sample is required to replicate and expand the current preliminary results.

In summary, the present study demonstrated significant gray matter reduction of the anterior cingulate gyrus in first-episode schizophrenia. We also suggested the possibility that such morphological change may exist prior to the onset of psychosis in some individuals, implying the potential role of neuroimaging methods in the prediction of future transition and effective intervention for high-risk subjects.

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Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain activity. Previous NIRS studies indicated the oxy-hemoglobin (oxy-Hb) increase during a verbal fluency task (VFT) is attenuated in patients with major depressive disorder (MDD) as compared with healthy controls. However, the possible relationship between depression symptom severity and oxy-Hb change on NIRS has not yet been elucidated. To examine this relationship, we recruited 30 patients with MDD and 30 age-, gender- and intelligence quotient-matched controls. All underwent NIRS during VFT. As expected, the oxy-Hb increase during the task was significantly smaller in patients than in controls. After false discovery rate correction using 31 channels, the mean increase in oxy-Hb during the task showed a significant negative correlation with the total score of the Hamilton Rating Scale for Depression 21-item version (ch25: rho = −.56; FDR-corrected *p*: .001). When each item of the HAM-D21 was examined individually, insomnia early in 9 channels (rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (rho = −.61 to −.57; FDR corrected *p*: .001 to .003) and psychomotor retardation in 12 channels (rho = −.70 to −.44; FDR corrected *p*: .000–.018) showed significant negative correlations with the mean oxy-Hb increase in the right frontal temporal region. Although it is possible that our results were affected by medication, these data suggest reduced right frontal temporal activation on NIRS during VFT is related to the symptom severity of MDD.

1. Introduction

Major depressive disorder (MDD) is a severe and common psychiatric disorder with a lifetime prevalence of 6.7 per 100 (Waraich et al., 2004). Although depressive symptoms per se do not specifically appear in MDD but also in other psychiatric disorders including bipolar disorders, we do not have an objective diagnostic marker to obtain a clear-cut diagnosis for those patients. In Japan, a relatively new neuroimaging method, near-infrared spectroscopy (NIRS) has been approved by the Ministry of Health, Labor and Welfare as a highly advanced medical technology to help distinguish between schizophrenia, depression and bipolar disorders in 2009. Verbal fluency task (VFT) is recommended as an activation task because of a relatively rich store of data. VFT is an easy task to examine the executive function and frequently used in neuroimaging studies (Alvarez and Emory, 2006) and is known to activate prefrontal cortex (PFC) in healthy subjects (Frith et al., 1991; Schlösser et al., 1998). Numerous neuropsychological studies suggest that patients with MDD show executive dysfunction (Gohier et al., 2009; Rose and Ebmeier, 2006; Fossati et al., 2003; Porter et al., 2003; Degl'Innocenti et al., 1998).

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, restraint-free functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain

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function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) changes with a high time resolution (.1 s). The concentrations of oxy-Hb and deoxy-Hb are assumed to reflect the regional cerebral blood volume (rCBV) changes, which was supported by the simultaneous NIRS and PET study (Villringer et al., 1997; Ohmae et al., 2006).

In fact, numerous studies have demonstrated that the oxy-Hb increase in the fronto-temporal regions during a VFT is significantly smaller in patients with MDD than in those with bipolar disorder or healthy controls (Pu et al., 2008; Kameyama et al., 2006; Suto et al., 2004; Matsuo et al., 2002). Moreover, NIRS studies using VFT have also demonstrated frontal lobe dysfunction in schizophrenia (Suto et al., 2004; Takizawa et al., 2008), and panic disorder (Nishimura et al., 2007). However, the relationship between depression symptom severity at the time of examination and oxy-Hb change on NIRS has not yet been clarified.

In neuroimaging studies using other methodologies, focusing on cortex level that NIRS reflects, positron emission tomography (PET) studies found that abnormal reductions of cerebral blood flow (CBF) and metabolism in patients with MDD in PFC (Kimbrell et al., 2002; Bench et al., 1995; Mayberg et al., 1994; Baxter et al., 1989). As for the relationship between executive function and CBF or metabolism, Elliott et al. (1997) showed activation in PFC was significantly attenuated relative to controls during the Tower of London planning task in PET study. In a functional magnetic resonance imaging (fMRI) study, depressed patients showed significant decreased prefrontal activation during VFT (Okada et al., 2003).

As for the relationship between depression symptom severity and frontal lobe function, Brody et al. (1999) found a positive correlation between change in Hamilton Rating Scale for Depression (HAM-D) scores and change in normalized inferior frontal gyrus (IFG) and ventrolateral PFC (VLPFC) metabolism, which indicates that IFG metabolism increased and VLPFC metabolism decreased as depression symptoms became better. Other initial studies also suggest that abnormal functions in dorsolateral PFC (DLPFC) are mood state dependent, attenuated during the depressed mood and reversing during symptom remission (Bench et al., 1995; Mayberg et al., 1994). In contrast, Drevets et al. (2002) showed the persistence of abnormal metabolic deficits using PET measures in the dorsomedial/dorsal anterolateral PFC in MDD during treatment. According to a review by Drevets (2000), a complex relationship exists between depression symptom severity and metabolic activity in the orbital cortex and VLPFC.

Findings obtained by more recent studies investigating cross-sectional relationship between depression symptom severity and brain function assessed by basal regional CBF and metabolism are also inconsistent. For example, Périco et al. (2005) reported that depression symptom severity was negatively correlated with regional CBF (rCBF) in the left amygdala, lentiform nucleus, and parahippocampal gyrus, and positively correlated with rCBF in the right postero-lateral parietal cortex, whereas Milak et al. (2005) showed only positive correlations in bilateral mesiotemporal cortex, parts of the ventral subgenual basal forebrain, and most of the thalamus, hypothalamus, ventral striatum, and midbrain. Accordingly more studies are warranted to clarify the relationship between depression severity and brain activity including frontal lobe function.

In the present study, considering the consistent finding of attenuated oxy-Hb changes during VFT in the fronto-temporal regions in depression, we hypothesized that oxy-Hb changes during VFT in NIRS could be objective indicators of depressive symptom severity. Thus, we used multi-channel NIRS to investigate the relationship between oxy-Hb changes and symptom severity in patients with MDD. Because NIRS can be measured easily and noninvasively in a restraint-free environment over a short amount of time we expect that NIRS can be widely used to assess objectively depressive symptom severity as a clinical examination.

2. Materials and methods

2.1. Subjects

The subjects were 30 patients with MDD, and 30 healthy volunteers matched for age, gender and premorbid intelligence quotient (IQ). Premorbid IQ was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native speakers of Japanese. All MDD subjects were outpatients of the National Center of Neurology and Psychiatry Hospital in Tokyo, Japan. They were diagnosed according to the Structured Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Disorders (SCID-I; First et al., 1995) by experienced psychiatrists. All patients were medicated with antidepressants. Twenty-seven out of 30 patients were prescribed with one or two antidepressants, 16 with SSRIs, 12 with tricyclics, 7 with milnacipran, 5 with tetracyclics, 2 with trazodone and 1 with mirtazapine. In addition, 20 patients were prescribed with anxiolytics, 16 with hypnotics, 7 with mood stabilizers and 9 with antipsychotics (Supplementary Table 1). Daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006) and anxiolytics/hypnotics to that of diazepam (Inagaki and Inada, 2006) for each patient. The controls were healthy volunteers recruited from the same geographical area through advertisements in free local magazines and our website announcement. They were interviewed using the SCID-I for MDD or SCID-NP for healthy volunteers and an unstructured interview for family history, and those individuals who had a current or past history of Axis I psychiatric disorder or a positive family history of Axis I psychiatric disorder within their first degree relatives were excluded. The exclusion criteria for both groups were previous head trauma, neurological illness, a history of electroconvulsive therapy, alcohol/substance abuse or addiction.

After the study procedures had been fully explained, written informed consent was obtained from every participant. This study was approved by the ethics committee of the National Center of Neurology and Psychiatry.

2.2. Clinical assessment

Depressive symptoms and the level of social functioning were evaluated by a single experienced psychiatrist using the GRID Hamilton Rating Scale for Depression 21-item version (GRID HAM-D21; Kalali et al., 2002) and Global Assessment of Functioning scores (GAF; American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data on the same day that the NIRS measurements were conducted. Sleepiness was evaluated as the score on the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).

2.3. Activation task

The activation task was a letter version of VFT similar to that described by Takizawa et al. (2008). During the VFT, changes in oxy-Hb and deoxy-Hb were measured. The VFT consisted of a 30-sec pre-task baseline, a 60-sec VFT, and a 70-sec post-task baseline. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/ and /o/ during the pre-task and post-task baseline periods. For the VFT, the subjects were instructed to generate as many words as possible.

One of the three initial syllables (A; 0–20 s /a/, /to/, or /na/, B; 20–40 s /i/, /ki/, or /se/, C; 40–60 s /o/, /ta/, or /ha/) was randomly

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presented on the computer display placed in front of the subjects, every 20 s during the 60-sec task. The number of possible combinations of syllables is 27 (A;3 × B;3 × C;3 = 27). We adopted 15 among the possible combinations. The number of correct words generated during the task was determined as a measure of task performance.

3. NIRS measurements

3.1. NIRS device

We used a 52-channels NIRS (ETG-4000 Optical Topography System; Hitachi Medical Co., Tokyo, Japan) which measures relative changes in oxy-Hb and deoxy-Hb using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). With this system, these Hb values include a differential pathlength factor (DPF). In the NIRS system, "hemoglobin concentration change*DPF" is calculated as a solution to the simultaneous equations based on the Beer–Lambert law, which cannot escape the effect of DPF. Although DPF varies among various brain regions Zhao et al., using a Monte Carlo simulation, reported the estimated DPF variation in the forehead region of adult humans was roughly homogeneous (Zhao et al., 2002).

The distance between a pair of source-detector probes was set at 3.0 cm and each area measured between a pair of source-detector probes was defined as a 'channel'. The NIRS device is considered to measure 'channels' at a 2–3 cm depth from the scalp, that is, at the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003, Toronov et al., 2001).

3.2. Probe positioning and measurement points

The NIRS probes were fixed with 3 × 11 thermoplastic shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The probes can measure Hb values from bilateral prefrontal and temporal surface regions. The measuring points were labeled ch1 to ch52 from right-posterior to left-anterior (Fig. 1). The correspondence between these NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical cranio-cerebral correlations (Okamoto et al., 2004) and presented on the basis of results obtained by the virtual registration method (Tsuzuki et al., 2007).

3.3. Measurement parameters

The rate of data sampling was .1 second (s). The obtained data were analyzed using integral mode; the pre-task baseline was determined as the mean over a 10 s period just prior to the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was then applied to the data between these two baselines. The moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied automatic rejection of data with artifacts separately for each channel (Takizawa et al., 2008).

According to the aforementioned measurement parameters for integral mode, the waveforms of oxy-Hb, deoxy-Hb and total-Hb

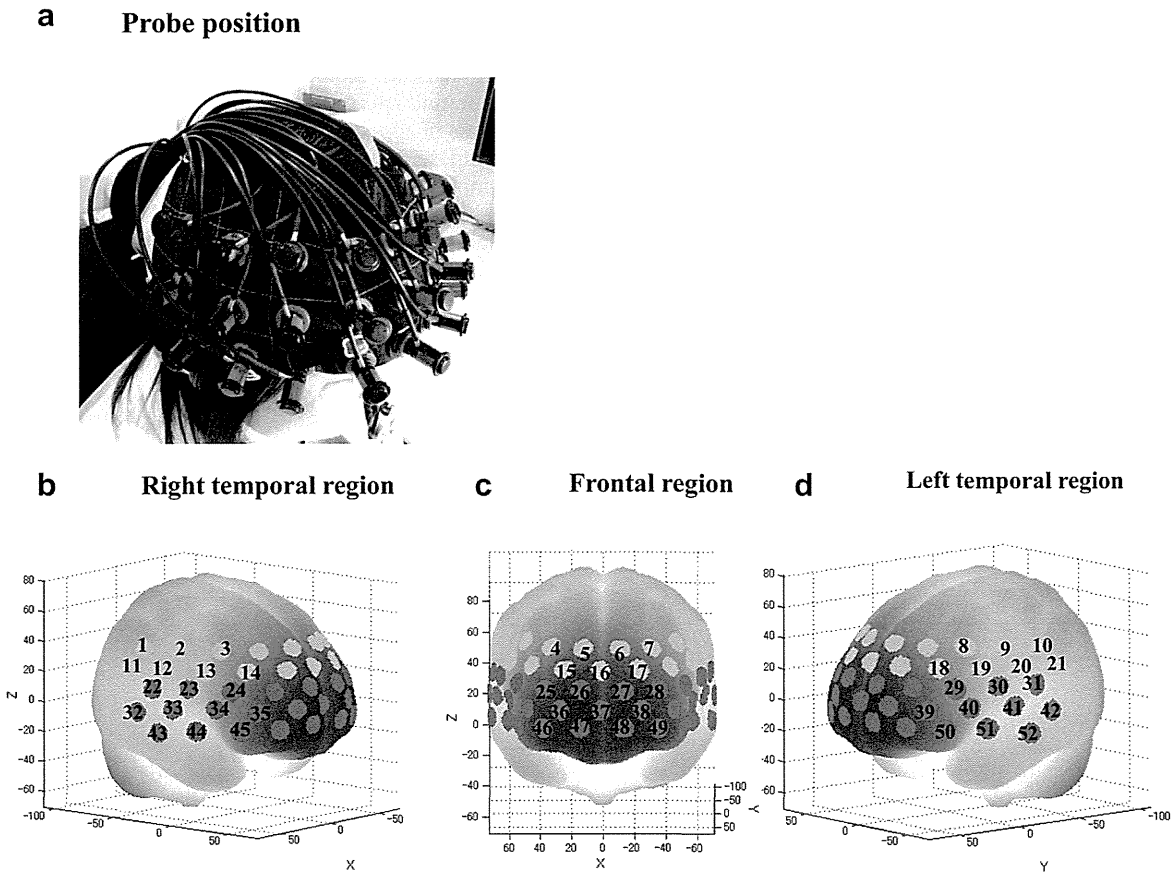

Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS) (a) Probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral frontal regions. (b–d) The 52 measuring positions of the NIRS device are superimposed on the 3D-reconstructed cerebral surface, based on magnetic resonance imaging. The 52 measuring positions are labeled ch1 to ch52, from the right posterior to the left posterior. The dimensional figures b, c and d indicate the right temporal, frontal and left temporal brain regions, respectively. Because acquired NIRS data from the 21 channels in the upper two rows (pink channels) clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ratio seemed to be low, they were excluded from statistical analyses.

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changes were acquired from each subject in all 52 channels during VFT.

3.4. Measurement environment

The subjects sat on a comfortable chair in a silent and day-lit room. They were instructed to minimize motions such as head movements, strong biting and blinking during the NIRS measurement, to avoid artifacts.

Data clearly containing motion artifacts, based on both our observations and the NIRS recording, were excluded from further analyses.

4. Statistical analysis

Because acquired NIRS data from the 21 channels in the upper two rows clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ration seemed to be low, they were excluded from statistical analyses.

The χ^2 test or Student's *t*-test was used to compare proportions and means, respectively, between the MDD and control groups.

As for the analysis of the NIRS data, we focused on oxy-Hb data, since oxy-Hb change (task period − pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean oxy-Hb changes were compared between the two groups (MDD and control) for each channel using Student's *t*-test. To examine the relationships between oxy-Hb changes and HAM-D21 total scores, HAM-D21 subscale scores, GAF, or other clinical variables, Spearman's rhos were calculated for MDD patients.

All statistical analyses were performed using SPSS for Windows, version 18.0.0 software (SPSS Japan, Tokyo, Japan). A value of $p < .05$ (two-tailed) was considered to be statistically significant. We set the value of q specifying the maximum false discovery rate (FDR) at .05, such that the false positive rate was no more than 5% on average in treating the oxy-Hb data obtained from multiple channels (Singh and Dan, 2006).

5. Results

5.1. Demographic and clinical data of patients and controls

Table 1 summarizes demographic characteristics of the patients and controls. The two groups did not differ significantly in age, gender, handedness, estimated premorbid IQ or SSS.

5.2. Task performance

The number of words generated did not differ significantly among the 15 combinations employed (15 combinations: $F[1, 45] = 1.1$, $p = .39$; three initial syllables: $F[2, 90] = 1.2$, $p = .31$) in either group. The number of generated words during VFT did not differ significantly (patients: 12.3 ± 3.9; controls 13.9 ± 4.3, $t = 1.5$, df = 58, $p = .13$) between the MDD and control groups.

5.3. Group comparison

As shown in Fig. 2, the MDD group had significantly smaller oxy-Hb increases than the control group in 22 channels (ch22–29, ch32–33, ch35–39 and ch44-50; FDR-corrected *p*: .000–.024) during VFT.

5.4. Relationship with symptom severity at the time of examination

As shown in Fig. 2, there were significant negative correlations between mean oxy-Hb changes during the task and HAM-D21 total scores in one channel (ch25: rho = −.56; FDR-corrected *p*: .001). Mean oxy-Hb changes during the task period showed significant negative correlations with three individual items of the HAM-D21 subscale scores (Fig. 3); insomnia early in 9 channels (ch23, ch25–27, ch36–37 and ch46–48: rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (ch44 and ch45: rho = −.61 to −.57; FDR corrected *p*: .001 to .003), and psychomotor retardation in 12 channels (ch22–24, ch32, ch35–36, ch41, ch43–ch45, ch47 and ch51: rho = −.70 to −.44; FDR corrected *p*: .000–.018). Mean oxy-Hb changes showed no significant correlations with the remaining HAM-D21 subscale scores (i.e., depressed mood, guilt, insomnia middle, insomnia late, psychomotor agitation, anxiety psychic, anxiety somatic, loss of appetite, somatic symptoms general, sexual interest, hypochondriasis, loss of weight, insight, diurnal variation, and obsessional symptoms;) (Fig. 4).

Furthermore, mean oxy-Hb changes showed no significant correlation with task performance during VFT or other clinical variables, such as age, duration of illness, and sleepiness (data not shown).

5.5. Relationships with medication

There were no significant correlations between the HAM-D21 total score and doses of antidepressants (rho = −.23, $p = .22$) or anxiolytics (rho = .25, $p = .18$). There were significant negative correlations between mean oxy-Hb changes during the task and doses of antidepressants in 6 channels (ch31, ch40–41, ch45, ch50–51: rho = −.57

Table 1
Demographic and clinical data of patients with major depressive disorder and controls.

Demographics	Patients with depression ($n = 30$)	Healthy controls ($n = 30$)	Group difference *p*-value
Age (years)	36.7 ± 11.6	35.1 ± 9.4	.871
Gender (female/male)	16/14	16/14	1.000
Edinburgh handedness inventory (%)	92.9 ± 9.7	92.0 ± 11.5	.753
Age at onset (years)	30.9 ± 10.8	–	–
Duration of illness (years)	5.8 ± 4.1	–	–
Duration of medication (years)	5.0 ± 3.6	–	–
GRID HAM-D21 total score	16.7 ± 4.8	–	–
Estimated premorbid IQ	105.7 ± 9.5	105.9 ± 8.3	.953
Sleepiness	3.3 ± 1.1	2.9 ± .9	.104
GAF	57.6 ± 9.3		
Medication			
Imipramine equivalent dose (mg/day)	141.9 ± 127.6	–	–
Diazepam equivalent dose (mg/day)	8.5 ± 11.6	–	–

The χ^2 test or *t*-test was used to compare these variables between patients and controls. GAF, Global Assessment of Functioning; GRID HAM-D21, GRID Hamilton Rating Scale for Depression 21 item; IQ, Intelligence Quotient.

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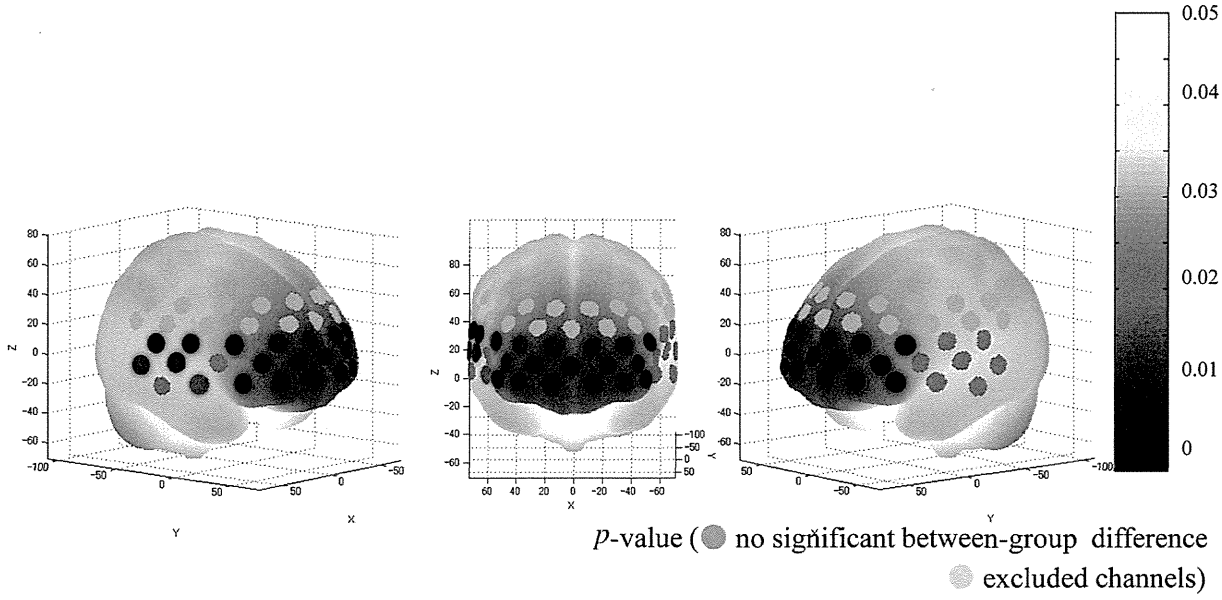

Fig. 2. *p*-value significance map of *t*-tests for oxy-Hb increases in patients with MDD compared with healthy controls during VFT using FDR correction. The warm colored circles represent significantly smaller oxy-Hb increases than in the control group at the channels indicated. There were 22 channels (ch22–29, ch32–33, ch35–39 and ch44–50; FDR-corrected *p*: 000–.024).

to −.48; FDR-corrected *p*: .002 to .007). Mean oxy-Hb changes showed no significant correlations with doses of anxiolytics.

6. Discussion

6.1. Task performance

The number of words generated during the VFT did not differ significantly between patients and controls, which is consistent with the majority of previous studies (Matsuo et al., 2002; Fossati et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Previous studies reported impairment on semantic fluency tasks in depression (Calev et al., 1989; Tarbuck and Paykel, 1995). However, on phonemic fluency task conflicting results patients showing normal or impairment performance in depression (Albus et al., 1996; Degl'Innocenti et al., 1998). Type of psychiatric disorder and task time setting may reflect the discrepancies (Fossati et al., 2003). In the present study, the time setting of VFT was three phonemes within 60 s, that is, 20 s for each phoneme, which differs from the standard VFT usually using 60 s for one phoneme. The time setting condition was designed as it is, so that the subjects were able to keep generating words regularly within the task period to avoid the effect of "not speaking". It is possible that the time setting condition in the present study caused the lack of significant between group-difference in task performance.

6.2. Between-group comparison of oxy-Hb activation

The present study showed oxy-Hb activation during VFT to be significantly smaller in the MDD group than in age-, gender- and IQ-matched healthy controls. This result is essentially consistent with those obtained using NIRS (Matsuo et al., 2002; Herrmann et al., 2004; Suto et al., 2004; Kameyama et al., 2006; Pu et al., 2008), single photon emission computed tomography (SPECT) (Mayberg et al., 1994) or functional magnetic resonance imaging (fMRI) (Okada et al., 2003).

6.3. Relationships with symptom severity at the time of examination

Mean oxy-Hb changes during the task period showed a significantly negative correlation with HAM-D21 total score at ch25. Ch25 is located approximately in the right DLPFC. The finding is in line with some initial studies (Bench et al., 1995; Mayberg et al., 1994) which suggest that abnormal functions in DLPFC are mood dependent. However, other more recent studies investigating cross-sectional relationship between depression psychopathology and brain function do not coincide with our result (Périco et al., 2005; Milak et al., 2005). One of the reasons for the discrepancy may arise from the different methodologies; in the present study we adopted VFT for activation whereas the previous studies observed the basal activity with no activation task. Although speculative as it is, the activation of PFC by VFT may have led to the significant relationship between oxy-Hb changes and depression symptom severity in the right DLPFC.

More interestingly, mean oxy-Hb changes during the task period showed significant negative correlations with three individual HAM-D21 items in a wider area than they showed with HAM-D21 total scores; insomnia early in nine, work and activity in two and psychomotor retardation in twelve channels. The nine channels correlating with "insomnia early" were located approximately in the right pre-motor area, DLPFC and frontopolar and orbitofrontal areas. The two channels correlating with "work and activity" were located approximately in the right DLPFC and temporopolar area. The twelve channels correlating with "psychomotor retardation" were located broadly in the fronto-temporal areas with right hemispheric dominance. Although these findings should be treated with care given the exploratory nature of multiple analyses, it is noteworthy that at least some subscale scores of HAM-D21 appeared to show stronger relationship with oxy-Hb changes than HAM-D21 total scores. It has been pointed out that HAM-D17 and/or HAM-D21 are not necessarily unidimensional, and thus not adequate to assess depression severity (Bagby et al., 2004). Licht et al. (2005) showed that a set of the HAM-D containing six subscales constitute a unidimensional scale measuring severity of

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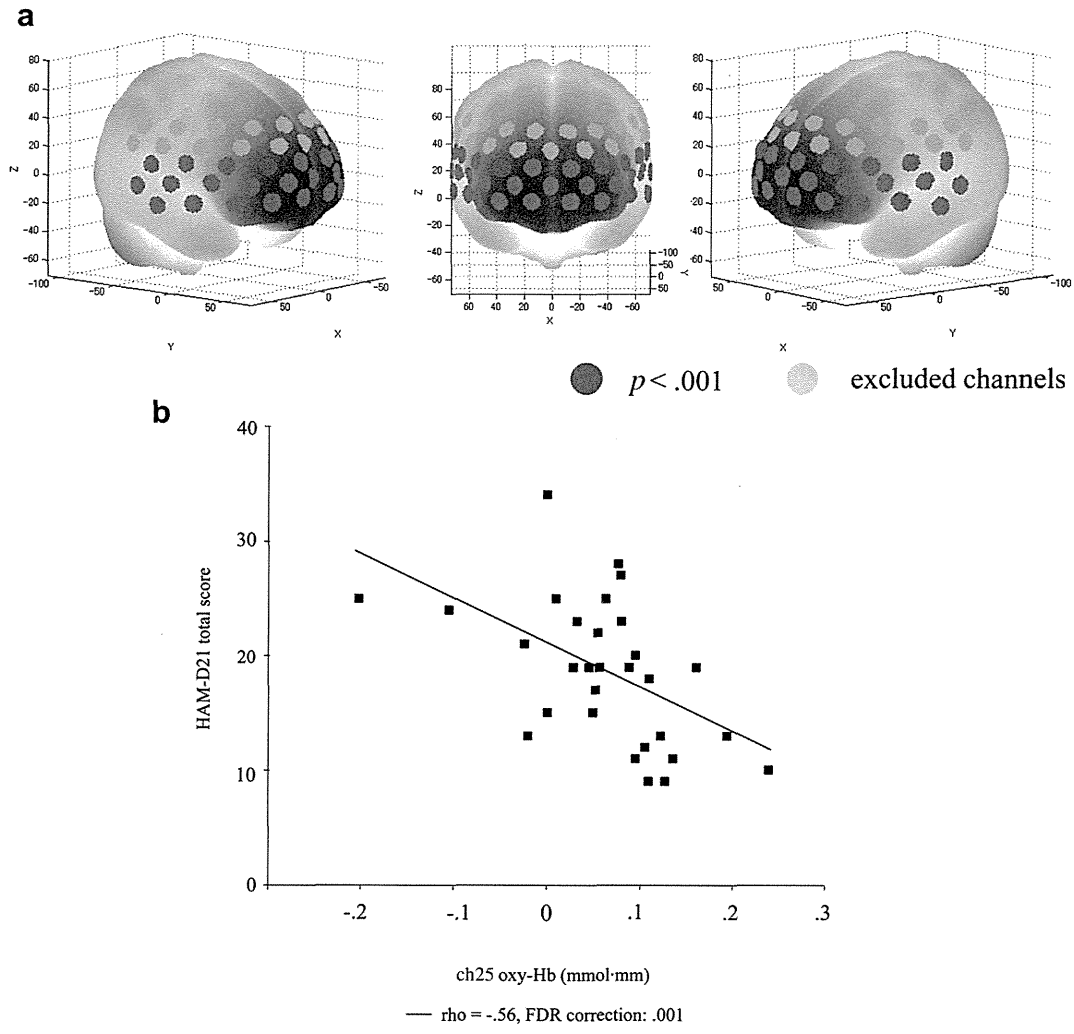

Fig. 3. (a) The channels with a significant correlation between oxy-Hb changes and HAM-D21 total score after FDR correction. (b) Scatter graph showing the relationship between HAM-D21 total scores and oxy-Hb activation in ch25.

depression, whereas the remaining items covering neurovegetative symptoms showed a problematic response somewhat insensitive to depression severity. In fact, the multidimensionality was highlighted in the unstable factor structure, which was demonstrated by a failure to replicate a single unifying structure across studies (Bagby et al., 2004). The relatively strong relationship indicated between HAM-D21 subscale scores and oxy-Hb changes in divergent areas, compared to HAM-D21 total scores may be due to the multidimensional properties of HAM-D21. Graff-Guerrero et al. (2004) also demonstrated that each HAM-D subscale score showed a significant correlation with the basal CBF in variant areas, in some cases showing positive correlation and others negative.

6.4. Relationships with medications

As all patients were taking antidepressants at the time of evaluation, the medication effect could not be ignored. Yet, there was no significant relationship between daily dose levels of antidepressants and the HAM-D21 total score. Although daily dose levels of antidepressants showed significant negative correlations with oxy-Hb changes in six channels, ch25, where a significant correlation between oxy-Hb changes and HAM-D21 total scores was observed, was not included in the six channels. Therefore, we suspect that the effect was small, if at all.

PET has been used to demonstrate that antidepressant medication normalizes both over-activity and under-activity in the frontal cortex (Kennedy et al., 2001, 2007; Mayberg et al., 2000; Goldapple et al., 2004). Unfortunately, our results could not clarify the relationship between medication and brain activation because our analysis was based on cross-sectional data. Although our data may reflect the more restraint-free, natural setting than those using fMRI or PET, further studies in drug-naïve patients are required to draw any conclusions as to the possible effects of medication on brain activation as measured by NIRS. Longitudinal studies investigating the relationship between the change in oxy-Hb data and symptom severity scores with a larger sample size are warranted to reach a conclusion on this matter.

The results of this study must be interpreted with caution due to certain limitations. First, because the analysis was based on cross-sectional data, causality cannot be determined. Longitudinal studies are needed to assess cause-and-effect relationships. Second, our sample size was not large, and is thus subject to type II error. Further studies with larger numbers of MDD patients are required. Finally, owing to the multidimensional properties of HAM-D21, assessment of depression symptom severity using HAM-D21 total scores may not be adequate, and thus, other scales such as Montgomery Asberg Depression Rating Scale (MADRS) or Beck Depression Inventory (BDI) should be tested in the future study.

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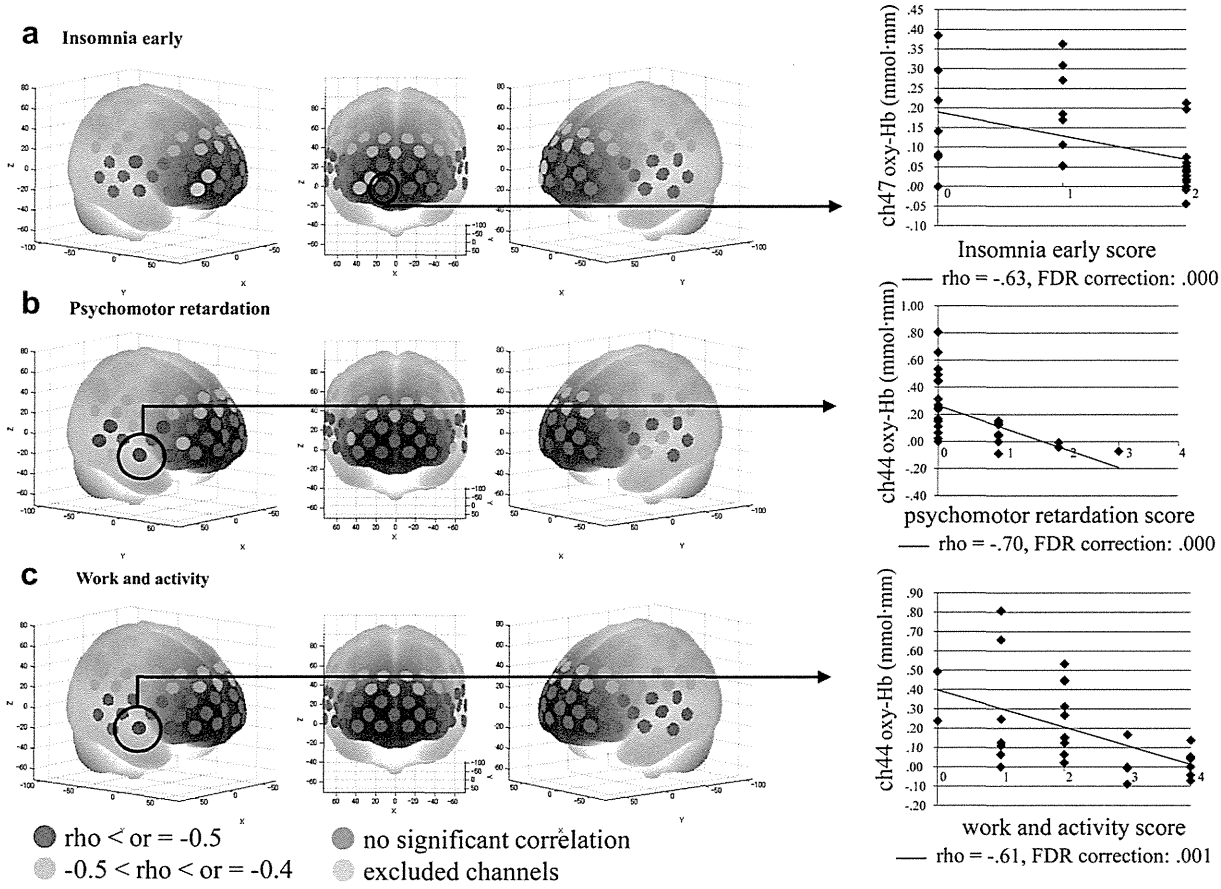

Fig. 4. rho-value map for the correlation between oxy-Hb activation in MDD patients and three individual HAM-D21 subscale scores after FDR correction. (a) insomnia early, (b) psychomotor retardation, and (c) work and activity.

7. Conclusion

In this study, we confirmed that the increase in oxy-Hb during a VFT task is significantly smaller in MDD than in age- and gender-matched healthy subjects. This difference could not be explained by a difference in task performance or premorbid IQ. The blunted increase in right DLPFC was associated with the symptom severity of MDD and therefore oxy-Hb changes during VFT in this region may be a state-dependent marker of depression.

Role of the funding source

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Contributors

T. Noda designed the study, wrote the protocol, assessment of depression severity, literature searches, statistically analyzed the data, and wrote the first draft of the manuscript. T. Matsuda was involved in patient recruitment and assessment of depression severity. H. Kunugi and S. Yoshida wrote the final version of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2012.04.001.

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Influence of Signal Intensity Non-Uniformity on Brain Volumetry Using an Atlas-Based Method

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Objective: Many studies have reported pre-processing effects for brain volumetry; however, no study has investigated whether non-parametric non-uniform intensity normalization (N3) correction processing results in reduced system dependency when using an atlas-based method. To address this shortcoming, the present study assessed whether N3 correction processing provides reduced system dependency in atlas-based volumetry.

Materials and Methods: Contiguous sagittal T1-weighted images of the brain were obtained from 21 healthy participants, by using five magnetic resonance protocols. After image preprocessing using the Statistical Parametric Mapping 5 software, we measured the structural volume of the segmented images with the WFU-PickAtlas software. We applied six different bias-correction levels (Regularization 10, Regularization 0.0001, Regularization 0, Regularization 10 with N3, Regularization 0.0001 with N3, and Regularization 0 with N3) to each set of images. The structural volume change ratio (%) was defined as the change ratio (%) = (100 x [measured volume - mean volume of five magnetic resonance protocols] / mean volume of five magnetic resonance protocols) for each bias-correction level.

Results: A low change ratio was synonymous with lower system dependency. The results showed that the images with the N3 correction had a lower change ratio compared with those without the N3 correction.

Conclusion: The present study is the first atlas-based volumetry study to show that the precision of atlas-based volumetry improves when using N3-corrected images. Therefore, correction for signal intensity non-uniformity is strongly advised for multi-scanner or multi-site imaging trials.

Index terms: *Atlas-based; Bias correction; Brain volumetry; Intensity non-uniformity; Non-parametric non-uniform intensity normalization*

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INTRODUCTION

Magnetic resonance imaging (MRI) and image analysis methods can track brain atrophy at multiple time-points, and have revealed fine-scale anatomical changes associated with cognitive decline (1, 2). An atlas-based method using three-dimensional T1-weighted magnetic resonance images (3D-T1WI) has been used to estimate local brain volume (3, 4). Signal intensity non-uniformity of 3D-T1WI is influenced by coil variation, repetition time (TR), and radio frequency uniformity (5, 6). Non-parametric non-uniform intensity normalization, commonly referred to as N3, was first proposed by Sled et al. (7) as a novel approach for correcting signal intensity non-uniformity in MRI (N3 software is publicly available at http://www.bic.mni.mcgill.ca/software/N3/). The correction is based on a non-parametric framework and thus operates without the presence of a statistical model for tissue classification. To explore suitable methods for correcting the signal intensity non-uniformity of 3D-T1WI, a previous study evaluating the performance of six correction methods was consulted, and reported that the N3 correction demonstrated a high degree of stability (8). Another study reported that the N3 correction reduced coil-type and pulse-sequence differences, indicating improved reproducibility using tensor-based morphometry (9). The N3 correction is the most commonly used method in comparative evaluation (10). None of these previous reports; however, investigated the effect of the N3 correction with regard to atlas-based volumetry (3, 4). The aim of the present study was to examine the change in the ratio of the compartment volume to assess whether the N3 correction and change in the bias correction setting in Statistical Parametric Mapping 5 (SPM5) (11) affect system dependency in brain volumetry using an atlas-based method.

MATERIALS AND METHODS

Subjects

A total of 21 healthy volunteers participated in this study (17 males, 4 females; mean age: 31.1 ± 7.4 years; age range: 23-47 years). Using 1.5- and 3-tesla MRI systems, 3D-T1WIs were obtained from each subject on the same day. The MR images were inspected by a board-certified radiologist (O.A.), who found none of the following findings in any subject: brain tumor, infarction, hemorrhage, brain atrophy, cognitive impairment, or white matter lesions graded higher than 2 using Fazekas's classification scale (12). The study protocol was approved by the Ethical Committee of our institution. After the study had been explained to each subject, written informed consent was obtained from all participants.

MRI Scanning Protocol

We employed the Alzheimer's Disease Neuroimaging Initiative (ADNI) (13) scanning protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml). MRI data were obtained using five systems: 1) The GE 3 tesla phased-array (GE 3T PA) coil / quadrature (QD) coil protocol was used when MRI data were obtained using a 3.0-T scanner (Signa EXCITE HDx, GE Medical Systems, Waukesha, WI, USA) for both protocols; 2) The GE 3T PA coil protocol was used when a phased-array coil was used for reception; 3) The GE 3T QD coil protocol was used when a quadrature head coil was used for send-receive. Otherwise, the conditions were the same for both protocols: three-dimensional magnetization-prepared rapid gradient echo (MP-RAGE) was used to obtain 170 contiguous sagittal 3D-T1WIs with a slice thickness of 1.3 mm, repetition time/echo time = 2300/2.8 ms, inversion time = 900 ms, flip angle = 8°, field of view = 26 cm, number of excitations = 1, and pixel matrix = 256 x 256; 4) MRI data were obtained via the GE1.5T protocol, which used a 1.5-T scanner (Signa EXCITE HDx, GE Medical Systems, Waukesha, WI, USA). A quadrature head coil was used for send-receive; 5) Three-dimensional MP-RAGE was used to obtain 184 contiguous sagittal 3D-T1WI with a slice thickness of 1.3 mm, repetition time/echo time = 3000/3.9 ms, inversion time = 1000 ms, flip angle = 8°, field of view = 24 cm, number of excitations = 1, and pixel matrix = 192 x 192.

Siemens protocol: MRI data were obtained using a 1.5-T scanner (MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany). A head matrix coil was used for reception. Three-dimensional MP-RAGE was used to obtain 160 contiguous sagittal 3D-T1WI with a slice thickness of 1.3 mm, repetition time/echo time = 2400/3.6 ms, inversion time = 1000 ms, flip angle = 8°, field of view = 24 cm, number of excitations = 1, and pixel matrix = 192 x 192.

Toshiba protocol: MRI data were obtained using a 1.5-T scanner (EXCELART Vantage, Toshiba Medical Systems, Tokyo, Japan). A quadrature coil was used for send-receive. Three-dimensional MP-RAGE was used to obtain 165 contiguous sagittal 3D-T1WI with a slice thickness of 1.3 mm, repetition time/echo time = 2400/4.0 ms, inversion

time = 1000 ms, flip angle = 8°, field of view = 24 cm, number of excitations = 1, and pixel matrix = 192 x 192.

Image Preprocessing for Atlas-Based Volumetry

We used SPM5 software for the volumetric analysis. In SPM5, 3D-T1WI in native space were bias-corrected, spatially normalized, and segmented into gray matter, white matter, and cerebrospinal fluid images. The voxel size of the spatially normalized images was 2 x 2 x 2 mm. During the modulation step in SPM5, we multiplied the voxel values of the spatially normalized gray and white matter images by a measure of the relative volumes of the warped and unwarped structures that were derived from the nonlinear step of spatial normalization (Jacobian determinant).

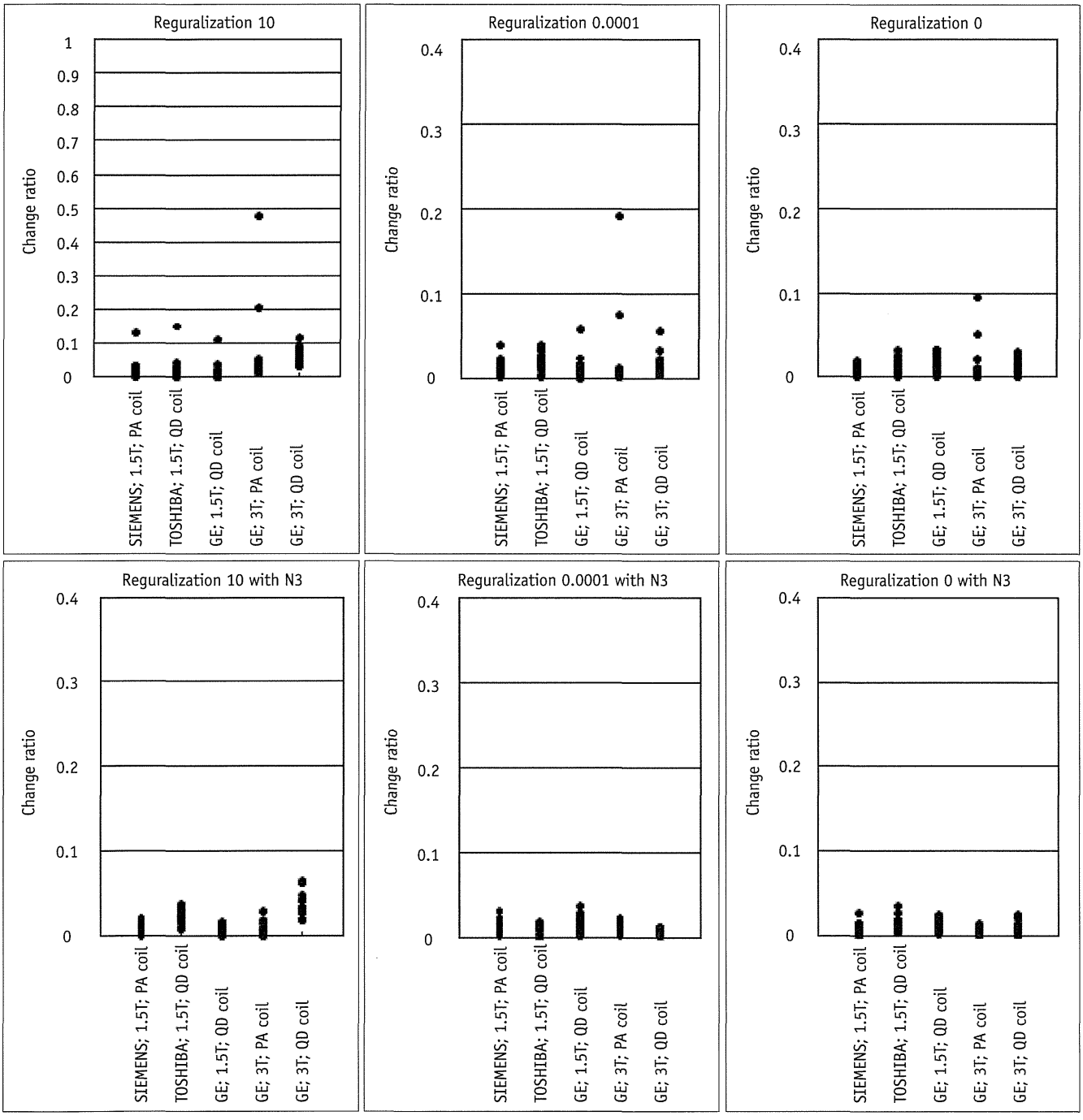

Fig. 1. Change ratio of structural volume of white matter, for each system. Bias-correction levels are shown at top of figure. Change ratios showed decrease in increasing bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3); this trend was strongest for GE 3T PA coil protocol. 3T = 3 tesla, PA = phased-array, QD = quadrature

We applied six different bias-correction levels in SPM5 preprocessing (Regularization 10, Regularization 0.0001, Regularization 0, Regularization 10 with N3, Regularization 0.0001 with N3, and Regularization 0 with N3) to each set of images, resulting in 60 prepared images for each subject (five magnetic resonance protocols x six bias-correction levels x spatially normalized gray matter and white matter). The options for the N3 method are that %nu_options = ("1.5","-normalize -stop 0.0001 -fwhm 0.05 -distance 150 -iterations 10000 -shrink 2", "3.0","-normalize -stop 0.0001 -fwhm 0.05 -distance 50 -iterations 10000 -shrink 2"). We used a default value with N3 because we wanted to retain the comparability with previous studies. However, we reduced the distance of the option for N3 in 3T because the

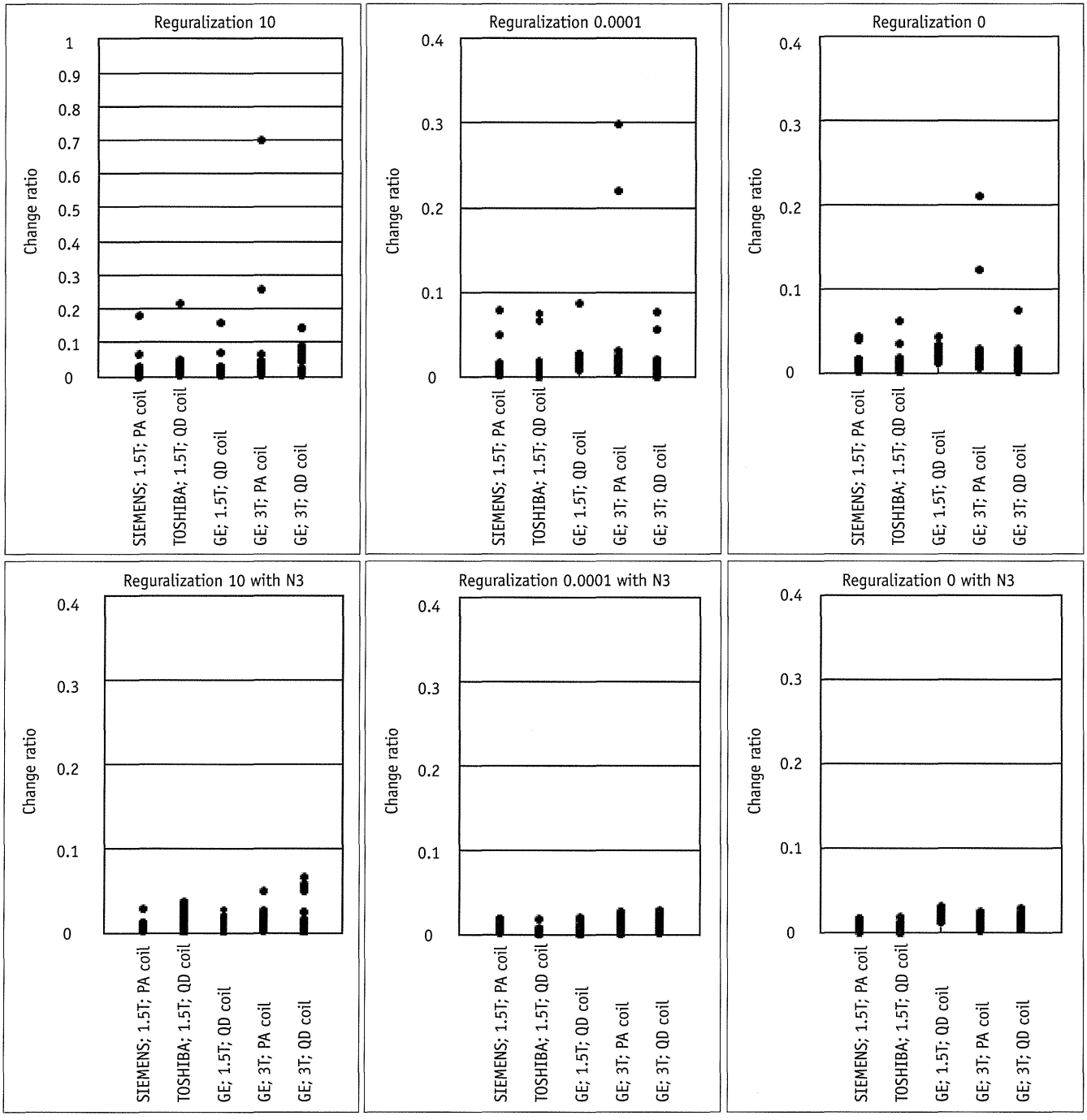

Fig. 2. Change ratio of structural volume of temporal lobe for each system. Bias-correction levels are shown at top of figure. Change ratios showed decrease with increasing bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3); this trend was strongest for GE 3T PA coil protocol. 3T = 3 tesla, PA = phased-array, QD = quadrature

signal heterogeneity of 3T image was large compared with the 1.5T image (7).

Measurement of Structural Volume Using the Atlas-Based Method

The region-of-interests (ROIs) for measurement of structural volume using the atlas-based method were obtained by WFU-PickAtlas (3, 4). The ROI labels used were those provided as default settings by the software: white matter, temporal lobe, parietal lobe, occipital lobe, and the hippocampus. White matter volume was measured using the normalized white matter data described in Section 'Image preprocessing for atlas-based volumetry'. The temporal lobe, parietal lobe, occipital lobe, and hippocampal volumes were

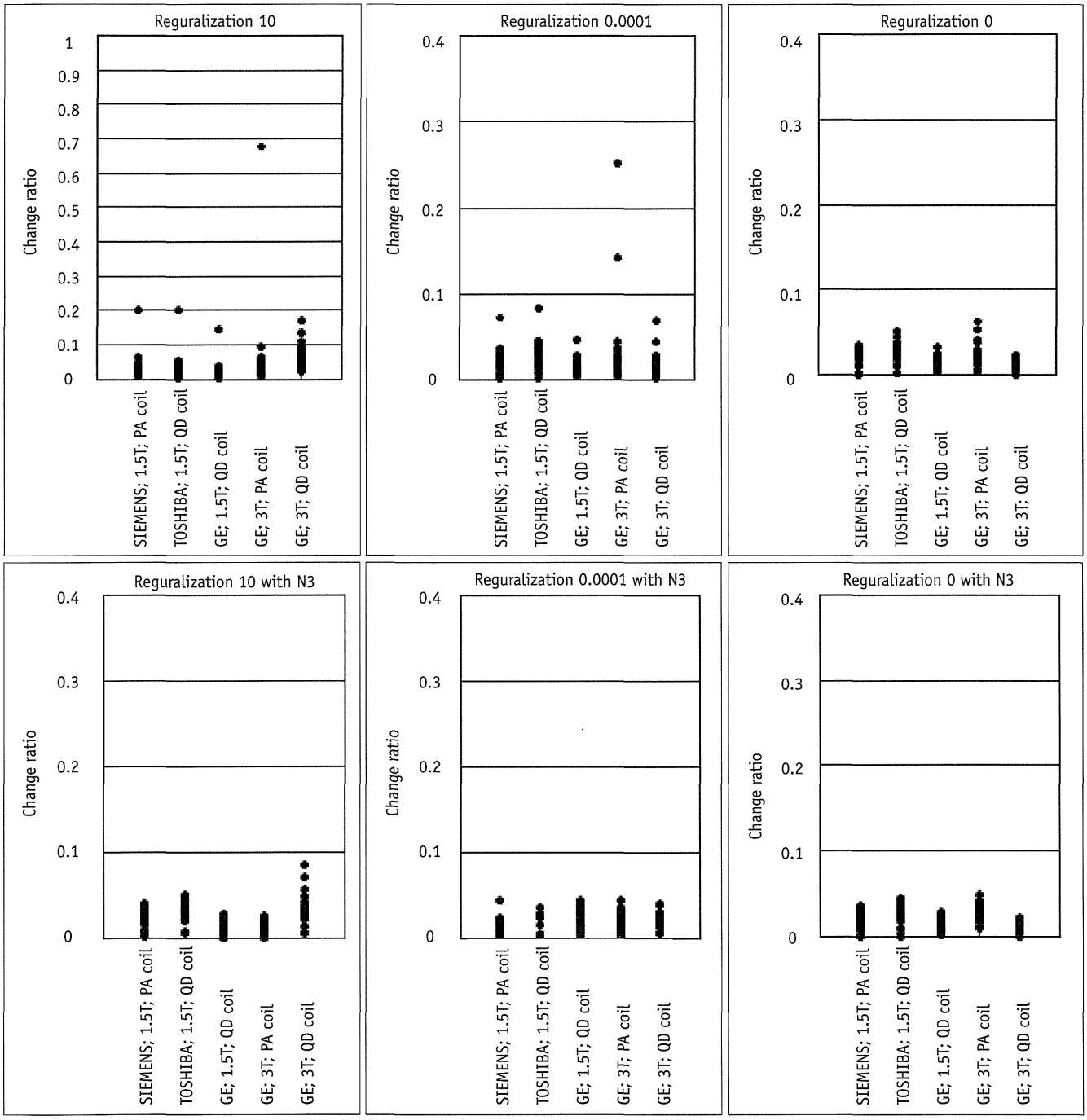

Fig. 3. Change ratio of structural volume of parietal lobe for each system. Bias-correction levels are shown at top of figure. Change ratios showed decrease with increasing bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3); this trend was strongest for GE 3T PA coil protocol. 3T = 3 tesla, PA = phased-array, QD = quadrature

measured using the normalized gray matter data described in Section 'Image preprocessing for atlas-based volumetry'.

The change ratio (%) of structural volume was defined as the change ratio (%) = (100 x [measured volume - mean volume of five magnetic resonance protocols] / mean volume of five magnetic resonance protocols) for each bias-correction level. A low change ratio is synonymous with lower system dependency.

RESULTS

The change ratio (%) of structural volume for each ROI is shown in Figures 1-5. Figure 1 shows the change ratio of structural volume for white matter. Visually, the smaller

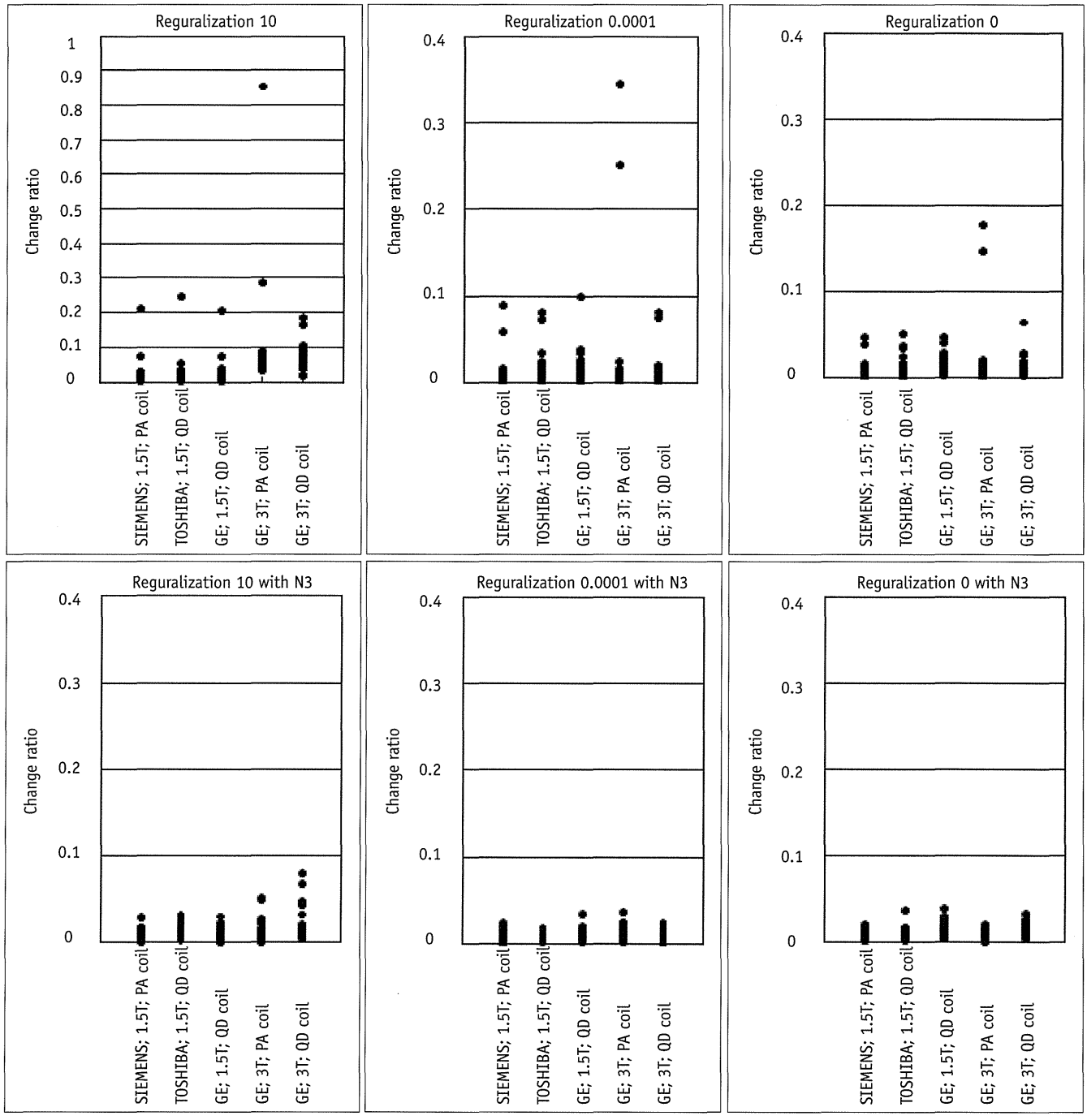

Fig. 4. Change ratio of structural volume of occipital lobe, for each system. Bias-correction levels are shown at top of figure. Change ratios showed decrease with increasing bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3); this trend was strongest for GE 3T PA coil protocol. 3T = 3 tesla, PA = phased-array, QD = quadrature

Regularization values had a decreased change ratio. That is, the result showed that increasing bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3) increased the effect on signal intensity non-uniformity correction; this trend was strongest for the GE 3T PA coil protocol. The lowest change ratio was achieved using "Regularization 0 with N3". Results in the temporal lobe (Fig. 2), parietal lobe (Fig. 3), occipital lobe (Fig. 4), and hippocampus (Fig. 5) show a similar trend. In addition, all figures were summarized in Table 1.

In white matter, the maximum value of the change ratio was 0.475% for the GE 3T PA coil protocol with Regularization 10; the maximum value for this protocol with Regularization 0 and with N3 was 0.015%. In the temporal

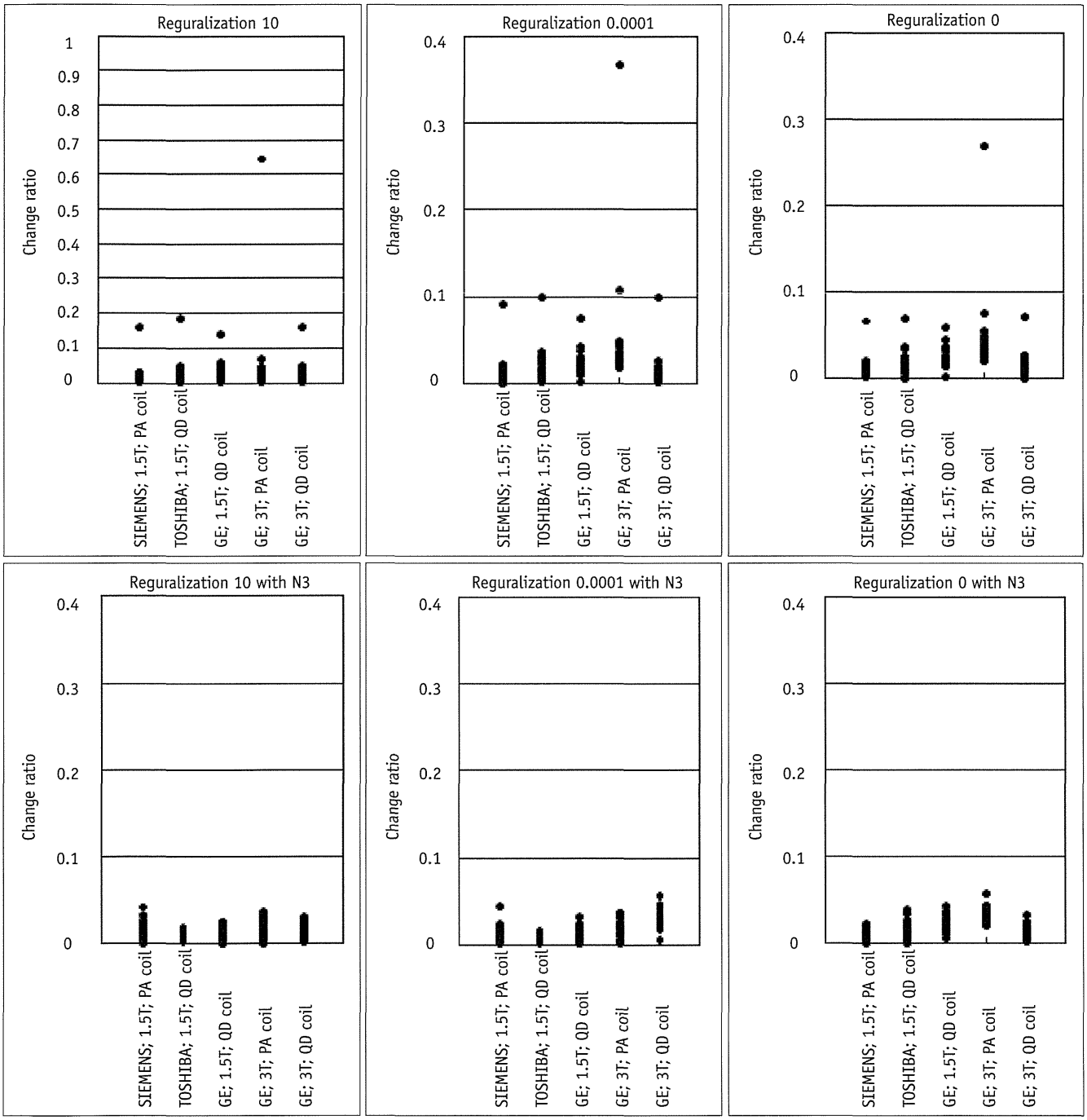

Fig. 5. Change ratio of structural volume on hippocampus, for each system. Bias-correction levels are shown at top of figure. Change ratios showed decrease with increasing bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3); this trend was strongest for GE 3T PA coil protocol. 3T = 3 tesla, PA = phased-array, QD = quadrature

Table 1. Average Change Ratios (%) Are Summarized in Upper Table. Region-of-Interest Names and Scanning Protocols Are Shown at Left Side of Table. Bias-Correction Levels Are Shown at Top of Table. Significant Statistical Differences (Paired Student's *t* Test) between Bias-Correction Revels Are Summarized in Lower Table

ROI Name	Scanning Protocol	Bias-Correction Levels					
		Regularization 10	Regularization 0.0001	Regularization 0	Regularization 10 with N3	Regularization 0.0001 with N3	Regularization 0 with N3
White matter	SIEMENS; 1.5T; PA coil	0.0223	0.0124	0.0102	0.0105	0.00989	0.00915
	TOSHIBA; 1.5T; QD coil	0.0243	0.0193	0.0153	0.0238	0.0174	0.0150
	GE; 1.5T; QD coil	0.0137	0.0134	0.0152	0.00774	0.0112	0.0135
	GE; 3T; PA coil	0.0574	0.0170	0.0120	0.00853	0.00489	0.00493
	GE; 3T; QD coil	0.0607	0.0179	0.0126	0.0347	0.0136	0.00865
Temporal lobe	SIEMENS; 1.5T; PA coil	0.0191	0.0121	0.0110	0.00887	0.00680	0.00940
	TOSHIBA; 1.5T; QD coil	0.0336	0.0141	0.0101	0.0199	0.00698	0.00582
	GE; 1.5T; QD coil	0.0228	0.0223	0.0227	0.0115	0.0178	0.0211
	GE; 3T; PA coil	0.0738	0.0388	0.0289	0.0138	0.0130	0.0128
	GE; 3T; QD coil	0.0548	0.0149	0.0155	0.0206	0.0103	0.0159
Parietal lobe	SIEMENS; 1.5T; PA coil	0.0354	0.0241	0.0223	0.0235	0.0221	0.0219
	TOSHIBA; 1.5T; QD coil	0.0314	0.0319	0.0279	0.0324	0.0296	0.0262
	GE; 1.5T; QD coil	0.0226	0.0156	0.0148	0.0126	0.0139	0.0153
	GE; 3T; PA coil	0.0636	0.0390	0.0275	0.0137	0.0256	0.0279
	GE; 3T; QD coil	0.0707	0.0204	0.0130	0.0367	0.0133	0.0107
Occipital lobe	SIEMENS; 1.5T; PA coil	0.0244	0.0131	0.0100	0.00788	0.00714	0.00713
	TOSHIBA; 1.5T; QD coil	0.0295	0.0192	0.0155	0.0191	0.0130	0.0106
	GE; 1.5T; QD coil	0.0255	0.0183	0.0170	0.0117	0.0142	0.0151
	GE; 3T; PA coil	0.107	0.0361	0.0234	0.0164	0.00774	0.00803
	GE; 3T; QD coil	0.0705	0.0138	0.0161	0.0242	0.00903	0.0158
Hippo-campus	SIEMENS; 1.5T; PA coil	0.0197	0.0128	0.0128	0.0104	0.00843	0.00933
	TOSHIBA; 1.5T; QD coil	0.0261	0.0180	0.0192	0.0118	0.0157	0.0165
	GE; 1.5T; QD coil	0.0286	0.0243	0.0247	0.0213	0.0205	0.0216
	GE; 3T; PA coil	0.0566	0.0494	0.0460	0.0101	0.0302	0.0313
	GE; 3T; QD coil	0.0258	0.0144	0.0145	0.0168	0.0102	0.0145
Average with 25 data in table		0.0408	0.0213	0.0183	0.0171	0.0141	0.0147
Standard deviation with 25 data in table		0.0234	0.0100	0.0082	0.0084	0.0069	0.0070
Regularization 10			$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Regularization 0.0001				$p < 0.001$	$p = 0.0573$	$p < 0.001$	$p < 0.001$
Regularization 0					$p = 0.311$	$p < 0.001$	$p < 0.001$
Regularization 10 with N3						$p = 0.059$	$p = 0.129$
Regularization 0.0001 with N3							$p = 0.130$

Note.— 3T = 3 tesla, PA = phased-array, QD = quadrature

lobe, the maximum value of the change ratio was 0.700% for the GE 3T PA coil protocol with Regularization 10; however, the maximum value in with Regularization 0 with and N3 was 0.024%. In the parietal lobe, the maximum value of the change ratio was 0.677% for the GE 3T PA coil protocol with Regularization 10, but the maximum value in with Regularization 0 with and N3 was 0.042%. In the occipital lobe, the maximum value of the change ratio was 0.854% for the GE 3T PA coil protocol with Regularization 10, but the maximum value with Regularization 0 and N3 was 0.020%. In the hippocampus, the maximum value of the change ratio was 0.646% in for the GE 3T PA coil

protocol with Regularization 10, but the maximum value with Regularization 0 with and N3 was 0.057%. In addition, T1WIs of the GE 3T PA coil protocol with native space were shown in the Figure 6, and normalized gray matter images of the GE 3T PA coil protocol were shown in the Figure 7.

DISCUSSION

While the increased statistical power inherent in multicenter studies can provide additional information over single-center studies, similar acquisition protocols must

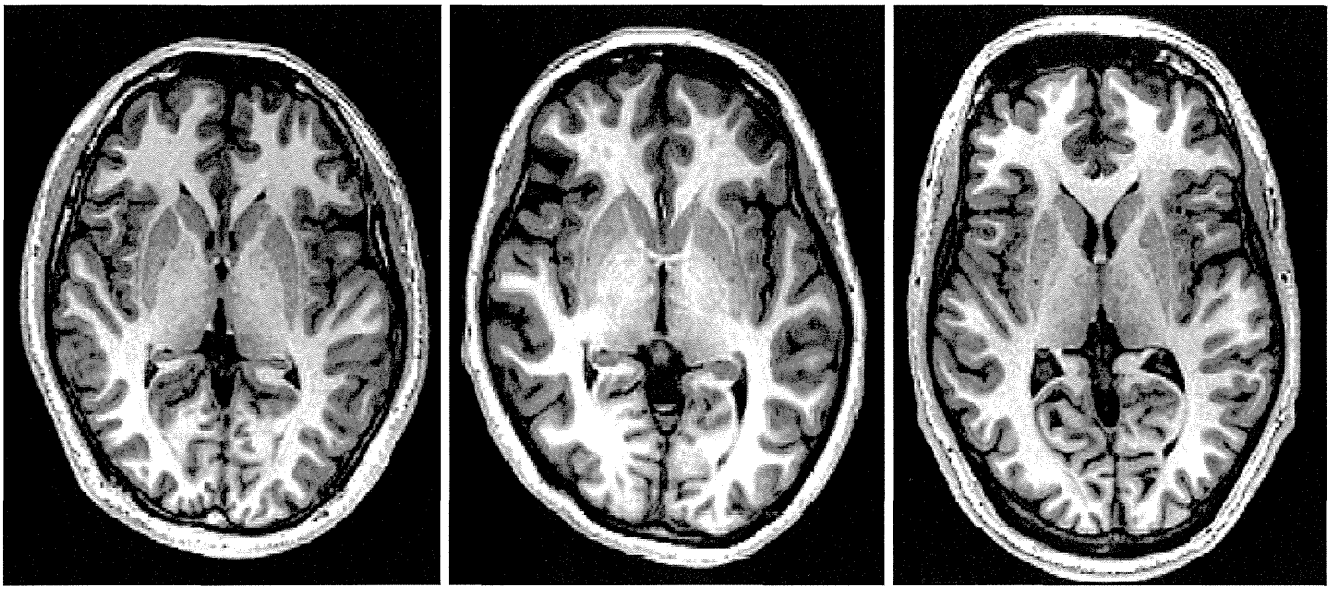

Fig. 6. T1 weighted-images of GE 3 tesla phased-array coil protocol with native space for three subjects. Subject C has more 0.1 change ratios, while subject A and B have less 0.1 change ratios.

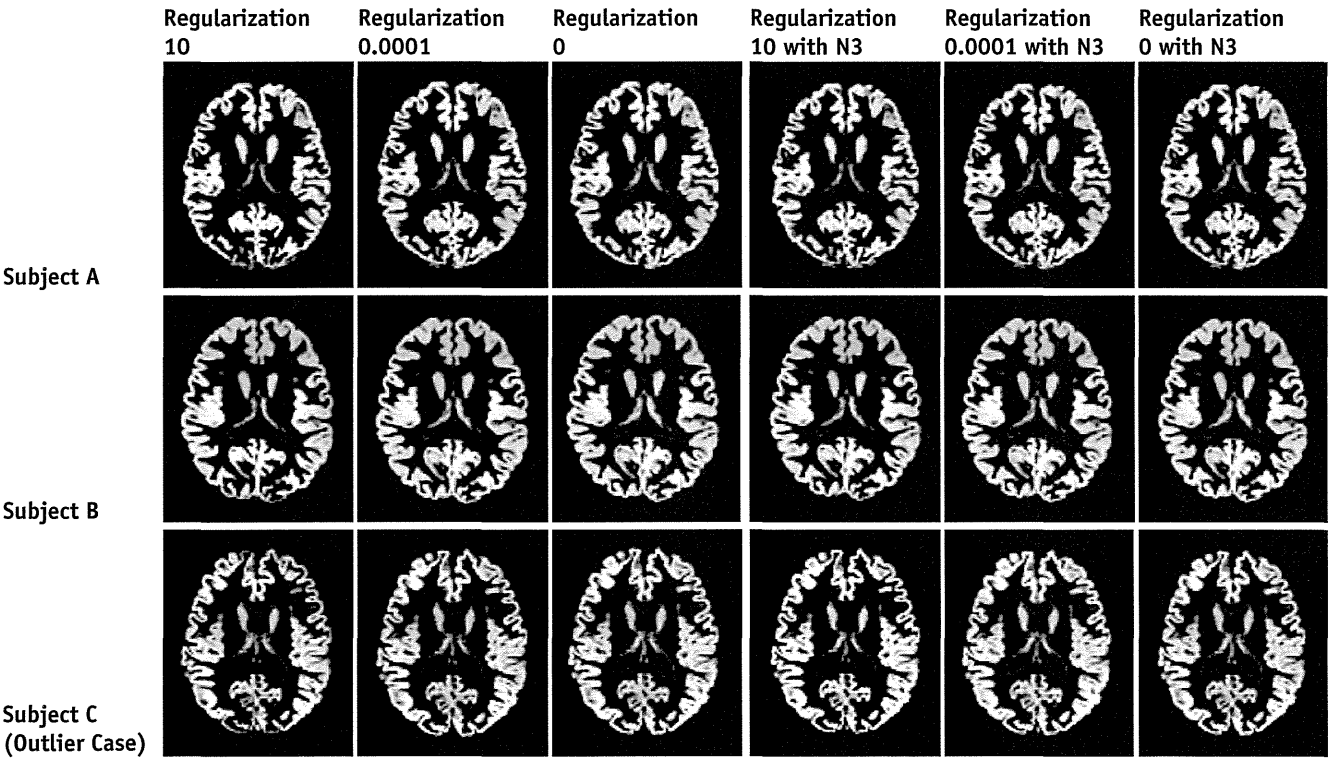

Fig. 7. Normalized gray matter images of GE 3 tesla phased-array coil protocol for three subjects. Subject C has more than 0.1 change ratios, and subject A and B have less than 0.1 change ratios. Bias-correction levels are shown at top of Figure.

be used in all cases to avoid possible system differences between sites (14). Building on the experience of previous multicenter studies in anatomical imaging (15, 16), the ADNI group took great care to define an optimized mandatory MP-RAGE imaging protocol across all sites (13), and employed correction for signal intensity non-uniformity differences. Accordingly, the precision of the computational analyses of compartment volume is affected by these differences (17).

Previous studies have shown low variability in volumetric measures obtained from repeated scans using the same protocol (17). It may be considered that the much higher variance that occurs across numerous protocols, which indicates the limited robustness of the segmentation procedure. To a lesser extent, combining images from different field strengths may be justified as a timesaving procedure that enables researchers to obtain a large number of images in a short time. However, variations in the imaging parameters, such as those caused by the use of different field strengths, may result in image changes that are independent of the biological characteristics of the tissue, instead of reflecting the physics of the imaging process (18). Therefore, because within-system variability is low, repeated scanning under the same conditions is strongly advised for a longitudinal study. However, variance in brain volume due to disease-related change is much less than that occurring naturally because of variance within a healthy population. For example, (1) there is natural variance in gender-related differences in brain volume of 8.9%, and (2) the difference in brain volume caused by disease-related change is 2.2% between Alzheimer's disease patients and healthy controls (19). Thus, it is important to improve the precision of MR imaging.

Computational analyses [i.e., boundary shift integral (20), voxel-based morphometry (21, 22), tensor-based morphometry (23), and atlas-based volumetry (3, 4)] used to evaluate brain volume have already been shown to be sensitive to image quality (i.e., signal-to-noise ratio, signal intensity non-uniformity, and image distortion) (9, 13, 24-27). Therefore, it is important to control the image quality in multi-scanner studies. In correcting the non-uniformity of signal intensity, Arnold et al. (8) previously reported that the root-mean-squared error is close to 4.0 for N3-corrected T1 images, which implies that the applied bias has been nearly completely removed. In addition, Boyes et al. (28) showed that the use of N3 correction resulted in a statistically significant improvement in signal intensity non-uniformity. Therefore, among several algorithms, we chose the N3 algorithm to correct for signal intensity non-uniformity.

The lowest change ratio for local brain volumetry using the atlas-based method was achieved using "Regularization 0 with N3", with all other parameters set at the same conditions. The results shown in Figures 1-5 are consistent with those of a previous study (9) that described the N3 correction effect for tensor-based morphometry in different scan systems. In addition, we found that decreased change ratios are correlated with increased bias-correction power (i.e., Regularization 10 < 0.0001 < 0 < 0 with N3). Brain of subject C is big and long compared with other subjects (Fig. 6). Therefore, we think that subject C had more 0.1 change ratios because of the improvement in signal intensity non-uniformity by the correction with SPM5 was insufficient.

The present study is the first to clarify the effect of bias-correction level on an atlas-based method with SPM5 preprocessing, and showed that system dependency is reduced by the N3 correction. This result does not prove that signal intensity non-uniformity correction completely erases system dependency, but it does provide an insight into understanding the necessity for using the signal intensity non-uniformity correction in multi-site studies. Even in a study using a single system, the analytical results are influenced by signal intensity non-uniformity because the distribution of signal intensity is influenced by the spatial placement of the coil center and the brain center, and this spatial placement in imaging differs among subjects (29).

A major limitation of the present study is that the reliability and robustness of the N3 algorithm for correcting non-uniformity could be improved by the optimal selection of brain masks and smoothing parameters (28).

The second limitation is an atlas-based method itself, for estimating volumes of specific areas, induces error from the true volume. Therefore, we must the understand deviation of the measured volume from the true volume, and must do work to decrease deviation. However, we cannot know the true brain volume. In the present study, we were able to demonstrate only how the system dependency was reduced by signal intensity non-uniformity correction in brain volumetry using the atlas-based method. We could not show that brain volumetry using the atlas-based method with signal intensity non-uniformity correction provides a more accurate estimate of brain volume. However, it is known that signal intensity/non-uniformity causes segmentation