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Quantification of perivascular spaces at 7 T: A potential MRI biomarker for epilepsy

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ABSTRACT

Purpose: 7 T (7T) magnetic resonance imaging (MRI) facilitates the visualization of the brain with resolution and contrast beyond what is available at conventional clinical field strengths, enabling improved detection and quantification of small structural features such as perivascular spaces (PVSs). The distribution of PVSs, detected *in vivo* at 7T, may act as a biomarker for the effects of epilepsy. In this work, we systematically quantify the PVSs in the brains of epilepsy patients and compare them to healthy controls.

Methods: T_2-weighted turbo spin echo images were obtained at 7T on 21 epilepsy patients and 17 healthy controls. For all subjects, PVSs were manually marked on Osirix image analysis software. Marked PVSs with diameter ≥ 0.5 mm were then mapped by hemisphere and lobe. The asymmetry index (*AI*) was calculated for each region and the maximum asymmetry index ($|AI_{max}|$) was reported for each subject. The asymmetry in epilepsy subjects was compared to that of controls, and the region with highest asymmetry was compared to the suspected seizure onset zone.

Results: There was a significant difference between the $|AI_{max}|$ in epilepsy subjects and in controls ($p = 0.016$). In 72% of patients, the region or lobe of the brain showing maximum PVS asymmetry was the same as the region containing the suspected seizure onset zone.

Conclusion: These findings suggest that epilepsy may be associated with significantly asymmetric distribution of PVSs in the brain. Furthermore, the region of maximal asymmetry of the PVSs may help provide localization or confirmation of the seizure onset zone.

1. Introduction

Ultra-high field magnetic resonance imaging (MRI) scanners, such as those operating at 7 T (7T), enable the visualization of the brain with very high resolution and contrast [1–3]. Positive identification of a lesion of epileptogenic potential on an MRI exam is an important component of determining the most promising treatment options for refractory epilepsy. The increased strength of the main magnetic field in 7T MRI generates a greater signal to noise ratio (SNR), which may be parlayed into enhanced conspicuity of abnormal structural features in epilepsy including those beyond the epileptogenic focus. There is increasing evidence that epilepsy is a complex network disease affecting brain functioning interictally and altering brain structure beyond the primary suspected seizure onset zone (SOZ) [4–8]. Subtle MRI features, now visible at ultra-high fields, may prove to be non-invasive biomarkers towards localizing and confirming the suspected SOZ, even when the features are not directly related to the epileptogenic focus.

Perivascular spaces (PVSs), also known as Virchow-Robin spaces [9], are small cerebrospinal fluid-filled areas between blood vessels and the pia mater, and can be visualized using high resolution T_2-weighted MRI sequences [10]. The brain lacks conventional lymphatic vessels and a growing body of research suggests that PVSs play an important role in a waste clearance, or glymphatic (glial + lymphatic), system [11–15]. Recent experiments indicate the involvement of PVSs in the recruitment of macrophages across the blood brain barrier [16,17]. Alteration in

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PVSs structure and appearance on high resolution MRI exams and may provide biomarkers for the altered macrophage activity associated with seizure onset [18].

Historically, PVSs have been visible on MRI only when grossly enlarged by diseases or disorders [19]. PVSs have been reported in previous investigations of epilepsy; however, the relationship between a patient's epilepsy and the presence of enlarged PVSs remains uncertain [20–23]. This has been true, in part, because even when enlarged, these spaces frequently remain below the threshold of *in vivo* detectability using MRI. Thus, in the past, smaller PVSs often had to be studied on biopsy specimens or post-mortem, and analysis may have been challenged by distortions of the physical dimensions of PVSs on *ex vivo* histological specimens. The enhanced contrast and resolution made possible by 7T MRI has enabled the noninvasive visualization and characterization of PVSs *in vivo* and high-resolution MRI experiments have begun to quantify PVSs as potential biomarkers for neurological disorders or diseases [24–26] as well as characterizing them in healthy volunteers [27]. The U.S. Food and Drug Administration has designated MR imaging scanners functioning at 8 T and below as non-significant risk1 and vendors are already building new 7T models that are slated for 510 K approval. In a recent study by our group, PVSs were observed in the brains of both healthy controls and in patients with focal epilepsy, and qualitative assessment suggested that the distributions of PVSs in the healthy controls were roughly symmetric while there was a trend towards asymmetry in the distributions of PVSs in vivo in epilepsy patients [28].

In this work, we performed a quantitative evaluation of the PVS distribution in epilepsy patients and healthy controls. In epilepsy patients with a localizable suspected SOZ, we also compared the asymmetric localization of PVSs to the suspected SOZ.

2. Methods

2.1. Subjects and recruitment

Institutional Review Board approval was obtained before commencing subject recruitment. Written informed consent was obtained from all subjects prior to scanning. Between July 2014 and October 2016, we recruited epilepsy patients and healthy volunteers, between 18 and 65 years of age at the time of scanning with no contraindications to 7T MRI. Epilepsy patients were recruited through their neurologist at the Epilepsy Center at Mount Sinai Hospital and had definite focal epilepsy identified through clinical signs and electroencephalogram (EEG) data. Patients were excluded if they had a traumatic brain injury or brain infection. All epilepsy patients were MRI-negative (no epileptogenic abnormalities identified) on previously-acquired diagnostic MRI scans. We scanned 21 subjects with focal epilepsy (13 males, 8 females, age 33 ± 11 years) and 17 healthy volunteers (11 males, 6 females, age 33 ± 9 years). The characteristics of both groups are reported in the supplemental material (Table e-1).

Axial T2-weighted turbo spin echo (T2 TSE) images were used for PVS tracing and quantification. Slices were defined along the plane of the anterior commissure-posterior commissure line and the acquisition volume extended from the top of the head to the cerebellum. These T2 TSE images were obtained as part of a comprehensive epilepsy 7T imaging protocol which also included T1-weighted and susceptibility weighted imaging sequences. T2 TSE sequence parameters were: TR = 6000 ms, TE = 69 ms, flip angle = 150°, Field of View = 202 × 185 mm2, matrix = 512 × 464, in-plane resolution 0.4 × 0.4 mm2, slice thickness = 2 mm, slices = 40, BW = 279 Hz/pixel, time = 6:50 min. Images were acquired on a 7T whole body MRI scanner (MAGNETOM 7T, Siemens Erlangen), equipped with a SC72CD gradient coil (Gmax = 70 mT/m and max slew rate = 200 T/m/s), using a single channel transmit and a 32-channel receive head coil (Nova Medical, Wilmington, MA).

2.2. Image processing

Image processing on the axial T2 TSE images was performed in Osirix (Pixmeo, Geneva) on bicubic interpolated images by a reader blinded to the status (epilepsy patient or control) of the subject. The location and cross-sectional diameter (d) of all PVSs in each slice were manually marked. To assist in registration and segmentation, 16 common and reproducible anatomical

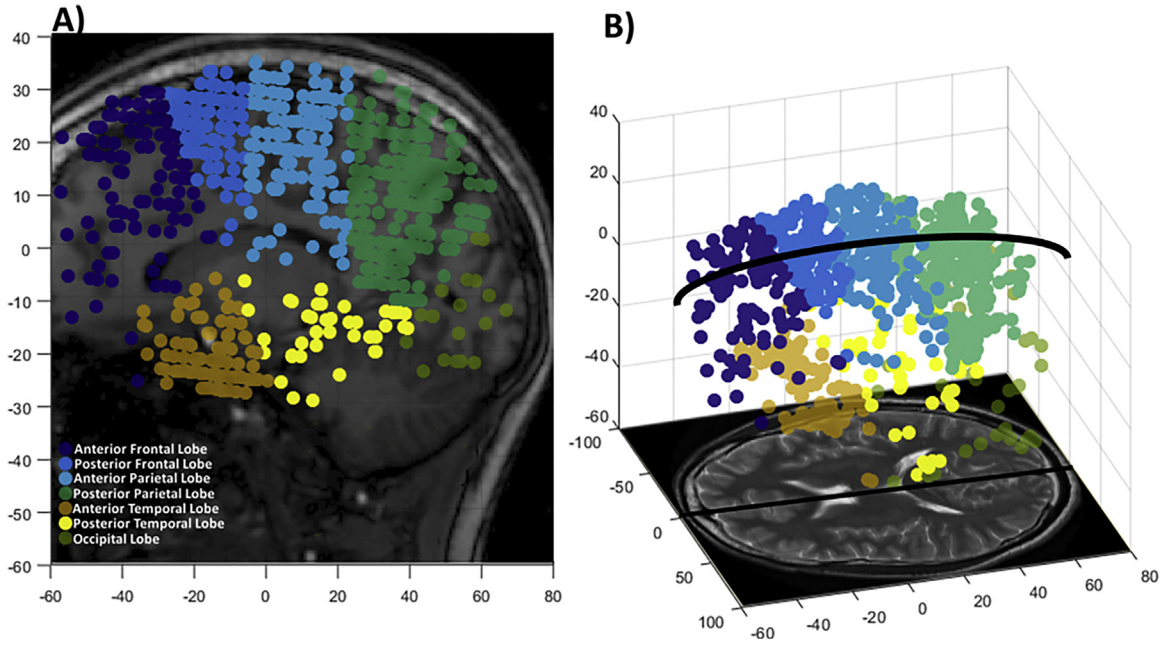

Fig. 1. Distribution of perivascular spaces (PVSs) in a healthy volunteer. Each PVS was marked, and its coordinates and diameter were recorded. The PVSs were binned into 7 different regions illustrated in A) a sagittal projection of all marked PVSs and B) and sagittal-oblique view showing the PVSs. Note: Circular markers are illustrative of the location and number of PVSs and not representative of PVS diameter.