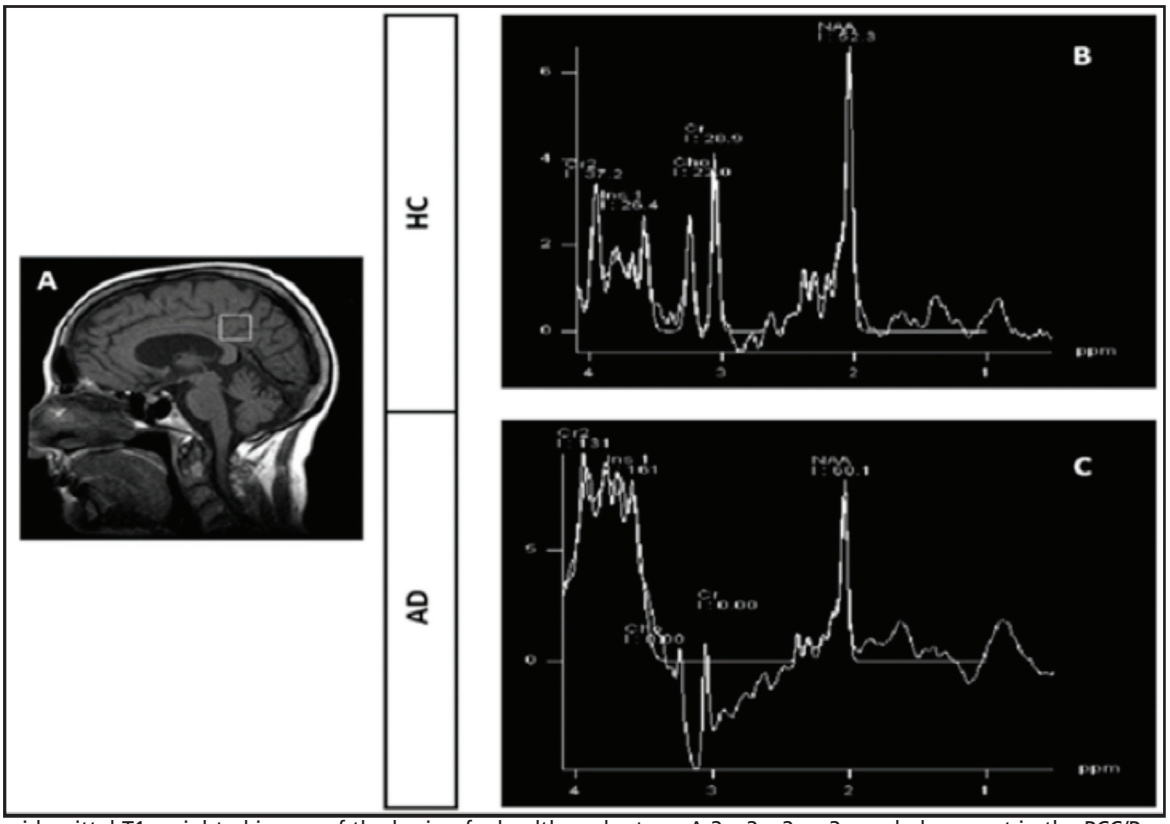

Fig. 3: A midsagittal T1-weighted image of the brain of a healthy volunteer. A 2 x 2 x 2 cm3 voxel placement in the PCC/Prec is shown in A. The difference in proton spectra and metabolites obtained from the region in healthy control and AD patients are shown in B and C. Notably, there is a significant decrease in the NAA peak in the AD subject. (This figure was reused with permission from ethical clearance received from our institutional ethical committee, reference number JKEUPM-2019-328 and Malaysian national ethical clearance number MREC (NMRR-19-2719-49105)).

high reproducibility. Nevertheless, caution needs to be exercised when comparing data from multicentre studies acquired using non-standardized protocols. Moreover, robust statistical analysis using AI could be hindered by data obtained from inferior software.

A point to consider is that the concentration of metabolites acquired using MRS is linearly proportional to the spectral peak area.[25] Under typical clinical MRS scan conditions (3T, using the shortest TE), there is bound to be overlap among metabolite spectra, including broad spectral overlap between metabolites and macromolecules in the baseline spectra. An example of a normal metabolites spectrum in healthy older adults generally has a tall N-acetyl aspartic acid (NAA) peak,[26] with some slight overlap of other metabolites that occur in lower concentrations (Figure 1).

Therefore, analysis methods based on the non-linear least squares fitting (NLSF) algorithm have been developed to address these problems, and the most common method is the Linear Combination (LC) Model proposed by Provencher et al.[27] (Figure 2). The model lays the in vivo spectrum as a fusion of pure, model spectra from each of the expected compounds in the brain.

The model also accommodates automatic phase and frequency correction and baseline correction. With the proper adjustment of each scanner and by using correct model solutions, the program returns metabolite concentrations (relative to an unsuppressed water signal or other internal metabolite references such as total creatine (tCr = creatine (Cr) + phosphocreatine (PCr)) or total choline (tCho = glycerophosphocholine (GPC) + phosphocholine (PCh)) as well as estimates of ambiguity.[27]

In NLSF, each metabolite's input to the overall spectrum is modelled as a single response function called the "basis set". Along with the LC Model, the development of software based on the NLSF algorithm has been steadily ongoing, and the following are representative examples: Tarquin,[28] Osprey,[29] Vespa,[30] INSPECTOR,[31] and jMRUI-QUEST among others have been designed by Graveron-Demilly,[32] Oeltzschner et al.,[33] Soher et al.,[30] Gajdošík et al.,[34] and Jabłoński et al.[35] as shown in Table I.

While attempts have been made to develop techniques for metabolite quantification and to apply MRS clinically, there are several limitations that make it difficult to use as a clinical tool. Specifically, the standard deviation of quantification results based on Cramér–Rao Lower Bound (CRLB) is commonly used as an error estimation indicator for quality control (QC) of results obtained using the NLSF method.

For example, according to the LCModel, it is not recommended to use results with a CRLB of 20% or more for statistics.[36] However, such CRLB-based QC can unintentionally lead to statistical bias, and furthermore, the

CRLB itself does not directly reflect the absolute error of quantification.[37] Additionally, there are large discrepancies in the analysis results between different software using various NLSF algorithm methods.

AI in Quantitative MRS Analysis.

The benefits of using AI have been widely discussed in the medical literature.[38] By using AI algorithms that resemble the network of neurons of the human brain, DL has been able to demonstrate excellent capability in pattern identification and denoising, thus providing a good-quality image for disease diagnosis, especially in AD. To address the technical issues in MRS analysis along with advances in AI, recent efforts in the MRS field have attempted to develop metabolite quantification techniques based on DL and ML.

Technically, various algorithms based on random forest,[39] autoencoder-based,[40] conventional convolutional neural network (CNN),[41] and Bayesian (BNN) have been developed, suggesting the feasibility of MRS analysis in clinical settings through these technical developments. On the other hand, one of the most significant technical challenges in applying ML/DL is to provide "uncertainty information" about the real-world data targeted inferences of the pre-trained model, allowing users to perform QC on the actual predicted quantification results.

Nevertheless, quantitative research achievements still lack empirical data on various diseases. Hence, further research is required to make MRS-based metabolite quantification potentially useful in a wide range of diverse clinical applications with the aid of ML/DL in the future.

AI in MRS for the Classification of Alzheimer's Disease Patients.

The use of AI techniques to improve MRS quantification has been increasingly adopted, along with the application of ML/DL for the classification of patients with cognitive impairment using MRS data by Munteanu et al.,[42] Ahmed et al.,[43] Kherchouche et al.,[44] and Wang et al.[45] as shown in Table II. The application of ML/DL in MRS can provide a potential avenue for early detection and treatment of dementia. For example, in the pioneering study by Munteanu et al., which was an MRS-AI-based classification of AD, multilayer perceptron was used on MRS data of 260 older adults, and the results extracted features such as metabolite derangements in the hippocampus that were similar to those of previous studies using structural MRI data.[42]

Recently, the development of end-to-end deep CNNs by Ahmed et al. and Kherchouche et al. have further advanced the field of dementia disease detection.[43,44] These types of CNN models have been able to accurately detect the presence of dementias using MRS data, suggesting that DL can be a powerful diagnostic tool by achieving 93.3% accuracy in 135 subjects (AD: 56, healthy control (HC): 79)[43] and 94% accuracy in normal and mild AD group and even 90% accuracy in normal and mild cognitive impairment (MCI) group in the diagnosis of these conditions.[44]

Furthermore, a study conducted by Wang et al.[45] demonstrated the effectiveness of classifying dementia patients by using both MRS and structural MRI data, achieving an accuracy rate of 96% to 98%, depending on the feature domain characteristics used in the classification. Hence, a noticeable focus lies in enhancing the accuracy of classifiers, limited by little to no discussion on generalisability, MRS data quality control, or broad applicability. Unfortunately, many studies employ analogous model architectures with scant comparisons between model structures.

Consequently, there is a need for multidisciplinary integrated research using ML/DL that not only improves the accuracy of metabolite quantification results inherent in MRS data but can also distinguish and link the severity of cognitive impairment with the pattern of the spectral data.

MRS Data Interpretation

Multiple metabolites are detectable at 1.5 or 3T with ^{1}H MRS in a normal human brain, including the prominent resonances of total NAA (tNAA), total creatine (tCr), total choline (tCho), and signals from myo-inositol (mI), glutamate and glutamine (Glx). Lactate is not usually seen in normal brains but is detectable in pathologies that cause its concentration to increase such as in brain abscesses and necrotic tissue.[17,46] Moreover, using MRS, one can detect characteristic patterns for AD because it has a unique metabolite pattern compared to other dementias when regional differences are taken into consideration.[47]

Total N-Acetyl-Aspartate

Total N-acetyl-aspartate (tNAA) is the largest metabolite signal in the spectrum[26] and is made up of the sum of N-acetyl-aspartate (NAA) and N-acetyl-aspartatyl-glutamate (NAAG). A very prominent signal at 2.01 ppm is usually shown by NAA corresponding to its methyl group.[20] "Neuronal marker," is another name given for NAA. This is because immunocytochemical studies have suggested that NAA is mostly tethered to the neurons, axons, and dendrites within the central nervous system. The decrease in NAA is one of the main findings in AD,[48] which is attributed to the loss of neuronal integrity that occurs in cells that undergo neuroinflammation and degeneration, as can be seen in Figure 3.

The most common VOI detected for the reduction of NAA has been reported in the medial temporal lobe, hippocampi, and PCC.[48] Even though NAA reduction is a well-known observation in AD, the outcome or findings are not consistent with those subjects having MCI, which is the prodromal stage of AD. Several studies claimed significant similarities between MCI cases and AD, whereas other studies found a significant difference between MCI and AD but not between MCI and HC.[49]

Total Creatine

Other than that, total Creatine (tCr) (3.01-ppm singlet and ~3.9-ppm singlet) arise from methyl and methylene group, respectively and is made up of the sum of creatine (Cr) and phosphocreatine (PCr), also known as energy metabolites. tCr is commonly used as an "internal reference" to quantify

other neurochemicals.[26] In a normal healthy brain, the level of tCr is found lower in WM compared to GM. Moreover, a greater level of tCr is found in the cerebellum in comparison with the supratentorial regions.

Total Choline

Referred to as choline-containing compounds (tCho) (3.21 ppm singlet arise from three identical methyl groups) in the human brain, it is involved in phospholipid synthesis and degradation, reflecting cell membrane turnover. tCho is mainly composed of Glycerophosphocholine (GPC) and Phosphocholine (PCh) and plays different functional roles in cell membrane formation and degradation. However, so far, there have been no consistent reports on the changes in Cho in either AD or MCI.

Myo-Inositol

Another commonly detected metabolite is myo-Inositol (mI). This metabolite produces one of the larger and strong coupled signals in short echo time spectra, which produces a signal at 3.5–3.6ppm. mI is much more abundant in glial cells as compared to neurons, and therefore it is increased in association with an increase in the glial component. Several recent studies related to MRS focused on MCI and AD have shown abnormal mI metabolite profiles. For example, a meta-analysis of MC and AD indicated decreased NAA and increased mI levels associated with MCI and AD, respectively.[49] Besides, NAA reduction and mI increase in AD compared to MCI and HC have also been detected, and this contributes to an increase in specificity and accuracy of the clinical diagnosis (100% for distinguishing AD from HC).[50]

Glutamate and Glutamine

Glutamate (Glu) and glutamine (Gln) (2.1–2.4- and 3.7-ppm multiplets) metabolites are complex (Glx = Glu + Gln); hence, their peaks are difficult to be distinguished, both from each other and from other compounds. At higher magnetic fields, like those used in preclinical studies, they can sometimes be resolved, depending on the spectral quality, but in general, it is difficult to obtain reliable measurements of these metabolites separately.[20] The most common brain region that shows a reduction in the level of Glx in AD is the anterior cingulate cortex, hippocampi, medial temporal lobe, and PCC.[49]

γ-Aminobutyric Acid and Glutathione

The primary inhibitory neurotransmitter in the brain is known as γ-aminobutyric acid (GABA) (1.9-, 2.3-, and 3.0-ppm multiplets). Due to the nature of the metabolites such as being very small and/or having overlapping peaks they are very hard to be detected routinely.[26] The concentration of GABA and glutathione in a normal brain are at relatively low levels (1.3–1.9 mmol/ kg weight),[13] which could also be a contributing factor to the difficulty of peak detection. Both GABA and Glutathione (GSH) have been reported to be observed at lower concentrations in AD compared to cognitively normal controls.

Metabolite Ratio (Semi-Quantitative Method)

Metabolite ratios have some instinctive benefits, such as accounting for partial volume effects or enhancing spectroscopic "contrast" in conditions where metabolites may change in opposite directions (e.g., tCho increases, tNAA decreases), however, the ratios may become inaccurate if all the metabolites are changing simultaneously.[26] The metabolite ratios that we commonly refer to are tNAA/tCr, tCho/tCr, mI/tCr, mI/tNAA, tNAA/mI, and Glx/tCr. AD patients exhibited a regional decrease in tNAA/tCr in the PCC and superior temporal lobe, and this reduction in demented patients compared with controls is due to the accelerated axonal damage.[50] Most of the previous research on AD and MCI have reported tNAA/tCr ratios to be consistently decreased.[50]

The reduction is caused by neuronal loss in addition to non-structural and physiological changes associated with impaired mitochondrial activity. Common findings in metabolite ratio for AD diagnosis are an increase in mI/tCr in AD followed by a decrease in tNAA/tCr and an increase in the ratio in tCho/tCr.[50] In addition, a systematic review done by Piersson et al.[50] had concluded that alterations in tNAA/tCr, tNAA/ml, and ml/tCr ratio may be potentially useful biomarkers that may highlight functional changes in the clinical stages of AD.

Automated Analysis of MRS Spectra

ML and DL have the potential to control spectral quality management and metabolite quantification, providing an automated analysis of MRS data. A study by Lee et al.[41] which was designed to develop a method for metabolite quantification with simultaneous measurement uncertainty estimation in DL-based 1H-MRS of rat's brains concluded that this method can be used for non-invasive metabolomics without additional data post-processing such as spectral fitting. They further stated that DL has great potential for the quantification of brain metabolites using 1H MRS data.

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