Construction of Periventricular White Matter Hyperintensity Maps by Spatial Normalization of the Lateral Ventricles

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Abstract: Subcortical and periventricular white matter hyperintensities (WMHs) may have different associations with cognition and pathophysiology. The aim of the present study is to develop an automated method for construction of periventricular WMH maps that enables the analysis of between-group differences in WMH location and characteristics in the periventricular region without the requirement of prior boundary definition. To avoid influence of WMHs on spatial normalization, a reference image of the lateral ventricles was constructed based on images of 24 subjects. Construction was not biased to a single subject. WMHs were segmented by k-nearest neighbor-based classification of magnetic resonance inversion recovery and fluid attenuated inversion recovery images. Cerebrospinal fluid segmentations of individual subjects were nonrigidly mapped to the reference image of the lateral ventricles. The subject's WMHs were transformed to the reference space accordingly. Spatial normalization accuracy was validated using measures of overlap and of displacement relative to the boundary of the lateral ventricles. After spatial normalization, the boundaries of the lateral ventricles closely matched the reference image and in an area of ~1 cm around the lateral ventricles the relative displacement was less than 1 mm. To illustrate the method, it was applied to 61 patients with Type 2 diabetes and 26 control subjects, whereupon periventricular WMH maps were constructed and compared. The proposed method is particularly suited to analyze WMH distribution differences at the level of the lateral ventricles between large groups of patients. *Hum Brain Mapp* 30:2056–2062, 2009. © 2008 Wiley-Liss, Inc.

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INTRODUCTION

White matter hyperintensities (WMHs) are frequently observed in the elderly [de Leeuw et al., 2001]. Age and vascular risk factors are associated with WMH severity [Jeerakathil et al., 2004; Longstreth et al., 1996], and WMHs are associated with cognitive decline [de Groot et al., 2002]. Periventricular and subcortical WMHs may differ with respect to pathophysiology [Fazekas et al.,

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1993; Hogervorst et al., 2002; O'Sullivan et al., 2002] and have different associations with cognitive function [de Groot et al., 2002], emotion [de Groot et al., 2000], and brain atrophy [Wen et al., 2006]. The use of quantitative volumetric methods may resolve some of the inconsistencies, but it has appeared difficult to reliably and consistently differentiate between periventricular and subcortical WMHs on magnetic resonance (MR) images [DeCarli et al., 2005]. Therefore, the analysis of differences in WMH distribution between groups would benefit from a method that does not require a priori differentiation between periventricular and subcortical WMHs.

The aim of the present study was to develop and validate an automated method for the creation of periventricular WMH maps. The proposed WMH mapping does not rely on a categorization into periventricular and subcortical WMHs, but uses spatial normalization to a reference image of the lateral ventricles to create WMH distributions. To illustrate its use, we have applied our algorithm to patients with Type 2 diabetes and to control participants.

MATERIALS AND METHODS

Participants and Imaging Protocol

A random sample of 26 control participants (65.8 ± 5.5 years) and 61 patients with Type 2 diabetes (67.8 ± 5.2 years) from the study population of the Utrecht Diabetic Encephalopathy Study (UDES) was selected to demonstrate the application of our method. UDES is a cross-sectional, population-based study on determinants of impaired cognition in diabetes. The design and detailed data on cognition and brain MRI of the UDES population have been reported previously [Jongen et al., 2007; Manschot et al., 2006]. Twenty-four MR fluid attenuated inversion recovery (FLAIR) images (same protocol as described below), from patients with vascular disease or vascular risk factors (average age 64.3 ± 9.2 years) included in a different study cohort, were used for the construction of a reference image of the lateral ventricles. Axial T1-weighted (T1), inversion recovery (IR), T2-weighted (T2), proton density (PD), and FLAIR MR images were acquired for all participants. Thirty-eight contiguous slices with a slice thickness of 4 mm and an in-plane resolution of 0.9 mm (field of view 230×230 mm; scan matrix 256×256) were acquired on a Philips Gyroscan ACS-NT 15 whole body system (1.5 Tesla, Philips Medical Systems, Best, The Netherlands). Scan parameters were T1: 234/2 ms (repetition/echo time); IR: 2,919/410/22 ms (repetition/inversion/echo time); T2: 2,200/100 ms (repetition/echo time); PD: 2,200/11 ms (repetition/echo time); and FLAIR: 6,000/2,000/100 ms (repetition/inversion/echo time).

The medical ethics committee of the University Medical Center Utrecht approved the study, and each participant signed an informed consent form.

Construction of a Reference Image of the Lateral Ventricles

To create maps of periventricular WMHs, spatial normalization of all images to a reference is necessary. In particular, accurate matching of the boundaries of the lateral ventricles is important. Fine-scale deformations are required to accommodate the lateral ventricle shape variation among subjects. WMH presence may influence the spatial normalization when using the full original MR images. Therefore, we created a reference image containing only the lateral ventricles. Lateral ventricles were manually segmented from 24 MR FLAIR images (see participants section) and interpolated to isotropic voxels using shape-based interpolation [Herman et al., 1992]. The reference image was constructed using an iterative approach to improve the robustness of the resulting reference lateral ventricles image and to reduce bias to a single image. All spatial normalizations were performed using normalized mutual information as registration criterion [Maes et al., 1997; Pluim et al., 2003; Viola and Wells, 1997]. First, a reference space was defined by determining the average lateral ventricles position and size using a subset of eight images. Then, all images were mapped to this reference space using linear transformations and the mapped images were averaged. This average image was used as the reference for nonrigid spatial normalization. The 24 images were mapped to the reference using a B-spline based algorithm [Rueckert et al., 1999] with a coarse control point spacing (32 voxels) to normalize global shape differences. The normalized images were summed and a threshold of eight was applied to create a binary reference image of the lateral ventricles including shape variations present in at least a third of the individuals.

WMH Map Construction

WMH maps were constructed by mapping a segmentation of each subject's CSF to the reference image of the lateral ventricles and then applying that transformation to the subject's segmented WMHs. First, inhomogeneities in the T1, T2, PD, and FLAIR images were automatically corrected [Likar et al., 2001], and for each subject the images were linearly aligned to the FLAIR image. Then, CSF was segmented using k-means clustering of the T1, T2, PD, IR, and FLAIR images. The CSF segmentations were interpolated to isotropic voxels. Using the entire CSF avoids the need of additional (manual) steps to consistently segment the lateral ventricles. Linear mapping of the CSF to the reference image of the lateral ventricles was followed by a nonrigid B-spline based mapping [Rueckert et al., 1999]. The deformations in each iteration were refined by halving the control point spacing from 64 voxels to a final resolution of 4 voxels.

WMHs were segmented using a probabilistic k-nearest neighbor-based classification of the FLAIR and IR images. This algorithm was designed for the same MR scan proto-

col as used in the present study. It has been extensively described and evaluated before [Anbeek et al., 2005]. To obtain a binary lesion map for each subject, a threshold of 0.5 was applied to the WMH probability images and single voxels were removed. The WMH segmentations were checked visually in all subjects. In 8 of the 87 subjects, a manual correction of the WMH segmentation was performed to eliminate voxels erroneously segmented as WMH because of motion-induced artefacts in six and noise and remaining intensity inhomogeneities in two of the patients' FLAIR images. On average, the procedure for checking and editing the segmentations took no more than 1 min per subject. WMH volumes were calculated by summing over the segmented images and multiplying with the voxel dimensions. The segmented WMHs were mapped to the lateral ventricles reference image by applying the transformations that registered the CSF segmentations to the reference image. Nearest-neighbor interpolation was used during this transformation. The transformed WMHs were summed to create WMH maps. Differences between WMH maps were examined voxel-by-voxel using the Lieberman quasi-exact test [Rorden et al., 2007; Seneta and Phipps, 2001].

Validation

Validation comprised three different aspects of the method. First, although a ground truth for spatial normalization of different subjects does not exist, an indication of the accuracy can be obtained by measuring the overlap between the mapped images. Because whole CSF segmentations of individual subjects were mapped to a constructed reference image that contained only ventricular CSF, we measured overlap with the constructed reference lateral ventricles and overlap with the background separately. The fraction of overlap of a subject's CSF with the reference lateral ventricles provides no information about overlap of the subject's lateral ventricles with the background. Therefore, overlap with the background was measured in four consecutive dilations of one voxel around the lateral ventricles. Although this measure should approach zero, some overlap will result from CSF close to and connected to the lateral ventricles.

Second, mapping accuracy may have been affected by the fact that whole CSF segmentations were mapped to a reference image containing only ventricular CSF. To investigate the influence, lateral ventricles were manually separated in three randomly selected subjects. Mapping accuracy was measured as described above and compared to the accuracy obtained when using whole CSF segmentations in these subjects.

Lastly, the assumption underlying our method is that the deformation that maps the lateral ventricles also maps the white matter around the lateral ventricles, and that the deformation of the tissue around the lateral ventricles should be similar to that of the boundary of the lateral ventricles. Therefore, we calculated, for every voxel, the

difference between its transformation and that of the closest voxel on the boundary of the lateral ventricles. The length of the resulting difference vector, the transformation difference, is an indication of the validity of our assumption of rigid coregistration for that voxel.

RESULTS

Validation

Figure 1 shows the overlap of the spatially normalized CSF segmentations with the reference lateral ventricles and the background. Maximal overlap of ventricles and minimal overlap with background were achieved at the smallest control point spacing, and the boundaries of the individual lateral ventricles were mapped within one voxel from the boundaries of the reference. The peak in the amount of overlap with the background, at a control point spacing of 32 voxels in Dilation 1 and to a smaller extent in Dilation 2, indicates a small initial dilation of approximately one voxel that is corrected in subsequent normalization steps. Results were similar for control participants and patients with Type 2 diabetes. Furthermore, results for the spatial normalization of the three manually separated lateral ventricles were similar to the normalization of the CSF of these subjects.

Figure 2 shows the averages of the difference in transformation of each voxel and the closest voxel on the lateral ventricles boundary. This difference was less than 1 mm in an area that extends to over 10 mm almost everywhere around the lateral ventricles.

WMH Maps

To illustrate the current method, maps of WMH distribution for a sample of control subjects and patients with Type 2 diabetes participating in the UDES are shown in Figure 3. This figure shows that frontal capping is the most common WMH type in both groups. For the majority of voxels, the relative WMH load was larger in the diabetes group. However, the prevalence of WMH for individual voxels in white matter areas slightly away from the lateral ventricles was low (<12.5%, Fig. 3). Voxel-by-voxel analysis of differences between the distributions of WMH in control participants and patients with Type 2 diabetes using the Lieberman quasi-exact test showed subtle differences in the frequency of frontal capping and WMHs along the body of the lateral ventricles, although these differences were no longer significant after correcting the α level for the number of distinct patient-lesion patterns ($n = 12.921$; α -corrected = $3.87E-06$) (Fig. 4).

DISCUSSION

The presented method to map periventricular WMHs enables a voxel-based analysis of group differences in WMH frequency and characteristics in the area around the

Figure 1.

Median overlap of CSF segmentations of individual subjects with the reference image of the lateral ventricles (Reference) and with the consecutive dilations of one voxel around the reference (Dilation 1 to 4) is shown at the different control point spacings (CPS) during the spatial normalization. Control participants are shown in white and patients with Type 2 diabetes are shown in gray. Error bars represent the interquartile range.

lateral ventricles. We applied this method to a sample of patients with Type 2 diabetes and control participants. This demonstrates the ability of our method to create periventricular WMH distribution maps of clinical samples.

Our WMH mapping method is the first that is based on the spatial normalization of the lateral ventricles to a reference image of the lateral ventricles. The advantage of this

approach is that the spatial normalization is not affected by the presence of WMHs. Previous studies on WMH patterns have registered whole brain T1-weighted [Wen and Sachdev, 2004a,b] or PD-weighted [Enzinger et al., 2006; Taylor et al., 2003] images to stereotaxic space. The WMH probability map for 477 healthy volunteers aged 60–64 years [Wen and Sachdev, 2004a] showed similar WMH

Figure 2.

Average of the difference between the transformation of each voxel and the transformation of the closest point on the boundary of the lateral ventricles calculated over all 87 participants. Colors indicate the average transformation difference: dark blue

0–0.5 mm, light blue 0.5–1 mm, green 1–1.5 mm, yellow 1.5–2 mm, orange 2–2.5 mm, red > 2.5 mm; bar length is 10 mm; slices shown are 5.4-mm apart. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 3.

White matter hyperintensity maps for control participants (top row) and for patients with Type 2 diabetes (bottom row). Colors indicate the percentage of subjects with white matter hyperintensity at that position: black 0%, dark blue 0–12.5%, green

12.5–25%, yellow 25–37.5%, orange 37.5–50%, red 50–62.5%; slices shown are 5.4-mm apart. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

patterns and prevalence as observed in the control participants of this study. Furthermore, studies directed at stroke [Wen and Sachdev, 2004b] and late-life depression [Taylor et al., 2003] showed WMH load differences between controls and stroke patients varying with brain region as well as different age-related WMH clusters in control and depressed subjects, which illustrates the importance of examining lesion topography.

WMH maps allow detailed analysis of confluent WMHs, smooth halos, and lining and capping of the lateral ventricles. It should be noted, however, that for the quantitative analysis of punctate WMHs that usually appear dis-

persed in the subcortical white matter at some distance from the ventricles and have no preferred locations, the construction of WMH maps has its limitations. First, at any given position in the subcortical white matter that is not in the direct vicinity of the ventricles the prevalence of WMHs is relatively low. This limits the statistical power to detect between-group differences in these regions and therefore, large sample sizes will be required for any WMH mapping strategy directed at deep WMH. Second, spatial normalization accuracy decreases with increasing distance from the lateral ventricles because no other structures are present in the reference image. Should mapping

Figure 4.

Differences in white matter hyperintensity pattern between control participants and patients with Type 2 diabetes on the same slices as shown in Figure 3. Colors indicate *P*-values obtained with the Lieberman quasi-exact test: red $P \leq 0.01$, orange

$0.01 < P \leq 0.05$, yellow $0.05 < P \leq 0.1$, green $0.1 < P \leq 0.2$; slices shown are 5.4-mm apart. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of deep of punctate WMHs be required, our approach could be extended by including a template of the outer brain boundary.

Lateral ventricles are rather variable in size. Spatial normalization to an average lateral ventricles image may therefore involve extension or shrinking of a subject's lateral ventricles. Differences between the transformation of voxels in the area surrounding the lateral ventricles and the boundary of the lateral ventricles were small and of subvoxel magnitude for all significant voxels. Furthermore, overlap between individual lateral ventricles and the reference image was good. This indicates good accuracy of mapping in the lateral ventricle area and therefore, bias resulting from differences in lateral ventricle volume is unlikely. Statistical analysis of differences in WMH maps has currently been performed using the Lieberman quasi-exact test, but other techniques, such as permutation-based nonparametric statistics [Enzinger et al., 2006], may also be used for analysis of the WMH maps created by our method. The differences between the WMH frequencies of patients with Type 2 diabetes and control participants were no longer significant after multiple comparison correction. This is mainly due to the, in general, small size of the lesions, the large differences in lesion load between individuals, and the relatively small differences in WMH volume between these groups [Jongen et al., 2007].

The advantages of the presented automated technique are most evident for large study populations. The proposed technique allows an efficient construction of WMH maps, not biased by WMH load, and is applicable to large numbers of scans. In large samples, this allows for quantitative assessment of hyperintensity distribution, which is of obvious benefit for studies into the causes and consequences of WMHs. The application of this approach to patients with Type 2 diabetes and control subjects indeed shows that the use of WMH maps provides insight into the distribution of WMHs and allows between-group comparison of WMH distribution and volume. WMH mapping will be a valuable tool for future studies into white matter disease.

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