NeuroImage 63 (2012) 1374–1383

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Investigation of the spatial correlation in human white matter and the influence of age using 3-dimensional variography applied to MP-RAGE data

Fabian Keil [a], Ana-Maria Oros-Peusquens [a], N. Jon Shah [a,b,*]

[a] Institute of Neuroscience and Medicine, Research Centre Juelich, 52425 Juelich, Germany
[b] Department of Neurology, Faculty of Medicine, JARA, RWTH Aachen University, 52074 Aachen, Germany

ARTICLE INFO

Article history:
Accepted 11 July 2012
Available online 23 July 2012

Keywords:
Spatial correlation
Variogram
White matter changes
Ageing
MP-RAGE

ABSTRACT

A novel method for the quantification of heterogeneity and spatial correlation in 3D MP-RAGE images of white matter is presented. The technique is based on the variogram, a tool commonly used in geosciences for the analysis of spatial data, and was tailored to the special requirements of MR image analysis. Influences from intensity non-uniformities, noise and arbitrary greyscale were quantified and considered in the calculations. The obtained variograms were fitted with spherical model functions to infer parameters that quantify heterogeneity and size of the correlation structures of the tissue. Numerically generated samples with well-defined correlation properties were employed to validate the estimation process and to provide an interpretation of the parameters obtained. It is shown that the method gives reliable results in an interval of correlation structures sized between 2 mm and 20 mm. The method was applied to 24 MP-RAGE datasets of healthy female volunteers ranging in age from 19 to 73 years. White matter was found to have two prominent correlation structures with sizes of approximately 3 mm and 23 mm. The heterogeneity of the smaller structure increases significantly with age ($r=0.83$, $p<10^{-6}$).

Introduction

Magnetic resonance imaging is an excellent tool for the non-invasive acquisition of in vivo images with high soft tissue contrast. By means of dedicated sequences one can exploit a variety of contrast mechanisms given by the interaction of magnetic fields and spins within the human body. Especially for brain imaging, MRI is the diagnostic method of choice for several neurodegenerative diseases (Polman et al., 2005) as well as for the investigation of normal brain structures in cross-sectional and longitudinal studies (Evans et al., 2006).

An important example for the diagnosis of structural changes of the brain is the observation of white matter hyperintensities (WMH) in MR images. WMHs can be caused by very different reasons. On one hand, they arise in the course of neurodegenerative diseases, such as multiple sclerosis, as a consequence of the inflammation process in regions of damaged myelin sheaths. On the other hand, WMHs can also be found in a multitude of elderly subjects not necessarily accompanied by any specific symptoms. These observations are commonly referred to as age-related white matter changes (ARWMC). Basile et al. (2006) found age, hypertension and lacunar stroke to be the most important determinants for the development of ARWMC. There are indications that these risk factors are connected to changes in the vascular structure of tissue (Pantoni, 2002). The underlying degenerative alterations are likely to be the result of a continuous process that cannot be observed directly in MR images before they manifest as ARWMC in an advanced state. This assumption is supported by several studies which investigated changes in human cerebral white matter (WM) structure using different advanced MRI methods such as diffusion tensor imaging (DTI), magnetisation transfer ratio (MTR) contrast and quantitative MRI techniques. Fractional anisotropy was found to decline with increasing age (Giorgio et al., 2010; Salat et al., 2005) while the mean diffusivity showed a positive correlation to age (Giorgio et al., 2010). Furthermore, Ge et al. (2002) demonstrated that the MTR starts to decrease in subjects older than 40 years. Neeb et al. (2006) analysed the distribution and voxel correlation in quantitative water content maps and found significant correlations of H_2O standard deviation and spatial correlation distance with age in white matter of male subjects. However, the abovementioned methods and studies require specialised sequences and demanding post-processing.

We demonstrate in this study a way of gaining information about the spatial heterogeneity of WM from a single 3D MP-RAGE image beyond that obtained from simple histogram analysis or observer dependent visual rating scales. Since the MR-RAGE sequence is a ubiquitous tool in neuroscientific applications, the variography method presented may be applied retrospectively to a huge body of existing data without the need for acquisition of new data with specialised MR protocols. We employ a technique similar to those widely used in geosciences, where they are subsumed by the term geostatistics. The first ideas in that field can be traced back to Krige (1960), and the first mathematical descriptions were given by Matheron (1963). Nowadays, these methods are

* Corresponding author at: Medical Imaging Physics, Institute of Neuroscience and Medicine - 4, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany. Fax: +49 2461 61 1919.
E-mail address: n.j.shah@fz-juelich.de (N.J. Shah).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2012.07.034

applied to the investigation of the distribution of minerals in an ore body, the amount of precipitation across a landscape or the soil contamination in a polluted area. These quantities are called regionalised variables (ReVs) (Journel and Huijbregts, 1991, p.27 ff.). For the spatial analysis of ReVs, so called variograms are employed which allow for the inference of parameters that quantify the heterogeneity and spatial correlation of the ReV.

In the following it is demonstrated that, in a similar way to the abovementioned examples, the greyscale values in an MR image of WM can also be regarded as a ReV. Alterations of WM, even on microscopic scales, locally influence the distribution of protons in the tissue as well as their relaxation behaviour and therefore determine the spatial distribution of measured intensities in simply T_1-, T_2- or proton density-weighted MR images. Although in most cases such local changes cannot be observed visually, variography can reveal structural alterations. The variographic analysis presented here takes up ideas from texture analysis (Castellano et al., 2004), such as co-occurrence matrices and the auto-regressive model, and extends them to the concept of ReVs. The resulting variograms provide an easily assessable relation between distance and intensity similarity of the voxels in a single diagram and reduce the information content of the whole image to a few significant and representative parameters. For applications to MRI data, the original, geoscientific methods were adapted to the requirements of MR image analysis in order to preserve the quantitative nature of the results and to allow for inter-subject comparability. That is, the effect of image non-uniformities, the influence of noise and the arbitrary greyscale had to be included in the analysis. In order to give some insight in the interpretation of the variograms, numerical samples were first generated and analysed. The results of the variographic analysis of 24 MP-RAGE datasets obtained in vivo from healthy female volunteers of different ages are presented. In order to demonstrate the utility of the method, the influence of age on the parameters obtained from the variograms of WM is investigated.

Theory

Variography

Comparing segmented WM in MP-RAGE images to an identical shape filled with Gaussian noise only, visual rating hardly allows for objective differentiation (Fig. 1). Even a closer look at the histograms of both intensity distributions does not reveal structure specific information. Nevertheless, the two samples differ in the essential property of spatial correlation: the intensities of two arbitrarily chosen voxels from the noise image vary independently of their separation while two voxels in WM tend to have more similar intensities if they are closer together. This might be expected intuitively since the measured intensity is the mean value over the internal substructure of a voxel. If the mean value in a given voxel is increased due to alteration processes in the microstructure of the tissue, it is likely that raised greyscale values in neighbouring voxels will also be found. Such a spatial correlation can be depicted by a semi-variogram, in the following abbreviated by variogram. A variogram illustrates the statistical variability of the intensity difference of two voxels that are separated by the distance d. To describe this variability mathematically, one has to interpret the image as a ReV which is defined by an intensity value, $i(x)$, at each measured location, x. Further, the ReV may be regarded as a particular realisation of a random process, $I(x)$, that is assumed to be intrinsically stationary:

$$E\{I(x_k)\} - E\{I(x_l)\} = 0, \forall (x_k, x_l) \tag{1a}$$

$$Var\{I(x_k) - I(x_l)\} = f(|x_k - x_l|) \tag{1b}$$

where E is the expectation value, Var the variance and the norm of $x_k - x_l$ denotes the Euclidean distance between locations x_k and x_l. This intrinsic hypothesis reflects, to some extent, the abovementioned idea of the spatial correlation of the ReV: neighbouring voxels have more similar intensities; distant voxels have a larger variability in their greyscale values. With these assumptions the variogram, $\gamma(d)$, of the image, $i(x)$, can be estimated by (Matheron, 1963):

$$\gamma(d) = \frac{1}{2N(d)} \sum_{k,l}^{N(d)} (i(x_k) - i(x_l))^2, \quad |x_k - x_l| = d\,. \tag{2}$$

Since it is crucial for the significance of the statistics to have a sufficiently large number of measured values for each distance, $\gamma(d)$ is usually obtained from all $N(d)$ data pairs separated by distances within an interval, $[d_{min}\ d_{max}]$, rather than from a single distance value. The nominal distance, d, is then the mean value over this interval:

$$d \to d = \bar{d} = \frac{1}{N(d)} \sum_{i}^{N(d)} d_i,\ d_{\min} < d_i \le d_{\max}. \tag{3}$$

Quantification of variogram parameters

Once a variogram is sampled for several distances, the resulting curve can be fitted to an appropriate model function in order to extract parameters that quantify the spatial correlation of the sample. The choice of the model function is not completely arbitrary. The theory of intrinsically stationary random processes demands conditional negative definiteness of $\gamma(d)$ (Journel and Huijbregts, 1991, p.35). There are several standard models fulfilling this condition which are used in the literature to describe the correlation of samples. One of these standard models is the spherical model that is employed in the present work to fit WM variograms. The spherical model is defined as:

$$\gamma_{sph}\left(d, \sigma^2, d_c\right) = \begin{cases} 0 & d = 0 \\ \sigma^2 \left(\dfrac{3d}{2d_c} - \dfrac{d^3}{2d_c^3} \right) & 0 < d \le d_c \\ \sigma^2 & d > d_c \end{cases}. \tag{4}$$

Here, σ^2 describes the behaviour of γ for large distances and is thus equal to the nominal variance of the ReV since the following holds (Journel and Huijbregts, 1991, p.37):

$$\gamma(d \to \infty) = Var\{i(x)\}. \tag{5}$$

The nominal variance is a measure for the width of the ReV distribution. A broader distribution, which corresponds to a larger σ^2, represents larger dissimilarities in the ReV values. Thus, σ^2 is referred to as heterogeneity. The parameter d_c denotes the distance where the variogram first reaches its plateau value, σ^2, and thus corresponds to the distance where spatial correlation vanishes. Consequently, a given value of the ReV is correlated to all values within the surrounding region of size d_c. Therefore, d_c is called the correlation distance in the following and is a measure for the size of the correlating structure. If d_c is smaller than the shortest measured distance, $\gamma_{sph}(d)$ equals σ^2 for all $d > 0$. This results in a discontinuity of γ at the origin, where the variogram is zero by definition. Such a discontinuity is called the nugget effect and can be due to the presence of structures in the ReV at length scales below the shortest measured distances (e.g. real nuggets in ore distributions). However, it can also be an indicator of measurement errors (Cressie, 1991) such as a finite signal-to-noise ratio (SNR).

In practice, and very likely in the case of WM, the use of a single correlation structure in the analysis can be an oversimplification. In order to find an appropriate variogram function for a more complex ReV, the model function can be generalised. The theory of random processes indicates that a linear combination of valid models is again a valid model (nested models, see Journel and Huijbregts, 1991, p.150 ff.). This