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REVIEW ARTICLE

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# MRS in neurodegenerative dementias, prodromal syndromes and at-risk states: A systematic review of the literature

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**Background:** In recent years, MRS has benefited from increased MRI field strengths, new acquisition protocols and new processing techniques. This review aims to determine how this has altered our understanding of MRS neurometabolic markers in neurodegenerative dementias.

**Methods:** Our systematic review of human in vivo MRS literature since 2002 pertains to Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease dementia, frontotemporal dementia (FTD), prodromal and 'at-risk' states. Studies using field strengths of 3 T or more were included.

**Results:** Of 85 studies, AD and/or mild cognitive impairment (MCI) were the most common conditions of interest (58 papers, 68%). Only 14 (16%) studies included other dementia syndromes and 13 (15%) investigated 'at-risk' cohorts. Earlier findings of lower *N*-acetylaspartate and higher myo-inositol were confirmed. Additionally, lower choline and creatine in AD and MCI were reported, though inconsistently. Previously challenging-to-measure metabolites (glutathione, glutamate and gamma-aminobutyric acid) were reportedly lower in AD, FTD and DLB compared with controls.

**Discussion:** Increasing field strength alongside targeted acquisition protocols has revealed additional metabolite changes. Most studies were small and regional metabolite differences between dementia types may not have been captured due to the predominant placement of voxels in the posterior cingulate cortex. The standard of data collection, quality control and analysis is improving due to greater consensus regarding acquisition and processing techniques. Ongoing harmonization of techniques, creation of larger and longitudinal cohorts, and placement of MRS voxels in more diverse regions will strengthen future research.

**Abbreviations:** AD, Alzheimer's disease; APOEe4, apolipoprotein e4 allele; Cho, choline; Cr, creatine; CRLB, Cramér–Rao lower bound; CSF, cerebral spinal fluid; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; Glx, glutamate + glutamine; GSH, glutathione; LASER, localization by adiabatic selective refocusing; MAPT, microtubule-associated protein tau; MCI, mild cognitive impairment; MEGA-PRESS, Mescher–Garwood point-resolved spectroscopy; mI, myo-inositol; MRSI, magnetic resonance spectroscopic imaging; MTL, medial temporal lobe; NAA, *N*-acetylaspartate; NMDA, *N*-methyl-D-aspartate; PCC, posterior cingulate cortex; PCr, phosphocreatine; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PD-MCI, Parkinson's disease mild cognitive impairment; PET, positron emission tomography; PRESS, point-resolved spectroscopy; PVC, partial volume correction; QC, quality control; rTMS, repetitive transcranial magnetic stimulation; SNR, signal-to-noise ratio; tCr, total creatine; tDCS, transcranial direct-current stimulation; $T_E$, echo time; $T_R$, repetition time.

KEYWORDS
Alzheimer's disease, dementia, Lewy bodies, mild cognitive impairment, MRS, Parkinson's dementia, proton spectroscopy

## 1 | INTRODUCTION

Functional brain changes in Alzheimer's disease (AD) and other neurodegenerative dementias precede structural and behavioural/cognitive changes by years or decades. For example, a recent review of preclinical AD populations suggested multiple functional changes, including hypometabolism in posterior cingulate and temporoparietal regions, using $^{18}$F-2-fluorodeoxy-D-glucose positron emission tomography (PET); reduced resting tissue perfusion, most markedly in posterior regions, using arterial spin labelling MRI; and reduced neuronal activity in response to a cognitive task, using blood oxygen level dependent signal on fMRI.[1]

MRS is a non-invasive method for measuring in vivo levels of neuro-metabolites, which are tightly related to brain functions. The method relies on the inherent resonance of protons within a magnetic field as protons precess and exchange energy with their surroundings. In this review we focus on single voxel proton MRS: protons resonate at subtly different frequencies depending on their local environment, giving metabolites a unique MRS 'fingerprint', which allows a number of neuro-metabolites with MRS-visible protons to be quantified either absolutely (using phantoms or water-scaling) or relatively (compared with another neuro-metabolite, typically creatine (Cr) or combined Cr and phosphocreatine, PCr (total creatine, tCr; note that the literature commonly refers to both Cr and tCr as creatine).[2]

Initially developed in the 1980s, proton MRS has been used to investigate changes in brain metabolites in dementia since the 1990s. Table 1 provides a brief summary of commonly measured metabolites and their relevance. A comprehensive review of MRS in neurodegenerative dementias and Parkinson's-related disorders from our group in 2002[10] found that all studies investigating dementia included an AD group (27 studies); of these, six included a vascular dementia group, one included a frontotemporal dementia (FTD) group and one included a group with non-AD dementia-like illnesses. No studies included dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD). In AD, studies consistently reported global reduction of *N*-acetylaspartate (NAA, a measure variously reflecting neuronal density, viability, function and metabolism[3]), with especially pronounced loss in the hippocampi, together with global increase in myo-inositol (mI, a putative marker of inflammation[5] and amyloid deposition[3]). Firbank et al. highlighted several methodological shortcomings of those studies to date, including the use of low MR field strengths (1, 1.5 and 2 T) and limited consensus regarding acquisition techniques, preprocessing and quality control (QC) measures.

MRS has progressed significantly in the last 20 years, not least due to the availability of higher-field-strength scanners (3, 4 and 7 T) and new acquisition techniques, including those specifically designed to detect previously difficult-to-measure molecules such as glutathione (GSH), glutamine (Gln), glutamate (Glu) and gamma-aminobutyric acid (GABA). The various acquisitions differ by virtue of their echo times ($T_E$), repetition times ($T_R$), flip angles and selective editing techniques, allowing metabolites with different MR properties to be selected for. Commonly used acquisitions include stimulated echo acquisition mode (STEAM), point-resolved spectroscopy (PRESS), Mescher–Garwood point-resolved spectroscopy (MEGA-PRESS), localization by adiabatic selective refocusing (LASER), semi-LASER and spin echo full intensity acquired localized spectroscopy (see Reference 11 for an explanation of these different acquisitions).

Many reviews published since 2002 have been narrative. Of the systematic reviews and meta-analyses, four have focused primarily on AD and/or mild cognitive impairment (MCI), with which the majority of published papers are concerned.[12–15] One, comprising only four papers, focused on DLB.[16] Four included studies with MRI scanner field strengths of 3 T or more alongside those at lower field strengths[13–15,17]; of these, one (from 2014) summarized findings at lower field strengths separately from those at higher fields[13] reporting that in AD NAA or NAA/Cr were lower in the medial temporal lobe (MTL) and posterior cingulate cortex (PCC), and that lower NAA and higher mI precede MTL atrophy, though lower NAA and higher mI were not consistently found simultaneously in the same voxel of interest. Differences in choline (Cho) and Cr in AD and MCI were not consistently found. This review also reported that in longitudinal studies of MCI NAA, glutamate + glutamine (Glx), Cho and Cr all decreased and that the decrease in NAA or NAA/Cr was greater in those who converted from MCI to AD. See Table 2 for a summary of AD and MCI MRS findings at field strengths of <3 T from this review. As 3 T scanners have become more widespread, relatively few groups have continued to publish MRS dementia studies at 1.5 T. A 2014 paper reported regional metabolite variation between AD and DLB, with lower PCC and frontal NAA/Cr in AD compared with lower occipital NAA/Cr in those with DLB.[18] This study also found that PCC Cho/Cr and mI/Cr were higher in patients than in controls. A number of longitudinal 1.5 T studies have been published since 2014, examining whether MRS metabolite changes could be used to predict conversion to dementia. In these papers, lower PCC NAA/Cr was found in those who converted from MCI to AD compared with those who converted to DLB,[19] and lower PCC NAA/mI was found in those who converted from MCI to AD[20] and from normal cognition to MCI, AD and DLB.[21] Additionally, in this third study MMSE scores at seven years were found to correlate with PCC mI/Cr and NAA/mI. Occipital mI and PCC Glx have also been found to predict conversion from MCI to AD with 46.1% sensitivity and 90.6% specificity.[22]

**TABLE 1** MRS metabolites.

| Metabolite | Abbreviation | Purported role/significance |
|---|---|---|
| *N*-acetylaspartate | NAA | • abundant in mitochondria and cytoplasm of neurons and possibly in oligodendrocytes[3]<br>• intermediary metabolite with no known primary function; precursor of aspartate and acetate, which become oxaloacetate and acetyl CoA as used in Krebs' cycle[3]; may also act as a reservoir for Glu[4]<br>• in MRS previously considered to be a 'neuronal marker' reflecting neuronal integrity and/or density, but this may be too simplistic an interpretation as levels may relate to mitochondrial density, and neuronal and mitochondrial viability and function[3] |
| Myo-inositol | mI | • present primarily in astrocytes in in vitro cultures but its consequent role in MRS as a marker of glial activation (thus suggesting an inflammatory process)[5] is sometimes disputed[3]<br>• a component of biomembranes, part of the second messenger system and an organic osmolyte<br>• in MRS it may be considered a marker of glial activation (see above) and oedema[3]; it may also be a marker of beta-amyloid deposition[3,7] |
| Choline | Cho | • signal principally consists of phosphocholine and glycerophosphocholine; present in low concentrations[3]<br>• Cho is taken up by cells for phospholipid synthesis (used in cell membranes)[3]<br>• in MRS Cho is a marker of non-steady-state cell membrane turnover, changes in cell density and possibly demyelination (phospholipids account for ~40% of myelin)[3] |
| Creatine | Cr | • combines with ATP to form PCr, ADP and $H^+$, thus has a role in energy storage[3]<br>• as used in the literature creatine often refers to total creatine (Cr + PCr), which is more properly abbreviated to tCr<br>• in MRS studies, commonly used as a reference metabolite; however, this approach is increasingly criticized as Cr concentration is not stable within the brain or between individuals[92] |
| Glutathione | GSH | • present throughout the brain though in relatively low concentrations[3]; difficult to measure due to spectral overlap with Cr, Glx, NAA and GABA[8]<br>• used for the synthesis and breakdown of proteins, the formation of the precursors of DNA, and the detoxification of reactive oxygen compounds[3]<br>• in MRS GSH is a marker of oxidative stress and mitochondrial function[3] |
| Glutamate | Glu | • the most plentiful amino acid and the principal excitatory neurotransmitter in the human brain[3,8]<br>• closely linked to metabolic activity and, therefore, in MRS concentration closely reflects neuronal excitation[3] |
| Glutamine | Gln | • present in brain and CSF in low concentration compared with Glu[7]<br>• the main precursor of both Glu and GABA[8]<br>• difficult to quantify due to significant overlap with Glu; levels of Glu and Gln are closely coupled[3]<br>• Gln and Glu are often combined as Glx[8] |
| Gamma-aminobutyric acid | GABA | • principal inhibitory neurotransmitter in the human brain but present in very small concentrations[7]<br>• a small amount is present as neurotransmitter, the remainder is an intracellular metabolic pool of GABA[3]<br>• in MRS concentration may better reflect overall GABAergic tone than simple inhibitory activity since activity at different GABA receptors may produce either increased or decreased overall activity[3] |
| Prefix t- (total) | e.g., tCho | • used when members of a common group are combined; e.g., tCho value combines all choline containing metabolites |

**TABLE 2** Summary of findings in AD and MCI at field strength of <3 T from Reference 13.

| | NAA | mI | Cho | Cr | Glx |
|---|---|---|---|---|---|
| AD | lower | higher | inconsistent | inconsistent | not reported |
| MCI | lower | higher | lower | lower | lower |

Given the ongoing advances in MRS and many new studies that take advantage of the higher MR scanner field strengths now available, the aim of this review is to build on previous reviews by summarizing high-field MRS findings in common neurodegenerative dementias since 2002. This review aims to determine how modern techniques have altered our understanding of MRS neurometabolic markers in neurodegenerative dementias and their prodromal and 'at-risk' states, as well as those examining the effects of treatments in dementias. By bringing studies together we aim to compare findings between dementias, examining the ways in which MRS metabolite changes are similar and different between dementia types. By considering only higher-field-strength MRS studies (≥3 T) we aim to understand how increasing field strength has altered our understanding of these diseases. Findings will be summarized and methodological issues including acquisition, processing, QC and analysis methods will be compared.

## 2 | METHODS

The initial search was completed in the PubMed and Embase databases using the search terms

'MRS', 'proton spectroscopy', '$^{1}$H spectroscopy'
'dementia', 'Alzheimer*', 'Lewy', 'Parkinson*', 'frontotemporal', 'mild cognitive impairment', 'prodrom* dementia'

Papers published between 1 January 2002 and 25 January 2022 were searched. 2002 was selected to find papers published since the previous Firbank et al. (2002) review, which included papers published up to 31 December 2001.

Manual review of titles and abstracts was performed to identify relevant papers according to the inclusion and exclusion criteria. Full papers were requested and each paper was reviewed. Manual review of references of relevant papers was used to identify further potentially relevant papers.

Inclusion criteria: published papers in English, human in vivo studies, MR field strength of 3 T or more, including participants with a neurodegenerative dementia or prodromal dementia syndromes (including MCI) or cognitively normal participants at increased risk of developing dementia. Papers that primary utilized $^{1}$H magnetic resonance spectroscopic imaging (MRSI, also known as chemical shift imaging) were not included.

Exclusion criteria: field strength of <3 T (or not stated), studies primarily comparing techniques rather than groups (for example, comparing effectiveness of acquisition technique A versus B) that did not report on group differences, and studies not meeting the inclusion criteria.

Data collected included condition under investigation, number of participants, mean ages of participants, MRS methods (voxel size and placement, metabolites of interest, scanner strength, acquisition protocol, analysis package used), main research question(s) and main significant finding(s).

Quality of papers was considered against the 2020 Öz et al. consensus criteria[23] for data acquisition and processing of high-field MRS. We could not expect studies performed prior to the publication of this paper to explicitly meet these criteria; however, we have included them as a marker of current best practice.

## 3 | RESULTS

A total of 85 papers are included in this systematic review. Figure 1 depicts the systematic review process.

### 3.1 | Participants and study design

Patient groups: the conditions of interest are summarized in Table 3. In most studies the condition of interest was AD and/or MCI (58 papers, 68%).

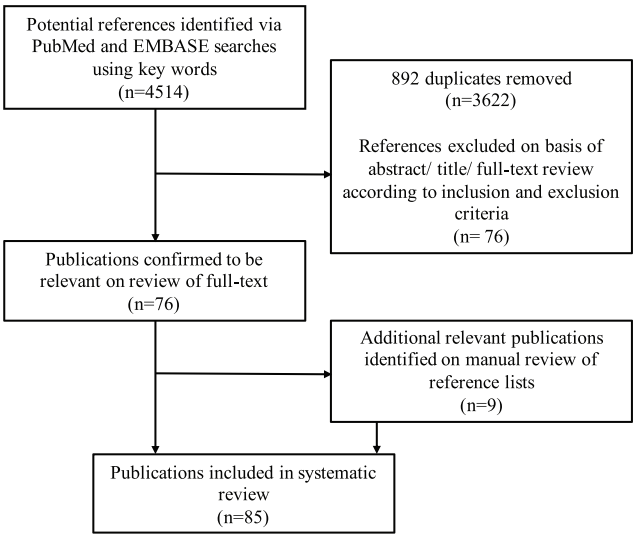


**FIGURE 1** Flow diagram depicting the systematic review process.

**TABLE 3** Summary of papers.

| Condition of interest | Number of studies | Further breakdown |
|---|---|---|
| AD versus HC (±MCI) | 31 | |
| MCI | 17 | |
| Effects of treatment | 11 | • 4 × anticholinesterases for AD<br>• 1 × NMDA receptor antagonists for AD<br>• 1 × anticholinesterase + NMDA receptor antagonist for AD<br>• 1 × riluzole (Glu modulator) for AD<br>• 1 × yoga and brain training for AD<br>• 1 × tDCS for primary progressive aphasia<br>• 1 × HD-tDCS in MCI<br>• 1 × rTMS for AD |
| Other dementia syndromes | 13 | • 6 × frontotemporal lobar degeneration including FTD (of these 1 FTD + AD)<br>• 2 × DLB (of these 2 DLB + AD)<br>• 5 × PDD/PD-MCI (of these 1 PDD, 1 PDD + AD, 1 PD-MCI, 2 PDD + PD-MCI) |
| 'At risk' of dementia cohorts | 13 | All papers considering cohorts 'at risk' of AD or unspecified dementia type. |

HC, healthy controls.

Participant ages: participants were generally aged between 65 and 75 years; the maximum mean age of a participant group was 87 years. Participants were generally younger in FTD studies than in other patient groups. Most studies reported age-matching or no significant difference in ages between patient group(s) and controls.

Participant numbers: aside from 'at risk' of dementia studies, numbers were mostly small, with around 10–30 participants in each group.

Longitudinal data: studies examining the effects of treatment included at least two scans acquired before and after a period of treatment; the majority of other studies were cross-sectional and only six non-treatment studies (7%) collected longitudinal data.

## 3.2 | Scanning methods

Field strength: we considered only studies using MRI scanners of 3 T or more. Of the 85 papers included, 76 used 3 T, two used 4 T and four used 7 T.

Acquisition: most studies (63, 74%) used PRESS; for MRS metabolites that are more challenging to measure by virtue of short $T_2$ relaxation times or spectral overlap (for example, Glx, GABA and GSH) alternative or additional sequences such as MEGA-PRESS (12, 14%) and semi-LASER (five, 6%) were used.

Voxel size: MRS voxels were commonly $2 \times 2 \times 2$ cm$^3$ but varied from $0.8 \times 0.8 \times 1$ cm$^3$ to $8 \times 8 \times 8$ cm$^3$.

Voxel placement: voxels were most often placed in the PCC (in 51, 60% of studies); voxels were also commonly placed in the hippocampus (22, 26%), frontal lobe (20, 24%) and anterior cingulate cortex (ACC, 15, 18%) (note: many studies included multiple voxels). In three studies (4%) automated or semi-automated voxel placement was used; otherwise, voxels were placed manually, with some papers making reference to the use of a consistent individual positioning the voxel or placement with reference to landmarks.

Water-referencing: although only 31 (36%) studies overall collected unsuppressed water data, since 2020 eight of 16 papers (50%) did so.

## 3.3 | Processing methods

Preprocessing: steps such as eddy current, phase and frequency correction, which improve the quality of the spectra prior to fitting and quantification of metabolite concentrations, were reported in 28 (33%) of papers.

Processing software: LCModel (which fits in vivo metabolite spectra using complete model metabolite spectra derived from simulations or in vitro solutions[24,25]) was most frequently used, in 34 (40%) of studies.

Assessment of data quality: QC measures were reported in 46 (54%) studies; relative Cramér–Rao lower bound (CRLB) (usually specifying a cut off of <20%) was the measure most frequently reported, in 37 (44%) studies. Other measures included visual inspection of spectra and use of spectral linewidth and signal-to-noise ratio (SNR).

Partial volume correction: PVC accounts for differences in metabolite concentrations in different tissue types, especially cerebral spinal fluid (CSF). Of the 31 papers reporting metabolite concentrations as 'absolute' or water-scaled values, 20 (65%) included PVC. Where

metabolite concentrations were reported as ratios to another metabolite (54, 64% of papers), the effects of CSF in the voxel were negated and PVC was not necessary.

### 3.4 | Summary of findings: AD, AD/MCI, MCI studies

See Supplementary Table S1: AD, AD/MCI, MCI studies. There was a general consensus in these 48 studies that NAA or NAA/Cr was lower in AD than in MCI and lower in MCI than in controls. Similarly, mI and mI/Cr were generally found to be higher in AD than in MCI and higher in MCI than in controls. Most studies placed voxels in the PCC (31, 65%), but lower NAA or NAA/Cr and higher mI or mI/Cr were also reported in wide ranging areas including hippocampal, occipital and motor regions. Eleven papers reported correlations between NAA or NAA/Cr and cognitive and functional symptoms.[26–36] Most papers reported no significant group differences in Cho or Cho/Cr between patient groups; four papers reported higher PCC Cho or Cho/Cr in patient groups than in controls.[37–40] Of the papers exploring changes in Glu, Glx, GSH and GABA, not all reported significant group differences; where group differences were found, Glu, Glx, GABA and GSH were found to be lower in patient groups.[31,32,41–52] In two papers GSH was found to differentiate AD from MCI and MCI from controls with a high degree of accuracy.[47,51] Ten studies considered Cr (or tCr) as a metabolite of interest: seven reported no significant results[26,29,32,42,46,50,53]; one found lower ACC and PCC Cr in AD and MCI groups compared with controls but no significant difference between AD and MCI groups[51]; another found lower left dorsal thalamic tCr in MCI compared with controls.[54] A functional MRS study found that changes in PCC tCr between three stimulation conditions differentiated between AD, MCI and controls with relatively high sensitivity and specificity (highest for AD versus controls, sensitivity 87.5, specificity 63.89).[94]

### 3.5 | Summary of dementia treatment study findings

See Supplementary Table S2: Treatment Studies. Of the 10 studies examining the effects of treatment in AD/MCI and one examining the effects of treatment in primary progressive aphasia (a dementia syndrome most commonly related to FTD pathology), all included at least two MRS scans, which took place before and after treatment. Six of the studies examined MRS changes with respect to AD treatment with anticholinesterases and/ or *N*-methyl-D-aspartate (NMDA)-receptor antagonists; the others examined the effects of yoga versus 'brain training', repetitive transcranial magnetic stimulation (rTMS), transcranial direct-current stimulation (tDCS) and riluzole (a Glu modulator usually used in the treatment of amyotrophic lateral sclerosis). Of the drug treatment studies, three studies did not include a control group[55–57] and in only two studies were participants and/or researchers blind to the treatment.[58,59] The numbers included in treatment studies were very small: the largest treatment group had only 22 participants[58] and two had 10 or fewer.[55,59] Cognitive function was not reported in two studies[56,60] and was found to be significantly different before and after treatment or between treatment groups in only two studies: one of galantamine (there was no control group in this study)[55] and one of rTMS.[61] All studies reported changes in MRS metabolites after treatment or differences in MRS metabolites between treated and untreated groups; however, the changes reported were mixed: after treatment with an anticholinesterase two studies reported higher NAA[56,62] and three lower NAA.[57,63,64] Changes in Glu, Glx or Glu/Cr were reported in three papers: in two studies Glu/Cr and Glx/Cr were found to be higher (in the right hippocampus and PCC respectively) following treatment with an anticholinesterase,[55,57] which in one correlated with a measure of general cognition.[55] PCC Glu was found to increase following treatment with riluzole and Glu concentration correlated with cognitive measures, although there was not a statistically significant difference in cognitive scores between treated and untreated groups.[58] Four papers considered concentrations of Cr: three studies of anticholinesterases[55,57,64] and one of tDCS for primary progressive aphasia[65] found no change in Cr before and after treatment.

### 3.6 | Summary of findings in studies of other dementia types

See Supplementary Table S3: Studies of degenerative dementias other than AD. Six studies included participants with FTD and/or related frontotemporal lobar degenerative conditions. One comparing FTD and AD reported similar reductions in NAA/Cr compared with controls but found differences in spatial patterns, with the FTD group showing a larger decrease in frontal regions and the AD group showing a larger decrease in posterior regions.[66] Three studies examined differences between symptomatic and non-symptomatic carriers of a microtubule-associated protein tau (MAPT) mutation that is linked to familial FTD.[67–69] Similar to the MCI and AD picture, NAA/Cr was found to be lower and mI/Cr higher in non-symptomatic MAPT carriers compared with controls and in symptomatic MAPT carriers compared with non-symptomatic carriers in PCC and frontal regions.[67,68] One paper reported an increased rate of decrease in PCC NAA/mI and increase in PCC mI/Cr around two years prior to symptom onset.[68] Another group found reduced GABA in the right inferior frontal gyrus but not the occipital lobe in patients with FTD, which correlated with a behavioural measure of impulsivity,[70] and reduced NAA and Glu in the right prefrontal cortex in FTD and progressive

supranuclear palsy, which was associated with executive dysfunction behavioural impairment.[71] One paper considered Cr as a metabolite of interest but found no difference between patients and controls after application of PVC.[71]

Five studies included participants with PDD or Parkinson's disease mild cognitive impairment (PD-MCI). There was a consensus that PCC NAA/Cr was lower in PDD than in PD-MCI and in PD-MCI than Parkinson's disease (PD) and controls. NAA/Cr was found to correlate with cognitive tasks including MMSE.[72,73] However, in a longitudinal study no changes in MRS metabolites were found as participants progressed through PD to PD-MCI and PDD.[74] Overall, no changes were found in PCC Cho/Cr or mI/Cr compared with controls. A paper comparing PDD and AD directly found that PCC Glu/Cr was lower in PDD than in AD or controls.[75]

Two studies included participants with DLB and both included an AD comparison group. One found occipital NAA and Glu to be lower in DLB and AD than controls[76] while another reported that both occipital NAA and Glu were lower in DLB than AD and could be used to differentiate between DLB and controls (with specificity 84% and sensitivity 83%) and DLB and AD (with specificity 84% and sensitivity 67%[77]). This group also reported lower occipital Cr in DLB than AD and controls, and associations between occipital NAA and Glu and global cognitive function in the DLB group.

## 3.7 | Summary of findings in 'at risk of dementia' cohorts

See Supplementary Table S4: Studies of cognitively normal groups 'at risk' of dementia. All studies but one[78] included older 'at-risk' cohorts with mean ages in their late 60s and 70s. Studies mostly had relatively large numbers of participants; the largest, with 594 participants, was also the only longitudinal study.[79] 'At risk' was defined in a variety of ways and included: carriers of the apolipoprotein e4 allele (APOEe4)[78–84] increased Pittsburgh B compound (PiB) PET retention (a measure of brain amyloid)[79,82,85] CSF amyloid and tau[81,86] subjective and objective memory deficits in the absence of clinically significant impairment[87,88] and presence of nocturnal hypoxaemia (due to obstructive sleep apnoea).[87]

Five studies compared MRS metabolites in cognitively normal participants with high or low brain amyloid. These studies found variously that significant amyloid deposition was associated with high mI/Cr,[79,85] NAA/mI[79] and Cho/Cr[85] and low GSH.[82] Only one study[79] found an association between brain amyloid and NAA/Cr; in addition, this study found that high mI/Cr and low NAA/mI (but not NAA/Cr) at baseline was associated with increased brain amyloid deposition over time. One study found no associations between brain amyloid and metabolite concentrations but found that higher brain tau was associated with lower NAA/Cr and Glu/Cr in females but not males[89]; this was the only study that measured brain tau deposition.

Overall, APOEe4 status was found to have little or no effect on MRS metabolite levels; for example, one study did not find that APOEe4 status had any modifying effects on the relationship between amyloid and MRS metabolite levels,[79] another did not find any APOE effect or APOE × age interaction when comparing MRS metabolites in young and old participants[83] and a third found no effect of APOEe4 status on the relationship between right hippocampal GABA and episodic memory, which was found in women but not men.[84] However, in a mid-life cohort (mean ages 53 for the APOEe4+ and 49 for APOEe4−), higher left hippocampal Glx was associated with poorer local neuronal interconnectivity in the APOEe4+ but not the APOEe4− group.[78]

## 3.8 | Discussion

We reviewed a total of 85 papers that used proton MRS at 3 T or more to measure metabolites in neurodegenerative dementias, prodromal dementia syndromes and 'at-risk' states. We found that, as in the earlier 2002 review[7] papers focused mainly on AD and/or MCI (58 papers, 68%). Across dementia types the most robust finding was that NAA/Cr was lower in dementias than in prodromal states and lower in prodromal states than in controls across brain regions. As NAA is a marker of neuronal integrity, density, function and metabolism, its decrease in dementia may reflect processes including neuronal loss, reduced metabolism and loss of myelin[3,90]

Increasing field strength to 3 T does not appear to have resulted in a change to the key findings from earlier studies regarding NAA/Cr (which is lower) and mI/Cr (which is higher) in AD and MCI. In addition, the increase in field strength has not fully resolved the question of changes in Cho and Cho/Cr in dementia, with most AD and MCI studies measuring Cho or Cho/Cr but only four papers reporting a significant increase in the PCC in MCI and AD compared with controls.[37–40] Cho is a marker of cell membrane degradation; it is not difficult to measure using MRS and an increase in its levels in dementia is biologically plausible and supported by some MRS studies[91]; therefore, the general lack of findings is perhaps puzzling. An explanation may be the widespread use of acetylcholinesterase medications, which appear to decrease levels of Cho (for example Reference 62), in the management of dementias including AD and DLB. Most studies included in this review did not control for whether participants were taking these medications; therefore, it is possible that they are responsible for reversing the increase in Cho that we might expect to see in patients compared with controls. As discussed below, small participant groups combined with a lack of adequate QC and PVC may also contribute to a lack of findings.

Metabolites such as GABA, GSH and Glu can be challenging to measure using MRS. GABA is present in low concentrations relative to other metabolites[8,9]; its multiplet signal results in three low-intensity peaks and there is spectral overlap with NAA, Cr and Glx, all of which are more abundant in the brain.[6,9] Although Glu is abundant, it overlaps with Gln, which makes it difficult to resolve, while GSH is present in low concentrations and overlapped by metabolites including Cr, Glx, NAA and GABA.[8] Spectral editing techniques such as MEGA-PRESS, which utilizes the *J*-coupled characteristics of these metabolites, is used to successfully measure them.[6] Additionally, increasing magnetic field strength results in improved SNR and greater spectral separation, producing more highly resolved spectra. Glu and GABA are excitatory and inhibitory neurotransmitters respectively and GSH is a marker of oxidative stress; in this review we found lower Glu, GABA and GSH in AD and MCI[31,32,46,47,51]; lower GABA and Glu in frontal regions in FTD, which correlated with measures of executive dysfunction[70,71]; and lower occipital NAA and Glu in DLB compared with AD and controls.[77] However, though atrophic brain changes are well established in these conditions, many studies did not report performing PVC/voxel tissue composition correction on their results, meaning that it is not necessarily clear whether reductions in metabolites are in fact due to the reduction in brain tissue in disease states. Most studies that presented relative metabolite concentrations rather than 'absolute' values did not include any form of PVC, since calculating ratios of two metabolites that are both present only in tissue negates the effect of CSF on the values and should, therefore, preclude any effects of atrophy. However, the presentation of the metabolite of interest as a ratio to Cr or tCr is itself problematic, as Cr may not be as stable in comparison with other metabolites as previously thought[92]; Cr has been found to increase with age[93] and with risk factors for dementia such as APOEe4.[83] Relatively few papers in this review calculated Cr concentration and most did not report significant results. Where differences were found, Cr was found to be lower in patient groups (AD, MCI and DLB) across a range of regions[51,54,77,94] but higher in older controls in 'at-risk' cohorts.[83,86] These results underscore the problem of using Cr as a reference region, especially within dementia research, as the relationship of Cr with disease and age is unclear.

The PCC was most commonly chosen for voxel placement, especially in studies of AD and MCI; studies of other dementias were more likely to include additional voxels, such as in the frontal cortex in FTD and the occipital cortex in DLB and PDD. Studies including voxels beyond the PCC suggest that differences in the relative distributions of metabolite changes are more pronounced than differences in the levels of metabolites themselves. For example, NAA/Cr is lower in both AD and FTD, but is lower in a frontal voxel than in the PCC in FTD while the opposite is seen in AD,[66] and lower NAA and Glu are more pronounced in the occipital lobe in DLB than in AD.[77] Different metabolite distributions are likely to reflect different distributions of pathology in these conditions; in addition, they may provide clues regarding the mechanisms underlying the different symptoms seen in these conditions. For example, in one FTD study lower GABA in the right inferior frontal gyrus was found to correlate with a measure of impulsivity, which is a key feature of the condition.[70] Similarly, changes in GABA or Glu may be related to hallucinations, which are a key feature of DLB.[95] Therefore, use of a single (or poorly chosen) voxel is a big limitation in MRS studies, as any results may miss or exaggerate true group differences. Particularly when comparing dementia types, it may be more interesting to look at the distribution of metabolites by comparing multiple voxels or by using MRSI which measures metabolites throughout a larger volume of interest or across the whole brain rather than within a single voxel, which is typically $2 \times 2 \times 2$ $cm^3$.

Of the 11 treatment studies, six investigated metabolite changes related to the administration of acetylcholinesterase and/or NMDA-receptor antagonists for the treatment of AD. The studies generally had methodological challenges, with extremely small treatment groups and a lack of comparison group or control group in some cases. Since functional or cognitive findings were not reported or not found to be significantly altered following treatment in most papers, the clinical relevance of any metabolite changes was difficult to interpret. Findings in these papers did not converge: for example, both increases and decreases in NAA/Cr following similar treatment were reported.[56,57,62–64] The lack of consensus is probably due to the very small sample sizes (meaning that the studies lacked statistical power) and differences in methodology—for example, the drug naivety or otherwise of participants and the length of the treatment course.

Thirteen papers reported on groups 'at risk' of dementia, by virtue of risk factors such as APOEe4 carriership or brain or CSF amyloid. The most commonly reported finding was of increased mI/Cr in those at higher risk, which is in keeping with the early-AD and MCI literature. Whilst most studies demonstrated an effect of brain amyloid deposition on MRS metabolites, changes associated with APOEe4 were not seen. An explanation is that carriership of the APOEe4 allele is a risk factor present from birth, which may or may not result in the development of dementia depending on many other genetic and environmental factors, while amyloid deposition in cognitively normal individuals may be a marker of a pre-clinical disease state. This may suggest that the MRS metabolite changes seen reflect amyloid deposition, or indeed deposition of other proteins such as tau or alpha-synuclein (which were rarely measured in these studies), rather than an early 'at-risk' state. A major source of bias in the 'at-risk' studies is the inclusion of older adults without cognitive impairment rather than of 'at-risk' populations in mid-life, as survivor bias is likely to mean that some of those at high risk of developing dementia are excluded, since by the time they are in their 70s they have already developed a dementia.

In comparison with the 2002 review,[10] which found changes in AD primarily in NAA/Cr and mI/Cr, this review has found additional differences between patients and controls, such as the reductions in GABA, Glu and GSH seen in patient groups compared with controls. However, in keeping with the previous review, differences in concentrations of Cho and Cr between those with dementia and controls have not been convincingly demonstrated in the studies reviewed here. The increase from 1.5 to 3 T and above is likely to have contributed to the improved SNR of these more recent studies. As SNR and spectral spread increase as field strength increases[96] 7 T MRS has the potential to be more sensitive in the measurement of challenging metabolites such as GABA and Glu.[96] Only four studies in this review were found to utilize 7 T MRS, and all but

one was published in or after 2019. Three of these studies included AD and/or MCI groups and variously found lower GABA/Cr, Glu and Glu/Cr in the cingulate cortex[31] and left hippocampus,[32] and higher ascorbate and Cho in the PCC.[53] These few papers suggest that the theoretical benefits of 7 T MRS may be realized, as GABA and Glu have generally been difficult to measure; however, a number of 3 T studies also successfully measured these challenging metabolites using acquisitions such as semi-LASER and MEGA-PRESS (see, e.g., References 50,70,84) and it may be that the acquisition protocol chosen is as important as (or more important than) the scanner field strength. The speculation that the choice of acquisition, processing and post-processing techniques impact more on the successful and accurate measurement of metabolites than field strength alone is supported by the findings of a 2003 paper that compared 1.5 and 3 T scanners directly without finding much benefit in the higher static field strength.[40]

A common difficulty when comparing imaging studies is a lack of consensus on acquisition and processing techniques; differences in MR acquisition, processing and QC criteria can result in large differences in findings and may be responsible for the variation in findings in the studies reviewed here. Although we could not expect studies performed prior to 2020 to explicitly meet the 2020 consensus criteria,[23] it is striking how few studies fulfil these criteria, which may now be considered the gold standard. For example, only 36% of studies collected an unsuppressed water acquisition within the same voxel and with the same $T_E$ as the MRS acquisition. This additional acquisition allows eddy-current correction to be performed, reducing spectral baseline artefacts, which can mask the signal from metabolites of interest.[2] It also allows water-scaling to be applied, which permits the calculation of metabolite concentration in millimolar, scanner or institutional units (often referred to as 'absolute' concentrations). Reporting water-scaled concentrations may have advantages over reporting values relative to another metabolite, since the denominator metabolite may also differ between groups, meaning that it is not ultimately possible to say which of the two metabolites is responsible for any group difference; limitations of Cr as a reference metabolite have been discussed. The lack of reported QC measures is also conspicuous, with almost half of studies reporting no QC. Relative CRLB with a cut-off of 20% was the most frequently reported QC measure; this has been standard practice historically, and considered to indicate acceptably reliable metabolite measurement[25]; however, more recently it has been found that the use of relative CRLBs may lead to the introduction of bias in cohort data, since higher relative CRLBs may systematically accompany lower metabolite concentrations.[97] Methods using absolute CRLB are now preferred, as reflected in the consensus criteria.[23] PVC is not included in the consensus criteria; however, in the specific case of dementia research it is likely to be important, as atrophy is prevalent in dementia cohorts and is a diagnostic feature of dementias such as AD[98] and FTD.[99] Without PVC or other correction for atrophy, any differences seen in metabolite concentrations may be attributable to changes in voxel tissue composition rather than to functional metabolic change.

### 3.9 | Limitations and strengths

This systematic review is a comprehensive search of the literature, using key terms. The references of papers that were identified as relevant were also searched. The search has captured a range of studies, including a variety or dementia types as well as treatment studies and 'at-risk' of dementia groups. It was not within the scope of this review to look at other related neurological disorders such as Down's syndrome dementia and PD.

Another general limitation of the current MRS literature is the lack of longitudinal studies. When attempting to establish prodromal and pre-clinical biomarkers and markers of 'at risk' states, the use of cross-sectional study designs severely limits the conclusions that can be made. Focus on large, longitudinal cohort study designs starting in mid-life (such as the PREVENT-Dementia study[100]) would allow the natural history of degenerative dementias with reference to MRS metabolites to be elucidated.

In conclusion, MRS studies in neurodegenerative dementias continue to focus on AD; there is a lack of papers considering other dementia syndromes and even fewer that compare dementia types directly. This review suggests that the MRS metabolite profiles in dementias such as FTD and DLB share similarities but also differences with AD. The similarities may reflect the changes that are common to these dementias (such as reductions in NAA due to a reduction in synaptic density), but the differences (such as differences in the distribution in metabolites) may help to illuminate the differing pathophysiologies and explain the different symptoms and functional challenges seen in these disorders. The lack of consensus in methodology has been a barrier to comparing papers, as any differences in findings may be due to methodological differences. The relatively recent publication of a consensus paper for MRS at 3 and 7 T,[23] which gives guidance regarding acquisition protocols and QC, may contribute to the resolution of these methodological differences. The increase from 1.5 to 3 T alongside the ongoing development of acquisition protocols and pre- and post-processing techniques has allowed the measurement of more challenging metabolites such as GABA; it will become apparent whether the theoretical benefits of MRS at 7 T will be borne out in practice as the use of 7 T scanners becomes more widespread. This systematic review has revealed the shortcomings of the current MRS degenerative dementia literature; focus on the creation of large, longitudinal cohorts, more varied voxel placement (especially in studies examining more than one dementia type), greater emphasis on non-AD dementias, and consensus regarding ideal MRS acquisition and processing techniques would address many of these limitations.

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## CONFLICT OF INTEREST

EM and LS declare no conflicts of interest. JOB reports personal fees from TauRx, personal fees from Axon, personal fees from GE Healthcare, personal fees from Novo Nordisk, non-financial support from Alliance Medical, personal fees from Roche, personal fees from Biogen, personal fees from GE Healthcare and grants from MSD.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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