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The Feasibility of Quantitative MRI of Perivascular Spaces at 7T

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Abstract

Background—Dilated brain perivascular spaces (PVSs) are found to be associated with many conditions, including aging, dementia, and Alzheimer's disease (AD). Conventionally, PVS assessment is mainly based on subjective observations of the number, size and shape of PVSs in MR images collected at clinical field strengths (3T). This study tests the feasibility of imaging and quantifying brain PVS with an ultrahigh 7T whole-body MRI scanner.

New Method—3D high resolution T₂-weighted brain images from healthy subjects (n=3) and AD patients (n=5) were acquired on a 7T whole-body MRI scanner. To automatically segment the small hyperintensive fluid-filling PVS structures, we also developed a quantitative program based on algorithms for spatial gradient, component connectivity, edge-detection, k-means clustering, etc, producing quantitative results of white matter PVS volume densities.

Results—The 3D maps of automatically segmented PVS show an apparent increase in PVS density in AD patients compared to age-matched healthy controls due to the PVS dilation (8.0 ± 2.1 v/v% in AD vs. 4.9 ± 1.3 % in controls, $p < 0.05$).

Comparison with Existing Method—We demonstrated that 7T provides sufficient SNR and resolution for quantitatively measuring PVSs in deep white matter that is challenging with clinical MRI systems (3T). Compared to the conventional visual counting and rating for the PVS assessment, the quantitation method we developed is automatic and objective.

Conclusions—Quantitative PVS MRI at 7T may serve as a non-invasive and endogenous imaging biomarker for diseases with PVS dilation.

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Graphical abstract

Keywords

perivascular space; MRI; perivascular drainage; Alzheimer's disease

1. Introduction

Perivascular spaces (PVSs), also called the Virchow-Robin spaces, surround small arteries and arterioles as they perforate the surface of the brain and extend into the brain tissue (Virchow 1851, Heier, Bauer et al. 1989). PVSs lie between the basement membrane around pericytes and the basement membrane at the surface of the glia limitans of the brain vessels. Although there are no perivascular spaces around arteries in the cortex (Zhang, Inman et al. 1990), there is a potential for dilatation of PVSs related to arteries in the cerebral white matter (Salzman, Osborn et al. 2005). Dilated PVSs are seen only in the white matter, basal ganglia, and brainstem (Salzman, Osborn et al. 2005).

The pathology of PVS dilation remains unclear. Studies have shown that enlarged PVS is associated with various neurological conditions, including aging, dementia, Alzheimer's disease (AD), traumatic brain injury, stroke, and other white-matter lesions (Miyakawa, Hattori et al. 1977, Braffman, Zimmerman et al. 1988, Fénelon, Gray et al. 1995, Poirier and Derouesné 1998, Achiron and Faibel 2002, Inglese, Bomsztyk et al. 2005, Patankar, Mitra et al. 2005, Zhu, Tzourio et al. 2010). Studies also suggested that PVS dilation may due to neuroinflammation (Rouhl, van Oostenbrugge et al. 2008, Wuerfel, Haertle et al. 2008), neurodegeneration (Kilsdonk, Steenwijk et al. 2014), demyelination (van Swieten, van den Hout et al. 1991, Patankar, Mitra et al. 2005), or cerebral small vessel disease (Doubal, MacLulich et al. 2010). Compared with other brain imaging features, PVS is relatively under-researched (Hernandez Mdel, Piper et al. 2013), likely due to the challenges associated with PVS quantitation.

Current assessments on brain PVSs mainly rely on the subjective observations of the number, size, and shape of PVSs on high-resolution and non-fluid-attenuated T₂-weighted MRI images at clinical field strengths (3T) (Doubal, MacLulich et al. 2010, Chen, Song et al. 2011). Since PVS structures in healthy subjects are typically < 2 mm, MRI with higher field strength is required to provide better signal to noise ratio (SNR) and therefore enable more quantitative information (Kwee and Kwee 2007). The emergence of high-field 7T whole-body MRI scanner can potentially increase our capability of quantitative PVS imaging. In this study, we aim to test the feasibility of quantitative PVS MRI at 7T. A

customized program for the automatic PVS segmentation will be developed to quantify PVS density in white matter and to compare PVS densities between AD and healthy subjects.

2. Materials and methods

T₂-weighted high resolution brain MR images were acquired on a 7T whole-body MR scanner (Siemens Medical Solutions, Erlangen, Germany) using a commercial 32 channel head coil. A 3D turbo spin echo (TSE) sequence based on SPACE (Sampling Perfection with Application optimized Contrasts by using different flip angle Evolutions) was used for the acquisition of 224 coronal slices covering the entire brain with TE/TR = 388/3000 ms, Echo Train Length = 274, slice thickness = 1 mm, matrix size = 426 × 448, in-plan-resolution = 0.42 × 0.42 mm², generalized autocalibrating partially parallel acquisitions (GRAPPA) R= 2, and acquisition time = ~7.5 min.

In this feasibility study, a total of eight subjects including five AD patients (78.2 ± 7.6 years old) and three age- and education-matched healthy subjects (69.3±18.0 years old, p=0.49) were studied. Informed consent was obtained before subjects were scanned under a protocol approved by the institutional review board. All participants were recruited from the Penn Memory Center, a specialty memory clinic at the University of Pennsylvania and the clinical core of the National Institute on Aging (NIA)-funded Alzheimer's Disease Center. Patients underwent extensive evaluation by a neurologist, psychiatrist, or gerontologist including physical and neurological exam, history from both patient and informant, and psychometric testing (Petersen 2004).

Using the MATLAB (R2012b, MathWorks, Natick, MA, USA) routine “imgradient” function, PVS were automatically segmented from voxels with high positive spatial gradient (magnitude heuristically set at >100 per pixel) in white matter regions to produce PVS images of the brain. For white matter segmentation, magnitude images were de-scalped by determining the largest object using MATLAB routine “bwconncomp”, B₁ field corrected, and then repeatedly (2×) segmented by using two rounds of three-level *k*-means clustering (Deoni, Rutt et al. 2007) algorithms to filter out cerebrospinal fluid (CSF) and gray matter sequentially. For B₁ correction, each magnitude image was divided by the relative B₁ field map, generated using only the central region of *k*-space obtained from the Fourier transform of the magnitude image. During the white matter segmentation procedure, hole-filling and edge-detection algorithms were applied to keep the PVS from being filtered out and to remove edge pixels with high spatial gradient, respectively.

Similar to our previous study (Cai, Shore et al. 2012), multi-slice PVS images were interpolated to create a 3D volume of isotropic voxels (0.4×0.4×0.4 mm³). The maximum intensity projection (MIP) of PVS images was then generated and color-coded using the cyan-hot colormap using ImageJ (U.S. National Institutes of Health, Bethesda, Maryland, USA). The total PVS volume, calculated from the count of segmented PVS pixels, was then divided by total volume of white matter to calculate the density of PVS in volume percentage (v/v%). Using visual counting as the standard, we calculated the false positive and false negative rates of our automatic segmentation method.

Two-tailed unpaired Student's t tests were performed to compare the PVS density between the healthy control and AD cohorts. The same test has also been applied to test the difference between the false positive and the false negative rates associated with the automatic segmentation of PVS pixels. Differences were considered to be significant at $p < 0.05$. Values are reported as mean $\pm$ standard deviation.

3. Results

In the high-resolution T₂-weighted brain MR images obtained from healthy elderly subjects at 7T, PVS were recognized as sparsely distributed hyperintense foci in white matter (Figure 1 a, c). While in AD patients, brain PVSs are mostly in the form of linear structures (Figure 1 b, d). Browsing all the brain slices from AD patients (Figure 2), we observed that PVSs appear to be fluid-filling micro-canals projecting from cortex to the lateral periventricular caps.

Figure 3 illustrates the major image processing procedures for the segmentation of brain PVSs. First of all, spatial gradient maps were generated as shown in Figure 3b. Pixels with high gradient magnitude in white matter were then segmented as PVSs (Figure 3c). The segmented PVSs were color-coded and overlaid onto the original brain image in Figure 3d. Figures 3 e,f depict the magnified images demonstrating the performance of PVS segmentation. Large white matter abnormalities with hyperintensity in T₂-weighted MR images can be filtered out using this algorithm as demonstrated in Figure 4.

The MIP images from multi-slice midbrain PVS images show an apparent increase of PVS density in AD patients compared to age-matched healthy controls (Figure 5a,b). The quantified white-matter PVS density in AD was significantly higher than controls (8.0 ± 2.1 v/v% vs. 4.9 ± 1.3 v/v%, $p < 0.05$) (Figure 5c). In addition, by comparing a representative PVS MIP image from an AD patient with a typical brain tractography generated by diffusion tensor MRI (Figure 5d), we observed that PVSs show the similar pattern and appears in parallel with white matter axonal tracts.

Compared to visual counting, using ten randomly selected brain slices from a subject, our automatic method yields an average of $10.4 \pm 5.0\%$ of false positives and $12.7 \pm 8.9\%$ of false negatives. There is no significant difference between the false positives and negatives of brain slices ($p = 0.50$).

4. Discussion

In this study, we demonstrated that PVS structures in white matter can be clearly observed on high-resolution T₂-weighted images collected using an ultra-high field 7T MRI system. Interestingly, comparing the PVS MIP images of AD patients with a typical brain tractography generated with MR diffusion tensor imaging, we found that PVS structures appears to be parallel with white matter axons, indicating PVSs along with their central arterioles travels along axons in white matter. We also reported a customized quantitative MRI method for the automatic segmentation of PVS in the brain. We then investigated the difference in quantified PVS densities between AD patients and age-matched healthy subjects. The PVS density is significantly higher in AD patients than healthy subjects due to

PVS dilation, consistent to previous observations (Doubal, MacLulich et al. 2010, Chen, Song et al. 2011).

Increased levels of the amyloid beta-peptide ($A\beta$), soluble and insoluble, are considered a major characteristic of AD due to the imbalance between $A\beta$ production and clearance. In terms of $A\beta$ clearance from the brain, there are several major mechanisms, including perivascular drainage, glial degradation, and transcytotic delivery (Weller, Subash et al. 2008, Saito and Ihara 2014). The central nervous system is devoid of conventional lymphatic vessels, which process various substances, such as wastes, fluid, proteins, and cells from tissues to lymph nodes. Instead, the lymphatic perivascular drainage system in the brain performs the main function performed by the systemic lymphatic vessels. Research shows that the perivascular drainage system contains immunocompetent cells (Bechmann, Priller et al. 2001) and apolipoprotein E (apoE) (Rolyan, Feike et al. 2011), the transporter of $A\beta$ peptides and proteins. Injection studies showed that tracers injected into grey matter diffuse through the extracellular spaces of the brain before they drain out of the brain along basement membranes within the walls of capillaries and arteries to lymph nodes (Weller, Subash et al. 2008, Weller, Galea et al. 2010).

Perivascular drainage system is driven by arterial pulsation for the clearance of interstitial fluid and solutes, including $A\beta$ peptides (Rolyan, Feike et al. 2011). Age-related changes in the walls of cerebral arteries including stiffening of those arteries and changes in the basement membranes appear to impair perivascular drainage. Deposition of amyloid in these pathways may also exacerbate the impaired drainage of $A\beta$ (Carare, Hawkes et al. 2013). It appears that such impairment of drainage may lead to the dilatation of perivascular spaces in the white matter (Roher, Kuo et al. 2003). Therefore, it is reasonable to believe that PVS dilation may reflect failure of $A\beta$ clearance, partially leading to $A\beta$ accumulation in AD brains. Our observations that AD patients have increased PVS volume density compared to healthy subjects may reflect impaired $A\beta$ clearance in AD patients.

Based on their punctuate or linear patterns, small PVS structures can be differentiated from clinical white matter hyperintensities (WMHs) detected with T_2 - weighted MRI. WMHs are associated with an increased risk of stroke, dementia, and death (DeBette and Markus 2010). However, WMHs are only detectable in 11-21% of adults aged ~64 years old (Ylikoski, Erkinjuntti et al. 1995, Garde, Mortensen et al. 2000); the severity of WMH varies widely in elderly adults (Brickman, Siedlecki et al. 2011). In addition, a fair portion of AD and mild cognitive impairment (MCI) subjects do not exhibit WMHs (Chen, Wang et al. 2006). Since dilated PVSs are detectable from all ages (Groeschel, Chong et al. 2006, Kim, Oh et al. 2007) and more elevated in the elderly (Barkhof 2004, Groeschel, Chong et al. 2006), PVS dilation is possibly an earlier biomarker for neurodegenerative diseases. As enlarged PVSs may co-exist with WMHs in AD, we demonstrated that large WMHs can be filtered out with our quantitative method that includes spatial-gradient and edge-detection algorithms (Figure 4).

Towards computational segmentation of enlarged PVS in brain, there are a few other methods being investigated (Hernandez Mdel, Piper et al. 2013), including a fully automatic method (Descombes, Kruggel et al. 2004) based on complex shape models and the marked

point process framework. Comparing the performance between our quantitation method and the previous published ones would be valuable, albeit, it is beyond the focus of this study on testing the feasibility of quantitative PVS MRI at 7T.

Most of the previous studies on developing computational methods for PVS validated their results against a visual rating scale or visual counting (Hernandez Mdel, Piper et al. 2013). There are multiple rating scales for enlarged PVS and white matter lesions, including the method published by Longstreth et al (Longstreth, Manolio et al. 1996), Breteler et al (Breteler, van Amerongen et al. 1994), van Swieten et al (van Swieten, Hijdra et al. 1990), Fazekas et al (Fazekas, Chawluk et al. 1987), Shimada et al (Shimada, Kawamoto et al. 1990), Wahlund et al (Wahlund, Agartz et al. 1990), and Victoroff et al. (Victoroff, Mack et al. 1994). These rating scales are based on visual observations of PVS images collected at clinical MRI systems (3T). For example, the Fazekas method uses a 0-3 scale for rating PVS: absence/caps or pencil-thin lining/smooth 'halo'/irregular PVS in deep white matter. With the high field 7T in this study, PVS are detectable in deep white matter from all subjects. Hence, some previous published rating scales may not work optimally for our datasets. As an alternative strategy, some previous studies validated their computational results with that from visual counting (Descombes, Kruggel et al. 2004, Wuerfel, Haertle et al. 2008). In this study, we also performed such comparisons to assess the false positive and negative rates associated with our automatic quantification method. Interestingly, we found that the averaged false positive and negative rates are close (~10%), indicating that our method is relatively balanced for assessing the overall PVS in the brain.

Note it is important to have consistent imaging setups and analyzing protocols for the automatic quantification of PVSs since factors such as image signal to noise ratio (SNR) may affect the quantification. Compared with clinical 3T, the ultra-high-field 7T being used in this study gains ~2 times in SNR, indicating higher resolution can be achieved with the same scanning time. On the other hand, compared with 7T, 3T offers a more homogeneous RF field homogeneity and uniform signal intensity that favor the PVS quantification based on spatial gradient. It remains to be tested if the quantitation method reported in this study may apply to clinical 3T.

There are a few limitations of this study. First, a limited numbers of subjects were scanned for this feasibility study. As age and gender are factors that may also affect PVS dilation (Zhu, Tzourio et al. 2010, Zhu, Dufouil et al. 2011), future large-scaled studies may help to evaluate the age and gender dependency of PVS dilation.

Also, in this study, we specifically quantified enlarged PVSs in white matter that are mainly associated with cerebral amyloid angiopathy (Roher, Kuo et al. 2003, Carare, Hawkes et al. 2013). Basal ganglia and brain stem may be excluded due to the white matter segmentation process utilized in our quantitation procedures. Our method may be modified to include these regions that typically contain enlarged PVSs (Salzman, Osborn et al. 2005).

In summary, we demonstrated that quantitative PVS MRI at 7T is feasible. Quantitative PVS MRI at 7T may help to characterize diseases that involve PVS dilation.

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Highlights

- Perivascular space dilation is associated with many conditions, including aging, dementia, and Alzheimer's disease (AD).
- We performed MRI of whole brain PVS at 7T. We also developed a computational method to quantify white matter PVS density.
- Our preliminary study confirmed that PVS density is higher in AD patients than healthy subjects.
- Quantitative PVS MRI at 7T may serve as an imaging biomarker for the A β clearance through PVS drainage system.

Figure 1.

The observation of brain perivascular spaces. A representative slice of T_2 -weighted high resolution brain MR image at 7T from a healthy subject (a) and an AD patient (b). (c) and (d) are magnified images from the regions of interest marked by yellow squares in (a) and (b) respectively. Red arrows show examples of PVSs with hyperintensity.

Figure 2.

The distribution of PVS in representative coronal slices (~10 mm gap) from an AD patient (zoomed in to show right-hemisphere). The majority of PVS appear to start from cortical brain and move towards lateral periventricular caps (red arrows).

Figure 3.

The illustration of brain PVS segmentation. (a) A representative brain slice from an AD patient. (b) Spatial gradient image. (c) Gradient image filtered with a white matter mask. (d) Segmented PVSs color-overlaid over the brain image. (e,f) Magnified partial raw brain image (e) and brain image with color-coded PVSs (f) demonstrate the performance of PVS segmentation.

Figure 4.

The segmentation method can avoid the selection of large areas of white matter hyperintensities. (a) A representative brain image from an AD patient with large regions of white matter hyperintensity (red arrows). (b) The brain image overlaid with color-coded PVS segments, showing large areas with white matter abnormalities are filtered out during PVS segmentation.

Figure 5.

Representative multi-slice MIP images of PVS generated from 25 continuous slices in the midbrain from a representative healthy subject (a) and an AD patient (b). (c) The summarized PVS densities among healthy subjects and AD patients (* $p < 0.05$). (d) Axonal fiber tracts typically detected using diffusion tensor MRI (Image cited from http://www.biomed.ee.ethz.ch/research/bioimaging/brain/diffusion_fiber_tracking).