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Mechanical properties of the *in vivo* adolescent human brain

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ABSTRACT

Viscoelastic mechanical properties of the *in vivo* human brain, measured noninvasively with magnetic resonance elastography (MRE), have recently been shown to be affected by aging and neurological disease, as well as relate to performance on cognitive tasks in adults. The demonstrated sensitivity of brain mechanical properties to neural tissue integrity make them an attractive target for examining the developing brain; however, to date, MRE studies on children are lacking. In this work, we characterized global and regional brain stiffness and damping ratio in a sample of 40 adolescents aged 12–14 years, including the lobes of the cerebrum and subcortical gray matter structures. We also compared the properties of the adolescent brain to the healthy adult brain. Temporal and parietal cerebral lobes were softer in adolescents compared to adults. We found that of subcortical gray matter structures, the caudate and the putamen were significantly stiffer in adolescents, and that the hippocampus and amygdala were significantly less stiff than all other subcortical structures. This study provides the first detailed characterization of adolescent brain viscoelasticity and provides baseline data to be used in studying development and pathophysiology.

1. Introduction

The study of viscoelastic mechanical properties of the healthy adult brain, through magnetic resonance elastography (MRE) (Muthupillai et al., 1995), has led to a quantitative understanding of the *in vivo* stiffness of neural tissue (Hiscox et al., 2016). Through advances in MRE technology, reports of reliable regional mechanical properties in the adult brain have been published, including data on different cerebral lobes (Murphy et al., 2013) and subcortical gray matter structures (Johnson et al., 2016). Stiffness and damping ratio data collected through MRE has theoretically and experimentally been correlated with microstructural brain health (Hiscox et al., 2016) as it provides a sensitive quantitative measure of biological factors such as white matter myelination and number of neurons (Sack et al., 2013). MRE studies of the adult brain have found brain stiffness to be affected by different neurodegenerative diseases (Murphy et al., 2016; Romano et al., 2012; Streitberger et al., 2012), and have also revealed correlations with fitness measures and cognitive tasks (Johnson et al., 2018; Schwarb et al., 2017, 2016). Adult brain MRE studies have also revealed changes in mechanical properties with age (Arani et al., 2015; Hiscox et al., 2018; Sack et al., 2011). Specifically, several studies have revealed a softening of brain tissue as it ages, with annual changes in stiffness between −0.3 and −1.0%, demonstrating how mechanical properties can be used to probe structural changes in the healthy brain.

Although considerable MRE data exists for the adult brain, no MRE studies examining the developing brain have yet been reported, despite the potential for mechanical properties to increase our knowledge of how brain structure matures (Johnson and Telzer, 2017). The brain undergoes many cellular level structural changes during adolescence, including volume variations both in total size and structure proportion, as well as a redistribution of gray and white matter (Gogtay et al., 2004; Raznahan et al., 2014) and myelination of white matter tracts (Lebel et al., 2017). Given significant structural brain changes during development, and the sensitivity of mechanical properties to neural tissue microstructure, MRE may provide a unique contrast for imaging the developing brain. It has been seen that MRE provides a complementary contrast compared to volumetric analysis for examining complex interactions of neuronal components (Wuerfel et al., 2010). Previous brain MRE studies have demonstrated the potential for measuring mechanical properties of the developing brain as these measures are expected to have higher sensitivity than many other common imaging contrasts (Mariappan et al., 2010).

The viscoelastic brain properties commonly reported by MRE are related to both the microstructural composition and organization of neural tissue (Sack et al., 2013). This is reflected in animal studies with MRE that have found changes in mechanical properties correlating with

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microstructural tissue characteristics, such as number of neurons in models of neurogenesis (Hain et al., 2016; Klein et al., 2014) and ischemic stroke (Freimann et al., 2013). Notably, viscoelastic properties measured with MRE are also sensitive to demyelination and remyelination (Schregel et al., 2012). Myelin specific MRI sequences have been developed to image the water content in the lipid bilayers of myelinated axons; however, these methods may artificially overestimate myelination (Alonso-Ortiz et al., 2015; Wang, 2012; West et al., 2016), and thus alternative and complementary approaches to examining myelin content are needed. Myelination of axons increases their mechanical strength (Shreiber et al., 2009), and brain stiffness increases with the number of intact myelinated axons (Weickenmeier et al., 2017), thus giving rise to white matter being stiffer than gray matter (Budday et al., 2015). The volume and proportion of white matter increases through development into adulthood (Paus et al., 2001), and local myelin distribution changes with age and functional need (Lenroot and Giedd, 2006), thus mechanical properties are expected to reflect these changes.

The volume and structure of gray matter also changes with development, including synaptogenesis and dendritic pruning, which are related to the maturation of cognitive functions. Gray matter density is often impacted in developmental disorders and their associated cognitive impairments (Toga et al., 2006). Recently, our group has demonstrated that MRE measures of gray matter regions can be highly sensitive to cognitive function, specifically viscoelasticity of the hippocampus as it relates to performance on memory tasks (Schwarb et al., 2017, 2016). This highlights the potential of MRE in mapping brain structure and function through mechanical properties.

This study aims to quantify the viscoelastic mechanical properties of the adolescent human brain *in vivo* using MRE. We report both global and regional property values quantified in lobes of the cerebrum and in subcortical gray matter structures. We further compare these adolescent properties to adult brain property values, collected and processed through a common protocol. To our knowledge, this is the first detailed characterization of the viscoelastic mechanical properties of the adolescent human brain measured *in vivo* with MRE. An understanding of healthy adolescent brain viscoelasticity at age of puberty will increase the knowledge of brain mechanics at an age where little is known about these properties, and can provide baseline data to be used in studying the pathophysiology and longitudinal development of the adolescent brain.

2. Methods

2.1. Participants

A total of 46 (22 male / 24 female) healthy, cognitively normal, right-handed adolescents, 12–14 years old and 20 healthy male, cognitively normal adults, 18–33 years old were included in the study. The adolescent data was collected as a subset of participants from a larger study where only a small portion completed the MRE scan. The adult data used for comparison was of the same subjects for two other adult MRE studies (Johnson et al., 2016; Schwarb et al., 2016) and was reprocessed for the purpose of direct comparison in this paper. Of the 66 collected datasets, four had low signal-to-noise ratio (SNR) (McGarry et al., 2011) or artifacts in the reconstructed property maps and two were determined to be outliers (see *Statistical Analysis* section, below), so the final sample included data from 40 adolescents (19 male / 21 female) and 20 adult males. This study was approved by the University of Illinois at Urbana-Champaign Institutional Review Board and all participants, and guardians of the adolescent participants, gave informed written consent prior to being studied.

2.2. Imaging data acquisition and processing

Each adolescent participant completed an imaging session on a Siemens 3 T Trio MRI scanner (Siemens Medical Solutions; Erlangen, Germany), with a protocol that included a high-resolution, T_1-weighted MPRAGE sequence (magnetization-prepared rapidly-acquired gradient echo; $0.9 \times 0.9 \times 0.9$ mm^3; TR/TI/TE = 1900/900/2.32 ms) for anatomical localization and an MRE acquisition. The MRE experiment involves vibrating the head to generate shear waves with micron-level amplitude that propagate through the brain. These waves are imaged with a phase-contrast motion-encoding MRI sequence synchronized to vibrations. By repeating the acquisition with different synchronization and motion-encoding gradient axes, 3D, full vector, complex displacement fields are captured across the entire brain. These displacement fields are used to estimate the brain mechanical properties through an "inversion" algorithm that uses a model of viscoelastic tissue behavior to create whole-brain property maps (Hiscox et al., 2016; Johnson and Telzer, 2017).

We acquired MRE data using a 3D multislab, multishot spiral sequence (Johnson et al., 2014). The resulting MRE images had $2.0 \times 2.0 \times 2.0$ mm^3 isotropic spatial resolution, and encoded displacements from 50 Hz vibrations delivered to the head *via* pneumatic actuator system with passive pillow driver (Resoundant, Inc.; Rochester, MN). Additional imaging parameters included: field-of-view = 240×240 mm^2; matrix = 120×120; 60 total slices (10 slabs; 8 slices per slab; 25% slab overlap); 1 in-plane spiral shot ($R = 3$); TR/TE = 1800/73 ms; bilateral, flow-compensated, matched-period motion-encoding gradients, 26 m T/m; 4 evenly-spaced phase offsets. Total acquisition time was 6 min. Iterative image reconstruction included field inhomogeneity correction, SENSE parallel imaging, and correction for small motion-induced phase errors between shots for a single imaging volume that may arise from subject motion or variations in applied vibration, as described in (Johnson et al., 2014). Data quality was confirmed after image reconstruction by the octahedral shear strain-based (SNR) (McGarry et al., 2011), where an SNR > 3 is sufficient for stable inversion and reliable property maps. This data quality check excluded datasets with too low displacement amplitude (*i.e.* from lack of sufficient head vibration) or data corrupted from excessive head motion.

The adult participants included in this paper underwent a nearly identical data collection procedure, however with a higher MRE spatial resolution (1.6 mm isotropic voxels). For comparison in this study, the higher resolution data was downsampled to 2.0 mm isotropic voxel size for comparison with the adolescent population. This downsampling occurred prior to inversion (next section) and all data was completely reprocessed using the identical pipeline. We have previously demonstrated that this downsampling had minimal effect on the population values recovered with MRE (Johnson et al., 2016).

The nonlinear inversion algorithm (NLI) was used to estimate brain tissue viscoelastic properties from MRE displacement data (McGarry et al., 2012; Van Houten et al., 2001). NLI returns whole-brain maps of the complex viscoelastic shear modulus ($G = G' + G''$), from which we calculate shear stiffness, $\mu = 2|G|^2/(G' + |G|)$ (Manduca et al., 2001), and damping ratio, $\xi = G''/2G'$ (McGarry and Van Houten, 2008). We also incorporated *a priori* spatial information during inversion through soft prior regularization (SPR) (McGarry et al., 2013) to improve the measures of subcortical gray matter regions. This involves providing masks of each subcortical region (see next section) over which property variation is penalized through SPR during NLI optimization. This is the same pipeline which was previously used for subcortical gray matter property estimation in adults (Johnson et al., 2016; Schwarb et al., 2016), and has been demonstrated to reduce variability in measures potentially arising from contamination of nearby cerebrospinal fluid (CSF).

2.3. Regional data analysis

Masks for mechanical property characterization of neuroanatomical structures were created using standard neuroimaging tools. Lobar