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Original Article

Bullseye's representation of cerebral white matter hyperintensities

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ABSTRACT

Background and purpose. – Visual rating scales have limited capacities to depict the regional distribution of cerebral white matter hyperintensities (WMH). We present a regional-zonal volumetric analysis alongside a visualization tool to compare and deconstruct visual rating scales.
Materials and methods. – 3D T1-weighted, T2-weighted spin-echo and FLAIR images were acquired on a 3 T system, from 82 elderly participants in a population-based study. Images were automatically segmented for WMH. Lobar boundaries and distance to ventricular surface were used to define white matter regions. Regional-zonal WMH loads were displayed using bullseye plots. Four raters assessed all images applying three scales. Correlations between visual scales and regional WMH as well as inter and intra-rater variability were assessed. A multinomial ordinal regression model was used to predict scores based on regional volumes and global WMH burdens.
Results. – On average, the bullseye plot depicted a right-left symmetry in the distribution and concentration of damage in the periventricular zone, especially in frontal regions. WMH loads correlated well with the average visual rating scores (e.g. Kendall's tau [Volume, Scheltens] = 0.59 CI = [0.53 0.62]). Local correlations allowed comparison of loading patterns between scales and between raters. Regional measurements had more predictive power than global WMH burden (e.g. frontal caps prediction with local features: ICC = 0.67 CI = [0.53 0.77], global volume = 0.50 CI = [0.32 0.65], intra-rater = 0.44 CI = [0.23 0.60]).
Conclusion. – Regional-zonal representation of WMH burden highlights similarities and differences between visual rating scales and raters. The bullseye infographic tool provides a simple visual representation of regional lesion load that can be used for rater calibration and training.

Abbreviations: BG, basal ganglia; CI, confidence Interval; FLAIR, fluid attenuated inversion recovery; ICC, intraclass correlation; IQR, interquartile range; IT, infratentorial regions; JC, juxtacortical; K_τ, Kendall's tau; MR, magnetic resonance; PV, periventricular; SD, standard deviation; WMH, white matter hyperintensities.

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Introduction

White manner hyperintensities (WMH) in the cerebral white matter on T2-weighted spin echo and FLAIR magnetic resonance (MR) images are commonly part of the spectrum of imaging findings in cerebral small vessel disease and normal aging. However, their precise etiology is still a subject of debate and likely multifactorial [1]. Histological findings in WMH include thinning or disruption of the myelin sheath, axonal loss and gliosis [2]. Close to the ventricles, increased water content in the extracellular spaces has been reported when the ependymal lining is damaged [2]. WMH are very prevalent and are associated with various clinical symptoms such as a decreased processing speed, altered gait, incontinence and depression [3]. Studies have demonstrated a link between the burden of WMH and cortical blood flow [4] as well as with cardiovascular risk factors such as hypertension [5] or diabetes [6]. In addition, the extent of WMH was recently shown to be an independent risk factor for periprocedural stroke in patients undergoing stenting of a carotid artery stenosis [7] and an indicator of prognostic outcome after ischemic stroke [8].

The majority of studies relating clinical findings with the burden of WMH have used visual rating scales. Such scales provide a semi-quantitative way to describe the burden and distribution of WMH in the brain without manual lesion delineation, a task that is cumbersome, time consuming and subject to inter- and intra-rater variability. A number of visual rating scales with various levels of complexity have been developed [9–14]. Compared to automatic global volumetric assessments, they remain popular especially when incorporating local burden information. The spatial information of WMH distribution, incorporated in the rating scales ranges from whole brain assessment (Manolio [9], simplified Fazekas [15]) to specific lobar lesion burden (Scheltens [16]). While spatial determination allows for differential clinical and pathophysiological explanatory pathways, the definition of the regional borders can be ambiguous and varies from one scale to another. With respect to the separation of periventricular and deep WMH, most methods are based on absolute distance to the ventricles and do not take into account additional age-related changes such as ventricular expansion [17]. Finally, few scales have been specifically defined for the longitudinal assessment of the WMH burden, whereas most are only intended to be applied cross-sectionally [18].

With the recent advances in the automated identification of WMH, lesion volume has been shown to be associated with clinical outcomes, sometimes allowing for a better differentiation between clinical subgroups than visual rating scales [19]. The correlation between visual scales is considerable [20] but heterogeneity between visual rating systems has also been put forward as a potential explanation for contradictory findings [21]. Methods involving the creation of voxelwise lesion maps have been proposed to investigate WMH spatial distribution across populations [22] or in relation to specific risk factors [23]. These strategies suffer however from a high noise level due to the sparsity of the lesions. In contrast, region based strategies generally consider a separation between zones based on the absolute distance to the ventricles and thus cannot account for the variability in atrophy across subjects [24].

This work presents a novel approach to analyze regional-zonal WMH burden. We used it to deconstruct the spatial loading of visual rating scales and determine in an objective manner similarities and discrepancies between such scales, but also to formally address interobserver variability. The bullseye infographic provides a simple visual tool to train raters or display disease effects.

Material and methods

Cohort imaging study

We used an imaging data subset of the SABRE study (UK Clinical Trials Gateway DRN 841, local ethical approval by Fulham REC ref: 14/LO/0108) comprising the first 84 consecutive participants a tri-ethnic population based study [mean (SD) age = 71.4 (5.7) years; 61.7% male]. This cohort study aims to assess the risks of diabetes and cardiovascular disease, including small vessel disease in the brain, in European, Indian Asian and African Caribbean men and women [25]. Surviving participants of 4972 individuals recruited in 1988–1990 from general practices in the London boroughs of Southall and Brent were all invited for this third round of investigations. Spouses of the participants were also invited to take part. Participants were excluded from the study on clinical ground if they were at a stage of terminal illness or if severe comorbidities affected their attendance and/or participation to the investigations.

All participants gave informed written consent and underwent MRI according to a standard protocol on a Philips Achieva 3.0-Tesla scanner. Imaging included the following pulse-sequences:

- 3D sagittal T1-weighted FFE: TR 6.9 ms; TE 3.1 ms; voxel size $1.0 \times 1.0 \times 1.0$ mm^3;
- 3D sagittal T2-weighted FLAIR: TR 4800 ms; TI 1650 ms; TE 125 ms; voxel size $1.0 \times 1.0 \times 1.0$ mm^3;
- 3D sagittal T2-weighted TSE: TR 2500 ms TE 222 ms; voxel size $1.0 \times 1.0 \times 1.0$ mm^3.

All images were reviewed for incidental pathology and scan quality. Two participants' scans were discarded from the analysis due to severe motion artifacts.

Regional-zonal WMH burden quantification

WMH were automatically segmented using a previously developed algorithm [26]. In brief, this iterative model selection framework uses simultaneously the three MRI pulse sequences to model both normal and outlier observations as a multivariate Gaussian mixture informed by anatomical atlases and constrained to ensure neighborhood consistency. Once the data model is fitted, the actual lesion segmentation is performed by voxelwise comparison to normal appearing white matter.

A patient-specific coordinate frame was created to localize the WMH burden. This coordinate frame considered radially the relative distance between the ventricles and the cortical grey matter discretized into four equidistant layers. As described by Yezzi and Prince [27], this distance was derived from the solution to the Laplace equation applied here between the ventricular surface and the white matter/cortical gray matter interface. By design, such distance is made agnostic to the level of observed atrophy. A division of the white matter into lobes provided the angular information. The division into lobes was based on the Euclidean distance maps resulting from the cortical parcellation obtained through the application of a label-fusion method [28]. Frontal, parietal, temporal and occipital lobes were delineated on the right and left side, while the basal ganglia, thalami and infratentorial regions from both sides were combined (BGIT region). By combining the 4 layers and the 9 lobar zones, 36 regions were defined in total.

The proportion of each region affected by WMH was used as a local feature and is referred to as regional WMH load hereafter. Once the local quantitative values are extracted, they are summarized as an infographic in a bullseye plot: the 4 layers are represented concentrically, the closest to the center being the most periventricular. The lobes are referred to by their first letters (Front,

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