High $b$ value $q$-space-analyzed diffusion MRI in vascular dementia: A preliminary study


Abstract

High $b$ value diffusion weighted magnetic resonance imaging (high-$b$ DWI) was used to characterize white matter changes in the brain of patients with vascular dementia (VaD). Hyperintense white matter areas detected by T2-weighted magnetic resonance imaging (MRI) represent lesions, also termed leukoaraiosis that are very common in VaD as well as in other types of dementia. Therefore, the role of white matter changes in the cognitive and memory decline that occurs in VaD patients is still under debate. High-$b$ DWI, analyzed using the $q$-space approach, is a more sensitive MRI method for detection of white matter changes. High-$b$ DWI revealed massive white matter loss in VaD patients that surpassed the boundaries of T2 hyperintensities. This technique, therefore, might serve as a better indication for the extensive nerve fiber loss in the white matter that is caused by vascular disease.

1. Introduction

Vascular dementia (VaD) is considered as the second most common cause of dementia. This heterogeneous group of disorders is difficult to define [1]. Several diagnostic criteria have been defined, several of which require demonstration of vascular brain disease by brain imaging. Imaging by CT and particularly by MR enables detection of structural vascular damage which is defined by infarcts (both cortical and lacunar), white matter signal abnormalities, decreased gray/white matter discriminability and enlarged CSF spaces. However, white matter changes, as detected by conventional MRI or CT are not specific to VaD and may occur in other types of dementia and normal aging as well. This is maybe due to the fact that CT and MRI are not specific imaging methods for identifying vascular infarcts. Undoubtedly, the introduction of more specific advanced MRI techniques will increase the ability of discrimination between white matter changes. Indeed, diffusion-weighted imaging (DWI) and magnetization transfer imaging (MTR) were shown to be more useful for the demonstration of white matter changes.

High $b$ value diffusion-weighted MRI and MRS in animal and human brains were shown to produce a non-mono-exponential water signal decay [2–4]. The multi-exponential signal decay has at least two diffusing components [2]. The first is a fast diffusing component representing water molecules capable of performing large displacements during a certain diffusion time. The second component, which exhibits an apparent slow diffusion, might represent a slow diffusing media or a restricted diffusion component [2–4]. Indeed, the slow decaying water component, apparent only at high $b$ value ($>3000 \, \text{s/mm}^2$) was also shown to be highly restricted [2–4]. It was suggested that this diffusing component mainly originates from restricted diffusion of water in the neuronal fibers due to the myelin layers that surrounds the fibers [5]. The $q$-space approach, developed by Cory and Garroway [6], is able to quantify and characterize such signal decay, enabling calculation of the displacement distribution profile of the molecules by Fourier transformation of the signal decay with respect to the $q$ values ($q$ defined as $\gamma \delta g / 2\pi$) [5,6]. This kind of analysis is especially powerful in cases of restricted diffusion since it provides a means of...
extracting structural information without resorting to complicated mathematical models [5–7].

In neuronal tissues, the $q$-space profiles can be used to characterize the slow diffusing component, which was found to be highly restricted [5,8]. Therefore, high $b$ value $q$-space-analyzed DWI can be used to follow changes and disorders in neuronal fibers, especially of the myelin. Indeed, using the $q$-space approach, high $b$ value diffusion experiments were shown to be very sensitive to neuronal maturation and degeneration in animal models [5,8].

The $q$-space diffusion-weighted imaging (QS-DWI) approach was recently shown to be applicable to in the human brain, albeit with some limitations [9]. The difficulties in applying this method to the human brain are due to the use of long gradient pulses (>50 ms) and the heterogeneity of brain tissue [9]. The use of long gradient pulses implies that one can extract only apparent displacement profiles. Although the absolute values are not accurate, the relative size does correlate with the relative size of the physical compartment. The heterogeneous neuronal fiber orientations in the brain requires measuring the diffusion in several directions in order to extract information on the perpendicular diffusion component in each pixel. Therefore, it was suggested to use a tensor analysis, similar to that used in DTI [10], to obtain a “displacement tensor” from which the narrowest displacement profile can be extracted. This displacement profile should represent the perpendicular diffusion component [9].

This new approach for analysis of diffusion MRI data was found to be very sensitive to subtle white matter changes in multiple sclerosis (MS) [9]. MS is characterized by focal white matter demyelination. Small hyperintense lesions are often detected in the white matter of MS brains using T2-weighted MRI [11,12]. However, it is known from MR and non-MR methods that demyelination occurs in areas that exceed these lesions [12,13]. Indeed, in MS brains, the QS-DWI images were shown to detect abnormal white matter areas which were larger than those detected by conventional techniques demonstrating the high sensitivity of this method towards white matter degeneration that conventional MRI method do not detect [9]. Therefore, we thought to use this method to characterize the white matter changes that may occur in VaD. Using this sensitive MRI method, we could address the question whether T2-weighted MRI maps all the white matter abnormalities in VaD, and whether or not the absence of these lesions indicates the presence of healthy white matter tissue. We present here our preliminary results on two VaD patients and two controls. Normal subjects had no history of neuronal disease. The local Helsinki committee approved the MRI protocol and informed consent was obtained from all subjects.

2. Methods

2.1. Subjects

MRI images were acquired from two clinically definite VaD patients and two normal healthy subjects that served as controls. MRI was performed on a 1.5-T GE Signa horizon echo speed LX MRI scanner (GE, Milwaukee, WI, USA). Five axial slices were selected—one at the level of the mid body of the corpus callosum (identified from a mid-sagittal view), two below it, and two above it with slice thickness of 5 mm (with 1-mm gap between slices). The MRI protocol included the following imaging procedures: Fluid Attenuated Inversion Recovery (FLAIR) images (TR/TE/TI = 8000/120/2000 ms), fast spin-echo T2-weighted images (TR/TE = 5300/102 ms), and inversion recovery T1-weighted images (TR/TE/TI = 1500/9/700 ms). The MRI protocol also included the acquisition of a set of 16 diffusion-weighted spin-echo EPI images in which the diffusion gradients were incremented linearly from 0 to 2.2 G/cm to reach a maximal $b$ value of 14,000 s/mm$^2$. This set of diffusion images was acquired for six gradient directions ($xy, xz, yz, -xy, -xz, y-z$). Other parameters of these experiments were as follows: TR/TE = 2000/178 ms, $A/\delta = 71/65$ ms and number of averages = 4. The duration of the entire MRI protocol was approximately 50 min.

2.3. Image analysis

$q$-space analysis of the high $b$ value DWI data was performed on a pixel-by-pixel basis as described previously [5,9]. Briefly, the data was zero filled prior to Fourier transformation (FT) in order to increase the resolution of the FT. After the FT, the displacement distribution function was obtained for each pixel in each direction. The calculation of two images from the displacement profile was suggested as a way to visualize the data—a displacement image and a probability for zero displacement image (probability image). The displacement images were calculated from the full-width at half-height of the displacement distribution profile and the probability images were calculated from the peak-height of the displacement distribution profile for each pixel [5,9]. After calculating the displacement and probability images for each of the six directions, a tensor analysis [14] was performed for the displacement and probability indices. From the displacement tensor analysis, the smallest eigenvalue was chosen to show the displacement that is perpendicular to the long axis of the neuronal fibers at each specific pixel. For the probability, however, the largest eigenvalue of the probability tensor analysis was taken.

3. Results and discussion

Alzheimer’s disease (AD) and VaD are the most common types of dementia and become a severe social problem in
developed countries [15]. While the two types of dementia lead to cognitive decline and memory impairment, the nature of the two diseases is different. In AD, the main pathologies occur in the cortical gray matter and are characterized by the accumulation of neurofibrillary tangles and senile plaques along with neuronal and synaptic loss [16]. In VaD, multiple ischemic lesions may cause a gradual development of the disease due to small vessel involvement resulting in lacunar infarctions in the subcortical gray matters and diffuse changes in the white matter [17]. These patients present diffuse periventricular hyperintensities on T2-weighted MRI known as leukoaraiosis [17,18].

In this work, we have used high $b$ value $q$-space-analyzed DWI to follow white matter integrity in VaD. Recently, we showed that high $b$ value $q$-space-analyzed diffusion imaging might be more sensitive to white matter changes in MS [9]. As the disease load in MS was found to be larger using the QS-DWI technique, we decided to apply this method to VaD as well, in order to delineate the extent of white matter changes in VaD patients. This might shed a light on the following questions: Are the white matter changes in VaD are limited to the area of leukoaraiosis alone? Are the white matter changes often seen in elderly subjects with cognitive impairment necessarily associated with VaD?

Fig. 1 show an example for high $b$ value $q$-space-analyzed images of a healthy control subject (F/62 years), along with a conventional anatomical FLAIR image. The $q$-space images show high contrast between the gray matter and white matter (see image blow-up, Fig. 1c). The contrast in the $q$-space probability images (Fig. 1b) is given by the intensity of the displacement distribution profile in each pixel and represents the probability for zero displacement. Higher intensity of the probability function (light blue on the color scale) means that there is a significant amount of water molecules whose diffusion is restricted and can diffuse only over small distances. Under the experimental conditions used is this study, this fraction of molecules will perform a net displacement of nearly zero during the diffusion time. On the other hand, low intensity in this image (dark blue, red and below on the color scale, see Fig. 1b) means that there is only a small fraction of water molecules for which the diffusion is restricted while a significantly higher fraction of water molecules can diffuse more freely and therefore can reach larger displacements. This result in good discrimination between gray matter, white matter and CSF. This can also be seen from the histogram of probability values shown in Fig. 2. These histogram values are the average of the two control subjects over all slices. Using the histogram, it is possible to quantify the number of pixels having normal probability values for

![Fig. 1. MRI data set of a normal control subject (F/62 years, cognitively intact, no neurological deficit). (a) FLAIR image, (b) $q$-space probability image, (c) a blow up of the left parietal lobe showing the ability of the QS-DWI images to distinguish between gray matter, white matter and CSF. The $q$-space probability image scale is in arbitrary units (a.u.). The color scale represents the peak of the displacement distribution profile (see text).](image)

![Fig. 2. A histogram of pixel values from the QS-DWI probability image of the two control subjects. The histogram shows three peaks that represent the white matter, gray matter and CSF.](image)
white matter without the need for image segmentation, as the differences between the values from the two tissues are significantly different.

In the VaD subjects, however, massive white matter abnormalities, expressed by a significant reduction in the apparent probability for zero displacement, are observed in the $q$-space images. This abnormality affects almost all areas of white matter. An example for one VaD subject (M/66 years) showing such abnormalities is given in Fig. 3 along with the FLAIR image (showing areas of leukoaraiosis). It is clear that the white matter changes, as observed in the $q$-space probability images, are much larger than those observed in the FLAIR image. This is clearly seen in the enlargement of a part of the brain (Fig. 3c). The reduction in the intensity of the displacement probability function in large areas of the white matter is characterized by dark blue and red colors in the QS-DWI probability image. This reduction implies that the water molecules in these areas, which in healthy tissue exhibit restricted diffusion due to the myelin membrane, show in the VaD brain a much smaller degree of restricted diffusion. This reduction in restricted diffusion might be attributed to axonal loss and demyelination processes, both known to occur in VaD. Interestingly, the areas that seem to be damaged in the QS-DWI probability image are larger than those observed in the FLAIR image. This indicates that only in cases of severe changes (infiltration of CSF or massive axonal loss) will hyper-intensity in the FLAIR images be observed. The fact that there is massive white matter loss in VaD brains is also manifested in the histogram of the two VaD patients (Fig. 4), showing an almost complete white matter loss in the VaD subjects with only minor changes in the gray matter.

To summarize, high $b$ value $q$-space-analyzed diffusion-weighted MRI introduces a new imaging contrast into VaD. These kinds of images show massive white matter loss in the brain of VaD patients, as compared to control subjects.

Leukoaraiosis itself, detected in the FLAIR images, does not represent the full extent of tissue damage in VaD, and might be a less specific measurement of the disease load in VaD. Further experiments on a much larger group of patients are needed in order to verify whether a correlation exists between the disease load as measured by the QS-DWI method and the cognitive and memory decline of VaD patients. In addition, an elaborate comparison of conventional DTI and high $b$ value $q$-space-analyzed diffusion MR images is required to verify if this new approach is more specific in detecting the disease load in VaD.

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Fig. 3. MRI data set of a vascular dementia patient (F/66). (a) FLAIR image, (b) $q$-space probability image, (c) a blow up of the left parietal lobe showing the massive changes in the white matter as compared with Fig. 1c. The $q$-space probability image scale is in arbitrary units (a.u.). The color scale represents the peak of the displacement distribution profile (see text).
References