Aims and objectives

The diffusion imaging sequences are commonly applied in neuroimaging, for both research and diagnostic purposes [1-4]. These sequences provide information about the microstructural architecture of the tissues through their high sensitivity to motion of water molecules within or around the cells. Several metrics have been derived to quantify the information provided by the diffusion imaging sequences. Of these, fractional anisotropy (FA), mean diffusivity (MD) and mean kurtosis (MK) are the three most commonly used metrics [3, 4]. FA and MD are the metrics derived from diffusion tensor imaging (DTI); the former represents the degree of directional coherence and the latter the magnitude of diffusion [5]. MK is the metric derived from diffusion kurtosis imaging (DKI), and it quantifies the degree of deviation from Gaussian distribution [6].

Precision and accuracy of diffusion measurements are important to allow reproducibility and correct interpretation of the tissue's microstructural integrity. To achieve precision and accuracy of the measurements, the imaging parameters which can influence the diffusion characteristics must be known and kept identical throughout acquisitions. There have been reports about the effect of cardiac pulsation and the benefit of cardiac gating on quantification of FA and MD [7-10]. However, the findings and conclusions drawn are inconsistent among the reports: while some studies report of significant difference in uncertainty about the FA and MD values between the gated and non-gated acquisitions, the others suggest that the effect is minimal and negligible for group studies. The effect of cardiac pulsation and gating on MK -- a recently introduced diffusion imaging metric thought to be more sensitive to the microstructural abnormalities than FA and MD, is still not known. In addition, the effect of respiration (i.e., another major physiological motion) and the benefit of respiratory gating on the major diffusion imaging metrics have not been reported.

To understand the effect of respiration and cardiac pulsation on the major diffusion imaging metrics and the benefit of gating, this study evaluated if MK, FA and MD of the brain varied between the respiratory or cardiac-gated and non-gated acquisitions.
Methods and materials

Participants

This prospective study was approved by the local institutional review board. Written informed consent was obtained from all participants.

Eleven healthy volunteers (10 men and 1 woman; mean age ± standard deviation = 28.50 ± 5.97 years; age range = 22-41 years) were included in the study. No participants had any history of cardiac or respiratory diseases. The gross abnormalities of the brain were excluded by the T2-weighted images of the brain.

Imaging

All magnetic resonance imaging (MRI) acquisitions were performed using a 3.0T scanner (Achieva TX, Philips Medical Systems, Best, the Netherlands) and a 32-channel head coil. Padding and fixation device were used to minimize head motion during acquisitions. A fast spin-echo echo-planar imaging sequence was used to acquire diffusion imaging. The major imaging parameters were as follows: repetition time (TR)/ echo time (TE) = 2000 ms (non-gated and cardiac-gated acquisitions) or 3000 ms (respiratory-gated acquisition)/ 35 ms, b-value (b) = 0, 1000, 2000 s mm\(^{-2}\), the number of diffusion gradient directions = 32, the number of excitation (NEX) = 1, field of view (FOV) = 224 x 224 mm, matrix size = 76 x 72. Gated and non-gated acquisitions were performed in ten healthy volunteers (all men; mean age ± standard deviation = 27.30 ± 4.55 years; age range = 22-35 years). For gated acquisitions, acquisitions were set to perform at diastole and end expiration, so as to minimize pulsation and gross motion artifacts. Three 3-mm thick axial sections were obtained at the level of centrum semiovale, the body of bilateral lateral ventricles, and foramina of Monro (Fig 1). The acquisition time for each condition ranged from 4.5 to 10 minutes. The gated and non-gated acquisitions were performed consecutively.
Fig. 1: A scout sagittal image showing the slice positions (a) and example of the axial sections for diffusion imaging (b-d; b = the centrum semiovale level, c = the level of the body of bilateral lateral ventricles, d = the foramina of Monro level). For the axial sections, the echo-planar images with no diffusion weighting (b = 0 s mm$^{-2}$) are given.

References: Department of Radiological Technology, Hokkaido University Hospital - Sapporo/JP

To access repeatability of diffusion measurements, a total of ten non-gated acquisitions were performed in a volunteer (a 41-year old woman), at different occasions. A total of 43 axial sections were obtained to cover the whole brain.
As TR varied among the acquisitions, the effect of varying TR on the major diffusion imaging metrics was tested. For this purpose, non-gated diffusion imaging with TR ranging from 1000~5000 ms (with an interval of 500 ms) was performed in a volunteer (a 32-year-old man). All other imaging parameters were kept the same as those for comparison of gated and non-gated acquisitions.

**Image processing and evaluation**

The image sections were checked for consistency of the slice position among acquisitions and to rule out gross artifacts. Correction for motion during each acquisition and eddy current-related distortions was performed at the operator console. The MK, FA and MD maps were then constructed from the diffusion images (Diffusion Kurtosis Estimator) [11]. Co-registration of the maps between the gated and non-gated acquisitions and among the repeated acquisitions was done to correct for any minimal motion among acquisitions (SPM8). To avoid inclusion of the cerebrospinal fluid (CSF) from evaluation, an exclusion mask of the CSF was created. This was done through measurement of the signal intensity of the CSF on the echo-planar images with no diffusion weighting (b = 0 s mm$^{-2}$). The mask was subsequently applied on the corresponding diffusion imaging metric maps (MRICron).

Histogram analysis was employed to compare the major diffusion imaging metrics. The histograms of brain parenchyma were constructed for each acquisition and metric (ImageJ) [12]. Two major measures of the histograms -- the normalized peak height and peak position, were extracted (Fig 2). Repeatability of the diffusion measurements was determined by the intraclass correlation coefficient (ICC) values. ICC > 0.80 was considered repeatable. Variation in the major diffusion imaging metrics between the gated and non-gated acquisitions was determined by using Friedman and post hoc sign tests. P < 0.05 was considered significant.
Fig. 2: An example of histogram. An MK histogram is given.

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The effect of varying TR on the major diffusion imaging metrics was tested by using Pearson's product-moment correlation analysis. P < 0.05 was considered significant.
Fig. 1: A scout sagittal image showing the slice positions (a) and example of the axial sections for diffusion imaging (b-d; b = the centrum semiovale level, c = the level of the body of bilateral lateral ventricles, d = the foramina of Monro level). For the axial sections, the echo-planar images with no diffusion weighting (b = 0 s mm-2) are given.

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Fig. 2: An example of histogram. An MK histogram is given.

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Results

Repeatability of the diffusion measurements

The ICC values among ten repeated acquisitions were 0.997, 0.966, and 0.999, for MK, FA, and MD, respectively. Excellent repeatability was achieved for all three diffusion imaging metrics.

The effect of varying TR on the diffusion imaging metrics

Fig 3 summarizes the results of correlation between the major diffusion imaging metrics and TR. The peak position of MK and MD increased significantly with increase in TR (P # 0.01). The peak height of all imaging metrics and the peak position of FA did not vary significantly with variation in TR.

Any further evaluation of the peak position of MK and MD was performed after correction for variation in TR.

![Graphs showing correlation between the histogram measures of the major diffusion imaging metrics and TR.]

Fig. 3: The scatterplots showing correlation between the histogram measures of the major diffusion imaging metrics -- the normalized peak height (a) and peak position (b), and TR.

References: Department of Radiological Technology, Hokkaido University Hospital - Sapporo/JP
The effect of respiratory and cardiac gating

The histogram measures of the major diffusion imaging metrics, for the gated and non-gated acquisitions, are given in Fig 4-6. The corrected peak position of MK histograms for non-gated acquisition was significantly larger than that for cardiac-gated acquisition ($P = 0.021$). The normalized peak height of FA histograms for non-gated acquisition was significantly higher than that for respiratory ($P = 0.007$) and cardiac-gated ($P = 0.028$) acquisitions. The normalized peak height of MD histograms for non-gated acquisition was significantly higher than that for respiratory ($P = 0.002$) and cardiac-gated ($P = 0.021$) acquisitions. The corrected peak position of MD histograms for non-gated acquisition was significantly smaller than that for respiratory-gated acquisition ($P = 0.021$).

**Fig. 4:** The box whisker plots showing the normalized peak height (a) and peak position (b) of MD histograms for gated and non-gated acquisitions. The whiskers indicate standard error. * indicates pairs with statistical significance.

**References:** Department of Radiological Technology, Hokkaido University Hospital - Sapporo/JP
Fig. 5: The box whisker plots showing the normalized peak height (a) and peak position (b) of FA histograms for gated and non-gated acquisitions. The whiskers indicate standard error. * indicates pairs with statistical significance.

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Fig. 6: The box whisker plots showing the normalized peak height (a) and peak position (b) of MK histograms for gated and non-gated acquisitions. The whiskers indicate standard error. * indicates pairs with statistical significance.

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Fig. 3: The scatterplots showing correlation between the histogram measures of the major diffusion imaging metrics -- the normalized peak height (a) and peak position (b), and TR.

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Fig. 4: The box whisker plots showing the normalized peak height (a) and peak position (b) of MD histograms for gated and non-gated acquisitions. The whiskers indicate standard error. * indicates pairs with statistical significance.
**Fig. 5:** The box whisker plots showing the normalized peak height (a) and peak position (b) of FA histograms for gated and non-gated acquisitions. The whiskers indicate standard error. * indicates pairs with statistical significance.

**Fig. 6:** The box whisker plots showing the normalized peak height (a) and peak position (b) of MK histograms for gated and non-gated acquisitions. The whiskers indicate standard error. * indicates pairs with statistical significance.
Conclusion

This study evaluated if the major diffusion imaging metrics of the brain varied between the respiratory or cardiac-gated and non-gated acquisitions. The results revealed significant variation in the histogram measures between the gated and non-gated acquisitions, for all three major diffusion imaging metrics. As repeatability of diffusion measurements was excellent, it is considered that the observed variations in the histogram measures are reflected by the effect of respiratory and cardiac gating on the major diffusion imaging metrics.

In this study, the normalized peak height of FA histograms was significantly lower with non-gated than gated acquisitions. The reverse was also true for the peak height of MD histograms. As variation in the peak height of histogram indicates variation in the proportion of voxels that contribute the maximum frequency, the observation of lower peak height of FA histograms is thought to reflect a larger degree of FA heterogeneity with non-gated acquisition [3, 13]. On the contrary, the higher peak height of MD histograms with non-gated acquisition may indicate constitution in the histogram of a large proportion of voxels with the same MD value. The observation of smaller peak position of MD histograms with non-gated acquisition, compared to respiratory gating, may suggest that the non-gated acquisition underestimates the MD value in the largest proportion of voxels. A larger peak position of MK histograms with non-gated acquisition, compared to cardiac gating, is indicative of larger deviation from Gaussian distribution with non-gated acquisition. Although the exact mechanisms that underlie variation in the histogram measures between the gated and non-gated acquisitions are not known, it is possible that pulsation-induced intravoxel phase dispersion and high signal intensity flow-related artifacts that propagate along the phase encoding direction are responsible [2, 14, 15]. The former results in signal attenuation of the affected voxels whereas the latter gives rise to signal increase within the voxels. The observation of discrepancy among the results of previous studies and ours may denote that both over- and underestimation of the major diffusion imaging metrics are possible with non-gated acquisition [7-10].

While the results of this study reflect a significant impact of respiratory and cardiac gating on the major diffusion imaging metrics, the observation of excellent repeatability among acquisitions may suggest that the diffusion measurements are repeatable and reproducible, provided the imaging parameters are kept identical. Although gated acquisition may be desired for improved accuracy, the non-gated acquisition with identical other imaging parameters can serve as a precise alternative. Considering increase in acquisition time with respiratory or cardiac gating, the non-gated acquisition may be preferred for clinical studies.

This study has several limitations. First, the effect of gating on the major diffusion imaging metrics was evaluated in three supratentorial sections only. The brain stem was not included in the evaluation because this structure is susceptible to several other
confounding artifacts such as susceptibility artifacts [16]. It is possible that variation in the major diffusion imaging metrics between the gated and non-gated acquisitions is more pronounced at the level of brain stem -- as CSF pulsations are accentuated at the cisterns that surround the brain stem [17]. The small volume of the brain stem may also lead to relatively large number of voxels affected by artifacts per unit volume. Second, variation in the effect of gating among the sections was not evaluated -- which is an ongoing work. According to a previous report, the effect of gating can be negligible at the cranial sections [18]. Third, repeatability was tested only for non-gated acquisition.

In conclusion, this study evaluated the effect of respiratory and cardiac gating on the major diffusion imaging metrics. The major diffusion imaging metrics are susceptible to artifacts related to respiration and cardiac pulsation. The knowledge that gating can affect quantification of the major diffusion imaging metrics would be valuable for correct interpretation of the metrics. Gating condition must be kept identical to achieve reproducible results.
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References


