

REVIEW ARTICLE

Magnetic resonance elastography of the ageing brain in normal and demented populations: A systematic review

Ana Coelho^{1,2,3}  | Nuno Sousa^{1,2,3,4}

¹Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

²ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal

³Clinical Academic Center—Braga, Braga, Portugal

⁴Association P5 Digital Medical Center (ACMP5), Braga, Portugal

Correspondence

Nuno Sousa, Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus Gualtar, 4710-057 Braga, Portugal.
Email: njcsousa@med.uminho.pt

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Abstract

The aim of this systematic review was to evaluate the ability of magnetic resonance elastography (MRE) to identify significant changes in brain mechanical properties during normal and pathological aging. PubMed, Web of Science and Scopus were searched for human studies using MRE to assess brain mechanical properties in cognitively healthy individuals, individuals at risk of dementia or patients diagnosed with dementia. Study characteristics, sample demographics, clinical characterization and main MRE outcomes were summarized in a table. A total of 19 studies (nine aging, 10 dementia), comprising 700 participants, were included. The main findings were decreased cerebral stiffness along aging, with rates of annual change ranging from -0.008 to -0.025 kPa per year. Also, there were regional differences in the age effect on brain stiffness. Concerning demented patients, differential patterns of stiffness were found for distinct dementia subtypes. Alzheimer's disease and frontotemporal dementia exhibited decreased brain stiffness in comparison to cognitively healthy controls and significant declines were found in regions known to be affected by the disease. In normal pressure hydrocephalus, the results were not consistent across studies, and in dementia with Lewy bodies no significant differences in brain stiffness were found. In conclusion, aging is characterized by the softening of brain tissue and this event is even more pronounced in pathological aging, such as dementia. MRE technique could be applied as a sensible diagnostic tool to identify deviations from normal aging and develop new brain biomarkers of cognitive decline/dementia that would help promote healthier cognitive aging.

KEYWORDS

aging, brain, dementia, elastography, mechanical properties, neuroimaging, stiffness

1 | INTRODUCTION

Normal aging is characterized by functional and structural changes in the brain with concomitant changes in cognition. Conventional neuroimaging techniques, such as magnetic resonance imaging (MRI), have

identified some recurrent patterns of alterations occurring in the brain during aging. These include gray (GM) and white matter (WM) atrophy accompanied by increases in cerebrospinal fluid and ventricular volumes (Fjell et al., 2014; Good et al., 2001; Resnick et al., 2003; Shaw et al., 2016; Storsve et al., 2014; Thambisetty et al., 2010; Vinke

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et al., 2018), increases in prevalence and severity of WM lesions (Breteler et al., 1994; Prins & Scheltens, 2015; Zupan, 2016), decreased WM microstructural integrity (Coelho et al., 2021; de Groot et al., 2015; de Lange et al., 2016; Lebel et al., 2012; Salat et al., 2005; Sexton et al., 2014; Vinke et al., 2018; Westlye et al., 2010) and functional dedifferentiation (Eyler et al., 2011; Koen & Rugg, 2019; Spreng et al., 2010; Turner & Spreng, 2012). Importantly, all these brain changes have been associated with alterations in cognition. The cognitive trajectories in aging present high inter-individual variability, with several factors (e.g., genetic, lifestyle, environmental) contributing to this differential response (Barter & Foster, 2018; Josefsson et al., 2012; Paulo et al., 2011; Santos et al., 2014). Thus, understanding the neural mechanisms which lead to either cognitive preservation or decline is of relevance to promote healthier cognitive aging and prevent the increased burden of neurodegenerative diseases, such as dementia.

Recently, magnetic resonance elastography (MRE) has emerged as a noninvasive imaging technique that quantitatively evaluates tissue stiffness. In comparison to traditional palpation it has the advantages of providing quantitative measures and allowing measurement of tissues that cannot be reached by hand (Murphy et al., 2019). It has been applied to study the mechanical properties of different tissues, namely the human brain in healthy and pathological conditions (Hiscox et al., 2016; Hiscox et al., 2021; Murphy et al., 2019). Alterations in the viscoelastic properties of the brain were proven to be representative of the composition and organization of the underlying microstructure (Guo et al., 2019; Sack et al., 2013; Yin et al., 2018). Prior to the neuronal loss typical of neurodegenerative diseases and the manifestation of symptoms, histopathological processes, such as amyloid depositions in Alzheimer's disease (AD), take place (Reiman et al., 1996; Selkoe, 2001). One neuroimaging technique which allows the non-invasive and in-vivo detection of amyloid plaques is amyloid-PET (Chételat et al., 2020; Kolanko et al., 2020). Although it has very high sensitivity and specificity, its cost is relatively high, its cost-effectiveness is currently under study, and there are also some side effects and radiation risk associated with the tracer (Chételat et al., 2020). In the MRI field, some techniques have been developed to image indirectly amyloid plaques through susceptibility effects. These acquisitions use either changes in relaxation times or in magnetic susceptibility of tissues, which are affected by the focal iron deposition accompanied with plaques (Yu et al., 2021). However, MRI imaging of amyloid plaques have not been applied to the living human brain yet, due to the long acquisition time. MRE could help circumvent these issues, since it is sensitive to changes in microstructural properties, which might be useful to detect amyloid aggregates. Moreover, it has a shorter acquisition time in comparison to most MRI imaging approaches to study amyloid plaques and, unlike PET, it has no radiation exposure. Therefore, MRE might potentially lead to the development of new in vivo brain biomarkers that could help identify, at earlier stages, individuals at risk of cognitive impairment. As an example, MRE metrics could be applied in a brain age prediction framework, in conjunction with other neuroimaging metrics, to identify individuals with high-risk of cognitive decline or neurodegenerative

diseases (Hiscox et al., 2021). However, the predictive value of MRE has not been evaluated yet.

The main goal of this review was to evaluate the ability of MRE to identify significant changes in brain mechanical properties during normal aging and in patients with dementia. Thus, this systematic review aimed to answer the following questions:

- i. Are there significant differences in brain mechanical properties, measured with MRE, during healthy aging?
- ii. Are there significant differences in brain mechanical properties, measured with MRE, in pathological aging, such as dementia?

2 | METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

2.1 | Literature search

PubMed, Web of Science and Scopus databases were searched using the following terms: ("Magnetic Resonance Elastography" OR "MRE") AND ("Brain") AND ("Ageing" OR "Aging" OR "Dementia"). The search was conducted across the entire time span until February 3, 2022. Two reviewers independently performed the literature search, and any disagreement were solved by consensus.

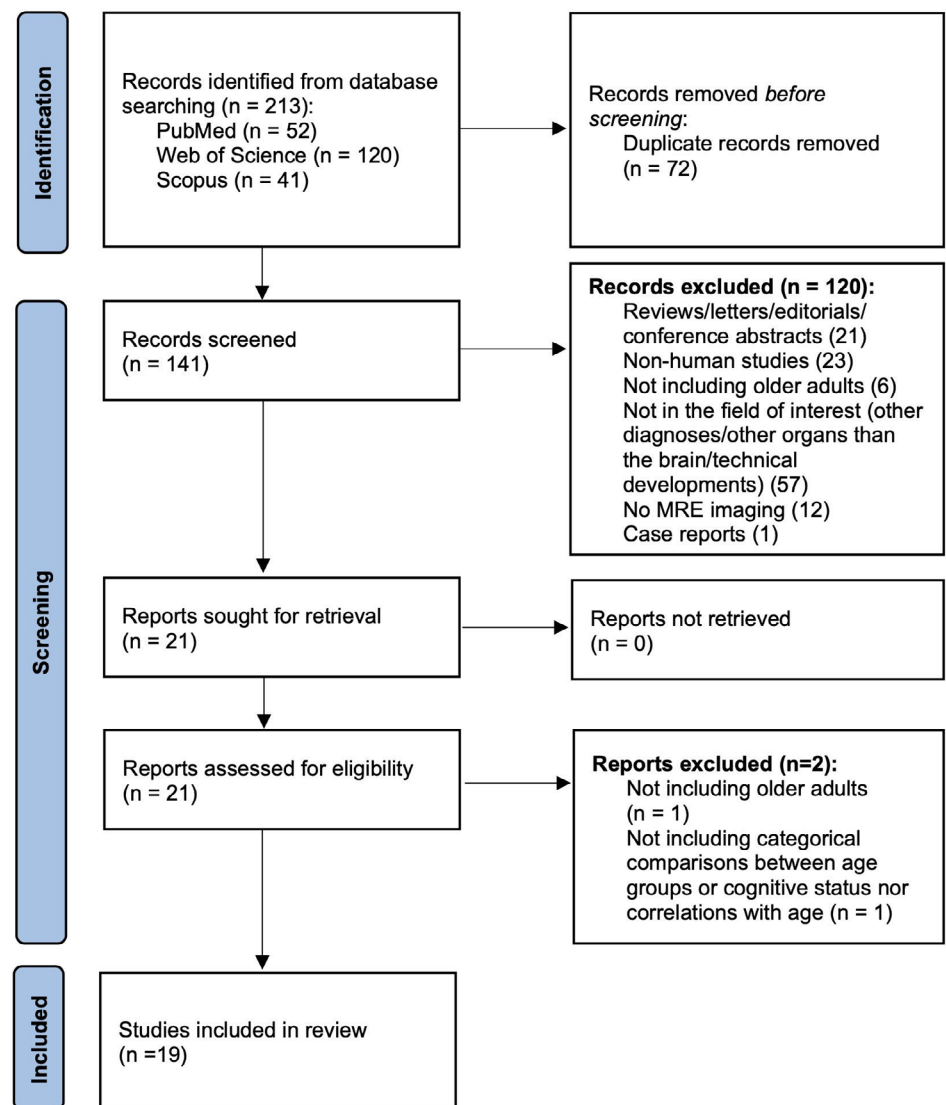
2.2 | Eligibility criteria

The included studies met the following inclusion criteria: i) cognitively healthy individuals, individuals at risk for dementia, patients diagnosed with mild cognitive impairment or dementia; ii) reporting imaging findings on MRE; iii) categorically comparing young and older adults or cognitively healthy and cognitively impaired patients on MRE imaging parameters or correlating MRE imaging parameters with age as a continuous variable. The exclusion criteria were the following: i) reviews, editorials or letters; ii) non-human studies; iii) articles not written in English; iv) other neurological diseases than dementia; v) studies not including older adults. Two reviewers independently determined eligibility and any discrepancy were solved by consensus. First, duplicates were removed and the title and abstract of the records were screened. Next, the full text of the remaining articles was retrieved, and studies were selected based on their evaluation against the inclusion and exclusion criteria.

2.3 | Data extraction

The following data was extracted from the selected studies: i) study characteristics: first author, year of publication, journal name and

FIGURE 1 PRISMA flow diagram describing article screening and selection process.



sample size; ii) sample's demographic and clinical characterization: age, sex, cognitive function, MRE acquisition protocol and parameters; iii) outcomes: MRE imaging findings. One reviewer extracted the data, and the second reviewer confirmed the data's validity.

3 | RESULTS

3.1 | Search results

A flow chart of the studies selection process is presented in Figure 1. The initial literature search identified 213 articles. After removing duplicates, the titles and abstracts of 141 articles were screened for eligibility. From this, 120 were excluded as they did not meet the inclusion criteria (21 reviews/letters/editorials/conference abstracts, 23 non-human studies, six studies not including older adults, 57 studies with irrelevant content, for example, other diagnoses, other organs than the brain, technical developments, 12 studies not reporting MRE imaging findings and one case

report). The full texts of 21 studies were retrieved and reviewed, which resulted in the exclusion of two articles (one study did not include older adults and one study did not perform categorical comparisons between age groups or cognitive status nor correlations with age). Hence, a total of 19 studies were included in this systematic review. These consisted of nine aging studies (Arani et al., 2015; Delgorio et al., 2021; Hiscox et al., 2018; Hiscox, Johnson, McGarry, Schwarb, et al., 2020; Kalra et al., 2019; Lv et al., 2020; Sack et al., 2009; Sack et al., 2011; Takamura et al., 2020) and 10 dementia studies (four with Alzheimer's disease [Gerischer et al., 2018; Hiscox, Johnson, McGarry, Marshall, et al., 2020; Murphy et al., 2011; Murphy et al., 2016], four with normal pressure hydrocephalus [Fattahi et al., 2016; Freimann et al., 2012; Perry et al., 2017; Streitberger et al., 2011], one with frontotemporal dementia [Huston et al., 2016] and one with multiple types of dementia [ElSheikh et al., 2017]), which altogether, and taking into account overlapping participants in some studies, comprised 700 participants (158 cognitively impaired or demented patients and 542 cognitively healthy controls).

3.2 | Aging studies

Table 1 provides a description of the nine MRE studies exploring the changes in brain mechanical properties during healthy aging. We observe some heterogeneity in terms of study design, MRE protocol and the brain structures investigated. Regarding study design, most of the studies used a sample with ages ranging from young to late adulthood. On the other hand, Hiscox and colleagues (Hiscox et al., 2018) performed group comparisons between a group of young adults (age range: 19–30 years) and a group of older adults (age range: 66–73), while in a later study from the same authors (Hiscox, Johnson, McGarry, Schwarb, et al., 2020) only the group of older adults was investigated. Similarly, Arani and colleagues (Arani et al., 2015) included only older adults in their analyses. Concerning MRE protocol, three studies (Lv et al., 2020; Sack et al., 2009; Sack et al., 2011) used multifrequency MRE and the remaining used single frequency MRE with the vibration frequency being 50 or 60 Hz. The MRE final resolution was very distinct between the studies and the most common inversion algorithms used were direct and nonlinear inversion. Finally, in terms of the brain structures investigated, with the exception of (Sack et al., 2009) that only examined the whole brain and (Delgorio et al., 2021; Hiscox, Johnson, McGarry, Schwarb, et al., 2020) which focused on the hippocampus, all the studies inspected both global and regional age-related changes in the mechanical properties of the brain by computing MRE parameters for the whole cerebrum and for different brain regions.

The common pattern across all studies is a decrease in global brain stiffness along aging, with the reported rate of annual change ranging from -0.008 to -0.025 kPa per year (Table 1). Regarding regional changes, significant age-related decreases in brain stiffness were found in frontal, temporal, occipital and parietal lobes, cortical GM and WM (Arani et al., 2015; Lv et al., 2020; Sack et al., 2011; Takamura et al., 2020), while no significant changes were found in the cerebellum (Arani et al., 2015; Takamura et al., 2020). Arani and colleagues (Arani et al., 2015) did not find a significant effect of age on brain stiffness in sensory motor regions and deep GM/WM, which could be explained by the sample being limited to older adults (age range: 56–89). In fact, Takamura and colleagues (Takamura et al., 2020) reported a significant age-effect of brain stiffness in these areas and a multiple comparisons test showed that the stiffness of sensory motor regions was significantly decreased in subjects in their 40s, 50s and 60s in comparison to subjects in their 20s, while for deep GM/WM, no significant decrease was found in the comparison between any age group (30s, 40s, 50s and 60s) and subjects in their 20s. Thus, the differences in the age range of the samples of the two studies might explain the different results obtained for these regions. In fact, we observe a shift in the rates of annual change in regional stiffness during aging. According to (Takamura et al., 2020), from 20 to 60 years old, the most prominent changes occur in sensorimotor regions, while the temporal and occipital lobes exhibit the smaller annual changes (Figure 2a). On the other hand, (Arani et al., 2015) demonstrate that from 60 to 90 years old there is an increased rate of softening of temporal and occipital lobes, while the sensorimotor

regions show smaller annual rates (Figure 2b). Concerning subcortical GM, Lv, and colleagues (Lv et al., 2020) found a significant negative correlation between age and stiffness in subcortical GM as a whole. When considering the individual subcortical structures, significant associations between age and brain stiffness were found in the caudate nucleus, putamen and thalamus, while no significant correlations were found in the hippocampus, amygdala and globus pallidum. Two other studies focused their analyses on the hippocampal region. Hiscox and colleagues (Hiscox, Johnson, McGarry, Schwarb, et al., 2020) did not find significant associations between age and hippocampus stiffness, which is in accordance with (Lv et al., 2020). On the other hand, Delgorio and colleagues (Delgorio et al., 2021) found a significant age-effect on the stiffness of hippocampal subfields; this significant result may be due to the high resolution MRE protocol adopted in this study, which was not used in any work before.

Hiscox and colleagues (Hiscox et al., 2018) used a different study design (i.e., comparisons between a group of young adults and a group of older adults) but reported similar results to the other studies. Namely, a significant effect of age in the stiffness of the whole cerebrum, with older subjects having lower cerebral stiffness than younger subjects, and a significant age-effect in the stiffness of all subcortical structures except for the hippocampus. The amygdala also lost the significant difference between age groups after controlling for volume size of the region. These results of lower global stiffness in older participants and no significant age effect in the stiffness of the hippocampus and the amygdala replicate the previously mentioned studies.

Finally, Kalra and colleagues (Kalra et al., 2019) only found a significant association between age and stiffness in the GM. The relatively low maximum age of 62 and the low sample size for a study spanning four decades of age might explain the lack of significant results for the other regions and the whole brain. This study also tried to measure anisotropic stiffness in the brain but once again only found significant results in GM and not in WM as it was expected.

3.3 | Dementia studies

A description of the 10 MRE studies investigating brain's mechanical properties changes in patients with dementia can be found in Table 2. Once again, there is heterogeneity in the MRE protocol as well as in the brain structures examined. Three studies used a MRE multifrequency protocol (Freimann et al., 2012; Gerischer et al., 2018; Streitberger et al., 2011), while the others applied single frequency MRE with 50 or 60 Hz as the vibration frequency. Regarding MRE resolution, half of the studies had isotropic 3-mm resolution and the remaining had varying resolutions. The most common used inversion algorithm was direct inversion. In terms of the brain structures investigated, except for (Freimann et al., 2012; Murphy et al., 2011; Streitberger et al., 2011) that only examined global changes and (Gerischer et al., 2018) which only analyzed the hippocampus, thalamus and WM, all the studies examined both global and regional changes of MRE parameters in demented patients.

TABLE 1 Overview of MRE studies investigating the mechanical properties of human brain in healthy aging.

Author	N	Age range	Sex (M/F)	Frequency (Hz)	MRE resolution	Inversion algorithm	Brain structure	Annual change in cerebral stiffness (kPa/year)
Sack et al., 2009	55	18–88	31/24	25, 37.5, 50, 62.5	$2.3 \times 2.3 \times 6 \text{ mm}^3$	Direct inversion + multifrequency fit	Whole brain	–0.015
Sack et al., 2011	66	18–72	31/35	25, 37.5, 50, 62.5	$1.5 \times 1.5 \times 6 \text{ mm}^3$	Direct inversion + multifrequency fit	Whole brain, cortical, inner, posterior, and frontal regions	–0.025
Arani et al., 2015	45	56–89	22/23	60	$3 \times 3 \times 3 \text{ mm}^3$	Direct inversion	Cerebrum, frontal, occipital, parietal and temporal lobes, sensory motor, deep GM/WM, and cerebellum	–0.011
Hiscox et al., 2018	24 (12 young vs. 12 old)	19–30 vs. 66–73	12/12	50	$1.6 \times 1.6 \times 1.6 \text{ mm}^3$	Nonlinear inversion	Cerebrum, amygdala, caudate, hippocampus, pallidum, putamen and thalamus	–8.47% (difference in stiffness between old vs. young)
Kalra et al., 2019	28	18–62	17/11	60	$2.5 \times 2.5 \times 2.5 \text{ mm}^3$	3D LFE inversion	Whole brain, GM, WM, thalamus, and corpus callosum	No significant correlation between age and whole brain stiffness
Hiscox et al., 2020	12	66–73	6/6	50	$1.6 \times 1.6 \times 1.6 \text{ mm}^3$	Nonlinear inversion	Left, right and bilateral hippocampus	No significant relationship between age and hippocampus stiffness
Lv et al., 2020	46	26–76	22/24	40, 60, 80, 90	$1.8 \times 1.8 \times 3 \text{ mm}^3$	Direct inversion + multifrequency fit	Cerebrum, cortical GM, WM, subcortical GM, hippocampus, amygdala, caudate, putamen, pallidum and thalamus	–0.012
Takamura et al., 2020	50	20–69	25/25	60	$3 \times 3 \times 3 \text{ mm}^3$	Direct inversion	Cerebrum, temporal, parietal, occipital and frontal lobes, sensorimotor areas, frontotemporal composite region, deep GM/WM, and cerebellum	–0.008
Delgorio et al., 2021	54	23–81	30/24	50	$1.25 \times 1.25 \times 1.25 \text{ mm}^3$	Nonlinear inversion	Hippocampal subfields	–0.011 (DG-CA3, CA1-CA2, SUB); –0.014 (ERC)

Abbreviations: CA1–3, cornu ammonis 1–3; DG, dentate gyrus; ERC, entorhinal cortex; GM, gray matter; LFE, local frequency estimation; SUB, subiculum; WM, white matter.

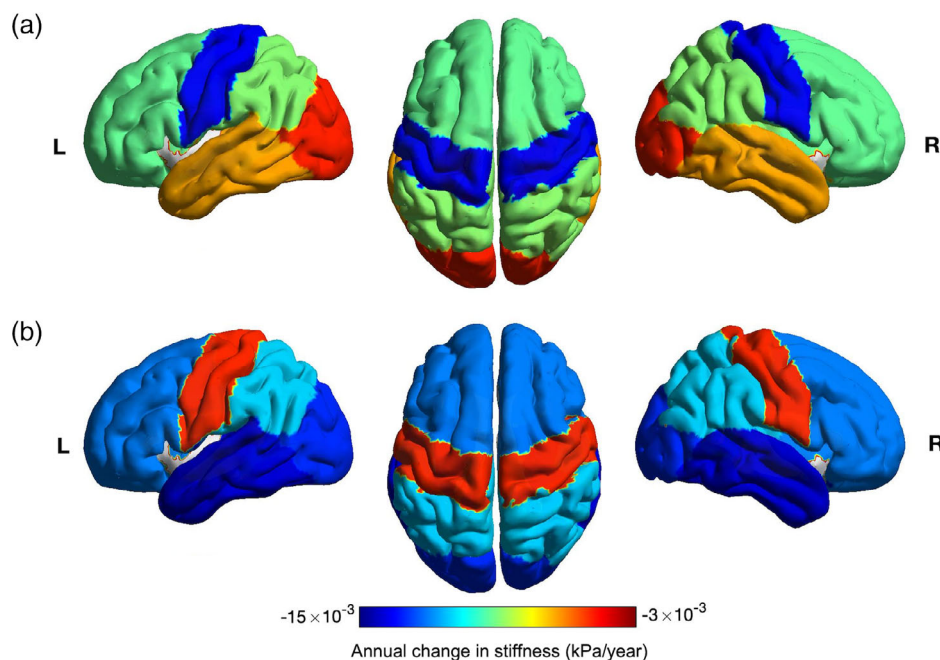


FIGURE 2 Annual changes in brain stiffness of the different lobes of the brain (frontal, occipital, parietal, temporal, and sensorimotor regions). Color bar indicates the annual change in stiffness in kPa/year. It is possible to observe a shift in the pattern of annual stiffness changes in the two studies, where study (a) comprises subjects between 20 and 60 years old and study (b) includes subjects between 60 and 90 years old. (a) Significant differences were found for all regions, with the most prominent changes occurring in sensorimotor regions and the least prominent occurring in temporal and occipital lobes (data from Takamura et al., 2020); (b) Significant differences were found for frontal, occipital, parietal and temporal lobes, with the most prominent changes occurring in temporal and occipital lobes. No significant differences found for sensorimotor regions (data from Arani et al., 2015).

The two studies exploring differences in brain stiffness between healthy controls and patients with frontotemporal dementia (FTD) reported decreased global brain stiffness for FTD patients, with the percentage of difference being -6.6% (Huston et al., 2016) and -7.0% (EISheikh et al., 2017). Regarding Alzheimer's disease (AD), the included studies also report decreased brain stiffness in patients in comparison to controls, with values of the difference ranging from -4.6% to -11% (EISheikh et al., 2017; Hiscox, Johnson, McGarry, Marshall, et al., 2020; Murphy et al., 2011; Murphy et al., 2016). The other cause of dementia examined was normal pressure hydrocephalus (NPH) and in this case, the studies describe conflicting results. While some (Freimann et al., 2012; Streitberger et al., 2011) report decreased stiffness in NPH patients, others (Fattahi et al., 2016; Perry et al., 2017) found increased stiffness in NPH patients and (EISheikh et al., 2017) also found increased stiffness although it did not reach statistical significance. These contrasting results may be due to differences in MRE protocol and in the delineation of the regions of interest. Lastly, the only study examining dementia with Lewy bodies (DLB) found no significant differences in cerebral stiffness between patients and controls (EISheikh et al., 2017).

Concerning regional changes, FTD studies showed decreased brain stiffness in frontal and temporal lobes of FTD patients, as expected (EISheikh et al., 2017; Huston et al., 2016). EISheikh and colleagues (EISheikh et al., 2017) also reported decreased stiffness of deep GM/WM in the FTD group.

In AD studies, consistent significant decreases in brain stiffness of AD patients were found in frontal, temporal and parietal lobes (EISheikh et al., 2017; Hiscox, Johnson, McGarry, Marshall, et al., 2020; Murphy et al., 2016). Changes in other brain regions are less coherent, with some (EISheikh et al., 2017; Hiscox, Johnson, McGarry, Marshall, et al., 2020) reporting decreased brain stiffness in sensorimotor regions, while another (Murphy et al., 2016) describes non-significant differences in these regions. Deep GM/WM also displays challenging results, with (EISheikh et al., 2017) showing significant softening of these regions in AD participants, while (Hiscox, Johnson, McGarry, Marshall, et al., 2020) reports only significant differences in WM and (Gerischer et al., 2018) in both WM and hippocampus, and in (Murphy et al., 2016) the differences did not reach statistical significance. Murphy and colleagues also showed that AD patients show decreased brain stiffness that is significantly different from amyloid-negative and amyloid-positive healthy controls, but the two control groups did not differ from each other (Murphy et al., 2011; Murphy et al., 2016). Moreover, they also demonstrated that brain stiffness was correlated with AD severity, as measured by hippocampal volume and amyloid load, and with functional connectivity within the default mode network (Murphy et al., 2016).

Regarding NPH studies, the common pattern observed is decreased brain stiffness in the periventricular region (Perry et al., 2017; Streitberger et al., 2011) and increased brain stiffness in parietal and occipital lobes in NPH patients (EISheikh et al., 2017;

TABLE 2 Overview of MRE studies investigating the mechanical properties of human brain in demented patients and cognitively healthy controls.

Author	Disorder	N	Age range	Sex (M/F)	Frequency (Hz)	MRE resolution	Inversion algorithm	Brain structure	% Difference in cerebral stiffness (patients vs. controls)
Streitberger et al., 2011	NPH	45 (20 NPH, 25 HC)	51–78	19/26	25, 37.5, 50, 62.5	1.5 × 1.5 × 6 mm ³	Direct inversion + multifrequency fit	Whole brain, periventricular region	–25.1
Murphy et al., 2011	AD	28 (7 AD, 7 HC+, 14 HC-)	73–94	20/8	60	4 × 4 × 4 mm ³	Direct inversion	Whole brain	–7.7 (AD vs. HC-); –5.4 (AD vs. HC+)
Freimann et al., 2012	NPH	20 NPH	51–85	8/12	25, 37.5, 50, 62.5	1.5 × 1.5 × 6 mm ³	Direct inversion + multifrequency fit	Whole brain	–26.8 (pre-shunt NPH vs. HC); –25.7 (post-shunt NPH vs. HC)
Huston et al., 2016	FTD	14 (5 FTD, 9 HC)	53–66	14/0	60	3 × 3 × 3 mm ³	Direct inversion	Cerebrum, frontal, occipital, parietal and temporal lobes, deep GM/WM, cerebellum, sensorimotor areas, and frontotemporal composite region	–6.6
Fattahi et al., 2016	NPH	31 (10 NPH, 21 HC)	67–80	15/16	60	3 × 3 × 3 mm ³	Direct inversion	Cerebrum, frontal, temporal, parietal and occipital lobes, deep GM/WM, and cerebellum	3.4
Murphy et al., 2016	AD	48 (8 AD, 8 MCI, 16 HC+, 16 HC-)	n/a	26/22	60	3 × 3 × 3 mm ³	Direct inversion	Cerebrum, frontal, occipital, parietal and temporal lobes, deep GM/WM, cerebellum, sensorimotor areas, and fronto-parietal–temporal composite region	–4.6
EISheikh et al., 2017	AD, DLB, FTD, NPH	84 (20 NPH, 8 AD, 5 DLB, 5 FTD, 46 HC)	54–89	49/35	60	3 × 3 × 3 mm ³	Direct inversion	Cerebrum, frontal, occipital, parietal and temporal lobes, deep GM/WM, sensorimotor areas, and cerebellum	–5.2 (AD vs. HC); –7.0 (FTD vs. HC); 0.8 (NPH vs. HC, non-significant); –0.4 (DLB vs. HC, non-significant)
Perry et al., 2017	NPH	30 (10 NPH, 20 HC)	67–80	13/17	60	3 × 3 × 3 mm ³	Direct inversion	Cerebrum, cerebellum, frontal, temporal, parietal, occipital, deep gray, and periventricular regions	3.4
Gerischer et al., 2018	AD	42 (21 AD, 21 HC)	66–80	22/20	30–60 (5 Hz increments)	1.9 × 1.9 × 1.9 mm ³	MDEV inversion	Hippocampus, thalamus, WM	–24.7 (hippocampus); –11.3 (WM); –6.2 (thalamus, non-significant)
Hiscox et al., 2020	AD	23 (11 AD, 12 HC)	66–87	10/13	50	1.6 × 1.6 × 1.6 mm ³	Nonlinear inversion	Cerebrum, WM, cerebral cortex, subcortical GM; voxel-wise analysis	–11

Abbreviations: AD: Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; HC, healthy controls; HC+: amyloid positive healthy controls; HC-: amyloid negative healthy controls; MCI: mild cognitive impairment; MDEV: multifrequency dual elasto-visco; NPH: normal pressure hydrocephalus.

Fattahi et al., 2016; Perry et al., 2017). Temporal and frontal lobes and deep GM/WM display distinct results. Fattahi and colleagues (Fattahi et al., 2016) report increased stiffness of the temporal lobe of NPH patients, while ElSheikh and colleagues (ElSheikh et al., 2017) found no significant differences in this region. Frontal lobe and deep GM/WM were found to be significantly softened in the NPH group in (ElSheikh et al., 2017), while Fattahi and colleagues (Fattahi et al., 2016) did not find statistically significant differences. Furthermore, Friemann and colleagues (Freimann et al., 2012) found a significant increase in the connectivity parameter in NPH patients after shunt treatment, with values within the range of the healthy control group. The connectivity parameter reflects brain tissue geometry or structure (Hiscox et al., 2016). On the other hand, stiffness remained unaltered after shunt placement and continued significantly different from healthy control values, which supports the hypothesis that the two parameters reflect two independent processes. Lastly, Perry and colleagues (Perry et al., 2017) investigated associations between brain stiffness and clinical outcomes. They reported associations between urinary incontinence and increased stiffness in cerebrum, frontal lobe and cerebellum, and decreased stiffness in periventricular region. Parkinsonism was found to be associated with increased occipital stiffness, while Mini-Mental State Examination (MMSE) score was inversely associated with parietal stiffness. Moreover, they show that postoperative failure was associated with decreased deep gray stiffness and increased stiffness of the temporal lobe.

A summary of the main findings regarding regional stiffness of the different causes of dementia is present in Figure 3.

4 | DISCUSSION

This review aimed at summarizing evidence of brain mechanical properties alterations, as measured with MRE, in normal and pathological aging. The available evidence revealed that normal aging is characterized by a decrease in brain stiffness spanning the different lobes (frontal, temporal, parietal and occipital) but not affecting the cerebellum. Regarding disorders causing dementia, distinct patterns of alterations were observed. AD and FTD patients showed decreased brain stiffness in comparison to cognitively healthy controls with significant decreases in regions known to be affected in each disease. NPH was characterized by decreased brain stiffness in the periventricular region and increased stiffness in parietal and occipital lobes, while the results for the whole brain were contradictory. The only study examining DLB found no significant differences in brain stiffness.

Another systematic review by Hiscox and colleagues (Hiscox et al., 2016), reviewed the alterations in brain mechanical properties in dementia caused by AD, FTD and NPH. The studies encompassed in their work were also part of the present review, but we additionally included recent studies, some with high resolution MRE, that reinforced previous results. Furthermore, we also investigated the available evidence regarding alterations in brain stiffness during normal aging, which despite having already been addressed in other reviews (Arani et al., 2021; Hiscox et al., 2021;

Yin et al., 2018), it was not the subject of any previous systematic review.

The exact biological mechanism behind the decreased brain stiffness in aging is not completely clarified. Several mechanisms were proposed as potential neuropathological correlates of the brain stiffness declines observed in aging. One of them is decreasing neuron-glia ratio (Kalra et al., 2019; Sack et al., 2009), since glia cells are softer than neurons (Lu et al., 2006) and with aging there is an increase in the glia/neuron ratio (Terry et al., 1987) leading to a softer brain. Another suggestion is GM composition (Arani et al., 2015; Delgorio et al., 2021; Sack et al., 2011; Takamura et al., 2020). In fact, Takamura and colleagues (Takamura et al., 2020) report that the age at which GM volume started significantly decreasing was the same age at which brain stiffness significantly declined. Thus, they hypothesized that these results possibly indicate that changes in cortical composition related to neuronal degeneration/volume loss contribute to the alterations observed in brain stiffness. Finally, Hiscox and colleagues (Hiscox et al., 2018) state that decreased brain stiffness is a result of the microstructural and metabolic changes occurring in the aging brain, given that stiffness reflects degree of myelination and neuronal density. In sum, all the different proposed mechanisms are related to brain tissue composition, which is in accordance with previous studies demonstrating that brain stiffness might reflect processes such as, neuronal density, myelination, mechanical matrix integrity, among others (Freimann et al., 2013; Guo et al., 2019; Klein et al., 2014; Munder et al., 2018; Sack et al., 2013).

Another important finding from elastography studies in aging is the larger effect sizes of MRE-derived parameters in comparison to volumetric measures from MRI. Previous studies found that decreases in brain stiffness during aging were 2 to 3 times greater than volumetric declines (Lv et al., 2020; Sack et al., 2011). This suggests that MRE may have higher sensitivity for detecting certain aging effects, and it can measure geometry-independent viscoelastic parameters which are related to intrinsic tissue structure (Hiscox et al., 2021; Sack et al., 2011). Furthermore, Hiscox and colleagues (Hiscox et al., 2018) found significant age-related decreases in brain stiffness even after controlling for the volume of the region, which demonstrates the additive value of MRE-derived parameters in elucidating changes in the aging brain not captured by standard neuroimaging methods. Lastly, Delgorio and colleagues (Delgorio et al., 2021) examined stiffness changes in hippocampal subfields and showed that the entorhinal cortex had the highest rate of annual change. However, this region showed low age-related variability of its volume in adulthood (Daugherty et al., 2016), which confirms the sensitivity of MRE to microstructural changes and that it can be used to identify earlier stages of age-related neurodegeneration.

Regarding pathological aging such as dementia, we observe pronounced changes in brain stiffness that distinguish them from the course of normal aging. For example, in AD, the reported stiffness reduction, found in both humans and animal models, is thought to reflect microstructural processes characteristic of the disease, such as disruption of the extracellular matrix due to amyloid deposition, loss of normal cytoskeletal architecture due to Tau hyper-phosphorylation

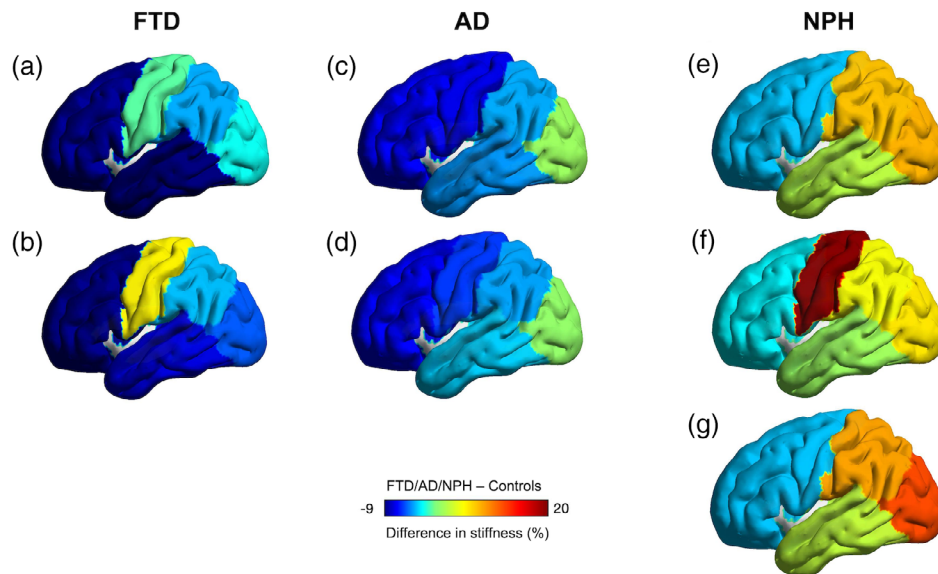


FIGURE 3 Summary of main findings of MRE studies investigating brain stiffness changes in different dementia subtypes. Color bar indicates percentage difference in FTD, AD, or NPH patients compared with healthy controls. FTD is characterized by decreased brain stiffness in frontal and temporal lobes (study [a]: Huston et al., 2016; study [b]: ElSheikh et al., 2017). Studies investigating AD display very similar patterns, with decreased brain stiffness occurring in frontal, temporal and parietal lobes. Regarding sensorimotor regions, although the percentage difference was similar in the two studies, in (c) it was not statistically significant (study [c]: Murphy et al., 2016; study [d]: ElSheikh et al., 2017). NPH studies also exhibit similar patterns of brain stiffness changes, with increased brain stiffness found in parietal and occipital lobes. Temporal and frontal lobes have similar percentage difference, but differences in frontal lobes were only significant in study (f), while for the temporal lobe, only study (g) found significant differences. Study (f) also investigated differences in sensorimotor regions and found increased stiffness of these regions in NPH patients (study [e]: Perry et al., 2017; study [f]: ElSheikh et al., 2017; [g]: Fattahi et al., 2016)

or altered synaptic connectivity (Munder et al., 2018; Murphy et al., 2012; Murphy et al., 2019). Furthermore, as in normal aging studies, Hiscox and colleagues (Hiscox, Johnson, McGarry, Marshall, et al., 2020) showed that alterations in brain volumes and stiffness had different spatial patterns in AD patients and stiffness changes remained significant after controlling for regional volume. Additionally, Gerischer and colleagues (Gerischer et al., 2018) demonstrated increased diagnostic accuracy of AD when hippocampal stiffness was incorporated with two other MRI-based hippocampal parameters (mean diffusivity and hippocampal volume). Also, different patterns of brain stiffness changes were observed between distinct subtypes of dementia (ElSheikh et al., 2017). In sum, all these findings show that MRE could be used to derive potentially new brain biomarkers of dementia and distinguish between its different types. Moreover, since it is sensitive to microstructural changes (Guo et al., 2019; Sack et al., 2013; Yin et al., 2018) and has some advantages over conventional neuroimaging techniques (e.g., no radiation exposure, short acquisition time, lower cost relatively to PET), it could help identify brain changes that occur at early stages of disease and thus help identify individuals at risk of dementia and evaluate the efficacy of new drugs or intervention therapies.

One limitation of this review is that we did not report results on viscosity. This is because not every study report results of this parameter. In fact, of the included studies only 10 (six aging, four dementia) have incorporated the viscosity parameter in their

analyses. Furthermore, the results are not robust as in brain stiffness, with some studies not finding significant effects of age or dementia (Hiscox et al., 2018; Hiscox, Johnson, McGarry, Marshall, et al., 2020; Hiscox, Johnson, McGarry, Schwarb, et al., 2020; Sack et al., 2009), while others find contradictory results, for example, increases with age (Delgorio et al., 2021) versus decreases with age (Lv et al., 2020; Sack et al., 2011). Future study employing high resolution MRE and larger sample sizes should investigate the age and dementia effects on this parameter to try to clarify if there exists an effect.

The field of MRE has gained recent interest and thus the number of studies is still very low. Future studies would benefit from using the latest technological developments (e.g., high-resolution MRE and improved inversion algorithms) and larger sample sizes in order to replicate previous findings and clarify some conflicting results. Additionally, to date there is no longitudinal study with MRE, which could help establish some causal relationships. In conclusion, this review demonstrated that MRE could be used as a sensitive diagnostic tool to identify deviations from normal aging. Additionally, it might help develop new brain biomarkers to identify individuals at risk of dementia and new intervention strategies to help promote a healthier cognitive aging.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Ana Coelho  <https://orcid.org/0000-0001-8489-5750>

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