ADC measurements at low and high $b$ values: insight into normal brain structure with clinical DWI

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Received 18 January 2007; revised 5 April 2007; accepted 21 April 2007

Abstract

Purpose: To demonstrate drop in brain ADC measurements from low to high $b$ values; to evaluate the structural information provided based on those changes; and to discuss the anatomical reasons for ADC differences.

Methods: Four cerebral ROI (precuneus-PRC, hippocampus-HIP, and the genu-GCC and splenium-SCC of the corpus callosum-CC) were drawn for ADC measurements with low (1000) and high (3000) $b$-value DWI in 50 normal subjects. ANOVA and Bonferroni correction tested ADC differences between areas, between both hemispheres, between GCC and SCC, and between $b$-value related ADC drop within areas. Pearson test evaluated dependence of interhemispheric and intercallosum ADC measurements obtained with the same $b$-value, dependence between areas of intrazonal drop, and the interhemispheric and intercallosum dependence of intrazonal drop.

Results: ADCs differed between areas ($P < 0.0001$). Interhemispheric ADC only differed in PRC with low $b$-value ($P < 0.027$). No HIP asymmetries occurred regardless the $b$-value. ADC drop within PRC and HIP was similar but differed ($P < 0.0001$) from ADC drop within both CC ROI. ADC drop was also different between GCC and SCC ($P < 0.0001$). In PRC and HIP, ADC showed a significant interhemispheric and intrazonal dependence ($P < 0.0001$). There was no GCC to SCC ADC dependence. Intrazonal dependence in the CC was only significant in the SCC ($P < 0.001$). Interhemispheric dependence of intrazonal drop was significant (PRC $P = 0.007$; HIP $P < 0.0001$) but failed to reach significance in the CC.

Conclusion: Low and high $b$-value measurements show different diffusion behaviours within different tissues, especially in a highly anisotropic structure as the corpus callosum. This fact can provide valuable information about brain structure and different diffusion compartments in clinical DWI.

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Keywords: $b$ value; Diffusion-weighted imaging; Brain; White matter; Gray matter; Corpus callosum

1. Introduction

Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique in which contrast between tissues depends mainly on the random motion of water molecules [1]. However, the final determinants of diffusion are not well understood [2–6]. The degree of diffusion weight in DWI determines MRI signal and depends on $b$ value [1,7,8]. The relationship between the motion of water molecules, the MRI signal and the $b$ value is described by the Stejskal–Tanner equation [9], which assesses diffusion by calculating the apparent diffusion coefficient (ADC). The standard $b$ value used in conventional DWI is $\sim 1000$ s/mm$^2$, and $b$ values of $\geq 3000$ s/mm$^2$ are considered high [2,8,10].

As the $b$ value increases, a progressive change in visual contrast between brain regions and an overall drop in ADC are noticed [2,7,8,10,11]. The drop in ADC cannot be adequately interpreted by monoexponential diffusion in tissues and is better explained by a biexponential model [2,8,11–16]. Supporting this model, the results of Niendorf et al. [14] and subsequently of others [2,7,8,10] demonstrated that there are fast and slow components of diffusion in the random motion of water molecules in brain tissues. On the basis of their results, Niendorf et al. [14] suggested that, using a low $b$ value, DWI signal is dominated by the fast component, and using a higher $b$ value, the DWI signal is dominated by the slow component. According to them [14], the fast and slow components corresponded to the extracellular and intracellular compartments, respectively. However, other studies have questioned whether the two components of diffusion are specifically related to those

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doi:10.1016/j.mri.2007.04.004
compartments [15,16]. Furthermore, they suggest that there are fast and slow components of diffusion in both intracellular and extracellular spaces that are determined by the distance between membranes and membrane permeability [17,18]. Despite this controversy, it seems that the use of different $b$ values in DWI can provide valuable microstructural information [2,12–16].

Many studies on the subject have been performed in animals or small samples of patients. In the present study, we used conventional clinical DWI and different $b$ values to obtain microstructural information from a large group of patients. Our objectives were to: (a) demonstrate quantitative differences in brain ADCs obtained with high and low $b$ values; (b) evaluate the structural information provided by DWI based on those ADC differences; and (c) discuss the anatomical reasons for ADC differences.

2. Materials and methods

2.1. Subjects

This retrospective study was conducted on a group of 700 consecutive patients who underwent conventional brain MRI and DWI between 2003 and 2005. The same imaging parameters were used for all patients. All patients provided informed consent for the procedure. A sample of 50 subjects with normal study was obtained by simple randomization. The criterion for normal study was the absence of morphological and signal abnormalities in all imaging sequences. For patients older than 50 years, a maximum of three supratentorial hyperintense $T_2$ foci with a maximum diameter of $<3$ mm (negligible in both $T_1$-weighted and DWI images) were considered normal. The demographic variables analyzed were age, gender, presence of vascular risk factors (VRFs) and relevant medical history.

The study group consisted of 26 men and 24 women with a mean age of $41.9 \pm 17$ years (men, $45.3 \pm 17.9$; women, $38.3 \pm 15.5$). None of the patients was cognitively impaired, according to the criteria of Petersen et al. [19]. Fourteen subjects had one or more VRFs. Eight of those had medically controlled hypertension. Of those, two had associated dyslipidemia, one had coexisting type 2 diabetes mellitus and one had a history of chemotherapy. Of the remaining six patients with VRF, one had type 2 diabetes mellitus and dyslipidemia, four had dyslipidemia or hypercholesterolemia and one was diagnosed with systemic lupus erythematosus and antiphospholipid syndrome. Since VRF could bias ADC assessment, a statistical comparison of the ADCs of non-VRF patients and VRF patients was performed prior to a full analysis of the data.

2.2. Imaging protocol

All patients were studied with a high-field MRI system 1.5 T (Signa MR/LX, Milwaukee, WI) using a double protocol.

Fig. 1. The images on the right are ADC maps upon which the ROI were drawn, using the corresponding $T_2$-weighted images for reference. For more detailed information, see García Santos et al. [22].
Conventional protocol included a sagittal \( T_1 \)-weighted spin-echo sequence (\( T_1/T_E=525/10 \) ms), an axial double-echo long \( T_1 \) fast spin-echo sequence (\( T_1/T_E=2000/30 \) ef ms; \( T_2/T_E=2000/112 \) ef ms), an axial \( T_2 \)-weighted fast Fluid Attenuation Inversion Recovery (FLAIR) spin-echo sequence (\( T_1/T_E=8000/120 \) ef/2200 ms) and a coronal \( T_2 \)-weighted fast spin-echo sequence (\( T_1/T_E=4500/80 \) ef ms). All images obtained in the conventional protocol were 5 mm thick with a 1-mm gap.

The DWI protocol included two sets of axial single-shot spin-echo echo-planar sequences, one with \( b=0 \) s/mm\(^2\) value of 1000 s/mm\(^2\), and the other with \( b=3000 \) s/mm\(^2\) and a \( b \) value of 5000 s/mm\(^2\). Both sequences were carried out with a 128 × 128 matrix, a 36 × 22 field of view, 5-mm thickness and no gap between sections. The number of averages was 1 and 4, respectively. Each DWI set included an axial sequence with a \( b \) value of 0 s/mm\(^2\) and three independent diffusion-sensitive sequences in each of the three main spatial axes (\( xx, yy \) and \( zz \)). Subsequently, diffusion data were automatically computed to obtain the pixelated ADC maps.

### 2.3. Data acquisition

Data were collected with commercially available software (GE Functool ADW 3.1, Milwaukee, WI). Variable ADC values calculated by different MRI systems [20] and interobserver variability in measuring the region(s) of interest (ROI) [21] inhibit us from comparing our results with those obtained in other MRI facilities. However, our goal was to make a structural assessment with a widely accessible basic research tool that is applicable in any MRI center, and not to establish reference values of brain diffusivity.

Isotropic images and \( T_2 \)-weighted images (\( b=0 \) s/mm\(^2\)) were transferred to a workstation (GE Advantage Windows 4.0, Milwaukee, WI). ADC maps were computed automatically for each patient with the GE Functool software, calculating the ADC pixel by pixel according to the Stejskal–Tanner equation. Once the ADC map had been obtained, the same radiologist (J.M.G.S.) drew six ROI (Fig. 1). In each hemisphere, two structurally well-known areas were selected: (a) the subcortical white matter of the medial parietal lobe/precuneus (PRC), behind the cingulate sulcus and anterior to the parieto-occipital sulcus and made up of intertwined fibers, and (b) the gray matter of the hippocampus (HIP), immediately behind the anterior edge of the temporal horn of the lateral ventricle. In addition to those ROI (hemispheric ROI), two additional ROI were drawn in the corpus callosum (CC; callosum ROI): genu of the corpus callosum (GCC) and splenium of the corpus callosum (SCC), including white matter comprised of compact fiber bundles.

Pixelated ADC maps were used to more easily identify those pixels that may be contaminated with cerebrospinal fluid (CSF). Accordingly, ROI were moved away from edge pixels that showed an intermediate signal between the CSF and the brain parenchyma. Since all DWI studies were performed in strict axial planes that were not corrected for craniocaudal tilt of the head, a simple previously reported method [22] was used to draw each ROI, assuring a similar position in all individuals.

### 2.4. Statistical analysis

Prior to analyzing the results, patients were assigned to one of two clinical groups: the VRF group and the non-VRF group. The mean values and standard deviations of the ADC for each clinical group are shown. The column on the left corresponds to quantitative data obtained with a low \( b \) value and the \( P \) value for the comparison between clinical groups in each particular ROI. On the right, diffusion data and \( P \) values correspond to ADCs obtained with a high \( b \) value.
group. Since VRF could bias the final results, after verifying the homogeneity of variances through the Levene test, the mean ADCs of the VRF and non-VRF groups were compared with one-factor analysis of variance (ANOVA).

Quantitative variables were expressed as means and standard deviations. They were first evaluated with Kolmogorov–Smirnov normality test. After verifying normality, we assessed the structure of the three selected areas by taking advantage of the expected nonmonoeponential behavior of diffusion. To that end, we analyzed diffusion behavior with two $b$ factors in each of the tissues, in two steps:

(a) Quantitative variables, considered dependent data, were compared with one-factor ANOVA. Statistical significance was set at $P<0.05$. Following ANOVA, multiple comparisons of all ADC ROI were carried out with Bonferroni correction. We assessed the diffusion differences between PRC, HIP and CC (interzonal comparisons) and between the ROI of symmetrical areas, including right versus left PRC, right versus left HIP, and GCC versus SCC (interhemispheric and intercallosum comparisons). Subsequently, the relationships between diffusion trends in both hemispheres and CC were assessed with parametric Pearson regression test. For this purpose, the interhemispheric dependence of ADC values and the correlation of GCC and SCC ADCs (interhemispheric and intercallosum correlation) were analyzed for the same $b$ values (right PRC ADC $b_{1000}$ vs. left PRC $b_{1000}$; right PRC ADC $b_{3000}$ vs. left PRC $b_{3000}$; right HIP ADC $b_{1000}$ vs. left HIP ADC $b_{1000}$; right HIP ADC $b_{3000}$ vs. left HIP ADC $b_{3000}$; GCC ADC $b_{1000}$ vs. SCC ADC $b_{1000}$; GCC ADC $b_{3000}$ vs. SCC ADC $b_{3000}$). Next, the relationships between diffusion trends within each ROI (intra-ROI correlations: right PRC ADC $b_{1000}$ vs. ADC $b_{3000}$; left PRC ADC $b_{1000}$ vs. ADC $b_{3000}$; right HIP ADC $b_{1000}$ vs. ADC $b_{3000}$; left HIP ADC $b_{1000}$ vs. ADC $b_{3000}$; GCC ADC $b_{1000}$ vs. ADC $b_{3000}$; SCC ADC $b_{1000}$ vs. ADC $b_{3000}$) were analyzed with the same statistical test.

(b) Because data were obtained with two different $b$ values and a drop in ADC was expected when DWI was carried out with a high $b$ value, we first assessed the significance of ADC drop within each ROI (intrazonal changes) by means of Student's paired $t$ test. Furthermore, intrazonal changes in different brain areas were compared with each other (PRC vs. HIP vs. GCC vs. SCC). For that purpose, in each anatomical area, low-$b$-value and high-$b$-value ADC means were subtracted, and the results were compared with one-factor ANOVA and Bonferroni correction in order to assess differences in the ADC drop between areas. Finally, the trend of intrazonal diffusion change within an ROI was compared with its corresponding ROI with Pearson parametric

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The column on the left and the row on top correspond to analyzed ROI. Each of the boxes represents one of the multiple comparisons performed and shows the mean difference of ADC means (in parentheses) and the $P$ value for the particular comparison. White boxes represent low-$b$-value comparisons. Gray boxes represent high-$b$-value comparisons.
regression test. The dependence of intrazonal changes (interhemispheric and intercallosum drop correlation: right to left PRC; right to left HIP; GCC to SCC) was evaluated in order to analyze the relationship of the ADC drop between left and right PRC; left and right HIP; and CC ROI. Statistical analyses were performed with SPSS for Windows software (Chicago, IL), version 13.0.

3. Results

In the preliminary analysis of the effect of VRF, ANOVA (Table 1) did not show significant ADC differences between the two clinical groups in any of the ROI compared. Therefore, it was assumed that VRF did not introduce changes in ADC measurements.

3.1. Interzonal, interhemispheric and intercallosum comparisons

The ANOVA for interzonal comparisons (PRC vs. HIP vs. CC) demonstrated significant differences between the ADCs of the three brain areas studied (P < 0.0001 for both b values) (Table 2A). Bonferroni correction (Table 2B) also showed a significant difference between the ADCs of PRC and HIP, and between the ADCs in the GCC vs. SCC. Besides the interzonal (white vs. gray vs. black bars) and interhemispheric and intercallosum (white vs. white; gray vs. gray; black vs. black) differences, note the different ADC values for low and high b values in the hemispheric ROI and the callosum ROI. While the intra-ROI ADC drop is similar for both the PRC and the HIP, it is far greater in the SCC and GCC. Dotted double arrows (*) indicate significant intrazonal changes (P < 0.0001 for all comparisons).

![Fig. 2. Intrazonal differences in PRC, HIP and CC ADCs according to b value. The graph represents the mean ADC values (vertical axis; in μm²/ms) of the left and right hemisphere ROI and callosum ROI (horizontal axis). White bars, PRC; gray bars, HIP; black bars, CC. High-b-value ADCs are represented by outer bars. Low-b-value ADCs are represented by inner bars. Besides the interzonal (white vs. gray vs. black bars) and interhemispheric and intercallosum (white vs. white; gray vs. gray; black vs. black) differences, note the different ADC values for low and high b values in the hemispheric ROI and the callosum ROI. While the intra-ROI ADC drop is similar for both the PRC and the HIP, it is far greater in the SCC and GCC. Dotted double arrows (*) indicate significant intrazonal changes (P < 0.0001 for all comparisons).](image)

![Fig. 3. Regression plots of interhemispheric and intercallosum correlations. (A and B) ADC values of right (columnwise) and left (rowwise) hemispheric ROI, and (C) ADC values of the GCC (columnwise) and SCC (rowwise) ROI. In each anatomical area, the upper and lower plots represent low-b-value and high-b-value measurements, respectively. The black box within each plot shows the r and P values for each analysis. The plots show significant moderate-to-strong interhemispheric ADC dependence at both b values. In contrast, the CC ROI did not show significant dependence with either low or high b values.](image)
and HIP. For both b values, the ADC was lower in the PRC than in the HIP (all differences P<.0001). However, diffusion values in the CC were different from those in the PRC and HIP, depending on the applied b value (Fig. 2). As a result, Bonferroni correction (Table 2B) showed that, with a low b value, the GCC, together with the HIP, had the greatest diffusion, showing a nonsignificant difference with the right HIP (P=.100) and the left HIP (P=.931), and a significant difference with the right and left PRC (both Ps <.0001). However, the ADC of the GCC was significantly lower than the ADCs of the PRC and HIP, with a high b value (all Ps <.0001). On the other hand, with a low b value, the ADC of the SCC was lower than the ADCs of the right and left HIP (all Ps <.0001), and was comparable to the ADC of the PRC (right PRC, P=.884; left PRC, P=1.000). However, with a high b value, the SCC showed the lowest diffusion (all Ps <.0001).

One-factor ANOVA for interhemispheric comparisons (Table 2A) indicated that, with a low b value, diffusion in the PRC was significantly higher in the left hemisphere than in the right hemisphere (P=.027). However, the ADCs of the left and right PRC did not differ with a high b value (P=.227). Bonferroni correction (Table 2B) did not demonstrate a significant interhemispheric difference in PRC (P=1.0), regardless of the b value. Disagreement between ANOVA and Bonferroni correction results may indicate that ADC asymmetry was scarce in PRC or that sample size was not large enough to obtain significance with the test of multiple comparisons. Although it is interesting for the analysis of asymmetries, we did not initially consider intra-ROI dependence. Right and left HIP ADC measurements were not significantly different according to ANOVA (b1000, P=.787; b3000, P=.498) and Bonferroni correction (for both b values, P=1.000). Diffusion within the CC (GCC vs. SCC) was always different (intcallosum comparisons) regardless of the b value (Ps <.0001 for ANOVA and Bonferroni correction) (Tables 2A and 2B).

The interhemispheric correlations of the PRC and HIP were positive and significant with both b values (Fig. 3). For a low b value, Pearson regression parametric test showed moderate dependence between the right and left HIP (r=.485, P<.0001), and strong dependence between the right and left PRC (r=.620, P<.0001). For a high b value, right-to-left dependence was moderate in the PRC (r=.566, P<.0001) and strong in the HIP (r=.675, P<.0001). Intercallosal correlations (GCC b1000 vs. SCC b1000; GCC b3000 vs. SCC b3000) were not significant at either b value (b1000, r=.232, P=.106; b3000, r=−.071, P=.625). Accordingly, we concluded that the ADC in one hemisphere depends on its counterpart, while the ADC at one end of the CC is independent of the ADC at the other end.

Intra-ROI correlation was positive and significant in both hemispheres (Table 3). Pearson test showed strong dependence in the right PRC and HIP (r=.612, P<.0001; r=.638, P<.0001), and moderate dependence in the left PRC and HIP (r=.510, P<.0001; r=.542, P<.0001). For the CC, intra-ROI dependence was moderate in the SCC (r=.455, P<.0001) but was not significant in the GCC (r=.277, P=.052). As a result, unlike hemispheric and SCC ROI,
3.2. Intrazonal changes

In all the anatomical areas assessed, when the applied \( b \) value was shifted from 1000 to 3000 s/mm\(^2\), the ADC measurement dropped significantly \( (P<.0001) \) (Fig. 2). One-factor ANOVA comparing intrazonal ADCs showed significant differences between the PRC, HIP, GCC and SCC \( (P<.0001) \) (Table 4). Bonferroni correction showed significant differences between hemispheric and CC intrazonal changes \( (P<.0001) \) and between GCC and SCC intrazonal changes \( (P<.0001) \) (Fig. 4). There were no differences between PRC and HIP (Fig. 4). As a result, we can conclude that, unlike the two brain areas (i.e., PRC and HIP) that did not differ in their \( b \)-value-related drop in diffusion measurements, the GCC and SCC, which are parts of the same structure, had quantitatively different diffusion drops from the PRC and HIP and also from each other.

Regarding the interhemispheric and intercallosum drop correlation, Pearson parametric regression showed weak positive dependence between the right and left PRC \( (r=.374, P=.007) \), and moderate dependence between the right and left HIP \( (r=.546, P<.0001) \). On the contrary, there was no significant dependence between GCC and SCC \( (r=.000, P=.999) \) (Fig. 5).

4. Discussion

Our results point out that, regardless of the \( b \) value used, different brain areas have different ADC measurements, and the use of different \( b \) values can provide information about subtle structural differences. Increasing the \( b \) value always produced a drop in ADC that varied depending on brain area. Accordingly, diffusion with low and high \( b \) values can be remarkably different in different tissues.

In agreement with previous reports [5, 23, 24], brain diffusion in our patients was different across the several areas analyzed. Since we assessed diffusion in gray matter and two different white matter regions, ADC differences also reveal differences in anatomical structure. As in other reports, interhemispheric asymmetries are occasionally

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**Fig. 5.** Regression plots of interhemispheric and intercallosum ADC drop correlations. The axes in each plot represent the subtraction of the mean ADC for the corresponding ROI. Within each plot, the black box shows the \( r \) and \( P \) values for each analysis. The plots show a significant interhemispheric correlation that is stronger in the HIP than in the PRC. There was no significant dependence in the intercallosum ADC drop.

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**Fig. 6.** The two upper longitudinal axons represent the right PRC, and the two lower axons represent the left PRC. Darker circles represent perpendicular axons in a tissue that is comprised of crossed fibers. Considering the difference in distance between the axons of the two PRCs (the right PRC is represented by a narrower extracellular space), the fast components of diffusion (represented by Molecule 1a) in the right PRC are more restricted than those in the left PRC (represented by Molecule 1b). On the other hand, because axons are of similar size in both PRCs, intracellular diffusion would be comparable in the two (Molecules 2a and 2b). However, if the slow components in clinical DWI also correspond to the extracellular space, the diffusion behaviors of Molecules 3a and 3b would be similar.
The idea that the result of increasing the attenuation represented by the fast (stressed by the low $b$ value) is simply a strengthening of diffusion. Indeed, it may state that the slow component represents diffusion in the extracellular space [14]. Using DWI with a $q$-space technique, recent work partially supports that idea and suggests that high $b$ values emphasize intracellular diffusion, but only within axons [2,12]. However, other reports do not support the intracellular and extracellular compartments hypothesis [17,18] and suggest that high $b$ values emphasize intracellular diffusion.

The ultrastructural reasons for ADC differences related to the $b$ value have not been elucidated. However, based on the present findings, double $b$ value DWI analysis may provide a useful investigative approach. We know from previous research that, in the PRC, the subcortical white matter is highly isotropic and is comprised of crossed fibers, with interhemispheric asymmetries in fractional anisotropy [23,28]. Thus, the weak interhemispheric drop dependence we detected in the PRC supports a right-to-left anisotropy difference. If we consider that the size of neuronal fibers is similar in both PRCs, the intracellular and extracellular compartments hypothesis could explain why the ADCs in both PRCs were similar with a high $b$ value (i.e., similar intracellular diffusion) but different with a low $b$ value (i.e., different extracellular diffusion) (Fig. 6). However, our findings could also be explained by a hypothesis based on extracellular diffusion, since the extracellular space did not hinder the slow component of diffusion in the PRCs, despite their asymmetry (Fig. 6). By the same reasoning and in agreement with the symmetry of HIP neuronal density [31,32], both theories would also explain the constant symmetric HIP diffusion and the stronger interhemispheric drop dependence we observed.

More than the hemispheric ROI, fiber differences in the CC can provide information about the final determinants of diffusion in conventional DWI. The GCC is comprised of thin poorly myelinated fibers, while thicker highly myelinated fibers comprise the SCC. As a result, the SCC has a wider intra-axonal space and more constricted and tortuous extracellular space [33,34]. The wider extracellular space in the GCC can facilitate parallel and perpendicular diffusion much more than the compact SCC. However, beyond mechanical confines, other proposed forms of compartmentation of extracellular water (linked to the fast exchange of water molecules in the myelin sheath or surface-versus-volume water) can also modulate signal differences in different types of tissue [35,36].

In summary, less restriction of the fast and slow diffusion components in the wider and less tortuous extracellular space of the less myelinated GCC can explain why its ADC values are higher than those in the SCC (Molecule 3b) as compared to the GCC (Molecule 3a). Fig. 7. In the CC, the GCC and the SCC differ in intracellular and extracellular spaces. The wider and less tortuous extracellular space in the GCC allows Molecule 1a to diffuse more freely than Molecule 1b in the extracellular space of the SCC. In fact, the anisotropy of the fast component would be much higher in the SCC. Accordingly, the GCC ADC is higher than the SCC ADC. On the other hand, the intracellular space is wider in the SCC. As a result, the intracellular diffusion of Molecule 2b in the SCC should be higher than that of Molecule 2a in the GCC. As the extracellular space is narrower and more tortuous in the SCC and the fibers in the SCC are highly myelinated, the slow components outside the axons must be more restricted in the SCC (Molecule 3b) than in the GCC (Molecule 3a).
was greater than that of SCC, independent of the b factor. It can also explain why GCC and SCC ROI had such different diffusion behaviors. On the other hand, if slow components of diffusion were representative of intracellular space and were detected by increasing the b value, they would have been more conspicuous in wider SCC fibers. Therefore, the hypothesis of intracellular and extracellular compartmental diffusion does not explain why, with a high b value, the GCC ADC is higher than the SCC ADC (Fig. 7). Thus, in diffusion does not explain why, with a high hypothesis of intracellular and extracellular compartmental diffusion behaviors. On the other hand, if slow components of diffusion were representative of intracellular space and that relative volume fractions and extracellular tortuosity; and that intracellular diffusion has minor influence [37,38].

This study has several limitations. First, patients with VRF were included and may have introduced uncontrolled bias to ADC measurements. However, no statistically significant ADC differences were detected between patients with and without VRF. Second, although ROI were carefully drawn, we cannot rule out CSF contamination, particularly in the PRC. Nevertheless, in contrast to more sophisticated and less accessible analytic models for the elimination of CSF effect, the use of conventional software makes our study easily reproducible in any MRI system. Third, we did not use diffusion tensor images, which would provide us with more information [39]. However, the simplicity of our design does not invalidate the results, particularly now that diffusion tensor imaging is less available, postprocessing is more complicated and data acquisition is longer than that of DWI [40,41]. Fourth, both DWI sequences were carried out using a different TE. Since the TE in the high-b-value sequence was longer, there was a difference in the signal/noise ratio in sequences that could interfere with ADC measurements. However, this effect would not account for the differences in diffusion that we observed. Finally, our two-point measuring method cannot achieve a full biexponential parameterization, and ADC results may differ depending on the specific b value selected. Parameterization is needed to explain the complex phenomenon of diffusion, including diffusion constants, relative fractions of fast and slow components, exchange time, extracellular tortuosity and intracellular diffusion restriction. However, parameterization is not easy to perform, is difficult to interpret and is beyond the scope of our design.

In conclusion, the analysis of ADC measurements with b values of 1000 and 3000 s/mm² makes the assessment of different brain structures possible in clinical DWI, probably emphasizing the distance between membranes, their degree of myelination and the complexity of extracellular space.

Acknowledgments

We would like to give thanks to Dr. Laura Oleaga for her comments to the final version of this article, and Dr. Andrés Carrillo, for his invaluable statistical support.

References


[38] Pfeuffer J, Provencher SW, Gruetter R. Water diffusion in rat brain in vivo as detected at very large b values is multicompartmental. MAGMA 1999;8:98–108.


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