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MR-elastography reveals degradation of tissue integrity in multiple sclerosis

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ABSTRACT

In multiple sclerosis (MS), diffuse brain parenchymal damage exceeding focal inflammation is increasingly recognized to be present from the very onset of the disease, and, although occult to conventional imaging techniques, may present a major cause of permanent neurological disability. Subtle tissue alterations significantly influence biomechanical properties given by stiffness and internal friction, that – in more accessible organs than the brain – are traditionally assessed by manual palpation during the clinical exam. The brain, however, is protected from our sense of touch, and thus our current knowledge on cerebral viscoelasticity is very limited. We developed a clinically feasible magnetic resonance elastography setup sensitive to subtle alterations of brain parenchymal biomechanical properties. Investigating 45 MS patients revealed a significant decrease (13%, $P<0.001$) of cerebral viscoelasticity compared to matched healthy volunteers, indicating a widespread tissue integrity degradation, while structure-geometry defining parameters remained unchanged. Cerebral viscoelasticity may represent a novel *in vivo* marker of neuroinflammatory and neurodegenerative pathology.

Introduction

The pathologic hallmarks of multiple sclerosis (MS) are inflammatory foci with demyelination, axonal degeneration, and reactive gliosis (Pittock and Lucchinetti, 2007). Although magnetic resonance imaging (MRI) has become the most important paraclinical tool for diagnosis and monitoring of MS, conventional MRI parameters correlate only modestly with the clinical course and neurological disability (Barkhof, 2002). Thus, new imaging modalities that provide a more specific measure of *in vivo* histopathological and cellular aspects of the disease process are needed (Miller et al., 2003). A direct measure of the tissue constitution could be based on the assessment of cell adhesion and tissue scaffold rigidity by measuring the macroscopic viscoelasticity of the brain parenchyma (Fung, 1993). Tactile measures of viscoelasticity are, for example, the stiffness or the softness of a given tissue, that can be obtained by simple palpation, as routinely employed during the physical examinations. The brain, however, is protected from our sense of touch, limiting the present knowledge on *in vivo* cerebral viscoelasticity and its relation to central nervous system pathologies. In a technical "palpation", known as magnetic resonance elastography (MRE), shear waves are applied with frequencies at the acoustic range, and a phase-sensitive MR sequence is used to detect propagating waves (Muthupillai and Ehman, 1996). Elastographic techniques have previously shown a high sensitivity for detecting subtle tissue alterations in skeletal muscle (Basford et al., 2002; Papazoglou et al., 2006), breast (McKnight et al., 2002; Sinkus et al., 2007) and liver (Asbach et al., 2008) pathologies. Cerebral MRE provides a unique tool measuring the viscoelasticity of brain parenchyma in its intact physiological environment (Kruse et al., 2008; Sack et al., 2008), circumventing the natural mechanical shielding through the skull, cerebrospinal fluid, and meninges. We recently developed a novel sensitive and highly reproducible setup that allows the calculation of global cerebral shear moduli and shear viscosities, based on a head-rocker actuator, the fast acquisition of scalar wave fields using echo planar imaging (EPI), and the analysis of complex-modulus inversion of time-resolved wave images (Sack et al., 2008). Here we investigated the potential of cerebral MRE to detect subtle diffuse parenchymal damage in mildly affected MS patients, that is not represented by macroscopically visible lesions.

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Patients and methods

We determined the complex modulus (G) in 79 participants, comprising 45 MS patients with mild relapsing-remitting disease course (mean Expanded Disability Status Score (EDSS) 1.6; range 0–4), and 34 age and gender matched healthy volunteers without neurological or psychiatric conditions, as presented in Table 1. The study was approved by the local ethics committee, and written informed consent was obtained from all subjects. Principles of our assay are presented in Fig. 1.

Every participant underwent an MRE examination of approximately 15 min duration in a standard 1.5 T-clinical MRI scanner (Siemens, Erlangen, Germany) in addition to a routine clinical MRI protocol: T2-weighted images (repetition time (TR): 5780 ms, echo-time (TE): 81 ms, 3 mm slice thickness and 44 contiguous axial slices).

In patients, conventional spin-echo T1-weighted images (TR: 1060 ms, TE: 14 ms, 3 mm slice thickness and 44 contiguous axial slices) were obtained before and 5 min after injection of 0.1 mmol/kg Gd-DTPA (gadopentate dimeglumine (Magnevist®), Bayer-Schering, Berlin, Germany). Blinded MRI data analysis was performed of conventional MRI data, following a semi-automatic procedure, which included an image coregistration (Jenkinson et al., 2002) as well as an inhomogeneity correction routine embedded into the MedX3.4.3 software package (Medical Numerics, Germantown, USA). Bulk white matter lesion load of T2-weighted scans as well as number and volume of hyperintense lesions on T1-weighted scans were routinely measured using the MedX v.3.4.3 software package, as described previously (Wuerfel et al., 2004, 2008). Brain parenchymal fraction (BPF) was calculated applying a fully automated software tool (Smith et al., 2002). In 16 healthy volunteers (5 females), a three-dimensional T1-weighted sequence (MPRAGE, TR: 2110 ms, TE: 4.38 ms, flip angle 15°, isotropic resolution 1 mm^3) replaced conventional spin-echo T1-weighted images.

The MRE protocol comprised a single-shot spin-echo echo planar imaging sequence with a sinusoidal motion-encoding gradient (MEG) in through-plane direction that was used to acquire three transversal image slices in a central slab through the cerebrum (Number of MEG cycles: 4, MEG amplitude: 35 mT/m, TR: 3.0 s, echo-time TE: 149 ms, field of view (FoV): 192 × 192 mm^2, matrix size: 128 × 128, slice thickness: 6 mm). The acquisition was repeated eighty times for each image slice with an alternating sign of motion sensitization, and an increasing delay between the onset of vibration and the motion-encoding.

A multifrequency vibration with a maximum amplitude of approximately 1 mm in parallel direction to the long axis of the magnet was fed into an actuator by a carbon-fiber piston. The resulting time-resolved wave images, $u(x,y,t)$ (with x and y as spatial coordinates), were Fourier-transformed for decomposition into complex wave images at driving frequency: $U(x,y,\omega)$, ($\omega/2\pi = 25$, 37.5, 50 and 62.5 Hz). Complex modulus images were obtained by wave inversion ($G(x,y,\omega) = -\rho\omega^2 U/\Delta U$, with Δ as the Laplace operator and ρ being the tissue's density of 1 kg/dm^3), spatially averaged within the segmented brain parenchyma and displayed on image slices (Fig. 2A). The resulting global modulus function was fitted by a least-square routine. A good match between model and multifrequency data was achieved by a combination of Voigt and Maxwell models given by the Zener model. However, the latter model incorporated an additional parameter – a second shear modulus – rendering the interpretation of viscoelastic constants rather cumbersome. The optimal tradeoff between physical significance and representation of the frequency dependency of our data was achieved by a two-parameter springpot model $G = \kappa(i\omega f)^{\alpha}$ that interpolated between springs and dashpots introducing a fractional element $\kappa = \mu^{1-\alpha}\eta^{\alpha}$, as also shown previously on healthy volunteers (Sack et al., 2009b). The

Table 1
Classification of 79 subjects included in our study with resulting viscoelastic parameters according to the springpot model.

	All subjects		Females		Males	
	MS	Controls	MS	Controls	MS	Controls
Number of individuals	45	34	23	17	22	17
Age						
Mean	37.84	37.00	37.8	34.5	37.9	39.5
Median	38	37	39	37	38	38
Range (in years)	21–51	18–59	22–50	18–55	21–51	21–59
CEL count						
Mean	0.6	–	0.9	–	0.3	–
SD	1.5		1.7		1.3	
Range	0–6		0–6		0–6	
CEL vol. (ml)						
Mean	33.8	–	55.1	–	11.5	–
SD	86.2		107.4		49.7	
Range	0–351		0–351		0–228	
T2 lesion vol. (ml)						
Mean	3870	–	3511	–	3906	–
SD	3312		3237		3457	
Range	25–11036		25–11036		61–9194	
T2 les. count						
Mean	17.7	–	18.9	–	16.5	–
SD	11.8		15.0		11.5	
Range	4–46		5–38		4–46	
BPF						
Mean	0.8579	–	0.8543	–	0.8628	–
SD	0.0241		0.0218		0.0269	
Range	0.7885–0.8939		0.8069–0.8939		0.7885–0.8939	
Mean structural Parameter α	0.266 (0.009)	0.266 (0.010)	0.267 (0.009)	0.267 (0.009)	0.266 (0.009)	0.265 (0.011)
Mean viscoelasticity μ (in Pa)	1865 (251)	2137 (314)	1875 (256)	2266 (307)	1853 (252)	2008 (271)
$\Delta\mu$	273 Pa		391 Pa		155 Pa	
	13%		17%		8%	
	$P<0.001$		$P<0.001$		$P=0.07$	

Tolerances given in brackets refer to the standard deviation. $\Delta\mu$ denotes age-adjusted differences in elasticity given by μ (MS) minus μ (controls). CEL = contrast enhancing T1-hyperintense lesions. BPF = brain parenchymal fraction.