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Neurochemical changes in the aging brain: A systematic review

Carlee Cleeland*, Andrew Pipingas, Andrew Scholey, David White

Centre of Human Psychopharmacology, Swinburne University of Technology, Hawthorn, Victoria, Australia

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ABSTRACT

Magnetic resonance spectroscopy (MRS) holds promise for understanding neurochemical mechanisms associated with human cognitive aging *in vivo*. Recent advances in magnetic field strength and methods provide the opportunity to examine neurometabolites with greater accuracy and detail. The current review summarizes recent literature on age-associated neurometabolite changes as measured by proton MRS, and the associations with cognition in non-clinical populations. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 179 studies were screened for review, of these, 42 were eligible. When a subset of studies were assessed based on voxel placement, magnetic field strength and sample size, *N* acetyl aspartate (NAA) concentration was consistently reduced with age predominantly in the frontal lobe and *Myo*-inositol (mI) concentration increased with age consistently in the posterior cingulate cortex (PCC). These findings are of particular interest as these NAA and mI changes mirror neurometabolite changes often seen in Alzheimer disease. The findings of this review provide further evidence of the potential for ^{1}H-MRS to track age-related neurometabolite changes.

1. Introduction

The adult brain undergoes a series of molecular, biochemical, structural and functional changes (Trollor and Valenzuela, 2001), which can result in a greater susceptibility to disorders that can affect central processes and cognition (e.g. Alzheimer's disease and mild cognitive impairment). Considerable research efforts have sought to understand healthy and pathological aging processes, whilst highlighting domains of functioning most affected. Candidate physiological changes which may contribute to age-related declines in cognitive performance include cardiovascular changes such as arterial stiffening, that can damage small cerebral vessels (Cooper and Mitchell, 2016; Pase et al., 2014; Singer et al., 2014), poor glucoregulation (Macpherson et al., 2015), inflammation (Marsland et al., 2015; Warren et al., 2018; Yin et al., 2016) and oxidative stress (Garcia-Mesa et al., 2016).

The application of magnetic resonance imaging (MRI) has greatly aided understanding of age-related neural changes (for a comprehensive review see Eavani et al., 2018). Structural MRI has reported consistent age-related changes, irrespective of individual variation (Vinke et al., 2018; Eavani et al., 2018). Functional MRI (fMRI) studies have revealed alterations in functional connectivity with age, particularly in regard to the default mode network (Eavani et al., 2018). While the physiological, functional and structural components of brain aging have been widely reported, less research attention has been directed to the neurochemical aspects of aging in healthy humans. The current known neurochemical profile of the brain has been primarily derived from non-human models and human post-mortem studies. The non-invasive nature of magnetic resonance spectroscopy (MRS) enables the *in vivo* study of neurometabolites in the human brain. The capacity to measure neurometabolites *in vivo* means it has the potential to further our understanding of neurodegenerative diseases like Alzheimer disease and may reveal candidate chemical processes to target in order to delay the onset of age-related decline.

2. Methods for assessing age-related neurochemical changes

2.1. Non-human research

The current understanding of neurometabolites and their action on the brain is largely derived from non-human research. The development of this methodology began early in the 18th century as a means to obtain neurochemical data via contemporaneous analysis of post-mortem brain tissue (Foley, 2007). Non-human research has used a variety of methods to extract and examine neurochemical data; however, the current review will focus on MRI-related methods only. In non-human research MRS has been to examine *in vivo* neurochemical changes. Many of these studies have used magnetic field strengths

* Corresponding author.
E-mail address: carleercleeland@gmail.com (C. Cleeland).

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greater than 3 Tesla (the current 'industry standard' in human studies) to separate the metabolite peaks more effectively (Hoyer et al., 2014; Febo and Foster, 2016). Other research has examined neurometabolites in association with Alzheimer's disease and dementia pathology in transgenic mice. Two canonical pathogenic events in Alzheimer disease are increases in amyloid beta deposition and neurofibrillary tangles in the brain (Selkoe, 1991). Neurochemical changes associated with amyloid beta markers include reduced NAA and increased myo-inositol (mI) concentration (Chen et al., 2013).

2.2. Human research

Before the advent of MRS, the understanding of neurochemical changes in the human brain was investigated more-or-less exclusively through autopsy (Hynd et al., 2003). While this method has yielded useful information regarding neurochemistry, there are certain drawbacks. Firstly, it is labor intensive and secondly, older autopsy techniques are error-prone as many neurotransmitters/neurometabolites are labile, deteriorating rapidly post-mortem. Additionally some of the earlier preservation techniques affected the samples. As this technique requires brain tissue, investigation of the healthy human brain *in vivo* is not possible.

Proton MRS (^{1}H-MRS) allows the potential for non-invasive investigation of neurochemistry *in vivo*. Like MRI, ^{1}H-MRS uses the signals emitted from hydrogen protons to measure neurometabolite concentrations as there is a natural high abundance of hydrogen (H) in the human brain (Novotny et al., 2003; Blüml and Ross, 1986). As the hydrogen protons act as an intrinsic contrast, no administration of contrast agents is required. The most readily studied resonance peaks using ^{1}H-MRS are *N*- acetyl aspartate (NAA), choline (Cho), creatine (Cr), glutamate/glutamine (Glx), and *myo*-inositol (mI). NAA has been speculated to act as a neuronal marker (De Graaf, 2007; Ross and Sachdev, 2004; Ross et al., 2005), as well as being implicated in many other neuronal processes (Duarte et al., 2014). It has also been speculated that NAA is closely linked to ATP production, and therefore may also be a potential measure of neuronal metabolic efficiency (Scavuzzo, Moulton & Larsen, 2018). Cho has been implicated as a membrane marker that may reflect alterations in membrane turnover or changes in cell density; fluctuating levels of Cho can potentially indicate changes in gliosis, myelination or inflammation (Chiu et al., 2014; Harris et al., 2014). Cr is suggested to play a key role in both brain energy homeostasis and second messenger functioning, as well as being an important brain osmolyte (Ross and Sachdev, 2004; Rae, 2014). Osmolytes are compounds that play a role in maintaining cell volume and fluid balance. Glutamate is the major excitatory neurotransmitter in the central nervous system and is involved in many aspects of brain functioning including cognition, learning and memory (Ramadan et al., 2013; Zahr et al., 2013). Quantification of glutamate is more challenging to quantify at magnetic field strengths of 3 T or lower, due to the overlap of glutamate and glutamine resonances, therefore their contributions are commonly combined when analyzing *in vivo* spectra and referred to as Glx. Myo-inositol (mI) has been suggested to act as an osmolyte in the brain and is potentially involved in functions of brain cell signaling (Hoyer et al., 2014; Novotny et al., 2003). Previous research has shown mI to also be implicated in glial proliferation (Fukuzako et al., 1997; Haris et al., 2011), however this is debatable as some studies have failed to find a correlation between pathology associated astrogliosis and mI (Duarte et al., 2014). This review will now focus on research examining how these ^{1}H-MRS -derived neurometabolites change in 'healthy' aging free of neurodegenerative disorders and other medical conditions known to have negative effects on cognitive aging.

An earlier review of MRS studies exploring aging, conducted by Haga et al. (2009) found that across multiple brain regions, the majority of studies found no change with age in NAA, Cr or Cho concentration. Three out of five studies showed an increase in mI concentration with age. However, Haga et al. (2009) also reported a meta-analysis of four studies reporting sufficient information, which found a decrease in frontal NAA and increases in parietal Cho and Cr. An important development since this previous review is the proliferation of higher field strength MRI scanners. The quality of the MRS signal is driven by a variety of factors including (but not limited to) shimming methods, signal to noise ratio, chemical shift displacement and excitation nonuniformity (Öz et al., 2014). To obtain an optimal MRS signal, these need to be addressed before and during the scanning procedure. Given the potential improvements in signal-to-noise ratio associated with increased field strength (Schmitt et al., 2004), and the fact that the aforementioned review contained results predominantly obtained using 1.5 T (and a maximum of 2 T), the present report provides an update of the literature incorporating the subsequent publications coinciding with the increased availability of MRI scanners of higher field strengths and improved methods. The aim of the current systematic review was to survey the literature using ^{1}H-MRS to study neurometabolite changes associated with aging. The current review also considers the methodology and data quality of related research, and the association between neurometabolite changes with age and neurocognition.

3. Methods

3.1. Search strategy

The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; see Fig. 1). The databases PubMed and Web of Science were searched for peer-reviewed published human ^{1}H-MRS aging studies. Publications were searched in any language using search terms: 'magnetic resonance spectroscopy AND ageing OR aging', 'spectroscopy AND ageing OR aging AND metabolite', 'magnetic resonance spectroscopy AND ageing OR aging AND brain'. Only studies that presented original data were included. Reference lists of included publications were also examined. The abstracts of the publications from the original search terms were read and excluded if they did not meet the inclusion criteria. The full articles were then assessed for eligibility.

3.2. Inclusion and exclusion criteria

Two reviewers independently searched and assessed each publication. The inclusion criteria included publications that reported original data related to ^{1}H-MRS and aging, and neurocognition associated with age-related neurometabolite changes. All included studies were non-clinical cohorts according to the criteria of the given publication and did not include studies using nuclei other than hydrogen to measure spectroscopy, as these nuclei require administration of invasive contrasts. Where multiple publications included the same dataset, the latest publication was included. Conventional single voxel spectroscopy (SVS) or multiple voxel spectroscopy (MVS) methods were the focus of the current review. The current review excluded editing methods (eg. J-difference methods such as MEGA-PRESS), choosing to focus on assessing the metabolites most readily quantified using ^{1}H MRS (NAA, Glx, Cr, Cho, mI). Studies that examined metabolites GSH and GABA were excluded due to evidence that quantification of GSH and GABA at 3 T may be problematic without the use of these spectral editing methods (Nezhad et al., 2016; Puts and Edden, 2012; for a review of GSH and aging see Saharan and Mandal, 2013). Reviews and studies that included participants younger than 18 years of age were excluded, as the current review is restricted to neurometabolite changes in the adult brain.

3.3. Data extraction

From the included studies, data was extracted using the PRISMA protocol. This included the total number of participants, and age range, the location of the voxel of interest (VOI), the metabolites measured/

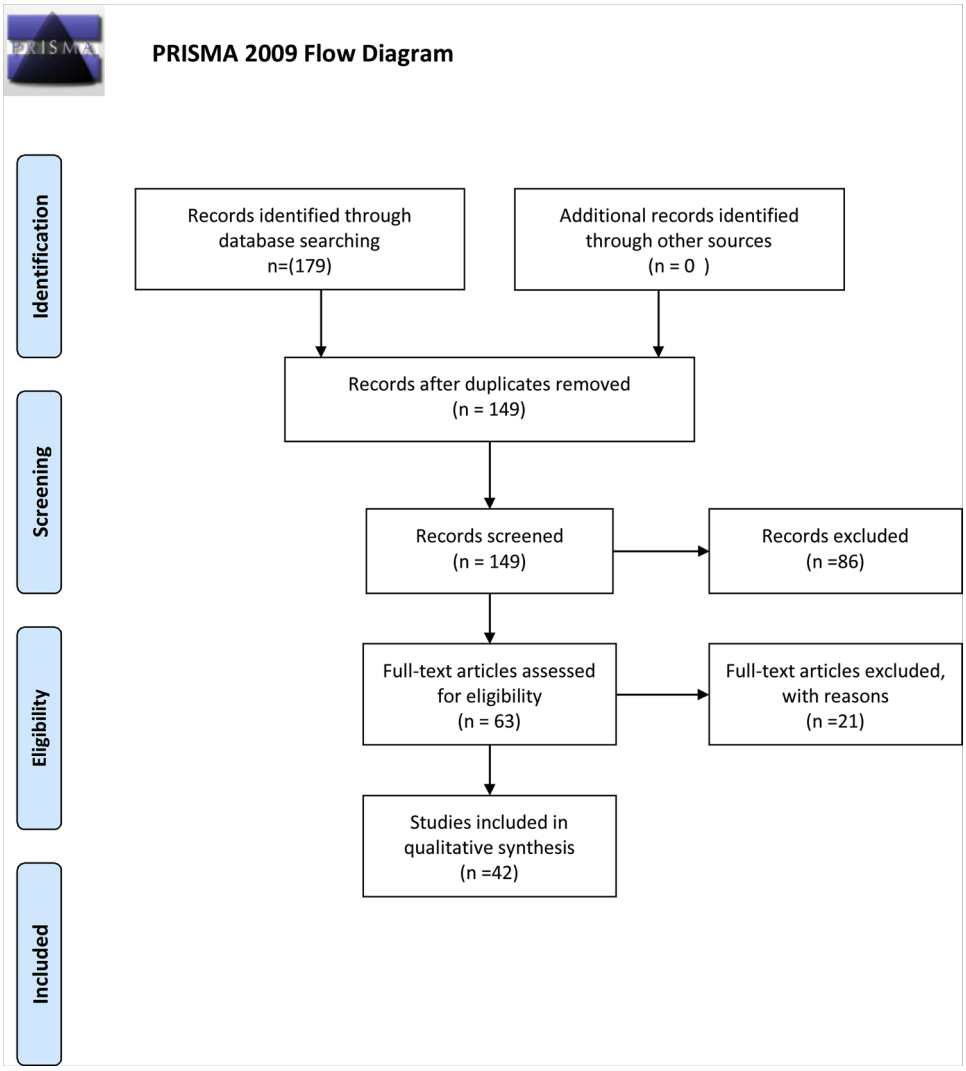

Fig. 1. PRISMA Flow Diagram.

reported (absolute value [using the unsuppressed water signal, replace and match method or institutional units] or reported as a ratio) and cognitive findings (see Table 1). Magnetic field strength, MRS sequences, correction for CSF and quantification methods are also reported (see Table 2).

3.4. Data quality assessment

A formal data quality assessment was not conducted for the current review. Assessing ^{1}H-MRS data quality can be difficult due to variability in study design and experimental approaches. For example, correcting for CSF is an important post-processing step in most studies due to CSF contamination; however, this becomes less important if the study VOI has a negligible amount of CSF within it. Magnetic field strengths also affect the spectra quality as the signal to noise ratio (SNR) tends to increase linearly with the magnetic field (Öz et al., 2014). Common artifacts that are seen in MRS spectra include unusual phase appearance, lines that are too broad or too narrow, or large residual water signals (Öz et al., 2014). These artifacts can be limited if correct acquisition methods are implemented, which include appropriate voxel location, optimal shimming methods, as well as implementing post-processing methods such as tissue segmentation and correcting for CSF within the VOI (Öz et al., 2014). Recent research has suggested that high Cramér Rao Lower Bounds (CRLB; gives a lower estimate for the variance of an unbiased estimator; Bottomley and Griffiths, 2016) should not be used as the main measure of data quality, as high CRLBs are also expected in the case of low levels of the measured metabolite (Kreis, 2016).

4. Results

4.1. Search results

One hundred and seventy-nine studies were identified from the literature using the search criteria. After the inspection of titles and the abstracts and removal of 30 duplicate studies, 63 studies remained. Subsequently, full-text inspection for inclusion/exclusion criteria was conducted, which resulted in 42 studies deemed eligible for inclusion in the current systematic review (see Fig. 1). Some of these publications overlap with Haga et al. (2009) review, however eight studies from their review were not included here as the publications either focused on disease or methodology, or had a sample under the age of 18, and therefore did not meet the inclusion criteria. The findings of the current review will be presented for each neurometabolite separately, after discussing the characteristics of the included publications.

4.2. Characteristics of included papers

Table 1 summarizes the ^{1}H-MRS findings of the 42 publications that were included in the current systematic review. These 42 publications

Table 1
MRS Findings from the Selected Studies.

Study	N	Age/Design	Regions Scanned	Metabolites Examined	R/A	Significant Effects of Age	Cog. Outcomes
Angelie et al. (2001)	32	21-69 C	Temporal, hippocampal, semioval, cortical (predom. GM)	NAA,Cho,Cr, NAA/Cho, NAA/Cr, Cho/Cr	Both	↓NAA ↓NAA/Cr (except hippocampal) ↓NAA/Cho (except hippocampal) ↑Cho (except hippocampal) ↑Cr (except hippocampal & temporal)	N/A
Bartres-Faz et al. (2002)	44	50-83 C	L MTL & L striatum (predom. GM)	NAA/Cr	R/Cr	No age effect	Memory Performance
Bozgeyik et al. (2008)	76	21-60 (study also included two additional groups aged between 0-20) B	Rostrum, Splenium, Genu & Corpus (predom. WM)	NAA/Cho Cho/Cr NAA/Cr	R/Cr & Cho	↓NAA/Cho (genu) ↑Cho/Cr (genu)	N/A
Brooks et al. (2001)	50	20-70 C	Medial frontal lobe (predom. GM)	NAA,Cr,Cho, NAA/Cr	Both	↓NAA ↓NAA/Cr	N/A
Chang et al. (1996)	36	19-78 C	Right Frontal WM & Medial frontal GM	Cho, Cr, NAA, mI, NAA/Cr	Both	↑Cho (GM) ↑Cr (GM) ↑mI (GM) ↓NAA/Cr (GM)	N/A
Charles et al. (1994)	34	Y (21-59) vs O (60-75) B	Basal ganglia (BG) & Corpus callosum	NAA,Cr, Cho NAA/Cho, NAA/Cr, Cho/Cr	Both	↓NAA (BG) ↓Cr (BG) ↓Cho (BG)	N/A
Charlton et al. (2007)	106	50-90 C	White matter in slice above ventricles (predom. WM)	Cho, Cr, NAA, mI	A	↑Cr	Executive function (pos. correlation with NAA)
Chen et al. (2013)	18	Y (18-27) vs O (55-75) B	Heschl's gyrus & Auditory cortex (bilateral)	NAA/Cr Glx/Cr	R/Cr	↓NAA/Cr (bilaterally) ↑Glx/Cr (R side)	N/A
Chiu et al. (2014)	30	22-82 C	ACC, PCC, Hippocampus (Bilateral)	Cho, Cr, NAA, mI	A	↑NAA (ACC & PCC) ↑Cr (ACC & PCC) ↑Cho (ACC & PCC)	N/A
Ding et al. (2016)	96	20-70 C	Whole brain	NAA,Cho,Cr, mI,Glx	A	↓NAA (all cerebral lobes) ↓Glx (R frontal lobe, L parietal lobe)	N/A
Driscoll et al. (2003)	32	Y (20-39) vs O (60-85) B	Axial slice through bilateral hippocampus (MVS) L & R frontal white matter (SVS)	NAA/Cr Cho/Cr	R/Cr	↓NAA/Cr (bilateral hippocampi; L & R frontal white matter)	Memory Tasks (pos. correlation with NAA/Cr)
Eylers et al. (2016)	60	21-70 (12 per decade) C	Whole brain	NAA, Cr, Cho	A	↓NAA (occipital GM, putamen, corpus collosum, ventral brain stem) ↓Cr (putamen & dorsal brain stem)	N/A
Erickson et al. (2015)	135	59-80 C	Inferior frontal gyrus, Insula, & BG	NAA Cr (as a covariate)	A	↓NAA (+ age x education interaction)	Digit span Task
Erickson et al. (2012)	137	58-80 C	Inferior frontal gyrus, Insula, & BG	NAA Cr (as a covariate)	A	↓NAA (+ age x fitness interaction)	Digit Span Task (pos. correlation with NAA) Spatial Memory Task
Fukuzako et al. (1997)	36	24-78 C	L frontal lobe & L MTL	NAA/Cr, NAA/Cho, Cho/Cr	R/Cr & Cho	No age effect	N/A
Gomar et al. (2014)	112	50-86 C	Precuneus/ PCC	Cho/Cr, mI/Cr, NAA/Cr	R/Cr	↑Cho/Cr (in APOE4 carriers) ↑mI/Cr (in APOE4 carriers)	Composite cognition (neg. correlation with Cho/Cr + mI/Cr)
Guan et al. (2008)	80	21-60 (Groups: 21-30; 31-40; 41-50; 51-60) B	Pons	NAA/Cr, NAA/Cho, Cho/Cr	R	No age effect	N/A
Gruber et al. (2008) seq. 1	10	Y (22-27) vs O (52-54) B	Frontal & Parietal WM, Semiovale, Thalamus, Caudate nucleus, lentiform nucleus	NAA/Cho, NAA, Cho/Cr, Cr, Cho, NAA/Cr	R	↓NAA/Cr (all WM regions) ↑Cho/Cr (Semioval, lentiform) ↓NAA/Cho	N/A

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Table 1 (*continued*)

Study	N	Age/Design	Regions Scanned	Metabolites Examined	R/A	Significant Effects of Age	Cog. Outcomes
						(all WM regions, Caudate & Lentiform)	
Gruber et al. (2008) seq. 2	7	20-65 C	Semiovale	NAA/Cho, NAA/Cr NAA, Cho/Cr, Cho, mI, mI/Cr	Both	↓NAA/Cho ↓NAA/Cr ↓NAA ↑Cho ↑Cho/Cr ↑mI ↑mI/Cr	N/A
Gruber et al. (2008) seq. 3 a	22	18-59 C	L & R Temporal Lobe	NAA/Cho, NAA, Cho/ Cr, Cr, Cho, NAA/Cr	Both	↓NAA/Cho	N/A
Gruber et al. (2008) seq. 3 b	24	19-59 C	L & R dorsolateral prefrontal WM	NAA/Cho, NAA, Cho/ Cr, Cr, Cho, NAA/Cr	Both	↑Cr ↓NAA/Cho	N/A
Hadel et al. (2013)	118	19-55 C	ACC & Hippocampus	NAA, Cho, Glu,Gln	A	↓NAA ↓Glu ↑Gln (ACC)	N/A
Harada et al. (2001)	50	20-70 C	L Frontal Lobe & Lentiform nucleus	NAA,Cr,Cho	A	↓NAA (Lentiform) ↓Cho (Lentiform)	N/A
Kaiser et al. (2005)	24	Y (25-28) [$M = 26 \pm 1$] vs O (45-65) [$M = 54 \pm 6$] B	Mesial Motor Cortex & Corona Radiata	NAA, mI, Cho,Cr, Glu, Gln	A	↓Glu (Mesial motor cortex) ↑Cho (Corona Radiata)	N/A
Kochunov et al. (2010)	38	57-90 C	Bilateral Frontal WM (Forceps minor)	NAA, Cho, Cr	A	↓NAA ↓Cr ↓Cho	Psychomotor Processing Speed (pos. correlation with Cr, Cho, & NAA)
Leary et al. (2000)	44	22-62 C	Parietal WM	NAA, Cr, Cho,mI	A	↑Cho ↑Cr	N/A
Marjanska et al. (2017)	33	Y (19-22) vs O (70-88) B	PCC/Precuneus & Occipital cortex	NAAG, NAA, PE, Cho, Asc, Glu, mI, Cr	A	↓NAAG (both voxels) ↓PE(both voxels) ↑Cho(both voxels) ↓NAA (occipital) ↓Glu(occipital) ↓Asc(occipital) ↑Cr(PCC) ↑mI(PCC)	N/A
McIntyre et al. (2007)	106	50-90 C	Centrum Semiovale	Cr, NAA, Cho, mI	A	↑Cr	N/A
Moreno- Torres et al. (2005)	57	Y (23-47) vs O (55-79) B	Midbrain Tegmentum (brain stem) & Pontine Tegmentum (brain stem)	NAA/Cr, NAA/Cho NAA/H_2O, Cr/H_2O, Cho/H_2O, NAA, Cho, Cr	Both	↓NAA/Cr (pons) ↑Cho/ H_2O (Pons) ↑Cr/ H_2O (pons)	N/A
Pfefferbaum et al. (1999)	34	Y ($M = 25 \pm 3$) vs O ($M = 73 \pm 4$) B	Whole brain	NAA, Cr, Cho	A	↑Cr (GM & WM) ↑Cho (GM)	N/A
Raininko and Mattsson (2010)	57	Y(33-52) v O(53-72) B	Supraventricular WM	mI, NAA, Glx, Cr, Cho	A	↓NAA ↑mI	N/A
Reyngoudt et al. (2012)	90	18-76 C	PCC & L hippocampus	NAA, Cr, Cho, mI, NAA/Cr, Cho/Cr, Ins/Cr Cr/H_2O, NAA/H_2O, Cho/H_2O, Ins/H_2O	Both	↑Cr/ H2O (PCC) ↑Cr (PCC) ↑Ins/ Cr (PCC & hippocampus) ↑Ins/H_2O (PCC & hippocampus) ↑Ins (PCC)	N/A
Ross et al. (2006)	40	58-84 P	L Frontal (predom. WM) & Occipitoparietal (predom. GM)	NAA,Cr, Cho, mI	A	↑mI (L frontal)	Visuospatial function
Ross et al. (2005)	59	58-85 C	L Frontal (predom. WM) & Bilateral Occipitoparietal (predom. GM)	NAA, Cho, Cr, mI	R/ Cr & H2O	↑NAA/H_2O (occipitoparietal) ↑Cr/ H_2O (occipitoparietal)	Composite processing speed (Pos. correlation in Frontal WM with NAA/ H2O)
Sailasuta et al. (2008)	50	21-71 C	BG, Frontal WM (FWM), Frontal GM (FGM) Parietal GM (PGM)	NAA, Cr, Cho, Glu	A	↓Glu (BG, FWM, PGM) ↓NAA (FWM) ↓Cr (BG) ↑Cho (FWM)	N/A
	30			NAA, Cr, Cho, mI	A	↑Cr (L parietal)	N/A

(*continued on next page*)

Table 1 (*continued*)

Study	N	Age/Design	Regions Scanned	Metabolites Examined	R/A	Significant Effects of Age	Cog. Outcomes
Saunders et al. (1999)		Y (20-60) vs O (60-89) B	L Occipital lobe (predom. GM) & L Parietal lobe (predom. WM)				
Schubert et al. (2004)	40	20-60 C	Frontal GM (ACC) & L Hippocampus	Glu, Gln, NAA, Cr, Cho	A	↓Glu ↓Gln (hippocampus)	N/A
Schuff et al. (1999)	24	36-85 C	Bilateral Hippocampus	NAA/Cho, NAA/Cr, Cho/Cr	R/Cr + Cho	↓NAA/Cho ↓NAA/Cr	N/A
Sijens et al. (2003)	271	60-90 P	A transverse plane above the ventricles (WM & GM)	NAA, Cho, Cho/NAA, NAA/Cr, Cho/Cr	Both	↓Cho/Cr ↓NAA/Cr	N/A
Suri et al. (2017)	147	Y (20-40) vs O (60-85) B	PCC/Precuneus	mI,Cr,Glu, mI/Cr, NAA/Cr, mI/NAA	Both	↑mI ↑Cr ↓Glu ↓NAA/Cr ↑mI/NAA	N/A
Szentkuti et al. (2004)	35	Y (22-27) vs O (60-70) B	Bilateral Hippocampus & bilateral MTL (predom. WM)	NAA/(Cr + Cho)	R/Cr + Cho	↓NAA/(Cr + Cho)	N/A
Yang et al. (2014)	43 (78 total, Two additional groups:0-5 & 6-20	Y (21-50) vs O (50-78) B	Pons	Cho/Cr, NAA/Cr, Cho/NAA	R/Cr	↑Cho/NAA	N/A
Yang et al. (2015)	80	Y(19-39) vs O (40-64) [7-18 Children's Group] B	Centrum semiovale, Thalamus, Hippocampus	NAA, Glx, mI NAA/Cr mI/Cr Glx/Cr, Cr,Cho,	Both	↓NAA ↑mI ↑Ins/Cr ↓NAA/Cr	N/A
Wu et al. (2012)	160	Y (20-44) v O (58-89) B	Whole Brain	NAA	A	No age effects	N/A
Zahr et al. (2013)	61	20-85 C	L or R Striatum, Central Pons & L or R Cerebellum	NAA, Glu, Cho, Cr	A	↓NAA (striatal) ↓Cr (striatal) ↓Glu (striatal) ↑Cr (cerebellum) ↑Cho (pons)	Working Memory (no corr.) Verbal Fluency (no corr.)

Note: Y = Young; O = Old; C = Continuous analysis; B = between groups analysis; P = Prespective study; L = left; R = Right; GM = Grey Matter; WM = White matter; CSF = Cerebrospinal Fluid; PCC = Posterior Cingulate Cortex; NAA = N acetyl aspartate; Cr = Creatine; Cho = Choline; Glx = glutamate/glutamine; Gln = glutamine; Glu = glutamate; mI = myo-inositol; PE = Polyethylene ; Asc = Ascorbic acid; H_2O = water.

included 2,848 participants, consisting of 1401 males, 1361 females and 86 participants across three studies that did not state their gender. The average age range across the 42 studies was 29.5–76.5 years, with 23 studies including subjects that were older than 75 years. Within the included publications, 17 compared neurochemical differences between young and elderly subjects as a between groups design, two were longitudinal studies and the remaining 23 papers assessed age as a continuous variable, looking at cross-sectional age-related differences over the adult lifespan.

Table 2 shows the MRS acquisition parameters that were applied across the included studies. Some studies reported multiple quantification methods and therefore multiple results for one metabolite. Of the 42 included publications, 12 studies reported ratios only, 18 studies reported absolute values only, and 12 studies reported both ratio and absolute values. The majority of included studies were performed using a field strength of 1.5 T (n = 22) or 3 T (n = 17), and three independent studies were acquired at 2 T, 4 T and 7 T, respectively. Single voxel spectroscopy (SVS) methods were used in 29 studies with 15 studies using multiple voxel spectroscopy (MVS) methods. Across the included studies, different ^{1}H-MRS sequences were utilized. Studies using SVS methods used the following MRS sequences: point resolved spectroscopy (PRESS; n = 15), stimulated echo acquisition mode (STEAM; n = 10), spin echo sequences not otherwise specified (n = 2), a single study acquired for each spectral inversion at lipid (SPECIAL; (Mekle et al., 2009; Near et al., 2013), constant time point resolved spectroscopy (CT PRESS; (Dreher and Leibfritz, 1999), multiple quantum filter (MQF; Thompson and Allen, 1998) and TE averaged PRESS sequences. Studies that investigated neurometabolites with MVS methods used the following sequences: PRESS (n = 4), STEAM (n = 1), chemical shift imaging not otherwise specified (CSI/MRSI methods; n = 5), volumetric spin echo planar spectroscopic imaging (n = 2; Maudsley et al., 2006, 2009) and one study used a spin echo sequence as specified by Adalsteinsson et al. (1995). A single study was acquired for non-localizing ^{1}H-MRS spectroscopy (Gonen et al., 1998) and turbo spectroscopic imaging (TSI; Duyn and Moonen, 1993; Martin et al., 2001; Yahya and Fallone, 2009). Across all methods, echo times (TE) ranged from 0 ms to 288 ms and repetition times (TR) ranged from 520 ms to 7000 ms.

CSF can be a major source of artefact and has implications for absolute quantification referenced to water if not corrected for during the pre-processing or post-processing stages. Differences in brain metabolite content in CSF have been reported in the literature, and as most MRS quantification methods assume there is no CSF in the VOI, it is important to apply a correction factor. From the included studies, only 19 corrected for CSF, which may have influenced neurometabolite findings. Having corrected for CSF was determined by either the purposeful selection of a voxel with a negligible amount of CSF within it or the correction of CSF manually post scanning.

4.3. Neurometabolite levels with aging (absolute value & ratio)

4.3.1. N- acetylaspartate

All publications (n = 42) examined NAA concentration across age (25 decreased, 2 increased, 15 no change). While the majority of studies found a reduction in NAA concentration, this pattern was most consistent in gray matter, whether reported as an absolute value or ratio. While there was some heterogeneity, the frontal lobe, hippocampus and temporal lobe were the most commonly examined regions for NAA concentration. The most consistent findings were in the frontal lobes (n = 9), hippocampus (n = 6), basal ganglia (n = 3), and centrum semiovale (n = 3), all finding a reduction in NAA concentration with age.

Table 2
MRS Acquisition Parameters for the selected studies.

Study	Tesla	MRS VOI	MRS Sequence	TE/TR(ms)	Adjust for CSF
Angelie et al. (2001)	1.5 T	MVS	PRESS	272/1500	✗
Bartres-Faz et al. (2002)	1.5 T	SVS	PRESS	144/1500 (Striatum) 35/1500 (MTL)	✗
Bozgeyik et al. (2008)	1.5 T	MVS	CSI (no further specification)	13/520	✗
Brooks et al. (2001)	1.5 T	SVS	STEAM	30, 72, 144, 216, 288/ TR varied to maintain constant relaxation delay of 2971.3	✓
Chang et al. (1996)	1.5 T	SVS	PRESS	30/3000	✓
Charles et al. (1994)	1.5 T	MVS	STEAM	270/2000	✓
Charlton et al. (2007)	1.5 T	MVS	PRESS	30/2000	✓
Chen et al. (2013)	3 T	MVS	PRESS	Not specified	✗
Chiu et al. (2014)	3 T	SVS	PRESS	39/2000	✓
Ding et al. (2016)	3 T	3D MVS	Volumetric spin echo planar spectroscopic imaging (Maudsley et al., 2006, 2009)	17.6/1550	✓
Driscoll et al. (2003)	1.5 T	MVS & SVS	PRESS	62/1500 (MVS) 40/2000 (SVS)	✗
Eylers et al. (2016)	3 T	3D MVS	Volumetric spin echo planar spectroscopic imaging (Maudsley et al., 2010)	70/1710	✗
Erickson et al. (2015)	3 T	SVS	Spin echo sequence (no further specification)	30/2000	✗
Erickson et al. (2012)	3 T	SVS	Spin echo sequence (no further specification)	30/2000	✗
Fukuzako et al. (1997)	2 T	SVS	STEAM	135/1500	✗
Gomar et al. (2014)	3 T	SVS	PRESS	30/1600	✗
Guan et al. (2008)	1.5 T	SVS	PRESS	144/1500	✗
Gruber et al. (2008) seq. 1	3 T	3D MVS	3D MRSI (Gruber et al., 2003)	135/1600	✗
Gruber et al. (2008) seq. 2	3 T	MVS	2D MRSI (STEAM; Gruber et al., 2005)	11/1600	✗
Gruber et al. (2008) seq. 3 a	3 T	SVS	STEAM	20/2500	✗
Gruber et al. (2008) seq. 3 b	3 T	SVS	STEAM	20/6000	✗
Hadel et al. (2013)	3 T	SVS	PRESS	80/3000	✓
Harada et al. (2001)	1.5 T	SVS	STEAM	18/7000	✓
Kaiser et al. (2005)	4T	SVS	STEAM	15/2000	✓
Kochunov et al. (2010)	3 T	SVS	PRESS	135/1500	✗
Leary et al. (2000)	1.5 T	SVS	PRESS	30/3000	✗
Marjanska et al. (2017)	7T	SVS	STEAM	8/5000	✓
McIntyre et al. (2007)	1.5 T	MVS	2D CSI (PRESS)	30 & 136/2000	✗
Moreno- Torres et al. (2005)	1.5 T	SVS	PRESS	135/1600	✗
Pfefferbaum et al. (1999)	1.5 T	3D MVS	Spin echo sequence (Adalsteinsson et al., 1995)	144/2000	✗
Raininko and Mattsson (2010)	1.5 T	SVS	PRESS	22/6000	✗
Reyngoudt et al. (2012)	3 T	SVS	PRESS (PCC) STEAM (L hippocampus)	30/1500 (PRESS) 20 &144/1500 (STEAM)	✓
Ross et al. (2006)	1.5 T	SVS	STEAM	30/1500	✓
Ross et al. (2005)	1.5 T	SVS	STEAM	30/1500	✓
Sailasuta et al. (2008)	3 T	SVS	TE averaged PRESS	TE: 32-195 (increments of 5 ms) Effective TE 82 ms/2000	✓
Saunders et al. (1999)	1.5 T	SVS	STEAM	30/2020	✓ (in GM)
Schubert et al. (2004)	3 T	SVS	PRESS MQF sequence (Thompson and Allen, 1998)	PRESS 50,80,135, 250, 330/3000 MQF Sequence Effective TE: 80/2800	✓
Schuff et al. (1999)	1.5 T	MVS	2D MRSI (PRESS)	135/1800	✗
Sijens et al. (2003)	1.5 T	MVS	2D CSI (PRESS)	135/1500	✗
Suri et al. (2017)	3 T	SVS	SPECIAL (Mekle et al., 2009; Near et al., 2013)	8.5/4000	✗
Szentkuti et al. (2004)	1.5 T	SVS	PRESS	135/1500	✗
Yang et al. (2014)	1.5 T	2D MVS	TSI (Duyn and Moonen, 1993; Martin et al., 2001; Yahya and Fallone, 2009)	288/1600	✗
Yang et al. (2015)	3 T	SVS	PRESS	30/2000	✓ (in hippocampus)
Wu et al. (2012)	3 T	MVS	Non-localising H-MRS (Gonen et al., 1998)	0/10000	✓
Zahr et al. (2013)	3 T	SVS	CT-PRESS (Dreher and Leibfritz, 1999)	Ave. TE: 139/2000	✓

Note: T = Tesla; SVS = Single Voxel Spectroscopy; MVS = Multiple Voxel Spectroscopy; PRESS = Point Resolved Spectroscopy; STEAM = Stimulated Echo Imaging; SPECIAL = Spectral Inversion at Lipid; MRSI = Multi voxel magnetic resonance spectroscopic imaging; R = Ratio; A = Absolute; TE = echo time; TR = repetition time; A = Absolute; R = Ratio.

4.3.1.1. Mixed tissue voxels. Four of the 42 studies used whole brain spectroscopy techniques, two of which found no change in NAA with age (Pfefferbaum et al., 1999; Wu et al., 2012) and the remaining two found that NAA was reduced with age (Ding et al., 2016; Eylers et al., 2016). One study examined a slice in multiple voxels on a transverse plane above the ventricles that contained a significant amount of both white and gray matter and found that NAA was reduced with age (Sijens et al., 2003).

4.3.1.2. White matter. Across all the white matter regions examined, 17 studies reported findings on NAA as both a ratio and absolute value (0 increase, 9 decrease, 8 no change; Angelie et al., 2001; Bozgeyik et al., 2008; Chang et al., 1996; Charles et al., 1994; Charlton et al., 2007; Driscoll et al., 2003; Gruber et al., 2008; Kochunov et al., 2010; Leary et al., 2000; McIntyre et al., 2007; Raininko and Mattsson, 2010; Ross et al., 2006, 2005; Sailasuta et al., 2008; Saunders et al., 1999; Szentkuti et al., 2004; Yang et al., 2015). NAA was sampled across the centrum semiovale, corpus callosum, frontal lobes, supraventricular white matter, and parietal lobe.

4.3.1.3. Gray matter. In gray matter, 30 studies reported findings on NAA, both as a ratio and absolute value (2 increase, 17 decrease, 11 no change; Angelie et al., 2001; Bartres-Faz et al., 2002; Brooks et al., 2001; Chang et al., 1996; Charles et al., 1994; Chen et al., 2013; Chiu et al., 2014; Driscoll et al., 2003; Erickson et al., 2015, 2012; Fukuzako et al., 1997; Gomar et al., 2014; Guan et al., 2008; Gruber et al., 2008; Hadel et al., 2013; Harada et al., 2001; Kaiser et al., 2005; Marjanska et al., 2017; Moreno-Torres et al., 2005; Reyngoudt et al., 2012; Ross et al., 2005; Sailasuta et al., 2008; Schubert et al., 2004; Schuff et al., 1999; Suri et al., 2017; Yang et al., 2015; Zahr et al., 2013; Yang et al., 2014). NAA was sampled across the temporal lobe, hippocampus, frontal lobe, basal ganglia, auditory cortex, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insula cortex, occipital cortex, brain stem and parietal lobe.

4.3.2. Creatine

Of the included publications, 33 examined Cr concentration across age (14 increased, 6 decreased, 13 showed no change). While there was some heterogeneity, the PCC was the most common region which investigated Cr concentration. The most consistent findings were in the PCC ($n = 4$), basal ganglia ($n = 3$), parietal lobes ($n = 2$), and centrum semiovale ($n = 2$), all finding a consistent increase in Cr concentration with age.

4.3.2.1. Mixed tissue voxels. Three of the 30 studies used whole brain spectroscopy techniques (Ding et al., 2016; Eylers, 2016; Pfefferbaum et al., 1999). Each of these studies found a different result, that Cr increases with age (Pfefferbaum et al., 1999), decreases with age (Eylers et al., 2016) and does not change with age (Ding et al., 2016).

4.3.2.2. White matter. In white matter, 14 studies reported findings on Cr (5 increase, 1 decrease, 8 no change; Angelie et al., 2001; Chang et al., 2013; Charles et al., 1994; Charlton et al., 2007; Gruber et al., 2008; Leary et al., 2000; McIntyre et al., 2007; Raininko and Mattsson, 2010; Ross et al., 2005, 2006; Saunders et al., 1999; Sailasuta et al., 2008; Yang et al., 2015). Cr was sampled across the centrum semiovale, supraventricular white matter, parietal lobe, corpus callosum and frontal lobe.

4.3.2.3. Gray matter. In gray matter, 19 studies reported findings on Cr (7 increase, 3 decrease, 9 no change; Angelie et al., 2001; Brooks et al., 2001; Chang et al., 1996; Charles et al., 1994; Chiu et al., 2014; Gruber et al., 2008; Harada et al., 2001; Kaiser et al., 2005; Marjanska et al., 2017; Moreno-Torres et al., 2005; Reyngoudt et al., 2012; Ross et al., 2005, 2006; Sailasuta et al., 2008; Saunders et al., 1999; Schubert et al., 2004; Suri et al., 2017; Yang et al., 2015; Zahr et al., 2013). Cr was sampled across the PCC, ACC, frontal lobe, occipital lobe, parietal lobe, basal ganglia, pons, temporal lobe and hippocampus.

4.3.3. Choline

Of the included publications, 36 examined Cho concentration across age (14 increased, 4 decreased, 18 no change). While there was some heterogeneity, the frontal lobe was the most common region that investigated Cho concentration, followed by the PCC and temporal lobes. The most consistent findings were in the PCC ($n = 3$) and centrum semiovale ($n = 2$), all finding an increase in Cho concentration with age.

4.3.3.1. Mixed tissue voxels. Three of the 42 studies used whole brain spectroscopy techniques, with two of these studies reporting no change in Cho concentration with age (Ding et al., 2016; Eylers et al., 2016), and one showing an increase in Cho concentration with age (Pfefferbaum et al., 1999). One study examined a slice in a transverse plane above the ventricles that contained a significant amount of both white and gray matter found that Cho was reduced with age (Sijens et al., 2003).

4.3.3.2. White matter. In white matter, 16 studies reported findings on Cho as both a ratio and absolute value (5 increase, 1 decrease, 10 no change; Angelie et al., 2001; Bozgeyik et al., 2008; Chang et al., 2013; Charles et al., 1994; Charlton et al., 2007; Driscoll et al., 2003; Gruber et al., 2008; Kochunov et al., 2010; Leary et al., 2000; McIntyre et al., 2007; Raininko and Mattsson, 2010; Ross et al., 2005, 2006; Saunders et al., 1999; Sailasuta et al., 2008; Yang et al., 2015). Cho was sampled across the centrum semiovale, corpus callosum, parietal lobe, frontal lobe, and supraventricular white matter.

4.3.3.3. Gray matter. In gray matter, 25 studies reported findings on Cho as both a ratio and absolute value (9 increase, 2 decrease, 14 no change; Angelie et al., 2001; Brooks et al., 2001; Chang et al., 1996; Charles et al., 1994; Chiu et al., 2014; Driscoll et al., 2003; Fukuzako et al., 1997; Gomar et al., 2014; Guan et al., 2008; Gruber et al., 2008; Hadel et al., 2013; Harada et al., 2001; Kaiser et al., 2005; Marjanska et al., 2017; Moreno-Torres et al., 2005; Reyngoudt et al., 2012; Ross et al., 2005, 2006; Sailasuta et al., 2008; Saunders et al., 1999; Schubert et al., 2004; Schuff et al., 1999; Yang et al., 2014, 2015; Zahr et al., 2013). Cho was sampled across the temporal lobe, frontal lobe, ACC, PCC, occipital lobe, pons, basal ganglia, hippocampus, and parietal lobe.

4.3.4. Myo-Inositol

Of the included publications, 18 studies reported findings on mI (9 increase, 0 decrease, 9 no change). While there was some heterogeneity, the PCC was the most common region mI concentration was examined. The most consistent findings were in the PCC ($n = 4$), centrum semiovale ($n = 2$) and the hippocampus ($n = 2$), all finding a consistent increase in mI concentration with age.

4.3.4.1. Mixed tissue voxels. One of the included studies used whole brain spectroscopy techniques to evaluate mI concentration, reporting no significant changes with age (Ding et al., 2016).

4.3.4.2. White matter. In white matter, 10 studies reported findings on mI, both as a ratio and absolute values (4 increase, 0 decrease, 6 no change; Chang et al., 1996; Charlton et al., 2007; Gruber et al., 2008; Leary et al., 2000; McIntyre et al., 2007; Raininko and Mattsson, 2010; Ross et al., 2005, 2006; Saunders et al., 1999; Yang et al., 2015). mI was sampled across the centrum semiovale, frontal lobe, supraventricular white matter and parietal lobe.

4.3.4.3. Gray matter. In gray matter, 11 studies reported findings on mI as both a ratio and absolute value (6 increase, 0 decrease, 5 no change;

Chang et al., 1996; Chiu et al., 2014; Gomar et al., 2014; Kaiser et al., 2005; Marjanska et al., 2017; Reyngoudt et al., 2012; Ross et al., 2005, 2006; Saunders et al., 1999; Suri et al., 2017; Yang et al., 2015;). mI was sampled across the frontal lobe, PCC, ACC, hippocampus and occipital lobe.

4.3.5. Glutamate

Of the included publications, eight studies reported findings on Glu (0 increase, 8 decrease, 0 no change; Hadel et al., 2013; Kaiser et al., 2005; Marjanska et al., 2017; Sailasuta et al., 2008; Schubert et al., 2004; Suri et al., 2017; Zahr et al., 2013). While there was some heterogeneity, the PCC was the most common region, which examined Glu concentration. All studies that reported Glu concentration, whether in gray or white matter, showed a reduction with age.

4.3.5.1. White matter. One study reported findings on Glu concentration in frontal white matter (0 increase, 1 decrease, 0 no change; Sailasuta et al., 2008).

4.3.5.2. Gray matter. In gray matter, seven studies reported findings on Glu (0 increase, 7 decrease, 0 no change; Hadel et al., 2013; Kaiser et al., 2005; Marjanska et al., 2017; Sailasuta et al., 2008; Schubert et al., 2004; Suri et al., 2017; Zahr et al., 2013). Glu was sampled across the PCC, ACC, hippocampus, basal ganglia, striatum, occipital lobe and frontal lobe, all of which reported a significant age-related decrease.

4.3.6. Glutamine

Of the included publications, three studies reported findings on Gln (1 increase, 1 decrease, 1 no change). Gln concentration was only examined in gray matter, across three different regions which yielded three different findings of Gln concentration changes with age. As there are only three studies examining Gln, there was heterogeneity across the regions. The ACC, hippocampus and frontal lobe were examined. In the ACC, an increase in Gln concentration was found, and in the hippocampus a reduction in Gln concentration was found. In the frontal lobe there was no change in Gln concentration.

4.3.6.1. White matter. No studies investigated Gln in white matter.

4.3.6.2. Gray matter. In gray matter, three studies reported findings on Gln (1 increase, 1 decrease, 1 no change; Hadel et al., 2013; Kaiser et al., 2005; Schubert et al., 2004). Gln was sampled in the ACC, hippocampus and frontal lobe.

4.3.7. Glx (consists of Glu & Gln)

Of the included publications, four studies reported findings on Glx (1 increase, 1 decrease, 2 no change). As there are only four studies examining Glx, there was heterogeneity across the regions. The frontal, parietal, temporal, auditory cortex and supraventricular white matter were examined. In the temporal lobe and supraventricular white matter, no change in Glx was found. In the auditory cortex, Glx increased with age, while in the frontal and parietal lobes Glx was reduced with age.

4.3.7.1. Mixed tissue voxels. One of the included publications used whole brain spectroscopy techniques to examine Glx. This study found a reduction in Glx concentration with age (Ding et al., 2016).

4.3.7.2. White matter. In white matter, one study reported findings on Glx (0 increase, 0 decrease, 1 no change). Glx was examined in supraventricular white matter.

4.3.7.3. Gray matter. In gray matter, two studies reported findings on Glx (1 increase, 0 decrease, 1 no change; Chen et al., 2013; Yang et al., 2015). Glx was examined in the auditory cortex which showed an increase in concentration and temporal lobe, which showed no change in concentration with age.

4.4. Magnetic resonance spectroscopy and cognition

Nine of the included publications assessed the relationship between cognition and age as part of their experimental paradigm (Bartres-Faz et al., 2002; Charlton et al., 2007; Driscoll et al., 2003; Erickson et al., 2015, 2012; Gomar et al., 2014; Kochunov et al., 2010; Ross et al., 2006, 2005; Zahr et al., 2013). Of these nine studies, six found a significant relationship when controlling for age between cognitive performance and neurometabolite levels (Charlton et al., 2007; Driscoll et al., 2003; Erickson et al., 2012; Gomar et al., 2014; Kochunov et al., 2010; Ross et al., 2005). From these studies, there was an association between NAA concentration and better performance on executive function tasks, digit span tasks, composite processing speed tasks, psychomotor processing speed tasks and memory tasks. These studies each assessed multiple cognitive domains, however only the significant findings will be discussed further.

Of these six studies, one found that there was a relationship between greater NAA in 1.6 × 1.6 cm voxels within a 7 x 7 cm slice of white matter above the ventricles and greater performance on a composite score of executive function derived from Trials, D-KEFS towers, letter fluency, category fluency, stroop and Wisconsin card sorting tasks (Charlton et al., 2007). Another study found an association between greater NAA concentrations and better performance on the digit span task of the Wechsler Adult Intelligence Scale (Erickson et al., 2012). For this study, a single 1.8 × 1.8 x 1.8 cm voxel was acquired in the right frontal cortex of predominately gray matter. Ross et al. (2005) found a relationship between increased concentrations of NAA/H_2O and greater speed of information processing within a 2 × 2x 2 cm voxel in the left frontal white matter and a 2 × 2.7 × 2 cm voxel in occipito-parietal gray matter. Speed of information processing was assessed with a composite processing speeds score, which derived from Trial Making Test Part A and Symbol Digit Modalities Test. Another study found an association between higher NAA/Cr concentration and better performance on the transverse patterning discrimination task, which is used to test learning (Driscoll et al., 2003) within two 13 × 13 x 13 cm voxels in the left and right frontal white matter and in a 15 mm slab including bilateral hippocampi. A significant association between higher NAA/Cr concentration and better performance on the Virtual Morris Water task was also evident in the left frontal white matter (Driscoll et al., 2003). Kochunov et al. (2010) found a relationship between higher concentrations of NAA, Cr and Cho and better performance on a psychomotor processing speed task, which was examined using the Grooved Pegboard. For this study, a 4 × 4x 4 cm VOI was placed in the forceps minor (Kochunov et al., 2010). Lastly, an association was evident between higher Cho/Cr and Cho/mI concentration and poorer performance on a composite score of global cognition (Gomar et al., 2014), which was examined in a mid-sagittal 2 × 2 x 2.7 cm voxel in the precuneus and posterior cingulate cortex. A global cognitive score was established from performance in tests that assessed memory (Rey Auditory Verbal Learning test), attention/executive function (Trial making test B and 1-back task), semantic fluency (animal naming version test) and speed of processing (digit-symbol coding test; Gomar et al., 2014).

5. Discussion

Since the 2009 review by Haga and colleagues, there has been a shift in methodology including the increase in the use of 3 T MRI scanners to examine neurometabolites. The aims of the current review were to summarize the MRS literature investigating the relationship between neurometabolite concentration and age, as well as to examine the MRS methodology utilized and the association between neurometabolites and cognition with age. The current review included 23 additional studies since 2009 that examined participants equal to or older

than 75 years of age, providing an updated overview of neurometabolite changes in healthy aging.

Sample sizes and voxel placement differ across studies; and publications with smaller samples may obscure consistent neurometabolite effects seen in higher-powered studies. By analyzing outcomes of larger scale studies (sample size ≥50 participants), that place the VOI in a homogenous area of gray or white matter, with a magnetic field strength of 3 T or higher, a more consistent pattern starts to emerge, indicating that NAA and Glu concentration is reduced with age and Cho and mI concentration is increased with age. These findings are consistent with studies that have identified a co-relation between NAA and Glu both in human aging (Atassi et al., 2017), and in rodent aging studies (Duarte et al., 2014).

Six studies examined the relationship between cognition and neurometabolite changes with age, in which there was a consistent association between NAA and better performance on cognitive tasks. This was observed across a range of VOIs and a range of domains including, executive function tasks, digit span tasks, composite processing speeds, memory tasks and psychomotor processing speed tasks. The neurometabolite changes that were seen across aging and inconsistencies in methodology will be further discussed below.

5.1. Human neurometabolite changes with aging

Overall, the 42 publications included in the current review have identified age–related influences on neurometabolite concentrations across different tissue types and brain regions. The most consistent finding was that of NAA concentration changes. Two studies found an increase in concentration, 25 studies found a decrease in concentration and 15 found no change in NAA concentration with age. However, sample sizes and voxel placement across studies are highly variable and those with smaller samples may obscure consistent effect with higher-powered studies. In line with this notion, the discussion will focus on outcomes of larger scale studies (sample size ≥50 participants), that place the VOI in a homogenous area of gray or white matter, with a magnetic field strength of 3 T or higher, to provide an overview of the most robust studies to explore neurometabolite changes with healthy aging.

Of the included publications, 11 studies measured NAA concentration at 3 T, in a region of interest (ROI) with predominately homogenous tissue composition and a sample size equal to or greater than 50 participants. Of this subset, nine studies found that NAA concentration was reduced with age and only two studies found no aging effects. While two studies found no significant aging effects, one of these studies demonstrated a trend showing the same pattern, that NAA concentration is reduced with age (Reyngoudt et al., 2012).

Therefore, the vast majority of studies have demonstrated reduced NAA concentration with age, and that variation seen in the overall results of the 42 publication may be a combination of the studies being underpowered or through the heterogeneity in methods.

A similar pattern is also evident in Cho concentration when examining studies with large sample sizes, a VOI of predominantly homogenous tissue composition and examined at 3 T or higher. Seven studies met this criteria when measuring Cho concentration. Five studies found that Cho concentration increased with age and two studies found a reduction in Cho concentration. Therefore, these results demonstrate that when examining higher-powered sample sizes, findings become clearer and more consistent, therefore the variation in results when considering the 42 papers may be partially a result of underpowered studies.

When examining select studies with larger sample sizes, a VOI of predominantly homogenous tissue composition and examinations at 3 T or higher, a pattern emerges in mI concentrations across age. Eight studies met this criteria when examining mI concentration and of these, five studies found that mI concentration increased with age and three studies found no change in mI concentration with age. Of these three studies that found no significant aging effects, one found a distinct trend in which mI concentration increases with age (Ding et al., 2016). Therefore, these findings demonstrate that studies that utilize a stronger magnetic field strength and have larger sample sizes tend to show an increase in mI concentration with age, a finding that is consistent with research in MCI and AD (Chen et al., 2012; Catani et al., 2001; Kantarci et al., 2004; Kantarci et al., 2000; Kantarci et al., 2002).

Studies that used a magnetic field strength of 3 T or higher were able to investigate both Glx and isolate Glu in healthy aging. All eight studies that looked at isolated Glu found it to be reduced with healthy aging. However, two of the four papers that examined Glx found no change with age, with one study finding an increase, and one study finding a reduction in Glx with age. Glu and Gln have different outcomes for both astrogliosis and neurodegeneration as they are two opposing neurotransmitters therefore the measurement of Glx (combination of Glu and Gln) may not be a true representation of the neurometabolite changes occurring in the brain. Therefore, future research should endeavor to examine Gln and Glu in isolation to obtain more accurate and robust findings.

Across the 42 studies included in this review, Cr concentrations varied, either increasing, decreasing or showing no change with age. When further examined by selecting studies with larger sample sizes, a VOI of predominantly homogenous tissue composition and examinations at 3 T or higher, Cr concentration still displayed an inconsistent pattern. Interestingly, the change in Cr with age was also a noted finding in a meta-analysis conducted by Haga et al. (2009) with studies predominantly using scanners with field strengths of 1.5 T. The authors found an increase in Cr concentration with age, however, it should be noted that only four studies were included in this meta-analysis. Findings on Cr concentration were more varied. Nevertheless, these changes in Cr concentration with age are important as Cr is often used as a 'reference' metabolite. This is most commonly used to determine metabolite ratios but Cr- can also be referenced in relation to absolute quantification, due to the assumption that levels remain relatively stable in the brain and unaffected by neurological diseases. Studies exploring age-related changes using metabolite ratios referenced to Cr risk conflating any change in the metabolite of interest with age-related shifts in Cr. While the use of ratios has some benefits including the avoidance of CSF partial volume effects (Jansen et al., 2006) there are some clear drawbacks. For example, if neurometabolites are expressed as a ratio and show a change with age, it is unclear within which the change occurred (Jansen et al., 2006). In the current review, six publications used Cr as a reference metabolite, and five of these studies found significant changes with age in these ratios. As these findings were presented as ratios, it is unclear which metabolite elicited this change with age, which highlights the need to understand which neurometabolites are driving these changes.

An overall reduction in NAA was evident in the current review when analyzing studies using the most robust methods (sample size ≥50 participants, VOI placement in a homogenous area of gray or white matter, with a magnetic field strength of 3 T or higher). A true reduction in NAA concentration could indicate an age-related reduction in synaptic density in the area of interest, which could assist in explaining the cognitive changes that occur with age (Woods et al., 2015). These changes in NAA may also be due to neuronal death or shrinkage (Peters et al., 1998; Terry et al., 1987), or a reduction in the density of microvasculature. Of the included studies, NAA was found to be linked with improved performance; however the results observed were across varied domains of cognition (Charlton et al., 2007; Driscoll et al., 2003; Erickson et al., 2012; Gomar et al., 2014; Kochunov et al., 2010; Ross et al., 2005). The results of the current review suggest that as humans age, NAA is reduced largely in the frontal lobes and hippocampus and there is a tendency for poorer cognitive performance. Future research should explore the association between NAA and cognition in age-related decline when accounting for regional volumetric changes with age and whether NAA partially mediates the age-related decline in

cognitive performance.

Reductions in NAA have also been shown to predict conversion from mild cognitive impairment to Alzheimer's disease (Kantarci et al., 2007). There are striking similarities between the findings in the current review and previous Alzheimer's research, which report significant reductions in NAA and increases in mI concentration (Chen et al., 2000; Engelhardt et al., 2001; Zhang et al., 2014). This reduction in NAA seen in AD is likely reflecting the disease-related neuronal loss/dysfunction (Zhang et al., 2014), but could also be due reduced neuronal metabolic efficiency (Scavuzzo et al., 2018). In non-human research, this reduction in NAA and increase in mI concentration is likely associated with amyloid beta markers, one of the two main pathogenic events that occurs in Alzheimer's disease (Selkoe, 1991).

As previous research has readily been able to differentiate MCI and AD from healthy aging using ^{1}H-MRS, this suggests that the changes in NAA and mI concentration respectively, are not necessarily transitional states, rather a continuum of age-related change, which potentially tracks pathological changes in the brain and the associated cognitive decline. This is supported by neuropathological studies, which have shown that individuals with MCI have a range of histological findings, some of which are seen in normal brain aging, and some that are used to characterize AD (Petersen, 2000), which emphasizes the concept of an aging continuum rather than transitional stages to pathological aging. These findings may be interpreted with the general conception of AD as a progressive condition in which brain changes are linked to the eventual clinical disease presentations taking place many years prior (Petersen, 2000). The findings of this review provide further evidence of the potential for ^{1}H-MRS to track these age-related neurometabolite changes.

5.2. Animal neurometabolite changes with aging

As animals such as rodents have a lower lifespan than humans, this allows for more rapid longitudinal studies examining neurometabolite changes in the aging brain. Duarte et al. (2014) conducted a longitudinal study in aging mice at 3, 6, 12, 18 and 24 months of age. They performed ^{1}H-MRS in the hippocampus, cortex and striatum and found that Glu was reduced with aging in all three voxels and NAA was reduced in the hippocampus and striatum. mI concentration was also found to be increased with age in the cortex and striatum. Similarly, using ^{1}H-MRS to examine neurometabolites in transgenic (APP-PS1) mice, an increase in mI, and a reduction in NAA and Glu was evident in the hippocampus (Chen et al., 2009). The neurochemical profile in animals suggests that aging may be associated with energy metabolism, synaptic transmission and/or cell membrane turnover alterations (Duarte et al., 2014). Furthermore, research has shown that while NAA and Glu may be relevant markers for neuronal density or function, mI is not necessarily a general marker of astrogliosis (Duarte et al., 2014).

As such, the most consistent findings observed in the human literature reviewed herein are largely in agreeance with these findings in lower mammals, in particular reductions in NAA and Glu, in addition to increased mI concentrations (Boumezbeur et al., 2010).

5.3. Methodology

5.3.1. Magnetic field strength

The magnetic field strength of the MRI machine used varied across publications. Older studies tended to use 1.5 T, which has a lower SNR than the more recent 3 T MRI studies, which makes it difficult to discern the overlapping spectra (an important consideration when examining isolate Glu) (Pamboucas and Nihoyannopoulos, 2006; Öz et al., 2014). The SNR increases approximately linearly with increasing magnetic field (Öz et al., 2014). For this reason, studies using lower magnetic field strengths do not generally investigate Glu due to the difficulty in separating the Gln and Glu metabolites. These metabolites can now be better isolated with a 3 T scanner using PRESS and a TE of 80 ms (Öz et al., 2014). Of the studies in the current review, a consistent pattern emerged showing a reduction in isolated Glu (7/7 of the reviewed studies to report on Glu observed this effect) across varied brain regions and tissue types.

5.3.2. Tissue relaxation and adjustment

Segmentation is the anatomical method for estimating the amount of CSF, white matter and gray matter in a given brain volume (Schuff et al., 1999; Schubert et al., 2004). Brain metabolite content are present in CSF; however, most quantification methods assume there is no CSF in the VOI. Therefore, by segmenting the different tissues in the region of interest, a more accurate measure of metabolite concentration is obtained. If the tissues in the VOI have not been segmented, natural age-related brain atrophy may give a false impression of reduced metabolite concentration. The importance of CSF correction differs across studies as some studies select voxel locations where there are negligible amounts of CSF, therefore little needs to be done to correct for this. Additionally, due to the large voxel sizes, larger brain regions or predominantly homogenous tissue such as the PCC and other regions of predominantly gray or white matter are more suitable for a higher quality MRS signal. Sufficient MRS signal quality becomes more difficult to achieve when studying small or irregular shaped regions such as the pons or hippocampus, in addition to those regions proximal to bone or other non-brain compartments (Dager et al., 2008). In the current review, 19 studies corrected for CSF contamination in the respective voxels.

It is also possible to correct for specific tissue type such as gray and white matter. This is useful in aging studies, as it is well known that GM and WM both atrophy with age (Pfefferbaum et al., 2000; Lockhart and DeCarli, 2014; Raz et al., 1997). However, gray and white matter do not necessarily atrophy at the same rate, therefore, if in a given region, GM reduces more rapidly, this will produce a different ratio of neurometabolites in that region. This is another source of variability, which may help to explain some of the mixed findings in the current review. To overcome this variability, results need to take the different rates of atrophy into account and adjust for GM and WM relaxation effects (Knight et al., 2016; Gasparovic et al., 2006). Only one of the included publications adjusted for tissue relaxation and found that even when controlling for relaxation effects and correcting for CSF, NAA still decreases with age (Ding et al., 2016). This suggests that there is an alternate cause for the reduction in NAA other than cortical atrophy (Ding et al., 2016).

5.3.3. Criteria for quality of acquisition and quantification

The current review did not use CRLBs as a formal measure of data quality as filtering based on relative CRLBs can lead to skewed data and therefore potentially incorrect conclusions (Kreis, 2016). CRLBs combine SNR and linewidth and turns them into an interpretable number (Kreis, 2016). Past studies have often used a relative CRLB cut off point (usually 20% or 30%) to include in the analysis, however, this leads to biased and skewed data (Kreis, 2016). While there are other ways to examine data quality such as residuals, lineshape, chemical shift artifact and voxel placement, Kreis (2016) also suggested the use of absolute CRLBs (from the original, unscaled data) might be a more optimal method to examine data quality than relative CRLBs.

5.3.4. Acquisition time/ scan time

Acquisition time is defined as the total amount of time required in the scanner to obtain spectroscopy data from that given VOI and is directly related to the number of averages performed in the sequence. The acquisition time also directly affects SNR and spatial resolution. Acquisition times for included studies ranged from 3.48 min to 60 min, with 25 studies not stating their acquisition times. It is important to note the acquisition time as the data obtained in a SVS 3.48 min scan is going to have a different quality and SNR than a 60 min SVS scan. While SNR can be improved by longer acquisition times, there are practical

limitations to increasing the scan time such as if the individual can no longer remain still (Blüml, 2013). The current review included 1D, 2D and 3D ^{1}H MRS study designs which makes it difficult to discern data quality based on acquisition time as each type of scan has a different 'ideal' acquisition time. Typically, a SVS scan in relatively large voxel of predominately homogenous tissue would take approximately 5–10 min in the scanner and a 3D ^{1}H MRS scan typically takes over 30 min (Golay et al., 2002).

5.3.5. Neurometabolites and cognition

Of the included publications, six studies examined the relationship between neurometabolites and cognition. While each study utilized different cognitive tasks and examined different VOI, a consistent association emerged between NAA concentration and cognition. More specifically, greater NAA concentration was associated with improved performance on executive function tasks, digit span tasks, composite processing speeds, memory tasks and psychomotor processing speeds. These relationships were examined in the supraventricular white matter, frontal GM, frontal WM and occipito-parietal GM, hippocampus and forceps minor, respectively. In addition, neurometabolites Cr and Cho also showed an association with improved psychomotor processing speeds in the forceps minor. Research examining Cho/Cr and Cho/mI in relation to cognition showed that greater concentration of these ratios was associated with poorer performance on composite cognitive tasks in the PCC. It has been further suggested that greater Cho/Cr concentration is associated with worse performance as this implies greater membrane turnover or cycling, in accord with degradation and demands for repair. Similarly, a greater concentration of the mI-Cr ratio has been suggested to indicate microglial activation as an indicator of neuro-inflammation- an early event in the pathogenesis of AD. Clearly, more research needs to be undertaken to examine the relationship between each neurometabolite and cognition, and whether these changes can predict the pathophysiology of dementia and related aging disorders.

5.4. Future directions and limitations of the converging literature

The authors recommend that future research utilize the best practice methodology based on current knowledge of ^{1}H-MRS which includes CSF correction, voxel placement in a homogenous area of gray or white matter and a large sample size. For a good quality ^{1}H-MRS signal, the VOI should be placed in a relatively large VOI of predominantly homogenous tissue with limited confounding factors such as bone. To pre-process this data, tissue segmentation should always be performed and concentrations corrected for CSF contamination. Absolute CRLBs should be used as a tool to analyze spectra quality during the pre-processing stage but not as a defining measurement of data quality (Kreis, 2016). Shimming is also an important aspect of signal quality, which should be taken into consideration. This was not assessed in the current review due to a lack of information provided in studies; however, future research should aim to comment on the impact of shimming procedures on neurometabolite quantification. In aging research, absolute metabolite concentrations should be reported by both age and brain region in order to establish a neurochemical baseline for aging adults. Researchers should consider reporting absolute values alongside ratios, as the interpretation of ratios is complicated due to some evidence of changes found in Cr with age. However, it should be noted that the results for the current review were quantified in terms of significant findings and not effect size, therefore, there may have been trends following similar patterns that were overlooked. Additionally, the current review used a largely qualitative method to analyse data in the included publications. Future research should endeavor to examine the neurometabolite changes in aging in a quantitative fashion to strengthen these findings. Only six studies found changes with MRS neurometabolite and cognition, while NAA concentration appeared to be associated with cognition, due to the limited studies more research in this area is required.

In conclusion, this systematic review of ^{1}H-MRS studies into healthy ageing has observed a reduction in NAA and Glu concentration, and an increase in mI concentration. These findings were particularly apparent in studies using the selected recommendations, closely mirroring the profile of neurometabolite changes in patients with Alzheimer's disease. This indicates that neurometabolite changes may be involved in this transitional process from healthy aging to Alzheimer's disease, and therefore, neurochemistry may be a key area in tracking this transition. NAA also appeared to be associated with cognitive performance. As only six studies investigated the relationship between neurometabolites and cognition, there is still a need for extensive research in this area, in order to gain a complete understanding of the neurochemical underpinnings of neurocognition in aging.

Conflict of interest statement

There are no conflicts of interest for the current manuscript.

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