Interimager Variability in ADC Measurement of the Human Brain

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Purpose: Routine clinical practice involves the application of diverse scanning parameters that can affect apparent diffusion coefficient (ADC) values. We evaluated interimager variability in ADC values with respect to their potential effect in clinical applications.

Methods: In 7 healthy volunteers, we obtained diffusion-weighted (DW) images using routine clinical parameters and 1.5- (n = 9) and 3-tesla (n = 3) magnetic resonance (MR) imagers from 5 different vendors, performing 84 MR imaging studies. To evaluate the differences in ADC values among the imagers, vendors, and magnetic field strengths, we measured the mean pixel values of the frontal white matter and thalamus (gray matter) in both cerebral hemispheres of the 7 volunteers and used repeated-measures analysis of variance for multiple comparisons.

Results: The laterality of ADC values in the bilateral structures ranged from one to 3% for the 12 imagers. Although the relative difference in ADC values of white matter was 7% for scanners yielding the highest and lowest mean ADC values (P < 0.01), it was within 2 to 4% for instruments from the same vendors. For gray matter, the interimager difference was 4 to 12%, even among the same vendors (P < 0.05). Among the 3T imagers, the difference for white and gray matter was approximately 3%.

Conclusions: There were significant interimager differences in ADC values, especially with respect to gray matter. Taking into consideration the existing laterality, however, the differences among our 3T imagers may be acceptable despite the use of diverse scanning parameters. In routine clinical practice, the existing variability must be considered imager by imager.

Keywords: apparent diffusion coefficient (ADC), diffusion-weighted (DW) imaging, interimager variability

Introduction

Diffusion-weighted (DW) imaging using the quantitative apparent diffusion coefficient (ADC) value has been widely used to characterize tissues in patients with acute ischemic stroke, brain tumors, and other disorders.1–10 However, earlier studies that measured the ADC values of white and gray matter encountered significant variability related to instrument vendors, imagers, coil systems, and field strengths used during magnetic resonance (MR) imaging.11–13 In 2008, Sasaki and associates12 reported approximately 15% lower ADC values generated by imagers from one vendor than other vendors. The authors also demonstrated average relative differences of 4 to 9% among imagers from the same vendors and intra-individual differences of 3 to 5% on repeat images acquired on the same scanner. In contrast, another study demonstrated a negligible difference between 1.5T and 3T imagers from the same vendor.14 In
these previous studies, the scanning parameters were set as identically as possible to ensure the comparability of the imagers.\(^{12-14}\)

Routine clinical practice involves the application of diverse scanning parameters that can affect ADC values.\(^15\) The variability in ADC values generated by different MR imagers with diverse scanning parameters in the same patient must be considered when consulting with other institutions, conducting follow-up at other institutions, and replacing imagers. We evaluated interimager variability in ADC values for its potential effects in clinical applications, enrolling 7 healthy volunteers and comparing ADC values routinely obtained using nine 1.5T and three 3T MR imagers.

### Materials and Methods

#### Subjects

Our institutional review board approved this study, and written informed consent was obtained from all subjects. We enrolled 7 healthy adult volunteers (5 men, 2 women) aged 21 to 45 years (mean age 24.7 years) at 9 institutions. Between March 13 and May 20, 2011, we acquired a total of 84 scans on 12 MR imagers—nine 1.5T and three 3T MR imagers from 5 vendors (Philips Healthcare, Best, The Netherlands [Imagers A, B, C, D, E]; Siemens Medical Solutions, Erlangen, Germany [Imagers F, G, H]; GE Healthcare, Milwaukee, WI, USA [Imagers I, J]; Hitachi Medical Corp., Tokyo, Japan [Imager K]; and Toshiba Medical Systems, Tokyo, Japan [Imager L]) (Table 1).

#### DW imaging

DW images were acquired in the transverse plane using a spin-echo echo-planar imaging sequence with 3 orthogonal motion-probing gradients. Taking into consideration clinical situations, we set all parameters except field of view (FOV) identical to those used in routine clinical examinations (Table 2); FOV was fixed at 220 mm. ADC maps were calculated on a pixel-by-pixel basis with the software program of each MR unit. The acquired data were anonymized and collected in the Digital Imaging and Communications in Medicine (DICOM) format.

#### Data analysis

Using a DICOM viewer (ViewR; Yokogawa Electric Corp., Tokyo, Japan), one of the authors (N.T.), with 7 years of experience in MR imaging of the brain who was blinded to subject and imager identity, measured the ADC values of the bilateral frontal white matter and thalamus (gray matter) in 3 manually placed regions of interest (ROIs) measuring 100 mm\(^2\), and results were averaged. In each subject, the ROIs were placed to match precisely as possible on ADC maps obtained with the 12 MR imagers. We calculated mean (± standard deviation)

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**Table 1.** Magnetic resonance imaging systems used in the multi-institutional study

| Imager* | Vendor                          | Field strength (tesla) | Coil channels | Maximum gradient strength (mT·m\(^{-1}\)) | Slew rate (T·m\(^{-1}\)·s\(^{-1}\)) |
|---------|--------------------------------|------------------------|---------------|-------------------------------------------|----------------------------------|
| A       | Philips Healthcare             | 1.5                    | 16            | 30                                        | 75                               |
| B       | Philips Healthcare             | 1.5                    | 1             | 30                                        | 150                              |
| C       | Philips Healthcare             | 1.5                    | 8             | 33                                        | 160                              |
| D       | Philips Healthcare             | 3                      | 8             | 80                                        | 200                              |
| E       | Philips Healthcare             | 3                      | 32            | 80                                        | 200                              |
| F       | Siemens Medical Solutions     | 1.5                    | 8             | 20                                        | 50                               |
| G       | Siemens Medical Solutions     | 1.5                    | 12            | 45                                        | 200                              |
| H       | Siemens Medical Solutions     | 3                      | 12            | 40                                        | 200                              |
| I       | GE Healthcare                  | 1.5                    | 8             | 33                                        | 120                              |
| J       | GE Healthcare                  | 1.5                    | 8             | 50                                        | 150                              |
| K       | Hitachi Medical Corporation   | 1.5                    | 8             | 33                                        | 150                              |
| L       | Toshiba Medical Systems       | 1.5                    | 5             | 35                                        | 200                              |

* A, Philips Gyroscan Intera 1.5T power; B, Philips Gyroscan Intera 1.5T Master; C, Philips Achieva 1.5T Nova Dual; D, Philips Achieva 3 T X-Series; E, Philips Achieva 3 T TX; F, Siemens MAGNETOM Symphony Syngo; G, Siemens MAGNETOM Avanto; H, Siemens MAGNETOM Trio, A Tim System; I, GE Signa HDxt 1.5T; J, GE Signa EXCITE HD 1.5T TwinSpeed; K, Hitachi ECHELON Vega; L, Toshiba EXCELART Vantage.
ADC values for the white and gray matter in 14 cerebral hemispheres and calculated the relative differences of laterality of the ADC values between bilateral structures in the 7 subjects to test the intraimager variability of the 12 MR imagers.

Statistical analysis
We assessed interimager variability in ADC values of white and gray matter for the different scanners, vendors, and magnetic field strengths. We calculated the absolute and relative differences for imagers that provided the highest and lowest mean ADC values among the imagers categorized by vendor and field strength (1.5T, 3T), used Wilcoxon matched-pairs signed rank test to compare differences between 2 scanners and repeated-measures analysis of variance and post hoc test to assess differences among 3 or more imagers. Statistical analyses were performed using the MedCalc (version 9.2.1.0; Mariakerke, Belgium) software program. \( P < 0.05 \) was considered statistically significant.

Results
We could obtain ADC maps using the 12 imagers in each subject (Fig. 1). ADC values on the 12 imagers ranged from \( 716 \times 10^{-6} \) to \( 769 \times 10^{-6} \) mm\(^2\)/s for white matter and from \( 683 \times 10^{-6} \) to \( 770 \times 10^{-6} \) mm\(^2\)/s for gray matter (Figs. 2 and 3, Table 3). The laterality of ADC values ranged from 1.0 to 2.3% for white matter and 1.3 to 2.9% for gray matter.

The relative interimager difference in the ADC value of white matter was 7.1% for scanners yielding the highest and lowest mean ADC values \( (P < 0.01) \). The relative difference in the ADC value of white matter on scanners from the same vendors was within 1.8 to 3.7%; this parameter was within 2.9% for the 3T imagers (Table 4).

For gray matter, the relative interimager difference was 4.4 to 11.9%, even for the same vendors \( (P < 0.05) \). Among the 3T scanners (D, E, H), the differences for gray matter were 3.4% (D versus E), 3.2% (D versus H), and 2.7% (E versus H).

Discussion
The ADC values generated from DW images represent a quantitative indicator that can be used as a clinical biomarker to assess diagnosis, prognosis, and tumor response to therapy.\(^{1-10} \) Although these parameters are thought to correlate inversely with tumor cellularity, their clinical value remains controversial because of the significant overlap in ADC values among different tumors and different grades of malignancy.\(^{6-10} \) Although earlier studies set scanning parameters as identically as possible to ensure comparability of the instruments, they pointed to interimager variability in ADC values.\(^{12-14} \) We were concerned with the marked variability between imagers using routine clinical settings and therefore designed the current volunteer study. Nevertheless, whether or not scanning pa-

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### Table 2. Scanning parameters for diffusion-weighted imaging

| Imager | TR (ms) | TE (ms) | Number of acquisitions | Reduction factor | Scan time (s) | Matrix size | Section thickness (mm) | Intersection gaps (mm) | Number of slices |
|--------|---------|---------|------------------------|-----------------|--------------|-------------|------------------------|------------------------|------------------|
| A      | 3229    | 79      | 1                      | 2               | 38.7         | 136 x 109   | 5                      | 1                      | 22               |
| B      | 3544    | 74      | 1                      | NA              | 24           | 112 x 89.6  | 5                      | 1                      | 22               |
| C      | 3486    | 52      | 1                      | 2               | 45           | 112 x 112   | 5                      | 1                      | 22               |
| D      | 3773    | 68      | 1                      | 2               | 45.3         | 176 x 144   | 5                      | 1                      | 22               |
| E      | 3270    | 63      | 1                      | 2.5             | 39           | 192 x 154   | 5                      | 1                      | 20               |
| F      | 3500    | 99      | 1                      | 2               | 58           | 128 x 115   | 5                      | 1                      | 19               |
| G      | 4500    | 85      | 3                      | 2               | 68           | 128 x 128   | 5                      | 1                      | 23               |
| H      | 3600    | 81      | 3                      | 2               | 56           | 128 x 128   | 5                      | 1                      | 22               |
| I      | 6000    | 82.8    | 2                      | 2               | 54           | 192 x 128   | 5                      | 1                      | 22               |
| J      | 8000    | 77      | 2                      | 2               | 64           | 192 x 128   | 5                      | 1.5                    | 22               |
| K      | 3300    | 87      | 4                      | 2               | 57           | 192 x 136   | 5                      | 1                      | 22               |
| L      | 5000    | 95      | 1                      | 1.8             | 30           | 160 x 128   | 6                      | 1.2                    | 20               |

Note: FOV, field of view; NA, not applicable; TE, echo time; TR, repetition time; reduction factor, reduction factor in parallel imaging. The imagers correspond to those listed in Table 1. With the exception of FOV, all parameters were identical to those used in routine clinical examinations using the 12 magnetic resonance imagers. The FOV was fixed at 220 mm.
Parameters differed, we found relative differences of 7% for white matter and 12% for gray matter between the select imagers that provided the highest and lowest mean ADC values. The relative difference in the ADC values of white matter, within 2 to 4% among the same vendors, was small and compatible with reported intraimager differences. Moreover, among our 3T imagers, the relative differences in ADC values of white and gray matter were approximately 3%.

To test intraimager variability, we evaluated the laterality of ADC values in bilateral structures and...
found laterality of one to 3% for the 12 imagers. Some authors have recommended evaluating diffusion abnormalities using the ADC ratio on the contralateral side but not the absolute ADC value.4–7,12 In contrast, Rumboldt and colleagues16 suggested that it is preferable to use absolute ADC value rather than ADC ratio for differentiating pediatric brain tumors because of brain changes with age, white matter anisotropy, and partial volume averaging effects. Laterality can affect the ADC ratio, and this must be recognized in clinical practice. Taking into consideration the existing laterality, the inter-

### Table 3. Apparent diffusion coefficient (ADC) values obtained with 12 magnetic resonance imagers for white and gray matter in 14 cerebral hemispheres

| Imager | Field strength (tesla) | ADC (10⁻⁶ mm²/s) White matter | Laterality (%) | ADC (10⁻⁶ mm²/s) Gray matter | Laterality (%) |
|--------|------------------------|-------------------------------|---------------|------------------------------|---------------|
| A      | 1.5                    | 738 ± 12                      | 1.4 ± 0.9     | 743 ± 12                     | 2.2 ± 0.9     |
| B      | 1.5                    | 738 ± 10                      | 1.1 ± 0.7     | 732 ± 21                     | 1.3 ± 1.1     |
| C      | 1.5                    | 727 ± 13                      | 1.1 ± 0.9     | 734 ± 21                     | 1.3 ± 1.5     |
| D      | 3                      | 718 ± 13                      | 1.4 ± 1.5     | 704 ± 19                     | 2.3 ± 1.7     |
| E      | 3                      | 716 ± 10                      | 2.3 ± 0.8     | 728 ± 28                     | 2.9 ± 0.9     |
| F      | 1.5                    | 737 ± 11                      | 1.0 ± 0.6     | 734 ± 22                     | 2.6 ± 1.4     |
| G      | 1.5                    | 756 ± 15                      | 1.2 ± 1.1     | 757 ± 16                     | 2.3 ± 1.3     |
| H      | 3                      | 731 ± 18                      | 1.7 ± 1.1     | 724 ± 22                     | 2.7 ± 1.0     |
| I      | 1.5                    | 769 ± 17                      | 2.1 ± 1.0     | 770 ± 23                     | 2.5 ± 1.4     |
| J      | 1.5                    | 768 ± 20                      | 1.4 ± 0.7     | 683 ± 12                     | 2.5 ± 1.5     |
| K      | 1.5                    | 719 ± 10                      | 1.6 ± 1.3     | 709 ± 16                     | 1.8 ± 1.1     |
| L      | 1.5                    | 730 ± 16                      | 2.2 ± 1.4     | 703 ± 29                     | 1.6 ± 1.4     |

The imagers correspond to those listed in Table 1. *We calculated the relative differences between bilateral structures in the 7 volunteers. The values indicate the mean ± standard deviation.

### Table 4. Absolute and relative differences in apparent diffusion coefficient (ADC) value among magnetic resonance imagers categorized by vendor and field strength

| Category | Imagers | ADC (%) White matter | ADC (%) Gray matter |
|----------|---------|-----------------------|---------------------|
| All imagers | E, I* | 53 ± 14 (7.1 ± 1.8) | I, J* | 87 ± 29 (11.9 ± 3.9) |
| Philips Healthcare | B, E* | 22 ± 13 (3.0 ± 1.8) | A, D* | 38 ± 22 (5.3 ± 3.1) |
| Siemens Medical Solutions | G, H* | 27 ± 16 (3.7 ± 2.2) | G, H* | 33 ± 23 (4.4 ± 3.1) |
| GE Healthcare | I, J | 14 ± 11 (1.8 ± 1.4) | I, J** | 87 ± 29 (11.9 ± 3.9) |
| 1.5T | I, K* | 50 ± 20 (6.7 ± 2.6) | I, J* | 87 ± 29 (11.9 ± 3.9) |
| 3T | E, H | 21 ± 15 (2.9 ± 2.1) | D, E* | 24 ± 17 (3.4 ± 2.3) |

Note: ADC = 10⁻⁶ mm²/s. The imagers correspond to those listed in Table 1. We compared differences between imagers that provided the highest and lowest mean ADC values among the categories. The values indicate the mean ± standard deviation.

* P < 0.05 (repeated-measures analysis of variance and post hoc test)
** P < 0.05 (Wilcoxon matched-pairs signed rank test)
imager differences among our 3T imagers may be acceptable.

Reported ADC values ranged from $650 \times 10^{-6}$ to $780 \times 10^{-6}$ mm$^2$/s for the frontal white matter and from $700 \times 10^{-6}$ to $800 \times 10^{-6}$ mm$^2$/s for the thalamus.12–14,17 We observed interimager variability in the ADC values of gray and white matter and a wide range of ADC values of gray matter that was probably attributable to tissue-specific characteristics. One histological difference between gray and white matter is capillary perfusion, as suggested by the intravoxel incoherent motion (IVIM) theory.20 Signal intensity of the thalamus may vary with some coil systems because of the location of the deep gray matter.21 Further investigations are required to resolve the current findings for gray matter.

Phantom studies have suggested an inverse relationship between field strength and ADC values of brain metabolites.11 Huisman’s group13 demonstrated significantly lower ADC values of white and gray matter at 3T than 1.5T. Although these data are compatible with our results, other studies concluded that the ADC values at 1.5T and 3T are almost identical.14,17 Interimager variability must be considered on an imager-by-imager basis.

In addition to the instruments themselves, coil systems,12 scanning parameters,15,22 and age of subjects18,19 elicit variations in ADC values. An animal study demonstrated that the diffusion time for the b-value affects the values of diffusion parameters, including the ADC.22 Although we fixed the b-value at 1,000 s/mm$^2$, diffusion times were dependent on tuning by the vendors. Because our study focused on the role of ADC values in the clinical setting, we used identical coil systems and parameters, except FOV, to those used in routine clinical studies performed with the 12 MR imagers. Because of the variability among imagers, scanning parameters must be tailored to individual instruments. In addition, consensus measurements for ADC values must be established because potential observer bias may affect reported ADC values.9,17 To eliminate interobserver variability in this study, a single observer measured ADC values. Technical improvements and diagnostic training may result in the acquisition of identical ADC values.

Our study has several limitations. Subjects were healthy volunteers because no suitable phantoms are currently available to facilitate ADC assessments, so physiologic fluctuations may have affected interimager variability. Although we placed ROIs as identically as possible on the ADC maps obtained with the 12 MR imagers in each subject, the ADC measurements may have yielded varying ADC values. Furthermore, we used 12 imagers to acquire scans in the course of approximately 2 months. Because we intended to simulate practical situations, such as consultations from and comparative follow-up examinations at other institutions as well as replacement of imagers, we do not believe the use of volunteers, manual placement of ROIs, and the 2-month term affected our findings. Finally, the results of this study were limited to data obtained with our 12 MR imagers; other imagers might yield different results. The existing variability should be evaluated with each MR imager even from the same vendors.

Conclusions

In this study, ADC values differed significantly among imagers, especially with respect to gray matter. However, taking into consideration the existing laterality of one to 3% in bilateral structures, the relative difference of 3% among our 3T imagers may be acceptable. In routine clinical practice using different MR imagers with diverse scanning parameters, the existing variability must be considered based on the imager used. Further investigations of intra- and interimager variability should provide the opportunity for technical improvements to generate identical ADC values.

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References

1. Nakamura H, Murakami R, Hirai T, Kitajima M, Yamashita Y. Can MRI-derived factors predict the survival in glioblastoma patients treated with postoperative chemoradiation therapy? Acta Radiol 2013; 54:214–220.
2. Murakami R, Sugahara T, Nakamura H, et al. Malignant supratentorial astrocytoma treated with postoperative radiation therapy: prognostic value of pretreatment quantitative diffusion-weighted MR imag-
3. Higano S, Yun X, Kumabe T, et al. Malignant astrocytic tumors: clinical importance of apparent diffusion coefficient in prediction of grade and prognosis. Radiology 2006; 241:839–846.

4. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. Radiology 2000; 217:331–345.

5. Desmond PM, Lovell AC, Rawlinson AA, et al. The value of apparent diffusion coefficient maps in early cerebral ischemia. AJNR Am J Neuroradiol 2001; 22:1260–1267.

6. Hayashida Y, Hirai T, Morishita S, et al. Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. AJNR Am J Neuroradiol 2006; 27:1419–1425.

7. Provenzale JM, Mukundan S, Barboriak DP. Diffusion-weighted and perfusion MR imaging for brain tumor characterization and assessment of treatment response. Radiology 2006; 239:632–649.

8. Murakami R, Hirai T, Kitajima M, et al. Magnetic resonance imaging of pilocytic astrocytomas: usefulness of the minimum apparent diffusion coefficient (ADC) value for differentiation from high-grade gliomas. Acta Radiol 2008; 49:462–467.

9. Murakami R, Hirai T, Sugahara T, et al. Grading astrocytic tumors by using apparent diffusion coefficient parameters: superiority of a one- versus two-parameter pilot method. Radiology 2009; 251:838–845.

10. Bode MK, Ruohonen J, Nieminen MT, Pyhtinen J. Potential of diffusion imaging in brain tumors: a review. Acta Radiol 2006; 47:585–594.

11. Guilfoyle DN, Suckow RF, Baslow MH. The apparent dependence of the diffusion coefficient of N-acetylaspartate upon magnetic field strength: evidence of an interaction with NMR methodology. NMR Biomed 2003; 16:468–474.

12. Sasaki M, Yamada K, Watanabe Y, et al. Variability in absolute apparent diffusion coefficient values across different platforms may be substantial: a multivendor, multi-institutional comparison study. Radiology 2008; 249:624–630.

13. Huisman TA, Loenneker T, Barta G, et al. Quantitative diffusion tensor MR imaging of the brain: field strength related variance of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) scalars. Eur Radiol 2006; 16:1651–1658.

14. Hunsche S, Moseley ME, Stoeter P, Hedehus M. Diffusion-tensor MR imaging at 1.5 and 3.0T: initial observations. Radiology 2001; 221:550–556.

15. Ogura A, Hayakawa K, Miyati T, Maeda F. Imaging parameter effects in apparent diffusion coefficient determination of magnetic resonance imaging. Eur J Radiol 2011; 77:185–188.

16. Rumboldt Z, Camacho DL, Lake D, Welsh CT, Castillo M. Apparent diffusion coefficients for differentiation of cerebellar tumors in children. AJNR Am J Neuroradiol 2006; 27:1362–1369.

17. Brander A, Kataja A, Saastamoinen A, et al. Diffusion tensor imaging of the brain in a healthy adult population: normative values and measurement reproducibility at 3T and 1.5T. Acta Radiol 2010; 51:800–807.

18. Ni JM, Chen S, Liu JJ, Huang G, Shen TZ, Chen XR. Regional diffusion changes of cerebral grey matter during normal aging: a fluid-inversion prepared diffusion imaging study. Eur J Radiol 2010; 75:134–138.

19. Engelter ST, Provenzale JM, Petrella JR, DeLong DM, MacFall JR. The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. AJR Am J Roentgenol 2000; 175:425–430.

20. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988; 168:497–505.

21. Wang J, Qiu M, Constable RT. In vivo method for correcting transmit/receive nonuniformities with phased array coils. Magn Reson Med 2005; 53:666–674.

22. Wu EX, Cheung MM. MR diffusion kurtosis imaging for neural tissue characterization. NMR Biomed 2010; 23:836–848.