Technical Note

Effects of the Use of Multiple Scanners and of Scanner Upgrade in Longitudinal Voxel-Based Morphometry Studies

Hidemasa Takao, MD,[1]* Naoto Hayashi, MD, DMSc,[2] and Kuni Ohtomo, MD, DMSc[1]

Purpose: To evaluate the effects of inter-scanner variability (bias) and of scanner upgrade on longitudinal changes in regional gray matter volume.

Materials and Methods: A total of 215 normal subjects were scanned twice, at an interval of approximately 1 year, using two 3.0 Tesla (T) scanners of the exact same model. Both scanners were simultaneously upgraded during the study period. The subjects were divided into four groups according to the combination of scanners used at the two time points. Using VBM, we evaluated longitudinal changes in regional gray matter volume in each group and the effects of scanner upgrade on longitudinal changes.

Results: The use of different scanners at two time points significantly influenced longitudinal changes in regional gray matter volume. Regional gray matter volumes were relatively stable within the same scanner, but significantly different between the two scanners. Scanner upgrade had effects comparable to those of using different scanners at the two time points.

Conclusion: The results of our study indicate that, even with scanners of the exact same model, the use of different scanners at different time points significantly influences longitudinal morphometric results, and that scanner upgrade has effects comparable to those of using different scanners at different time points.

Key Words: gray matter volume; multi-center; multi-scanner; reliability; reproducibility; variability
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OUR CURRENT KNOWLEDGE of the effects of normal aging and neurodegenerative disorders on brain structure is derived mostly from cross-sectional studies. The large amount of between-subject variability that exists in normal brain morphology, however, reduces the sensitivity of methods to detect any changes in brain volume. Multi-center studies have more power than smaller studies in conducting sophisticated studies of basic neuroanatomy and neurodegenerative disorders (1). They provide researchers with larger datasets by pooling data from different sites and hence improve the statistical power; however, multi-center studies also introduce a between-center variance component.

Longitudinal studies avoid some of the problems of secular trends and between-subject variation. They limit the variance associated with individual differences in brain morphology by using each subject as his or her own control. The statistical power to detect brain structure changes can, however, be limited by measurement errors. To precisely quantify the rates of changes in brain volume from serial magnetic resonance imaging (MRI) scans, it is important that the acquisitions at baseline and at later time points are as similar as possible (1). Any change in voxel size that is introduced by scanner instability and/or errors may either mimic or obscure true changes (2,3).

There has recently been growing interest in longitudinal, multi-center studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) study (1), which is a longitudinal multi-center observational study of healthy elders, mild cognitive impairment (MCI), and Alzheimer's disease (AD). The large number of subjects that results from pooling multi-scanner datasets increases sensitivity, thus allowing detection of subtle effects, and offers increased reliability and confidence regarding effect size by averaging out unforeseen confounds. One important confound of combining images obtained from different scanners, however, is the potential for scanner effects (scanner-dependent geometrical inaccuracies, image intensity variability, etc.) to introduce systematic error, thus making the interpretation of results difficult.

Numerous previous studies have evaluated the effects of different scanners on cross-sectional or longitudinal morphometric results (4–22). We are not, however, aware of any study that has investigated the

[1]Department of Radiology, Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo, Japan.
[2]Department of Computational Diagnostic Radiology and Preventive Medicine, Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo, Japan.
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*Address reprint requests to: H.T., Department of Radiology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: takaoh-tky@umin.ac.jp
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Table 1
Subject Characteristics

	Group A (1/1)	Group B (1/2)	Group C (2/1)	Group D (2/2)	χ^2	*P*
N	67	44	56	48		
Sex					2.24	0.52
Female	17	12	15	18		
Male	50	32	41	30		
Age (yr)	57 ± 9	57 ± 10	57 ± 10	56 ± 9	0.10	0.99
Upgrade (-)	56	30	31	34		
Sex					0.94	0.82
Female	15	9	8	12		
Male	41	21	23	22		
Age (yr)	56 ± 9	57 ± 10	56 ± 9	56 ± 9	0.15	0.99
Upgrade (+)	11	14	25	14		
Sex					2.30	0.51
Female	2	3	7	6		
Male	9	11	18	8		
Age (yr)	59 ± 10	57 ± 9	57 ± 10	57 ± 8	0.59	0.90

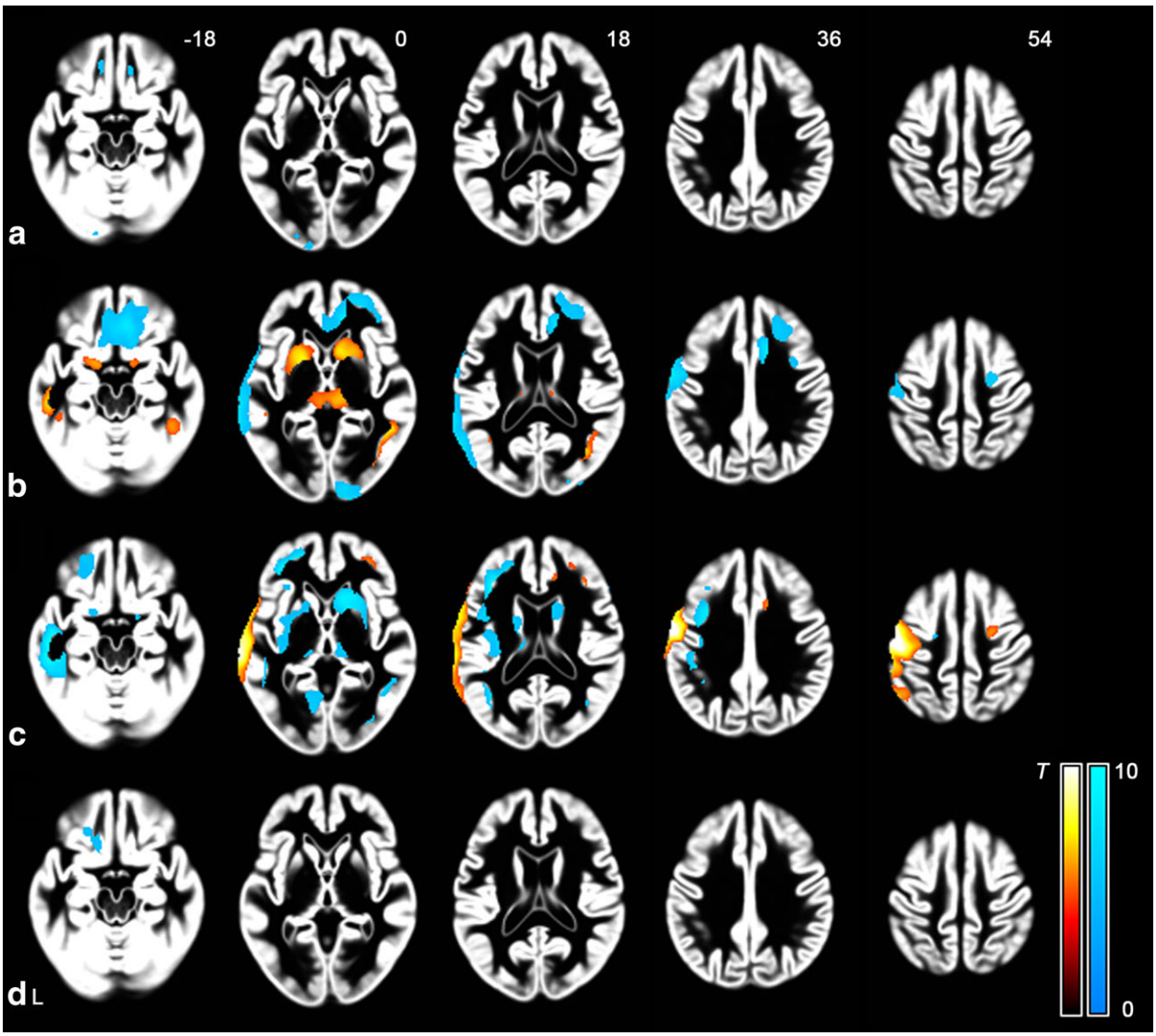

Figure 1. Voxel-based morphometry (VBM) analysis of longitudinal (1-year) gray matter volume changes. The rows show an analysis for each group (A–D). **A**: Baseline and follow-up images were obtained on scanner 1. **B**: Baseline images were obtained on scanner 1 and follow-up images were obtained on scanner 2. **C**: Baseline images were obtained on scanner 2 and follow-up images were obtained on scanner 1. **D**: Baseline and follow-up images were obtained on scanner 2. The color bars represent the t score at each voxel (red, increase in volume; blue, decrease in volume).

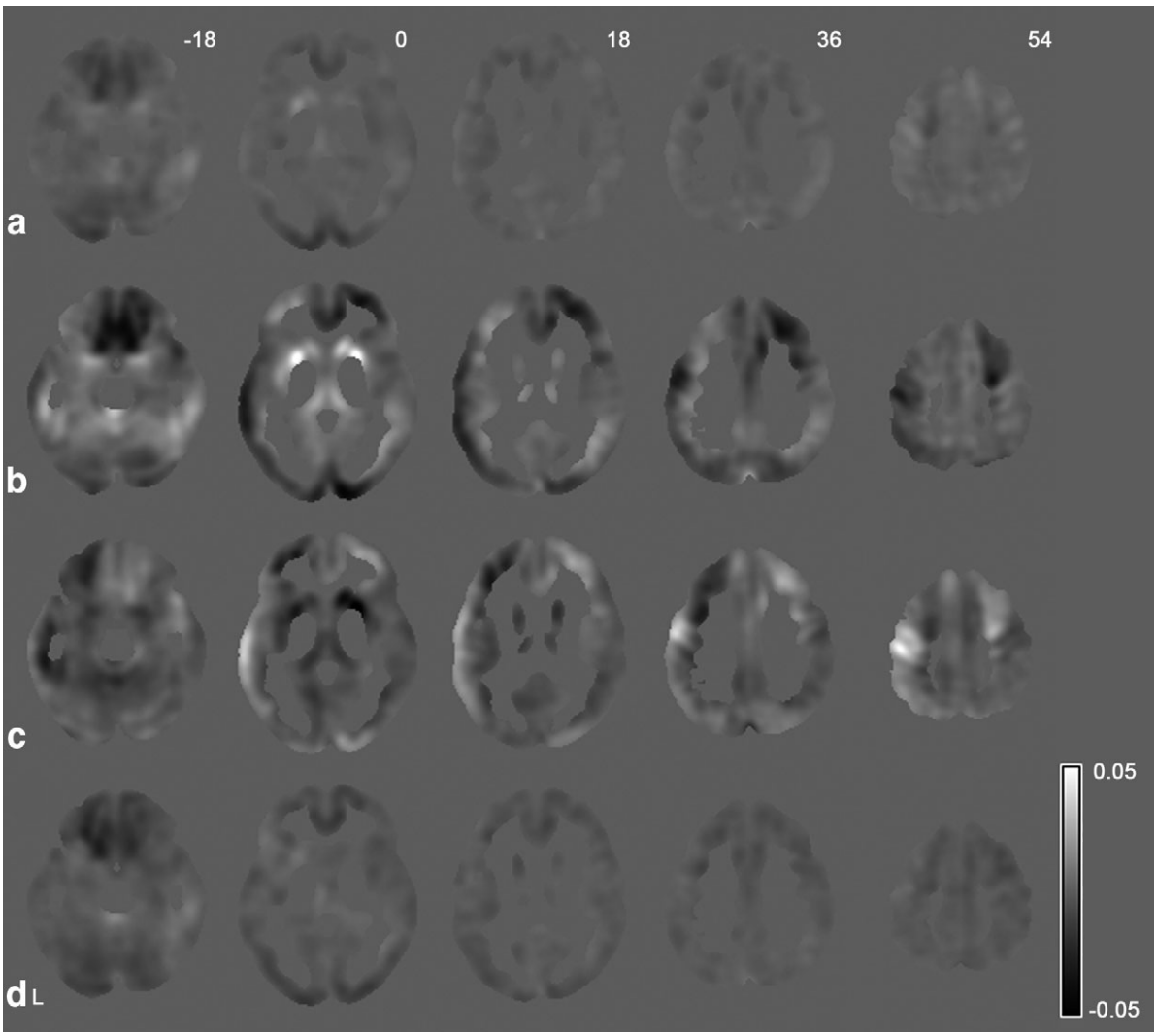

Figure 2. A–D: Voxel-based morphometry (VBM) analysis of longitudinal (1-year) gray matter volume changes: beta images, which represent longitudinal changes in each group with the effects of scanner upgrade, age, and sex removed.

effects of inter-scanner variability on longitudinal morphometric results in relation to the effects of scanner upgrade, using scanners of the exact same model. In the present study, we evaluated the effects of inter-scanner variability (bias) and of scanner upgrade on longitudinal changes in regional gray matter volume using voxel-based morphometry (VBM) and longitudinal (1-year) data obtained on two scanners of the exact same model at one institution.

MATERIALS AND METHODS

Subjects

A total of 215 normal subjects (62 females and 153 males, mean age = 56 ± 9 years, age range = 40–83 years) were included in this study. None of the subjects had a history of neuropsychiatric disorder, including serious head trauma, psychiatric disorders, or alcohol/substance abuse or dependence. Mean Mini-Mental State Examination (MMSE) score was 29.6 ± 0.7 (range = 27–30). Each subject was scanned twice, at an interval of approximately 1 year (mean interval = 1.0 ± 0.1 years, range = 0.6–1.3 years). A board-certified radiologist reviewed all scans (including T1-weighted and T2-weighted images) and found no gross abnormalities such as infarct, hemorrhage, or brain tumor in any of the subjects. Fazekas score (range, 0–3) was 0 (absence) or 1 (caps, pencil-thin lining, and/or punctuate foci) (23). The ethical committee of the University of Tokyo Hospital approved the study. After a complete explanation of the study to each subject, written informed consent was obtained.

Imaging Data Acquisition

MR data were obtained on two 3.0 Tesla (T) Signa scanners (GE Medical Systems, Milwaukee, WI) with an eight-channel brain phased array coil. Both scanners were the exact same model, and were simultaneously upgraded from HDx to HDxt during the study period. Software alone was upgraded; hardware remained unchanged. The subjects were grouped as follows: Group A, baseline images were obtained on scanner 1 and follow-up images were obtained on scanner 1 (n = 67); Group B, baseline images were

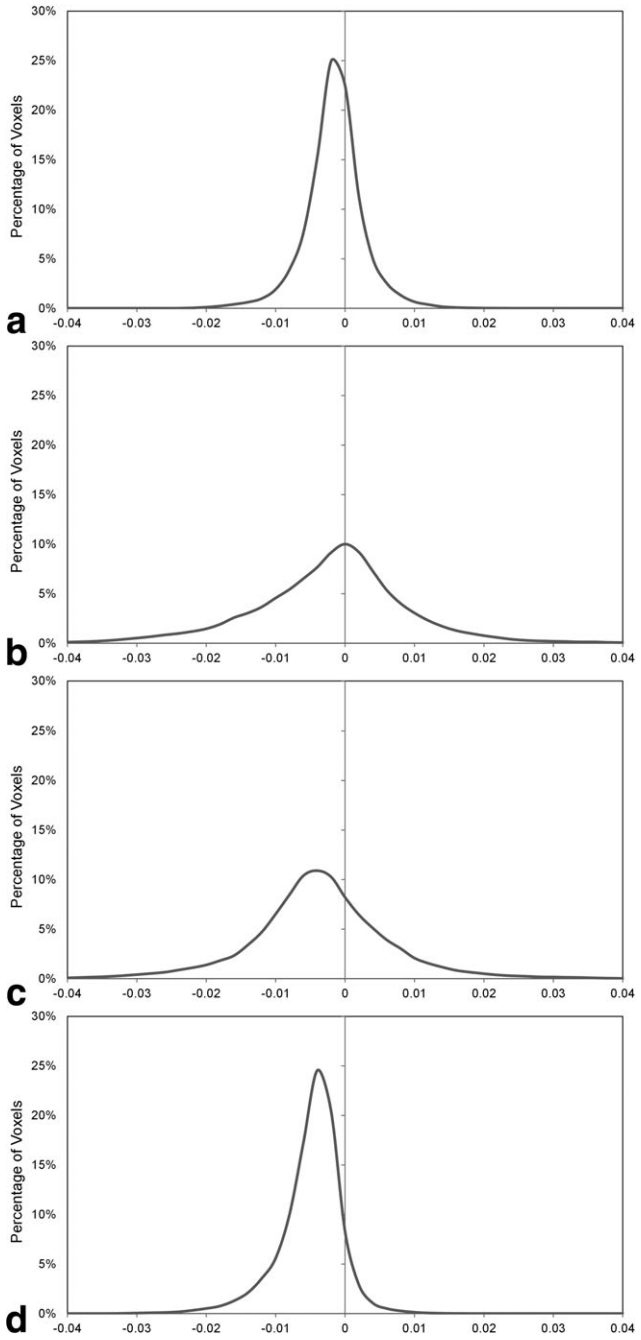

Figure 3. A–D: Voxel-based morphometry (VBM) analysis of longitudinal (1-year) gray matter volume changes: histograms of beta images.

obtained on scanner 1 and follow-up images were obtained on scanner 2 (n = 44); Group C, baseline images were obtained on scanner 2 and follow-up images were obtained on scanner 1 (n = 56); and Group D, baseline images were obtained on scanner 2 and follow-up images were obtained on scanner 2 (n = 48) (Table 1). Of the 215 subjects, 151 underwent baseline and follow-up scans before upgrade, and the remaining 64 underwent a baseline scan before upgrade and a follow-up scan after upgrade (Table 1).

T1-weighted images were acquired using three-dimensional (3D) inversion recovery prepared fast spoiled gradient recalled acquisition in the steady state (IR-FSPGR) in 176 sagittal slices (repetition time = 5.3–5.4 ms; echo time = 1.7 ms; inversion time = 450 ms; flip angle = 15°; field of view = 250 mm; slice thickness = 1.0 mm with no gap; acquisition matrix = 256 × 256; number of excitations = 0.5; image matrix = 256 × 256). Parallel imaging (ASSET; Array Spatial Sensitivity Encoding Technique) was used with an acceleration factor of 2.0. Voxel dimensions were 0.977 mm × 0.977 mm × 1.0 mm. The images were corrected for spatial distortion due to gradient nonlinearity using "grad_unwarp" (24–26) and for intensity nonuniformity using the nonparametric nonuniform intensity normalization algorithm N3 (25–27).

Image Processing

Image analysis was performed using statistical parametric mapping (SPM) 8 software (http://www.fil.ion.ucl.ac.uk/spm) developed in the Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, running in MATLAB 7.13.0 (Mathworks, Sherborn, MA).

The IR-FSPGR images were segmented into gray matter, white matter, and cerebrospinal fluid using an integrated generative model (unified segmentation) (28). The International Consortium for Brain Mapping (ICBM) gray matter, white matter, and cerebrospinal fluid templates were used as priors to segment the images. The Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (29) was used to spatially normalize the segmented images. The normalized gray matter images were modulated to correct voxel signal intensity for volume displacement during normalization and reflect brain volume (30), and smoothed using an 8-mm kernel. The baseline gray matter images were then subtracted from the follow-up gray matter images. The resulting subtraction images were fed into voxel-based statistical analysis.

Statistical Analyses

Subtraction images were analyzed with SPM 8 using the framework of the general linear model (31). First, we identified areas with significant longitudinal changes in gray matter volume in each group (A–D). Scanner upgrade, age, and sex were included as covariates of no interest. Next, we identified areas where there was a significant effect of scanner upgrade on longitudinal changes. Significance levels for t tests (one-tailed) were set at $P = 0.025$, corrected for multiple comparisons using the family-wise error (FWE) rate (voxel-level). We computed two t contrasts (positive, negative) for t-tests. Only voxels with a volume greater than 0.1 were included in analyses.

RESULTS

Effects of Scanner on Longitudinal Changes

Voxel-based analysis of subtraction images revealed several regions with a significant increase or decrease

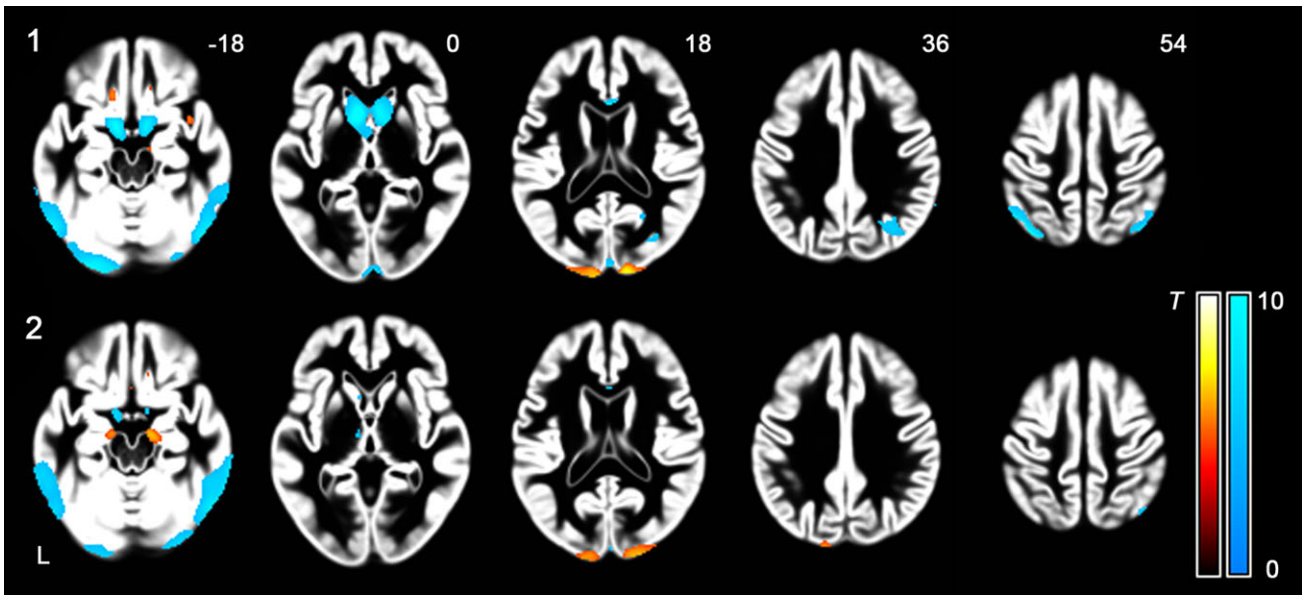

Figure 4. 1,2: Voxel-based morphometry (VBM) analysis of the effects of scanner upgrade on longitudinal (1-year) gray matter volume changes. The rows show the results of analysis of the effects of upgrade for each scanner.

in gray matter volume in groups in which the baseline and follow-up images were obtained on different scanners (B and C) (Fig. 1). There was a trend for opposite directions of change in these two groups (B and C). In groups in which both the baseline and follow-up images were obtained on the same scanner (A and D), however, only small regions showed significant longitudinal changes (Fig. 1).

Figure 2 shows beta images obtained from the above analysis, which represents longitudinal changes in each group with the effects of scanner upgrade, age, and sex removed. Figure 3 shows histograms of the beta images (histogram bin width, 0.002; range, −0.1 to 0.1). In groups in which both the baseline and follow-up images were obtained on the same scanner (A and D), almost no voxels showed a change of less than −0.02 (A, 0.0%; D, 0.8%) or more than 0.02 (A, 0.0%; D, 0.0%). In groups in which the baseline and follow-up images were obtained on different scanners (B and C), however, approximately 8% of voxels showed a change of less than −0.02 (B, 5.5%; C, 4.7%) or more than 0.02 (B, 3.3%; C, 2.2%).

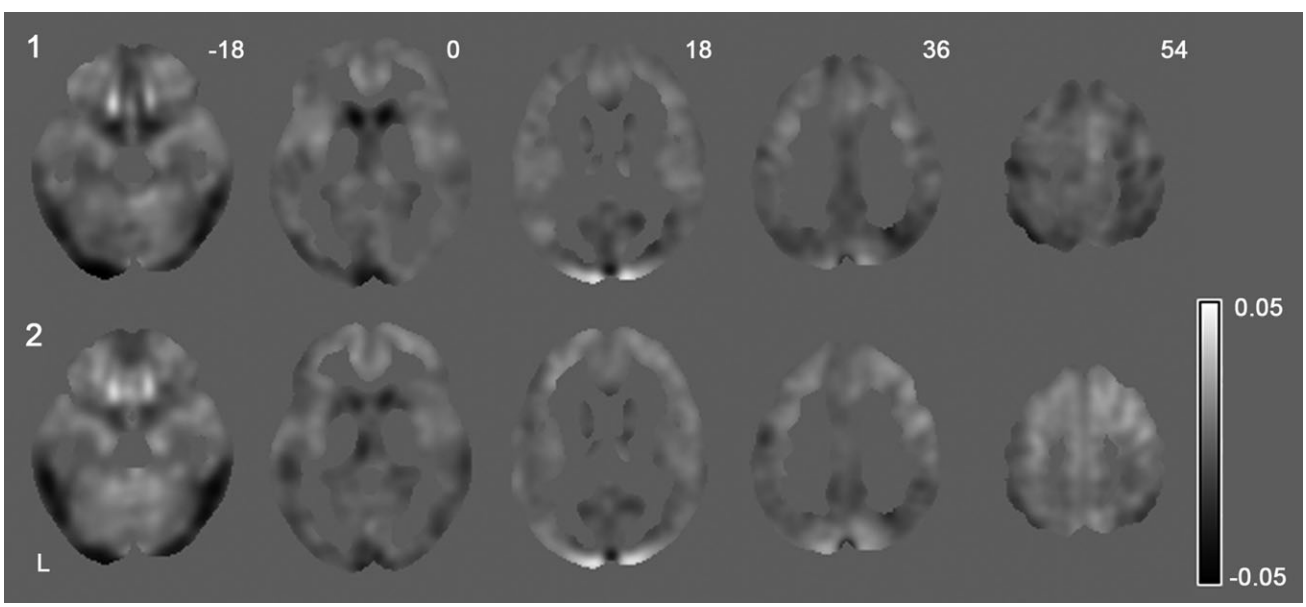

Figure 5. 1.2: Voxel-based morphometry (VBM) analysis of the effects of scanner upgrade on longitudinal (1-year) gray matter volume changes: beta images, which represent changes due to upgrade of each scanner with the effects of group, age, and sex removed.

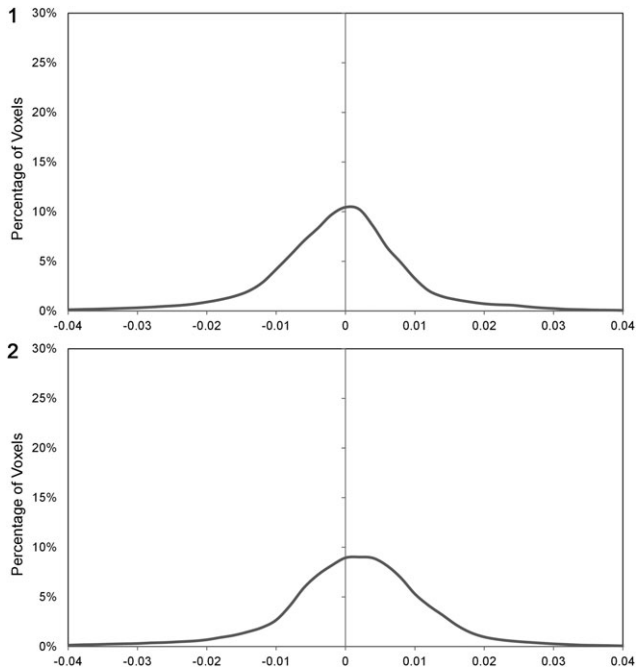

Figure 6. 1.2: Voxel-based morphometry (VBM) analysis of the effects of scanner upgrade on longitudinal (1-year) gray matter volume changes: histograms of beta images.

Effects of Scanner Upgrade

Voxelwise analysis of the subtraction images revealed several regions with a significant effect of scanner upgrade on longitudinal changes in gray matter volume (Fig. 4). There were both positive and negative changes due to scanner upgrade. The effects of upgrade of scanner 2 were similar to those of upgrade of scanner 1 (Fig. 4).

Figure 5 shows beta images obtained from the above analysis, which represents changes due to scanner upgrade with the effects of group, age, and sex removed. Figure 6 shows histograms of the beta images (histogram bin width, 0.002; range, −0.1 to 0.1). Approximately 8% of voxels showed a change of less than −0.02 (upgrade of scanner 1, 4.0%; upgrade of scanner 2, 3.6%) or more than 0.02 (upgrade of scanner 1, 3.5%; upgrade of scanner 2, 4.1%).

Standard Deviation Maps

Figure 7 shows standard deviations of longitudinal changes in gray matter volume for each group. Figure 8 shows histograms of the standard deviation maps (histogram bin width, 0.002; range, 0.0 to 0.2). Most voxels showed a standard deviation of less than 0.05 (A, 99.5%; B, 98.5%; C, 99.1%; D, 99.3%).

DISCUSSION

We examined the effects of inter-scanner variability (bias) and of scanner upgrade on longitudinal changes in regional gray matter volume, using longitudinal (1-year) data obtained on two scanners of the exact same model at one institution. Even with scanners of the exact same model, the use of different scanners at different time points significantly influenced longitudinal morphometric results. Regional gray matter volumes were relatively stable within the same scanner, but significantly different between the two scanners. In addition, scanner upgrade had effects on longitudinal morphometric results comparable to those of using different scanners (of the exact same model) at different time points. The scanner upgrade included a software upgrade alone; hardware remained unchanged. It is unclear which software components influenced morphometric measurements; however, recalibration, which is commonly performed as part of a system hardware or software upgrade, might be a major cause of disruption of gradient stability. Recalibration causes discrete changes that may be larger than observed system drift over periods of months (17).

Brain atrophy accelerates with increasing age, and its rate depends on the age range of the sample (32). Annual atrophy rates vary across the cortex, but are typically ~0.5% in the aged (33). Atrophy in Alzheimer's disease patients is much larger than in normal subjects, with most areas showing 1% annual change or more (33). In the present study, the effects of scanner and of scanner upgrade were larger than annual atrophy rates in normal aging and Alzheimer's disease.

To demonstrate the feasibility of multi-scanner studies, numerous groups have previously analyzed the effects of different scanners on cross-sectional or longitudinal morphometric results (4–22). Inter-scanner variability of volumetric measures is generally larger than intra-scanner variability. Most studies evaluating intra- or inter-scanner variability of morphometric measures investigated reliability by performing repeated scans on a few subjects, with imaging acquired within short scan intervals. With short scan intervals, however, the effect of drift in scanner hardware on variability is underestimated, which is an important potential source of error in actual longitudinal studies. Scanner drift is under-recognized and is sometimes ignored in longitudinal imaging studies (2,3).

Several studies have previously evaluated the effects of scanner upgrade on morphometric results (8,13,34,35); however, only a few studies have investigated the effects of scanner upgrade in relation to longitudinal morphometric changes (34,35). Gunter et al evaluated the effects of gradient hardware upgrade on global atrophy rates in AD and normal subjects using the brain boundary shift integral (BBSI) method and structural image evaluation, using normalization, of atrophy (SIENA) (34). They found that major changes in hardware had a negligible effect on the observed rates of atrophy in each group, which may be because they used 9 degrees of freedom (9 DOF) registration (which allows voxel size scaling) to register the images at two time points.

Shuter et al evaluated the effects of scanner software upgrade on signal-to-noise ratio (SNR) (35), and concluded that SNR changes caused by scanner

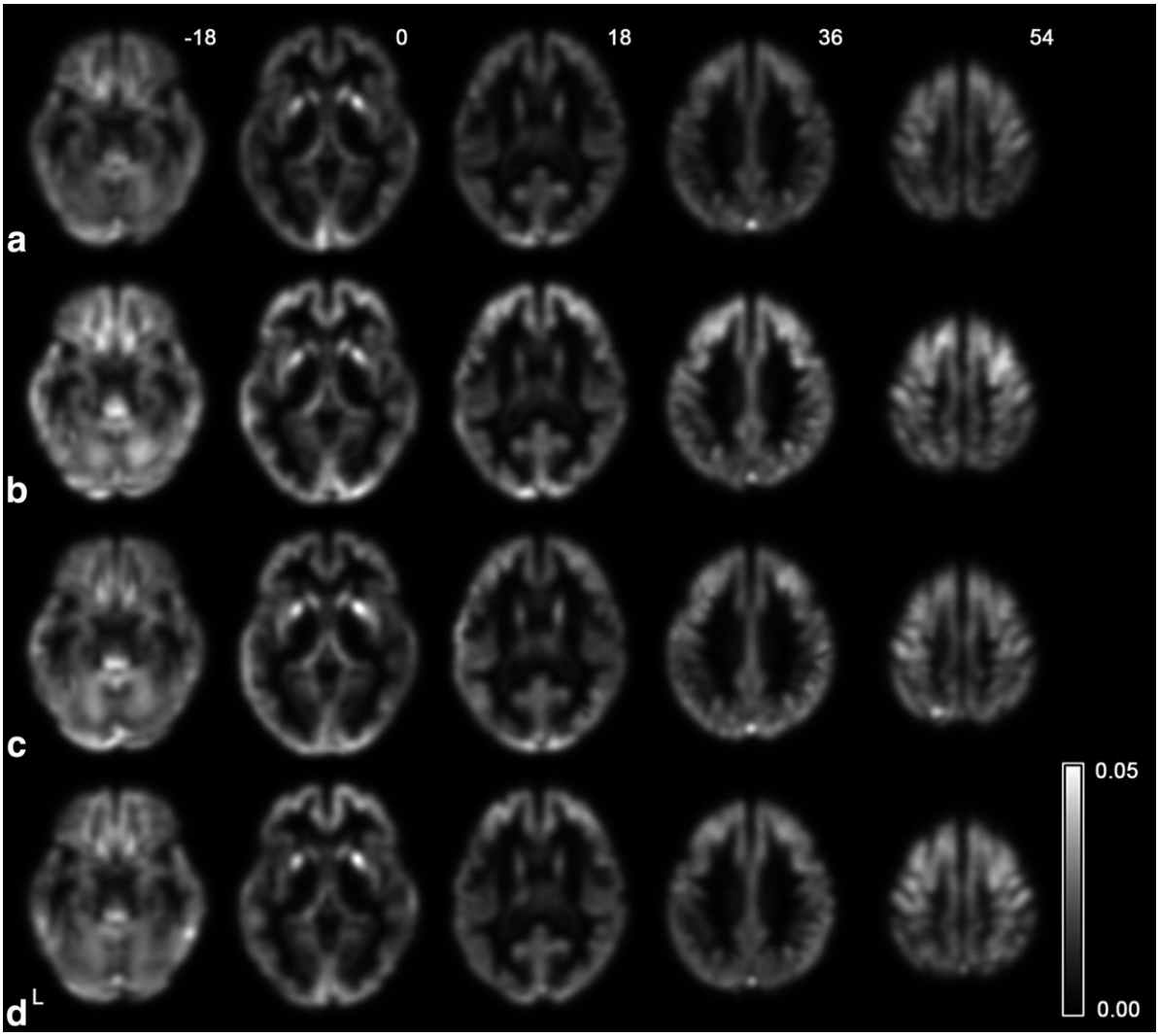

Figure 7. Standard deviations of longitudinal (1-year) gray matter volume changes in each group (**A–D**).

upgrade significantly influence VBM-derived gray matter volumes. In our previous study, we examined the effects of drift in scanner hardware and inter-scanner variability on longitudinal brain volume changes (20), but because the scanners were upgraded between the two scans in all subjects, we could not evaluate the effects of scanner upgrade on longitudinal changes. In the present study, scanner software upgrade had effects on longitudinal morphometric results comparable to those of using different scanners (of the exact same model) at different time points.

Scanner upgrades generally improve scanner performance, which is desirable in the clinical situation. To maintain consistency in longitudinal morphometry studies, scanner upgrade should be postponed; however, upgrade may be inevitable, especially when clinical scanners are used for the study. Pfefferbaum et al examined whether structural data acquired at different field strengths could be merged, and concluded that application of a regression-based correction function improved correspondence in regional volume estimations (22).

In the ADNI study, imaging of a geometric phantom is included with every set of scans, to enable correction for differences in scanner voxel sizes due to drift in scanner performance and for inter-scanner variability (1). Repair or replacement of phantoms between scans, however, is a confounding factor (17). ADNI phantom measurements are at this time mainly used to identify scanner errors through central monitoring (17). Clarkson et al compared voxel scaling correction using a phantom with correction using 9 DOF registration algorithm (36), and concluded that 9 DOF registration was comparable to geometric phantom correction. Voxel scaling using a phantom or 9 DOF registration algorithm, or including scanner/scanner upgrade as a covariate in the statistical analysis may be useful to eliminate the effects of scanner and of scanner upgrade.

In conclusion, the results of the present study indicate that, even with scanners of the exact same model, the use of different scanners at different time points significantly influences longitudinal morphometric results, and that scanner software upgrade has effects comparable to those of the use of

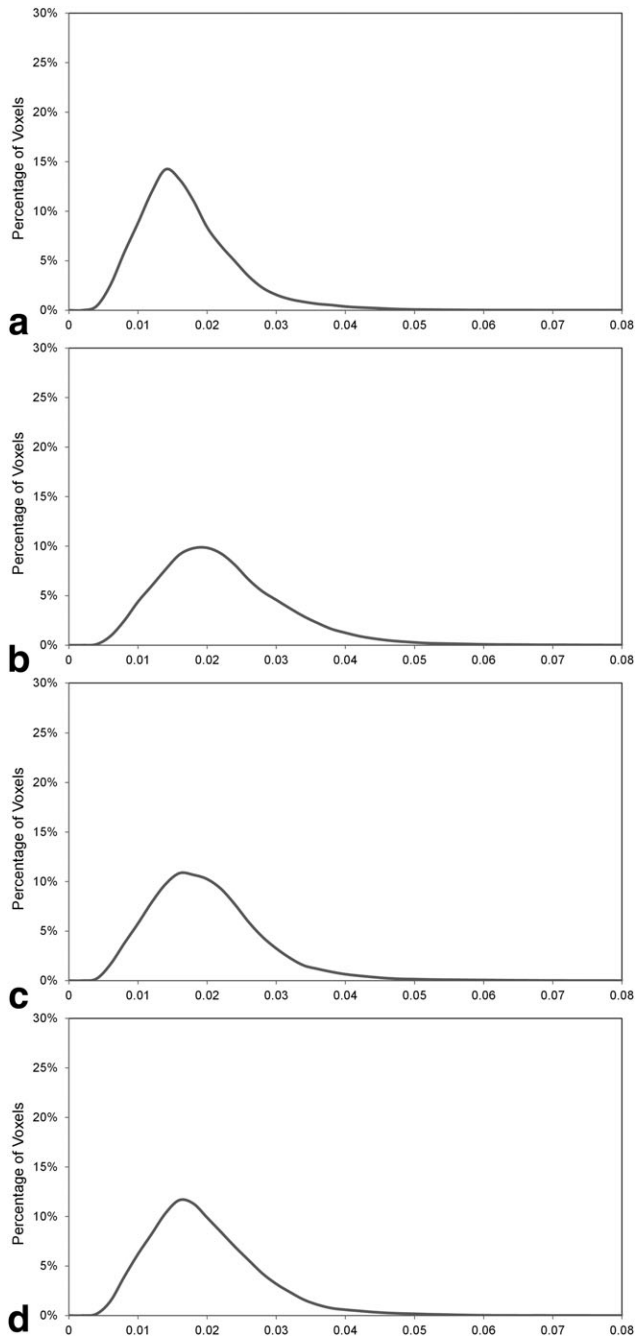

Figure 8. A–D: Histograms of standard deviation maps of longitudinal (1-year) gray matter volume changes.

different scanners (of the exact same model) at different time points. To maintain consistency in longitudinal morphometry studies, scanner upgrade should be postponed if at all possible. The results of the present study are useful for planning not only longitudinal studies but also multi-center cross-sectional studies.

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