Research article

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Tissue structure and inflammatory processes shape viscoelastic properties of the mouse brain

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Magnetic resonance elastography (MRE) is an imaging method that reveals the mechanical properties of tissue, modelled as a combination of "viscosity" and "elasticity". We recently showed reduced brain viscoelasticity in multiple sclerosis (MS) patients compared with healthy controls, and in the relapsing–remitting disease model experimental autoimmune encephalomyelitis (EAE). However, the mechanisms by which these intrinsic tissue properties become altered remain unclear.

This study investigates whether distinct regions in the mouse brain differ in their native viscoelastic properties, and how these properties are affected during chronic EAE in C57Bl/6 mice and in mice lacking the cytokine interferon-gamma. IFN-$\gamma^{-/-}$ mice exhibit a more severe EAE phenotype, with amplified inflammation in the cerebellum and brain stem. Brain scans were performed in the sagittal plane using a 7 T animal MRI scanner, and the anterior (cerebral) and posterior (cerebellar) regions analyzed separately. MRE investigations were accompanied by contrast-enhanced MRI scans, and by histopathology and gene expression analysis *ex vivo*.

Compared with the cerebrum, the cerebellum in healthy mice has a lower viscoelasticity, i.e. it is intrinsically "softer". This was seen both in the wild-type mice and the IFN$\gamma^{-/-}$ mice. During chronic EAE, C57Bl/6 mice did not show altered brain viscoelasticity. However, as expected, the IFN$\gamma^{-/-}$ mice showed a more severe EAE phenotype, and these mice did show altered brain elasticity during the course of disease. The magnitude of the elasticity reduction correlated with F4/80 gene expression, a marker for macrophages/microglia in inflamed central nervous system tissue.

Together these results demonstrate that MRE is sensitive enough to discriminate between viscoelastic properties in distinct anatomical structures in the mouse brain, and to confirm a further relationship between cellular inflammation and mechanical alterations of the brain. This study underscores the utility of MRE to monitor pathological tissue alterations *in vivo*. Copyright © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

Cranial magnetic resonance elastography (MRE) is an emerging method that can yield information about the mechanical properties of brain tissue (1). MRE achieves a non-invasive "virtual palpation", by using an external vibration source to induce shear waves in the tissue, and detecting these waves using motion-sensitive gradients. The resulting complex-valued shear modulus G^* includes the real component G' (the storage modulus), which reflects tissue elasticity, and the imaginary component G'' (the loss modulus) (2), which reflects tissue viscosity. Decreased values of G^* indicate a reduction in the mechanical rigidity of tissue, i.e. a "softening" of the tissue. Changes in the loss tangent given by the phase angle φ, calculated as $\arctan(G''/G')$, indicate an alteration of the tissue complexity, which may be associated with more severe tissue remodeling and tissue destruction (3).

Inside the central nervous system (CNS), interactions between neurons, glia, the vasculature and the extracellular matrix, as well as the interstitial and cerebrospinal fluid compartments, contribute to establishing the mechanical properties of CNS tissue. The fact that the brain is composed by different structures with

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Abbreviations used: *ANOVA, analysis of variance; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; FoV, field of view; IFNγ, interferon-gamma; MOG, myelin oligodendrocyte glycoprotein; MRE, magnetic resonance elastography; MS, multiple sclerosis; MSG, motion sensitizing gradient; qPCR, quantitative polymerase chain reaction; SJL, Swiss Jim Lambert; WT, wild type.*