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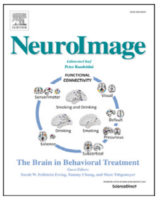

Double dissociation of structure-function relationships in memory and fluid intelligence observed with magnetic resonance elastography

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ABSTRACT

Brain tissue mechanical properties, measured *in vivo* with magnetic resonance elastography (MRE), have proven to be sensitive metrics of neural tissue integrity. Recently, our group has reported on the positive relationship between viscoelasticity of the hippocampus and performance on a relational memory task in healthy young adults, which highlighted the potential of sensitive MRE measures for studying brain health and its relation to cognitive function; however, structure-function relationships outside of the hippocampus have not yet been explored. In this study, we examined the relationships between viscoelasticity of both the hippocampus and the orbitofrontal cortex and performance on behavioral assessments of relational memory and fluid intelligence. In a sample of healthy, young adults (N = 53), there was a significant, positive relationship between orbitofrontal cortex viscoelasticity and fluid intelligence performance ($r = 0.42$; $p = .002$). This finding is consistent with the previously reported relationship between hippocampal viscoelasticity and relational memory performance ($r = 0.41$; $p = .002$). Further, a significant double dissociation between the orbitofrontal-fluid intelligence relationship and the hippocampal-relational memory relationship was observed. These data support the specificity of regional brain MRE measures in support of separable cognitive functions. This report of a structure-function relationship observed with MRE beyond the hippocampus suggests a future role for MRE as a sensitive neuroimaging technique for brain mapping.

Introduction

Measuring the *in vivo* mechanical properties of the human brain with magnetic resonance elastography (MRE) (Muthupillai et al., 1995) has recently found clinical applications in radiology, neurology, and neurosurgery (Hiscox et al., 2016; Johnson and Telzer, 2017). MRE studies have revealed softening of neural tissue in several neurological disorders associated with neurodegeneration (Huston et al., 2016; Murphy et al., 2016; Romano et al., 2014; Streitberger et al., 2012), and the assessment of intracranial tumor stiffness has shown promise in surgical planning (Hughes et al., 2015; Hughes et al., 2016). Part of the success of MRE is owed to the high sensitivity of mechanical properties to microstructural tissue health; indeed, viscoelastic parameters relate to tissue composition and organization (Sack et al., 2013) and compositional and organizational changes accompanying viscoelastic property changes have been observed in animal models of demyelination (Schregel et al., 2012), inflammation (Riek et al., 2012), and neuronal loss (Freimann et al., 2013). Beyond disease, MRE has also revealed differences in viscoelasticity in the healthy aging brain (Arani et al., 2015; Sack et al., 2011), presumably reflecting natural changes in brain health.

The high sensitivity of brain tissue viscoelasticity to microstructure has also motivated its use in answering cognitive neuroscience questions about structure-function relationships, as it is well documented that across the brain, the health and integrity of the underlying tissue can influence cognitive function and success (Raz, 2000). Our group has recently reported a positive relationship between the relative viscosity of the hippocampus (HC) measured with MRE and relational memory performance assessed with a spatial reconstruction (SR) task (Schwarb et

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al., 2016). We have also observed that the HC viscoelasticity measured from MRE appears to convey the benefits of aerobic fitness and exercise training on memory performance (Sandroff et al., 2017; Schwarb et al., 2017). Taken together, these studies highlight an exciting new role for MRE that harnesses its inherent sensitivity to tissue microstructure to explore structure-function relationships in the brain; however, to date, HC structure-function relationships remain the only such relationships explored with MRE. This is in part due to the challenges associated with localizing MRE property measures to specific regions of cortical gray matter due to its very thin structure and sulcal discontinuities. Overcoming these limitations requires high resolution imaging and mechanical inversion techniques (Johnson et al., 2013b; Johnson et al., 2016), and we hypothesized that, by adopting a high-resolution MRE scheme for assessing the cortex, we could observe other structure-function relationships with MRE.

We tested this by examining the viscoelasticity of the orbitofrontal cortex (OFC) and its relationship with fluid intelligence performance assessed with a figure series (FS) task (Cattell, 1971; Daugherty et al., 2018). Fluid intelligence is the ability (Carroll, 1993; Cattell, 1971) that supports flexible, abstract, and adaptive thinking (Barbey et al., 2013; de Abreu et al., 2010; Jaeggi et al., 2008; Masunaga et al., 2008). Traditionally, damage to the prefrontal cortex (PFC) generally has resulted in impairment on tasks designed to measure fluid intelligence (Barbey et al., 2013; Duncan et al., 1995; Woolgar et al., 2010). Of course, the PFC is a large, non-homogeneous region comprising many structurally and functionally differentiated subregions, including the lateral PFC, anterior cingulate cortex, and OFC, which have been identified as particularly important for fluid intelligence (Barbey et al., 2013; Woolgar et al., 2010; but see Tranel et al., 2008). Different measures of fluid intelligence also engage different PFC regions. Functional neuroimaging studies of canonical FS reasoning tasks of fluid intelligence (e.g. the Cattell Culture Fair task; CCF) engage middle frontal gyrus and OFC (Duncan et al., 2000; Masunaga et al., 2008). Volumetric studies on older adults have also been informative in localizing PFC contributions to fluid intelligence performance highlighting the role of the OFC. Gong and colleagues reported that after controlling for the effects of age, volume in the medial PFC extending into the OFC correlated with performance on a figure series task (Gong et al., 2005). Raz and colleagues corroborated and further refined these findings, and demonstrated that, after controlling for age, sex, and vascular risk factors, OFC volume specifically predicted performance on the CCF task (Raz et al., 2008). Based on these previous findings, the current experiment focused on OFC viscoelasticity and figure series task measures to explore its relationship with fluid intelligence.

Further, we hypothesized that observed structure-function relationships dissociate with each other. We therefore compared the OFC-fluid intelligence relationship with the previously-established HC-relational memory relationship. The hippocampus is critically involved in relational memory abilities (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001) and we have previously shown that MRE derived measures of HC viscoelasticity are sensitive to relational memory success among healthy young adults (Schwarb et al., 2016; Schwarb et al., 2017). Derived primarily from behavioral and lesion studies, the gold standard for identifying dissociable and selective structure-function relationships is the double-dissociation (Bigler, 2009; Fama and Sullivan, 2014; Freedman et al., 1984; Teuber, 1955). Generally, a double dissociation necessitates that brain region A relates to or impacts cognitive process X, but not (or to a significantly lesser extent) cognitive process Y; while brain region B relates to or impacts cognitive process Y, but not (or to a significantly lesser extent) cognitive process X. In the current study, we apply this framework to our MRE measures of microstructural integrity predicting that among healthy, young adults, HC viscoelasticity will show a significant relationship with performance on measures of relational memory, but not fluid intelligence; and that OFC viscoelasticity will show a significant relationship with performance on measures of fluid intelligence, but not relational memory. Together, these data provide the first evidence to support the specificity of structure-function relationships from MRE, and motivates the use of MRE in mechanically mapping the human brain to understand its structure, function, and health.

Methods

Participants

Participants were recruited from the Urbana-Champaign community as part of a larger cognitive training intervention study designed to assess the efficacy of different intervention modalities on cognitive performance in healthy adults ($N = 384$). A small number of participants ($N = 64$) volunteered to complete an optional additional imaging session that included an MRE scan. The University of Illinois Urbana-Champaign Institutional Review Board approved all aspects of the study and participants provided informed consent at enrollment. All participants were right-handed with normal or corrected-to-normal vision without color blindness, reported no previous neurological disorders or surgeries, were not on medications affecting central nervous function, and were not pregnant. Participants received monetary compensation for their participation. Only those participants who completed MRE scans are included in this report. A subsample of this population has previously been reported (Schwarb et al., 2017).

As such, data were collected from 64 participants ages 18–35 (mean age = 22.7) and included 32 males and 32 females. Five participants were excluded as they did not complete the hippocampal-dependent SR memory task. Due to significant skewness in some of our variables of interest, median absolute deviation (MAD) methods were used to detect statistical outliers (Hampel, 1974; Leys et al., 2013). A conservative criterion of 3 times the MAD was used for outlier detection (Miller, 1991). As such, five participants were removed based on their memory performance measures and an additional participant was excluded due to hippocampal MRE viscoelasticity measures. The resulting sample included 53 participants ages 18–35 (mean age = 22.8) and included 26 men and 27 women.

All participants completed a behavioral assessment session and an MRI scanning session. The MRI session was completed on a Siemens 3T Trio scanner with 32-channel head coil (Siemens Medical Solutions; Erlangen, Germany).

MRE acquisition and analysis

We acquired MRE displacement data using a 3D multislab, multishot spiral sequence (Johnson et al., 2014). Imaging parameters included: 2 in-plane, constant density spiral shots ($R = 2$) (Glover, 1999); 1800/73 ms repetition/echo times; 240 mm field-of-view; 150×150 matrix; 60 slices at 1.6 mm thickness (acquired in 10 slabs of 8 slices each with 25% overlap). The final imaging resolution was $1.6 \times 1.6 \times 1.6\ \text{mm}^3$. Images were reconstructed using an iterative algorithm (Sutton et al., 2003) that included parallel imaging with SENSE (Pruessmann et al., 2001), field inhomogeneity correction with an auxiliary field map (Funai et al., 2008), and motion-induced phase error correction (Johnson et al., 2013b; Johnson et al., 2014).

The MRE sequence captured displacements using motion-sensitive gradients synchronized to applied 50 Hz vibrations, which were delivered to the head using a pneumatic actuator with soft pillow driver (Resoundant, Inc.; Rochester, MN). Gradients were applied separately in three directions, with both positive and negative polarity to remove background phase, and with varying synchronization to vibration to sample four time points evenly spaced over one period. The total acquisition time was approximately 12 min. Following image reconstruction and data processing (including phase subtraction, temporal filtering (Manduca et al., 2001), and phase unwrapping (Jenkinson, 2003)), complex, full vector displacement fields were generated for mechanical property estimation.