Neurobiology of Aging 65 (2018) 158–167

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

High-resolution magnetic resonance elastography reveals differences in subcortical gray matter viscoelasticity between young and healthy older adults

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ARTICLE INFO

Article history:
Received 27 July 2017
Received in revised form 10 January 2018
Accepted 16 January 2018
Available online 6 February 2018

Keywords:
Brain
Magnetic resonance elastography (MRE)
Viscoelasticity
Healthy aging
Subcortical gray matter
Elasticity imaging techniques
Elastography

ABSTRACT

Volumetric structural magnetic resonance imaging (MRI) is commonly used to determine the extent of neuronal loss in aging, indicated by cerebral atrophy. The brain, however, exhibits other biophysical characteristics such as mechanical properties, which can be quantified with magnetic resonance elastography (MRE). MRE is an emerging noninvasive imaging technique for measuring viscoelastic tissue properties, proven to be sensitive metrics of neural tissue integrity, as described by shear stiffness, μ and damping ratio, and ξ parameters. The study objective was to evaluate global and regional MRE parameter differences between young (19–30 years, n = 12) and healthy older adults (66–73 years, n = 12) and to assess whether MRE measures provide additive value over volumetric magnetic resonance imaging measurements. We investigated the viscoelasticity of the global cerebrum and 6 regions of interest (ROIs) including the amygdala, hippocampus, caudate, pallidum, putamen, and thalamus. In older adults, we found a decrease in μ in all ROIs, except for the hippocampus, indicating widespread brain softening; an effect that remained significant after controlling for ROI volume. In contrast, the relative viscous-to-elastic behavior of the brain ξ did not differ between age groups, suggesting a preservation of the organization of the tissue microstructure. These data support the use of MRE as a novel imaging biomarker for characterizing age-related differences to neural tissue not captured by volumetric imaging alone.

1. Introduction

The use of medical imaging to identify and quantify brain tissue atrophy (i.e., neuronal cell loss) has been influential in aiding the prediction of onset and progression of many neurodegenerative disorders. Traditional diagnostic magnetic resonance imaging (MRI) is based on the radiologist grading of atrophy, often semi-quantitatively, through visual inspection of structural images, whereas research institutes or centers involved in clinical trials, typically use manual, semiautomated or fully automated techniques to study volume changes (i.e., macroscopic size), of regions of interest (ROIs). As an example, the European Medicines Agency has deemed low hippocampal volume an acceptable selection marker for clinical trials of people in the early stages of Alzheimer's disease (AD) (European Medicines Agency, 2011).

Despite the apparent relationship between brain atrophy and clinical syndromes, the association is not simple and linear; atrophy does not necessarily predict clinical symptoms or indeed their severity. Meta-analysis of results from 33 studies found a surprisingly weak positive relationship between hippocampal size and episodic memory ability in older adults, in addition to extreme variability among participants (Van Petten, 2004). One possible reason for this weak relationship is that most age-associated behavioral impairments appear to result from region-specific changes in dendritic morphology, cellular connectivity, axonal integrity, gene expression, or other factors that ultimately alter the network dynamics of neural ensembles that support cognition (Burke and Barnes, 2006; Smith et al., 2004). Accordingly, volumetric MRI is the most basic of neurobiological metrics; a gross proxy of tissue composition and integrity that is not specific to

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https://doi.org/10.1016/j.neurobiolaging.2018.01.010

microstructural tissue characteristics. As a result, volumetric measurements are unlikely to characterize presymptomatic neuronal dysfunction, thus limiting the utility of volumetry as a clinical biomarker for the early detection of neurological disorders.

Prior to neurodegeneration, pathological processes, which cause a reduction to, for example, cellular connectivity, are reflected in the biophysical characteristics of brain tissue such as mechanical properties like stiffness and viscous energy dissipation. The mechanical properties of soft tissue may vary over a dynamic range much greater than other physical properties such as magnetic resonance relaxation time (Mariappan et al., 2010), and thus the ability to directly image properties such as tissue stiffness offers the prospect of an imaging technique with high sensitivity. Magnetic resonance elastography (MRE) is being actively developed to noninvasively measure the mechanical properties of the brain in vivo. MRE combines MRI with mechanical wave propagation and records harmonic displacements of soft tissue in MRI phase images using motion-sensitive magnetic field gradients, which are then inverted to estimate underlying viscoelasticity (Muthupillai et al., 1995; Muthupillai and Ehman, 1996). Alterations in the mechanical properties of the brain, therefore, provide a unique contrast mechanism that appears to reflect the integrity of the underlying microstructure and health of brain tissue (Sack et al., 2013). The sensitivity of MRE measures is confirmed by the observation of tissue softening in many neurological diseases (Gerischer et al., 2017; Huston et al., 2015; Lipp et al., 2013, 2018; Murphy et al., 2011, 2016; Romano et al., 2014; Streitberger et al., 2012), for a review, see Hiscox et al. (2016) or Murphy and Huston (2017), with animal studies linking this softening to degree of myelin content (Schregel, 2012; Weickenmeier et al., 2016, 2017), inflammation (Riek et al., 2012), and a reduction in neuronal density related to a decrease in neurogenesis (Freimann et al., 2013; Klein et al., 2014). In general, tissue stiffness parameters likely reflect the composition of the tissue microstructure, whereas viscosity measures, including the phase angle and damping ratio, instead have been suggested to provide information regarding microstructural organization (Sack et al., 2013; Schwarb et al., 2016).

Understanding normal mechanical changes in brain tissue with respect to healthy aging is necessary before determining the efficacy of MRE for neurological disease diagnosis and therapy monitoring. Previous MRE studies into healthy aging have assessed either the global cerebrum (Sack et al., 2009), parcellated slices (Sack et al., 2011), or lobar regional effects (Arani et al., 2015). All studies reveal significant softening to the brain with increasing age, with brain softening occurring at a faster relative rate than brain volume loss with aging (Sack et al., 2011). In contrast, viscosity parameters remain constant suggesting a global preservation of the alignment of the tissue microstructure (Sack et al., 2009, 2011). However, no previous MRE studies into aging have investigated specific neuroanatomical structures, including subcortical gray matter (SGM) ROIs such as the hippocampus. Lying deep within the medial temporal lobes, the hippocampal formation is one of the most studied neuronal systems in the brain due to its implication in memory-specific disorders such as AD and mild cognitive impairment. Rapid improvements of MRE imaging protocols have now transitioned MRE into a high-resolution technique, capable of acquiring whole-brain MRE displacement data at an isotropic resolution of 1.6 mm to enable the study of small brain structures (Johnson et al., 2014). Aging effects have also never been studied with nonlinear inversion (NLI); formulated around a finite-element implementation of the full viscoelastic wave equation, NLI allows for local inhomogeneity and wave reflection effects (McGarry et al., 2012; Testu et al., 2017).

In this current cross-sectional exploratory study, we aim to use these methodological developments to assess the viscoelasticity of the cerebrum globally and 6 SGM matter structures (to include the amygdala [Am], hippocampus [Hp], caudate [Ca], pallidum [Pa], putamen [Pu], and thalamus [Th]), in both young and cognitively healthy older adults. First, we will assess the acceptability of the MRE examination by administering a questionnaire to all participants after the scanning procedure. Second, based on findings from previous work, we predict that the brain will be softer in older adults (i.e., show lower shear stiffness, μ), throughout the cerebrum and all SGM regions. Third, we predict that the global cerebrum will not differ between age groups in its relative viscous-to-elastic behavior (i.e., damping ratio, ξ). It is currently unknown whether age-related differences for ξ will be detected in SGM regions, and thus our analysis is an exploratory one. Finally, we will take into consideration the volume of the cerebrum and each SGM region within our statistical analyses to investigate whether MRE results persist even once ROI volume has been accounted for. MRE results that remain significant after controlling for ROI volume would suggest that MRE parameters provide additive value over volumetric measures alone.

2. Material and methods

2.1. Participants

Thirty-one apparently healthy participants were recruited from the Join Dementia Research database; 13 were young adult participants aged between 18–30 years and 18 were older participants aged between 65–75 years. Criteria for exclusion included history or current diagnosis of a severe medical, neurological, or psychiatric disorder, history of major head injury, and contraindications for undergoing MRI (such as claustrophobia or the presence of an implanted pacemaker). To ensure older participants, in particular, had no significant underlying memory problems, all were required to complete the Montreal Cognitive Assessment and score within the normal range (>26/30) (Nasreddine et al., 2005). MRE data quality was measured by octahedral shear-strain–based signal-to-noise ratio (OSS-SNR) (McGarry et al., 2011), (see Section 2.4). Overall, 1 young adult was excluded due to OSS-SNR < 3, and 6 older participants were excluded from the analysis: 3 participants had OSS-SNR < 3, 2 participants scored below the required level set for the Montreal Cognitive Assessment, and 1 participant was excluded due to the presence of significant white matter abnormalities, as determined by a consultant radiologist. As a result, the final sample included 24 participants (12 young adults [mean age $= 25.2 \pm 3.0$ years] and 12 older adults [mean age $= 69.4 \pm 2.5$ years]). An equal number of female and male participants were recruited into each group. All participants completed the Edinburgh Handedness Inventory and National Adult Reading Test to measure handedness and IQ, respectively (see Table 1). The study was approved by the National Health Service (NHS) Lothian ethics committee and all study participants gave written, informed consent before the examination.

2.2. MRI scanning

MRI data were collected using a Siemens 3T Verio whole-body MRI scanner with a 12-channel head receive coil (Siemens Medical Solutions; Erlangen, Germany). The imaging protocol included high-resolution T_1-weighted and MRE series. T_1-weighted images were acquired using an MPRAGE sequence (magnetization-prepared rapid gradient echo; $1 \times 1 \times 1$ mm^3 voxel size; 2400/1000/2.97 ms repetition/inversion/echo times). The MRE acquisition used a 3D multislab, multishot spiral sequence to capture high-resolution displacement data (Johnson et al., 2014). Imaging parameters included the following: 1800/75 ms repetition/echo times; 240 mm square field of view; 150×150 imaging matrix; and sixty 1.6-mm thick slices acquired in 10 overlapping slabs. The resulting imaging