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Intensity ratio to improve black hole assessment in multiple sclerosis

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ABSTRACT

Background: Improved imaging methods are critical to assess neurodegeneration and remyelination in multiple sclerosis. Chronic hypointensities observed on T1-weighted brain MRI, "persistent black holes," reflect severe focal tissue damage. Present measures consist of determining persistent black holes numbers and volumes, but do not quantitate severity of individual lesions.

Objective: Develop a method to differentiate black and gray holes and estimate the severity of individual multiple sclerosis lesions using standard magnetic resonance imaging.

Methods: 38 multiple sclerosis patients contributed images. Intensities of lesions on T1-weighted scans were assessed relative to cerebrospinal fluid intensity using commercial software. Magnetization transfer imaging, diffusion tensor imaging and clinical testing were performed to assess associations with T1w intensity-based measures.

Results: Intensity-based assessments of T1w hypointensities were reproducible and achieved > 90% concordance with expert rater determinations of "black" and "gray" holes. Intensity ratio values correlated with magnetization transfer ratios (R = 0.473) and diffusion tensor imaging metrics (R values ranging from 0.283 to −0.531) that have been associated with demyelination and axon loss. Intensity ratio values incorporated into T1w hypointensity volumes correlated with clinical measures of cognition.

Conclusions: This method of determining the degree of hypointensity within multiple sclerosis lesions can add information to conventional imaging.

1. Introduction

Hypointense areas of white matter (WM) on T1-weighted (T1w) magnetic resonance images (MRIs) persisting for at least 12 months are markers of focal tissue injury in MS known as "persistent black holes" (PBH) (Riva et al., 2009). The pathologic correlate of a PBH is severe axon loss and matrix destruction (Bitsch et al., 2000; van Walderveen et al., 1998, 2001). Some investigators label less hypointense BHs as "gray holes" (GHs) to reflect a lower degree of axonal loss. Acute contrast enhancing lesions (CELs) may also display decreased intensity on the concurrent non-contrasted T1w images. These "acute black holes" are due primarily to inflammation and edema, as most resolve within months of contrast resolution (Naismith et al., 2010).

PBHs have relevance to clinical outcomes and disease progression (Truyen et al., 1996). Several studies have shown that PBH numbers or volumes correlate with worse clinical test scores (van Walderveen et al., 2001; Truyen et al., 1996; van Waesberghe et al., 1999). MS lesion "burden" has often been reported as the sum of lesion volumes, but the degree of tissue destruction may vary between lesions (Brex et al., 2002; O'Riordan et al., 1998). A quantitative method to define the degree of hypointensity in individual MS lesions could improve patient monitoring, allow for better correlations to clinical measures, and may prove useful as an outcome measure in clinical trials of potential reparative therapies (van Waesberghe et al., 1999).

Our goal was to develop a simple and objective method to identify and distinguish PBHs and PGHs and to estimate the severity of the underlying tissue damage in these lesions based on degree of T1w hypointensity.

2. Methods

2.1. Subject population and clinical testing

Human Studies Committee approval was obtained. All 38 MS

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subjects contributing data gave informed consent. The following clinical tests, all validated for MS, were performed at times of imaging: Expanded disability status scale (EDSS), 25 foot timed walk (25FTW), nine-hole peg test (9HPT) and the 3- and 2-second versions of the Paced Auditory Serial Addition Test (PASAT).

2.2. Image acquisition

Human Studies Committee approval was obtained and all subjects gave informed consent. Patients were imaged on a 3.0 T Siemens Trio scanner (Siemens, Erlangen, Germany). T1w was acquired using the following parameters: Repetition Time (TR) = 600 ms; Echo Time (TE) = 9 ms; slice thickness = 2 mm; in-plane resolution = 1 × 1 mm^3; total acquisition time = 4 min. T2w was acquired using the following parameters: TR = 7500 ms; TE = 210 ms; TI = 2500 ms; slice thickness = 1 mm; in-plane resolution = 1 × 1 mm^3; total acquisition time = 10 min. Magnetization Transfer (MT) images were acquired with the following parameters: TR = 38 ms; TE = 11 ms; Flip Angle = 15 degrees; slice thickness = 3 mm; in-plane resolution = 1 × 1 mm^3; total acquisition time = 8 min. Magnetization Transfer Ratio (MTR) maps were calculated pixel-by-pixel using the equation: $MTR = (S_{off}–S_{on})/S_{off} \times 100$, where S_{on} and S_{off} were signal intensities with and without saturation pulse. Axial Diffusion Weight images (DWI) covering the whole brain were acquired using a multi-b value diffusion weighting scheme (99 directions, maximum b-value 1500 s/mm^2) and the following parameters: TR = 10,000 ms; TE = 120 ms; slice thickness = 2 mm; in-plane resolution = 2 × 2 mm^3; total acquisition time = 16 min. Eddy current and motion artifacts of DWI were corrected, then susceptibility-induced off-resonance field was estimated and corrected. Whole brain voxel-wise DTI analyses were performed on DWI images by the in-house software developed using MATLAB (Wang et al., 2015).

2.3. MS lesion classification

Areas of hypointensity on pre-gadolinium T1w images that met the definition of “persistent” by being present for at least 12 months were identified in the MS subjects. Amira 6.0.1 visualization and analysis software (FEI, Hillsboro, OR) was used to provide quantitative intensity values for each hypointense lesion on each scan, with lower values reflecting darker voxels. Lesion intensity assessment requires consideration of baseline intensity for each scan, to control for scan-to-scan variations. As cerebrospinal fluid (CSF) is not changed by MS pathology, CSF was used to provide a baseline for each individual scan.

Selection of voxels representative of CSF intensity consisted of starting inferiorly and moving superiorly on axial slices, until the initial appearance of both anterior horns of the lateral ventricles. The axial slice 15 mm superior to this was located (typically where the anterior horns of the lateral ventricles were widest), and was used to determine the median “Baseline Intensity” for CSF for that scan (Fig. 1). After initially testing 1, 5, 20 and 40 voxels, using the median of 20 ventricular voxels was found to be representative of CSF and a feasible number to select, time-wise.

To ensure exclusion of any voxels containing choroid plexus or partial volume effect from ventricle edge, the 20 lowest intensity, not necessarily contiguous, voxels within the CSF of the right and left anterior lateral ventricles at this level were selected. Voxels within one voxel distance from the ventricle edge were excluded to avoid voxels within periventricular lesions. In the rare situation of the baseline slice not containing 20 voxels unaffected by choroid plexus, the adjacent inferior axial image was also used to ensure a sample of 20 lowest intensity voxels within CSF.

For each MS lesion, the “Lesion Intensity (LI)” was defined as the median of the 5 lowest intensity voxels on all T1w slices where the lesion was visible (Fig. 2). This number of voxels was chosen to be representative of the lowest intensity voxels. It took less than 1 min to identify the median of the 5 lowest intensity voxels. Moreover, small lesions of few voxels could usually be accommodated using 5 voxels.

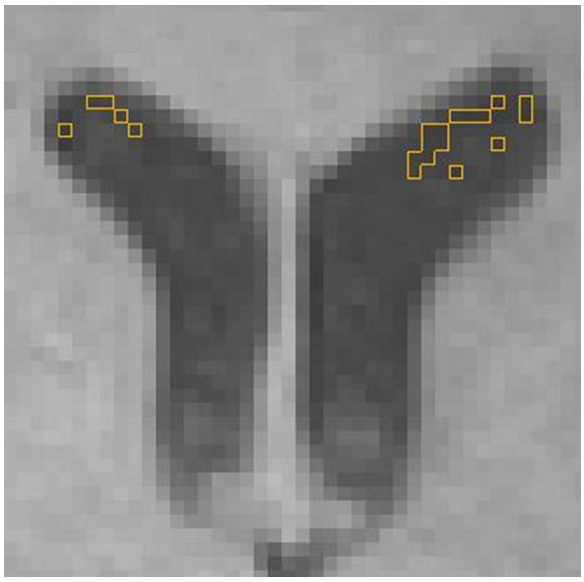

Fig. 1. Illustration of determining “baseline intensity.” The median value for the 20 voxels of lowest intensity (identified by yellow lines) within the lateral ventricles at an axial slice 15 mm superior to the initial appearance of the lateral ventricles determined BI. Only voxels that were more than one voxel away from the ventricle edge were used. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

This value was divided by the BI for that scan to obtain an “Intensity Ratio (IR)” for the lesion relative to CSF:

$$\mathbf{IR} = \frac{\mathbf{LI}}{\mathbf{BI}}$$

Lesions were selected from throughout the brain. The only exclusion criterion for size was that a lesion have a minimum of 5 voxels, for intensity determinations. Lesion volumes were determined based on the voxel dimensions and the total number of voxels within each lesion ROI. Total WM volumes for each patient were generated using the SIENAX tool.

A single rater identified a region of interest (ROI) for a total of 181 chronic T1w hypointense MS lesions, 189 non-hypointense T2w hyperintense lesions and 113 normal appearing white matter (NAWM) areas, and determined IR for each hypointense lesion. Three of the 38 subjects had no PBH or PGH lesions.

2.4. Tests of reproducibility

For intra-rater reproducibility determination, one examiner used the method on a single scan from each of 6 MS (2 RRMS, 2 SPMS, 2 PPMS) subjects. At two time-points one week apart, BI was determined and LI was determined for 20 lesions on the 6 scans.

For inter-rater reliability, another rater replicated the instruction protocol on 5 scans with 25 lesions from 5 subjects. We determined how potential differences in perceiving the initial appearance of the anterior lateral ventricles might affect the baseline slice chosen and the results. Thus, BI was determined on the 2 slices immediately adjacent to the baseline slice (1 inferior slice, 1 superior slice) for all 38 subjects in the study. Bland-Altman plots were used to compare the BI of the baseline slice to the BI of each of the adjacent slices (Bland and Altman, 1986, 1999).

While at least 12 months was required to designate lesions as PBH, PGH or non-hole T2w lesions (NBH), some patients with multiple scans had intervals between consecutive scans of as few as 3 weeks, ranging to 54 weeks, with an average interval of 9.2 months. Reproducibility across these scans was assessed to determine whether scan-to-scan