High b-value diffusion imaging of dementia: Application to vascular dementia and alzheimer disease

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Abstract

Alzheimer's disease (AD) and Vascular Dementia (VaD) are the most common types of dementia and are progressive diseases affecting millions of people. Despite the high sensitivity of MRI to neurological disorders it has not thus far been found to be specific for the detection of either of these pathologies. In the present study high b-value q-space diffusion-weighted MRI (DWI) was applied to VaD and AD. Controls (N=4), VaD patients (N=8) and AD patients (N=6) were scanned with high b-value DWI, which emphasizes the water component which exhibits restricted diffusion. VaD patients were found to present major WM loss while, in AD, the major pathology found was GM changes, as expected. Also, WM changes in VaD and AD were of a different pattern, more specific to frontal and temporal areas in AD and more widespread in VaD. This pattern of WM changes may be utilized as a diagnosis criterion. Conventional diffusion tensor imaging did not show significant changes between either of the groups and controls. These results demonstrate the potential of high b-value DWI in the diagnosis of dementia.

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1. Introduction

Alzheimer’s disease (AD) and vascular dementia (VaD) are considered the two leading forms of dementia. AD is assumed to be a diffuse cortical dementia that preferentially involves the temporal and parietal brain regions [1]. AD affects nearly 50% of demented patients and is a severe social problem in developed countries, affecting nearly half of the people of 85 years of age [1]. VaD is a group of dementing disorders arising from various vascular etiologies [2]. VaD is a progressive disease with either repeated strokes or gradual involvement of small vessels causing lacunar infarctions in the basal ganglia and diffuse changes in the white matter [1]. AD and VaD together are considered responsible for about 80% of all dementia cases [3].

Despite the high sensitivity of magnetic resonance imaging (MRI) to neurological disorders, it is not specific for the detection of dementia. Also, poor correlation was found between conventional MRI (T1, T2) and the cognitive decline associated with dementia [4,5]. Temporal and parietal brain atrophy is usually found in AD, with signal abnormalities in the periventricular WM, but these abnormalities do not usually exceed what is seen in a population of the same age [1]. Many VaD patients show multiple ischemic lesions, cortical and subcortical. However, not all such lesions are symptomatic. In VaD, as in other pathologies, many patients present periventricular hyperintensities (Leukoariosis), but these are not specific to any specific pathology, especially in younger age groups [6]. In addition, a postmortem study [7]
found no association between the extent of periventricular WM hyperintensities and AD or stroke. Diffusion-weighted MRI (DWI) is a valuable tool for obtaining contrast, studying structures, and characterizing pathologies in the central nervous system [8,9]. DWI and diffusion tensor imaging (DTI) have been used to study white matter (WM) changes in many neurological disorders, including dementia [10,11]. In VaD, those studies showed an ADC increase and low diffusion anisotropy, indicative of cellular disintegration [12] in areas of leukariosis, but these findings did not correlate with the clinical condition of the subjects [2,13]. In AD, some loss of WM tract integrity in association fibers was found using DTI [14], presumed to be secondary to Wallerian degeneration of fiber tracts in cortical association areas [15]. There has been some controversy regarding changes of diffusion anisotropy in AD patients. Some found that AD patients demonstrated reduced anisotropy in the posterior WM [16], and reduced anisotropy in the temporal lobe, anterior and posterior cingulate bundles and posterior portion of the corpus collosom [17] but their findings did not correlate with dementia severity. Yoshiura and coworkers, for example, found a significant correlation between the Mini-Mental State Evaluation (MMSE) score and mean diffusivity and also the three eigen values but not FA [18], and Bozzali et al. found a good correlation between the MMSE and diffusivity as well as FA [15]. Conventional DWI and DTI (b ≤ 1500 s/mm²) are generally considered to be sensitive to all water components in the studied tissue. So, if the pathologies we expect to encounter involve only one compartment, the effect is averaged and not always detectible, although some pathologies, such as stroke [19,20] are reliably detected by DWI for example.

High b-value DWI is highly sensitive to WM changes. The signal decay at high b-values (b > 3000 s/mm²) DWI deviates from mono exponential behavior [21,22,23]. The apparent slow diffusing component, observed in neuronal tissues, seems to originate, at least partially, from water molecules exhibiting restricted diffusion. This restricted population is thought to mainly represent water in the intra-axonal compartment. This tentative assignment is based on the facts that this water component appears restricted to a compartment size of a few microns and is found to be more abundant in WM than in GM [24]. In addition, the displacement of this component was found to barely change when the diffusion time is increased [24,25]. Due to the non-mono-exponential nature of the water signal decay at high b-values, different approaches to it’s analysis were developed [21,23,26,27], including the q-space approach [28], originally developed by Cory and Callaghan [29,30]. Indeed, high b-value q-space DWI was used to study WM maturation [31], degeneration [32], and spinal cord trauma [33]. For example, diffusion images, when analyzed using the q-space approach, show areas of abnormal WM in multiple sclerosis (MS) not detected by other MRI methods like T2, T1-weighted imaging, FLAIR, and DTI [34,28]. In addition, high b-value q-space DWI was shown to have an improved detectability in experimental allergic encephalomyelitis (EAE) as compared with conventional MRI [35]. In this work we sought to apply high b-value q-space analyzed DWI to VaD and AD. In VaD, mainly WM deterioration was presumed to occur, while in AD the main pathology was presumed to be in the GM, with a variable amount of the WM pathology. The signal decay at high b-values reveals a slow decaying component that was hypothesized to allow differentiation between WM and GM effects.

2. Methods and materials

2.1. Subjects

MRI scans were acquired from six patients diagnosed with probable AD and eight patients diagnosed with probable VaD. The patients were diagnosed and evaluated by two neurologists. Four normal healthy subjects served as controls. The average age of the AD group was 74±10, of the VaD group 69±8, and of the controls was 61±4. The control subjects had no history of neuronal disease. The local Institutional Review Board (IRB) committee approved the MRI protocol, and informed consent was obtained from each subject (AD, VaD patients and controls).

2.2. MRI methods

Imaging was performed on a 1.5T GE Signa horizon echo speed LX MRI scanner (GE, Milwaukee, WI, USA). The patient’s head was fixed with foam pads to reduce motion during the imaging process. The MRI protocol included the following clinical 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 protocol also included the acquisition of a set of 16 diffusion-weighted spin-echo EPI images in which the diffusion gradient was incremented linearly from 0 to 2.2 G/cm to reach a maximum b-value of 14,000 s/mm². This set of diffusion images was acquired for six gradient directions (x1, x2, yz, −x1, −xz, y−z). Five axial slices were selected — one at the level of the mid body of the corpus callosom (identified from a mid-saggital view), two below it, and two above it with a slice thickness of 5 mm (with 1-mm gap between slices) and a matrix dimension of 128 × 128 (interpolated to 256 × 256 with final resolution of 0.9 × 0.9 mm²). Other parameters of these experiments were as follows: TR/TE=2000/178 ms, Δ/δ=71/65 ms and the number of averages was 4. The duration of the entire MRI protocol was approximately 50 min. The high b-value protocol itself lasted ~ 20 min.

A DTI data set was also acquired using a spin-echo DW−EPI sequence with the following parameters: TR/TE=6000/90 ms, Δ/δ=31/25 ms, gmax of 2.2 G/cm (where gmax is the maximal value of the diffusion gradient pulse), a matrix dimension of 128 × 128 (interpolated to 256 × 256), with 4
deviation. Tests were marked significant for NS stands for non-significant. All results presented as average±standard deviation. Tests were marked significant for $p<0.05$ in comparison with the control group.

averages and 24 slices (5 of them being aligned in the same position as the q-space imaging slices). The diffusion images were acquired along the aforementioned diffusion gradient directions with a maximal $b$-value of 1000 s/mm$^2$. The DTI data set consisted of seven images (six diffusion images and one with no applied diffusion gradients). The total acquisition time for the DTI data set was 3 min.

2.3. Image processing

Fractional anisotropy (FA) images were produced from the diffusion tensor imaging data set as described previously [36]. q-space analysis of the high $b$-value diffusion data was performed on a pixel-by-pixel basis as described previously [31,34,28]. For each image pixel, the diffusion signal decay was transformed into displacement distribution profiles (using Fourier transformation), to produce the displacement–distribution profile for each pixel in the images (for more details see Fig. 13 in Ref. [28]). Two images were calculated from the imaging data: an apparent displacement image (subsequently referred to as the displacement image) and an apparent probability for zero displacement image (subsequently referred to as the probability image). The apparent displacement images were calculated from the full-width at half height (FWHH) of the displacement distribution profile and the probability images were calculated from the peak height of the displacement distribution profile for each pixel. As the short gradient pulse (SGP) approximation cannot be met using a clinical imaging system, only apparent mean displacement and probability for zero displacement can be determined. It should be noted that our data was not corrected for head movement of cardiac pulsation.

2.4. Data analysis

Histogram analysis of the displacement maps resulted in three peaks for the control data sets, as did the probability maps. In the displacement maps one peak was centered around 12 μm and most probably represents the CSF, second peak centered around 8 μm was assigned to the gray matter and the third peak, centered around 4 μm was assigned to the white matter (see control values in Tables 1–3). Using spectral analysis (which fits the histogram to pre-determined Gaussian shaped peaks, provided by Origin ©), data of peak center, width at half height, and area were calculated for the displacement and probability data. In order to compare high $b$-values with conventional FA maps extracted from DTI we created anisotropy maps based on the anisotropy from the q-space images. We used the 6 displacement images as input for a tensor-like analysis from which we calculated the q-space displacement anisotropy index. DTI histograms were not analyzed using spectral analysis as no separation of WM and GM was achieved. All results are presented as the mean±standard deviation. A paired $t$-test was used to compare the parametric variables, with a value of $p<0.05$ considered significant. In addition, correlation analysis was performed between the histograms of the different patients groups (AD, VaD and control) for each parameter (FA, probability and displacement) in order to test for similarity between the indices.

2.5. Psychiatric evaluation

Evaluation of all AD and VaD patients was performed using the MMSE, which is the most widely used standardized cognitive screening test for assessing dementia [37]. Although, it was never meant to be used for the diagnosis of dementia, the MMSE has been extensively used in the field of dementia [38]. The benefits of the MMSE include its
brevity (10–15 min to administer), and the fact that it is a global assessment of many cognitive and mental domains including: orientation to time and place perception, memory, attention, and language. The standardized MMSE has been used to look at disease progression as well as relating it to areas of functional impairment. In AD, it is quite established to use scores ranging from 25–30 for controls, 21–24 for mild AD, 14–20 for moderate AD, and less than 13 in severe

Fig. 1. A representative healthy volunteers (female age 59) data set, including (A) FLAIR image, (B) ADC map, (C) DTI FA image, (D) q-space displacement image, (E) q-space probability image and (F) displacement anisotropy map, all for one representative slice. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. A data set for a VaD patient (male, age 76 MMSE 20), including (A) FLAIR image, (B) ADC map, (C) DTI FA image, (D) q-space displacement image, (E) q-space probability image and (F) displacement anisotropy map, all for one representative slice. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
AD. It is a useful tool in the initial assessment as well as the ongoing follow-up of patients with AD [39].

3. Results

Fig. 1 shows a representative healthy volunteer’s data set, including a FLAIR image (Fig. 1A), an ADC map (Fig. 1B), a DTI FA image (Fig. 1C), q-space displacement (Fig. 1D) and probability images (Fig. 1E), and a displacement anisotropy map (Fig. 1F), all for one representative slice (female, age 59). The FLAIR image (Fig. 1A) shows the anatomy, with no significant neuroradiological abnormalities. Neither does the ADC map (Fig. 1B), which doesn’t give good WM/GM contrast. The FA map however highlights areas of WM, which appear as white, as expected for a healthy subject, with no abnormalities apparent (Fig. 1C). The probability image (Fig. 1E) shows healthy WM with control values similar to our database, as does the displacement image (Fig. 1D, Table 1). The displacement and probability images (Fig. 1D and E, respectively) also show the expected values for healthy GM (Table 2), and Table 3 shows displacement and probabilities values for control CSF. The displacement anisotropy map (Fig. 1F) also highlights the areas of WM, as does the FA map, while giving better contrast to GM areas than the FA map.

In Fig. 2, a matching data set is shown for a VaD patient (male, age 76 MMSE 20). The ADC map (Fig. 2B) shows the WM ADC to be slightly elevated. Some areas of periventricular hyperintensity can be observed in the FLAIR images (Fig. 2A). These areas appear in the FA and q-space displacement maps as areas of reduced diffusion anisotropy (Fig. 2C and D, respectively). However, in the displacement image (Fig. 2D), not only do those areas of FLAIR hyperintensities appear as areas of increased displacement (WM areas appear bluish in Fig. 2D instead of the orange-red of control healthy WM areas in Fig. 1D, for example), but some WM areas that appear normal in the FLAIR and FA maps also show increased displacement, although to a lesser degree (exhibited in the shift to dark blue from orange-red color, see Fig. 2D). The same trends appear in the probability image of the patient with the FLAIR hyperintensity. Areas in the probability image show decreased probability (color changing to orange-red (Fig. 2E) from blue in the healthy control (Fig. 1E)), and some normal appearing WM (NAWM) areas also show, though to a lesser degree, decreased probability. The displacement anisotropy map (Fig. 2F) shows the same trends as the FA map, showing reduced anisotropy in areas of leukariosis, with better contrast for GM and WM areas with reduced anisotropy.

Fig. 3A–C shows the average displacement, probability, and FA histograms for all controls and VaD patients studied, respectively. The q-space displacement histogram of the controls (Fig. 3A, black squares) shows three peaks representing: WM (centered at 4.06±0.35 μm), GM (centered at 8.04±0.47 μm), and CSF (centered at 13.40±0.56 μm). When we look at the average displacement histogram for the VaD patients (Fig. 3A, green circles), we see that the WM peak has declined significantly (see Table 1, from a peak height of 3.26±0.80 for controls to 0.93±0.53 for VaD patients) and the average displacement has shifted significantly to 5.26±0.19 μm (see also Table 1) while the GM peak appears increased, although not significantly (Table 2). There is also a significant increase at the CSF peak height, from 0.58±0.06 for controls to 1.11±0.27 for VaD patients, and a shift in it’s center from 13.40±0.56 for controls to 11.66±0.77 in VaD. Generally, the displacement of VaD patients differs from that of control subjects in the WM peak area. Indeed, a dramatic decrease appears in the WM peak area (from 8.54±2.40 to 3.03±2.11, p<0.005, see Table 1). The other tissue type showing significant change in the area of the displacement is the CSF (in the range from 10 μm to 16 μm). The changes in the q-space probability histogram of the VaD patients vs. controls (Fig. 3B) follow the same trends as the displacement histogram changes. The average probability histograms show changes in the WM area and CSF areas, like in the displacement histograms. Fig. 3C, in contrast, shows that the FA histograms of the VaD patients, obtained from conventional DTI, overlap much more with the FA histogram of the controls.

Fig. 4 shows a similar data set for an AD patient (female, age 55). Some areas of periventricular hyperintensity can be observed in the FLAIR image (Fig. 4A). These areas appear.

Fig. 3. (A) Average displacement histogram for controls and VaD patients. The histogram of the controls appears in black while the VaD histogram appears in green in all graphs. (B) Average probability histogram for controls and VaD patients. (C) Average FA histogram for controls and VaD patients obtained from low b-value conventional DTI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
in the respective FA map (Fig. 4C) as areas of reduced diffusion anisotropy. Other than atrophy, the ADC map (Fig. 4B) shows no abnormalities, as expected. In the displacement (Fig. 4D) and probability (Fig. 4E) images of the same patient, the FLAIR hyperintensity areas appear as areas of increased displacement and reduced probability, correspondingly. The displacement and probability images of the WM of the AD patients (see Fig. 4D and E) seem more like that of the healthy controls (Fig. 1D and E). The GM of the same patients, however, seems less similar to that of controls as compared to the appearance of the GM of the VaD patients (compare Fig. 4D–E and Fig. 2D–E with Fig. 1D–E). This is apparent both in the displacement and matching probability images (Fig. 4D–E). Fig. 4D–E show the much more pronounced changes on the q-space characteristics of the GM of the AD patient than the VaD patient as compared with the control. Again, the displacement anisotropy map (Fig. 4F) shows the areas of leukariosis as areas of reduced anisotropy, much like the FA map, but with improved contrast between GM and WM with reduced anisotropy.

These phenomena are also apparent in the displacement, probability, and FA histograms of the AD patients, shown in Fig. 5A, B, and C, respectively. When we look at the WM peak of the AD patients displacement histogram (Fig. 5A, in red), we notice that its height is reduced, in comparison with that of the control, from 3.26±0.80 for controls to 1.55±0.80 for AD patients (Table 1, p<0.01). The GM peak shows a reduction trend, although not significant, from a height of 3.26±0.50 for controls to 3.09±0.63 for AD patients.
controls, VaD patients and AD patients. Correlation analysis of the DTI, displacement, and probability graphs of the different groups (Table 4) showed that the DTI values for both the VaD group and the AD group were well correlated with control values ($R=0.993$ and $R=0.997$ respectively). The values for the displacement analysis were poorly correlated, with a correlation of $R=0.850$ between the AD group and the control group and a worse correlation between the VaD group and controls ($R=0.622$). The probability values were also not well correlated between the AD group and controls, and the VaD group and controls, with the later group showing poorer correlation, as was the case for the displacement values. The data for the displacement analysis were least correlated, explaining it’s better utility as a screening method for the data.

Table 4

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<th>Displacement</th>
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<td>$R=0.951$</td>
<td>$R=0.997$</td>
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<tr>
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<td>$R=0.993$</td>
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4. Discussion

High $b$-value q-space DWI seems to be very sensitive to both WM and GM changes in dementia. The increased sensitivity of high $b$-value DWI to WM in general [18] and high $b$-value q-space DWI in particular has been documented [34,40,28,41]. The present high $b$-value q-space diffusion results show that the loss of white matter integrity is the major change observed in VaD patients. This effect is apparent both in displacement images and probability images of the patients, where it is manifested as a decrease in probability values and an increase in displacement values of WM. This agrees with findings by Jones et al. that showed that VaD patients exhibit increased ADC and decreased diffusion anisotropy in areas of leukariosis [12]. This effect is accompanied by a smaller decrease in probability values and a smaller increase in displacement values of WM that appears normal in FLAIR and FA maps.

These changes in NAWM are more apparent in the probability/displacement images than in the matching DTI maps and are also supported by findings by O’Sullivan et al. that showed changes in VaD patients extending to WM tracts beyond areas of $T_2$ abnormalities [42]. The displacement and probability histograms of patients studied in this work corroborate the results of O’Sullivan et al. but also extend them to a more general form. The current work looks at all the pixels within the MRI slice, not only in a ROI as in O’Sullivan’s work, and analyzes the changes in the brain tissue as a whole, WM, GM, and CSF together and as distinct populations. The ROI approach can show that there are changes in the displacement and probability values of specific NAWM pixels, but the q-space approach allows us to discern such changes in more extended regions of WM in VaD patients (up to all brain regions in $3T$ MRIs). Indeed, such wider spread changes are suggested by postmortem studies of WM pathology, in which a combination of infarcts and diffuse perifocal rarefaction were observed for VaD.

In AD, the main effect apparent is GM shrinkage, and the WM effects are less profound. This effect is apparent both in displacement and probability images of the patients, where the GM pixel values turn to CSF values, as well as in the displacement histogram where the AD patients show a trend for a decrease in the GM peak, and an increase in the peak size of the CSF. In AD patients, WM hyperintense areas show a decrease in probability values and an increase in displacement values which are smaller than those found for VaD patients. For example, a reduced anisotropy in the posterior WM was found [16], which agrees with the small changes observed in the current work. These changes were mostly found in areas of WM hyperintensities, similar to the way these hyperintensities are presented in VaD.

Another advantage of q-space analysis of high $b$-value diffusion imaging is the improved discrimination between different types of tissue, i.e. WM, GM, and CSF. This is easily illustrated by looking at the displacement histogram of
the healthy volunteers that presents three distinct peaks, for WM, GM, and CSF. Using the displacement histograms the changes affecting the different tissue types are more noticeable. In the matching displacement histograms the WM peak in VaD patients is significantly decreased from controls, both in area and height, while the GM peak isn’t. The center of the WM peak is also shifted from control values. The FA histograms of the VaD group vs. controls are not significantly different. When we compare the displacement histograms for AD patients the WM peak is also significantly reduced from controls, both in height and area, but to a lesser degree than VaD patients. However, in contrast to the case of VaD, the center of the WM peak of AD patients is not shifted from the value found for normal controls, indicating the maintenance of some normal tissue characteristics for remaining WM tissue in AD, consistent with the scenario of axonal loss, in contrast to VaD, where the decline in the WM peak is accompanied with its shift, implying a degenerative process in the form of demyelination. This is accompanied by a complementary increase in the area of the CSF peak, in both pathologies. In VaD, the increase in CSF peak area and height, consistent with brain atrophy, is accompanied with a significant change in the CSF peak center while in AD, the significant increase in the CSF peak area and height isn’t accompanied by such a shift in the peak center from control values. Again, the FA histograms of AD patients were not significantly different from controls.

Widespread atrophy and degeneration of GM, as expected in AD, is impressively highlighted in this study. Indeed, the atrophy apparent in the FLAIR images is further enhanced in the probability and displacement images, where the dramatic shrinkage of the GM is even more impressive, as the thin layer of GM, surrounding the relatively intact WM, is emphasized. This is in good agreement with finding by Sandson et al., that show increased ADCav in the hippocampus and posterior GM of AD patients and with findings by Yoshihura et al., that show increased diffusivity in ROI’s in the temporal lobes of AD patients (relative to occipital lobe diffusivity of the same patients), although their results are not specific to GM. Interestingly, Yoshihura et al., also found increased contrast between AD and controls with increasing b-value. A comparison between MRI and histopathology of in-vitro AD-affected brains was documented in an interesting paper by Bronge and coworkers [43], where the authors found that WM changes were more extensive on a myelin stained neuropathology exam than on postmortem MR images. While their findings imply an increase in tissue water content, even before myelin loss or axon loss occur, a phenomenon to which they expect MRI to be sensitive, they didn’t observe such changes by MRI as they didn’t employ diffusion-weighted MRI techniques that are sensitive to water content and movement changes. A study that employed low b-value DWI in AD linked MRI WM hyperintensities with loss of myelinated axons and gliosis in the deep WM [44]. This study suggested that independent of periventricular changes, WM degeneration of the secondary Wallerian type, which has been identified to correlate with pathologic cortical conditions in AD, may coexist in AD patients.

The increased sensitivity of high b-value q-space analyzed diffusion imaging, as compared with low b-value imaging, allows us to track changes in brain tissue even on the single patient level. When we consider a typical VaD patient, as illustrated in Fig. 2, and compare displacement (Fig. 2D), probability (Fig. 2E), and displacement anisotropy (Fig. 2F) maps to controls, we are immediately aware of the major observed change in VaD, i.e. WM degeneration and loss. Correspondingly, when we consider the matching images for a typical AD patient (Fig. 4D–F), we are immediately struck by the extensive GM loss and the comparative retention (in comparison with VaD) of WM integrity. These striking observations are very important, especially in the light of the great heterogeneity of both discussed pathologies, VaD and AD. Not only do those pathologies affect different brain regions in different patients, but these regions also change during the course of the disease. This variability in pathology location, and the extensive variability in the changes occurring in the course of the disease, only serves to highlight the need for widespread analysis of the brain tissue of the patient. ROI analysis, while allowing us to track specific areas of tissue for analysis, often fails to address the whole range of changes affecting all the brain tissue during the development of such pathologies. A global view of these changes is desirable, especially if there is to be an attempt to distinguish between pathologies on a patient-by-patient basis. While the present study did not provide a full analysis of all brain tissue, an extensive part of the brain was covered (five 5-mm slices with 1-mm inter-slices distance), probing a wide range of functional and anatomical structures, impractical using the ROI technique.

5. Conclusion

In conclusion, high b-value q-space analyzed DWI has been shown to be more sensitive to changes in WM and GM in these types of dementia that are not apparent using conventional imaging, low b-value DWI, and DTI. This increased sensitivity seems to provide a more complete estimation of the disease load and, more importantly, enable one to distinguish radiologically between AD and VaD patients on a single basis patient level. Clearly, the present diffusion study demonstrates the much significant changes in the WM in the cases of VaD as compared to larger changes in the GM for cases of AD.

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