

The relationship between Aging and T1 relaxation time in deep gray matter: A voxel-based analysis

Gosuke Okubo, MD¹⁾, Tomohisa Okada, MD, PhD¹⁾, Akira Yamamoto, MD, PhD¹⁾,
Yasutaka Fushimi, MD, PhD¹⁾, Tsutomu Okada, MD, PhD¹⁾, Katsutoshi Murata, MS²⁾,
Kaori Togashi, MD, PhD¹⁾

¹⁾ Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan.

²⁾ Siemens Healthcare KK, Ohsaki, Tokyo, Japan.

Abstract

Purpose: To investigate age-related changes in T1 relaxation time in deep gray matter structures in healthy volunteers using magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE).

Materials and Methods: 70 healthy volunteers (aged 20–76, mean age 42.6 years) were scanned at 3T-MRI. A MP2RAGE sequence was employed to quantify T1 relaxation times. After the spatial normalization of T1 maps with the diffeomorphic anatomical registration using exponentiated Lie algebra algorithm, voxel-based regression analysis was conducted. In addition, linear and quadratic regression analyses of regions of interest (ROI) were also performed.

Results: With aging, voxel based analysis (VBA) revealed significant T1 value decreases in the ventral-inferior putamen, nucleus accumbens, and amygdala, whereas T1 values significantly increased in the thalamus and white matter as well ($P < 0.05$ at cluster level, false discovery rate). ROI analysis revealed that T1 values in the nucleus accumbens linearly decreased with aging ($P = 0.0016$), supporting the VBA result. T1 values in the thalamus ($P < 0.0001$), substantia nigra ($P = 0.0003$), and globus pallidus ($P < 0.0001$) had a best fit to quadratic curves, with the minimum T1 values observed between 30 and 50 years of age.

Conclusion: Age-related changes in T1 relaxation time vary by location in deep gray matter.

Keywords:

T1 relaxation time; aging; deep gray matter; nucleus accumbens; thalamus

The deep gray matter (GM) of the human brain plays important roles in motor control, cognitive function, emotion, among others (1,2). Diseases may disrupt deep GM functioning and physiological aging is known to alter its microstructure (3-9). In addition, iron accumulates in deep GM with aging (6). Iron transport to the brain, accumulates in oligodendrocytes and is essential for myelin production and management, is mediated by transferrin and H-ferritin (8). Excess accumulation of iron results in neurodegeneration and myelin breakdown as observed in Alzheimer's disease, Huntington's disease, and Parkinson's disease (3,4).

T1, T2 and T2* may provide presumptive inference about underlying tissue microarchitecture (7). T1 relaxation time mainly reflects the myelination of axons, and previous research on quantitative T1 values have focused on white matter (WM) (9-11). Aging changes in GM have predominantly been investigated based on T2/T2*-weighted signal changes and quantitative susceptibility mapping (QSM) to detect iron deposition (12,13). However, the deposition of iron and manganese also alters the T1 relaxation time of the tissue (14,15). As the concentration of iron is higher in deep GM than WM, the correlation of age and T1 values in deep GM is expected to differ from that for WM.

Many current brain investigations have been conducted voxel-wise, to objectively detect localized changes in many brain regions within the brain. Voxel-based analysis

(VBA) requires high-resolution imaging of the whole brain, which has typically not been affordable for quantitative imaging studies. However, a recent advance in MR imaging has brought a new scan method, magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE), which derives a three-dimensional (3D) T1 map in a clinically practical way. In MP2RAGE, two 3D gradient echo images are acquired at different inversion times, yielding a T1-weighted image and a whole brain T1 map free from coil sensitivity inhomogeneity (16).

Considering these factors, we hypothesized that VBA would reveal age-related changes in deep GM based on quantitative T1 values, and employed MP2RAGE to investigate this.

Materials and Methods

Subjects

This study was approved by the institutional review board of our hospital, and written informed consent was obtained from all subjects. Seventy-one subjects without any previous history of severe head trauma, neuropsychiatric disorders or severe illnesses participated, but one subject was excluded due to a historical asymptomatic lacunar infarction in the left putamen. No other major lesions were observed on either

fluid-attenuated inversion recovery or T2-weighted imaging, although these sequences are not highly sensitive to microbleeds that may affect the analysis. The remaining 70 subjects were enrolled (age range, 20–76 years; mean age, 42.6 ± 16.0 years; 50 males).

MR Imaging

A 3T MR scanner (MAGNETOM Skyra; Siemens Healthcare GmbH, Erlangen, Germany) with a 32-channel phased array head coil was used. MP2RAGE imaging was conducted in sagittal orientation with 1 mm isotropic resolution. It yielded a pair of images acquired at two inversion times (TIs), from which a T1 relaxation time map, as well as a T1-weighted image, was calculated. The details of the acquisition parameters are as follows: 160 slices, FOV = 224×216 mm, TR = 4000 msec, TE = 2.11 msec, TIs = 600 and 1800 msec, and flip angles = 4° and 5° , GRAPPA acceleration factor 3 based on a previous study by Marques et al. (16,17). The acquisition time was 6 minutes and 10 seconds. The T1 value of each pixel was estimated using Bloch simulations as described by Marques et al. (16).

Image Processing

Data processing and analysis was conducted using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) running on Matlab R2015b (Mathworks, Sherborn, MA, USA). T1-weighted images were segmented into GM, WM and cerebrospinal fluid (CSF), and probability maps for each segment were obtained. Spatial normalization was conducted on GM probability maps using the diffeomorphic anatomical registration using exponentiated Lie algebra (DARTEL) algorithm (18). Using the flow fields obtained in the DARTEL process, T1 maps derived from MP2RAGE scans were normalized to MNI space preserving concentrations of measured T1 values. These values were then smoothed with an isotropic Gaussian kernel of 3 mm full width at half maximum and used for VBA. Region-of-interest (ROI) based analysis was conducted on the T1 maps without smoothing. The averaged image of normalized T1 maps of all subjects was used for determining ROIs.

Voxel-Based Analysis

For VBA, a brain mask was used to prevent artifacts derived from CSF partial volume effects. The brain mask was generated by including voxels that had a GM plus WM probability of more than 90% and a CSF probability of smaller than 5% (Fig. 1a).

A voxel-wise linear regression analysis was conducted using SPM12 with age as a

covariate of interest. A statistical threshold of $P < 0.005$ was applied at voxel level, with $P < 0.05$ at cluster level, after correction for multiple comparisons by false discovery rate (FDR).

ROI-based analysis

Of the deep GM structures, the following substructures were selected for ROI analysis: the putamen, globus pallidus, thalamus, caudate head, substantia nigra and nucleus accumbens. Each ROI for these structures was placed on a single mid-slice of each structure on the population averaged T1 map (Fig. 1b), referencing the SPM12 ROI atlas (labels_Neuromorphometrics). Additionally, ROIs of the frontal WM (fWM) and the genu of corpus callosum (gCC) were set as representative WM areas. The correction positioning of each ROI was checked on each T1 map. Mean T1 values for each ROI were measured.

A previous study clarified that the relationship between WM T1 values and aging show a good fit to a quadratic curve, with the lowest T1 values between 30 and 50 years old with increases thereafter (19). In previous reports, linear and quadratic fitting were employed to investigate the relationship between the T1 values of brain tissues and aging (20-22). In terms of iron accumulation in deep GM (12), consistent decreases in

T1 values with aging is expected, as iron shortens the T1 value (14). In our study, both linear and quadratic polynomial regression analyses were performed for the mean T1 values of each ROI with age. Following Bonferroni's correction for multiple comparisons, $P < 0.0031$ was considered statistically significant. These regression analyses were performed using JMP 12 (SAS Institute Inc., Cary, NC, USA).

Results

VBA

A significant positive linear correlation between T1 values and aging was observed in the bilateral ventral areas of the thalamus, and a significant negative correlation was found in the bilateral ventral-inferior putamen, nucleus accumbens, and amygdala. The deep WM and the internal capsule had significant increases in T1 values and the left temporal WM showed a significant decrease. ($P < 0.05$ at cluster level, FDR). Each anatomical location was determined using an atlas in SPM12 (labels_Neuromorphometrics.nii). No significant correlations were detected in the caudate nucleus, globus pallidus, or substantia nigra (Fig. 2).

ROI-based Analysis

Mean T1 values for each ROI are shown in table 1, along with comparisons with previous reports (16,23-25). While there were variations in the T1 values between these studies, the results of this study were in agreement with the T1 values measured using MP2RAGE reported by Marques et al (16). The T1 values of the ROIs were plotted versus age, and the results of regression analyses are summarized in Fig. 3 and Table 2. The T1 value in the nucleus accumbens decreased significantly in association with aging ($P = 0.0016$). The caudate head also had a trend towards monotonic decline, but this was not significant ($P = 0.0044$).

Significant quadratic regressions were found for the thalamus ($P < 0.0001$), globus pallidus ($P < 0.0001$), and substantia nigra ($P = 0.0003$). T1 values for the gCC and fWM had significant linear and quadratic fits. The R^2 better fitted the quadratic curve, although the P value of the gCC was lower for the linear regression. The T1 values of these structures decreased in the first half of the age range investigated and then inverted to increase during the latter. The ages of the minimum T1 values were between 30 and 50 years, with the exception of the gCC.

Discussion

This study has demonstrated that the T1 values of deep GM vary by location. We also

found a linear increase in WM T1 values, which is consistent with a previous study (26), although the case for a non-linear relationship has also been argued (19). Our VBA revealed that T1 values in the nucleus accumbens, ventral-inferior putamen, and amygdala significantly linearly decrease with aging. ROI analysis confirmed that a monotonic decline of T1 in the nucleus accumbens accompanies aging. VBA of the thalamus revealed significant T1 elongation with aging, as in the WM in this study. In the ROI analysis, T1 values in the thalamus, globus pallidus, and substantia nigra decreased in the first half of the life and then switched to increase during the latter half, although former studies have reported contradictory results (20,21).

For T1 analysis with aging, quadratic regression analysis is expected to yield better fitting in many areas based on the previous studies. However, in this study VBA revealed sub-regional differences. For example, a significant positive area was found in the thalamus, but not in the pulvinar (Fig. 2a). In addition, significant negative areas in the ventral-inferior putamen and inner part of the amygdala (Fig. 2b) may not be readily detected by applying predefined ROIs. Therefore, VBA analysis is complementary to ROI-based analysis.

There are several methods for acquiring a T1 map. Although the inversion recovery method is the gold standard for T1 mapping, clinical application is difficult due to the

long acquisition times required (27). The variable flip angle method is vulnerable to errors in B1 mapping (27,28). B1 inhomogeneity is one of the large factors increasing errors, especially in high magnetic fields. In the MP2RAGE used in this study, two gradient echo images were acquired at different inversion times, yielding a T1-weighted image and a whole brain T1 map free from coil sensitivity inhomogeneity. (16). Although several variations are reported in these methods for T1 measurement, the reliability of the MP2RAGE sequence has already been validated (17). However, Marques et al. suggested further optimization of MP2RAGE for high resolution T1 maps on 7T MRI (29). MP2RAGE on 3T may also have room for improvement, contributing to higher resolution.

Myelin and iron concentrations in brain tissue contribute to T1 relaxation time. Increased demyelination elongates the T1 value, and iron accumulation shortens it (14,30). Although deep GM has higher iron concentrations than WM, this varies between deep GM structures. Despite high iron accumulation in the substantia nigra, globus pallidus, and putamen (6,12,31), T1 mapping of these structures did not reveal any significant decreases in this study, both in VBA and ROI analyses. Previous reports have demonstrated that age-related increases in iron levels in the globus pallidus and substantia nigra reach a plateau in early adulthood (6,13). However, those results are not

consistent with other studies (20,21,32). Badve et al. (20) demonstrated a negative linear correlation between age and T1 value in the left substantia nigra, a quadratic trend in the right substantia nigra, and no significant correlation in the globus pallidus. Jara et al. (21) reported a positive linear correlation in the globus pallidus. The differences in the ages and number of subjects in these studies may explain these inconsistencies.

Dilatation of perivascular space (PVS) is another factor that influences T1 relaxation time, especially in the putamen and globus pallidus. This is because PVS is common in the basal ganglia along the lenticulostriate arteries, and the incidence of PVS increases with aging (33,34). In the aging brain, the capacity for eliminating interstitial fluid is limited, which leads to dilatation of PVS and leukoaraiosis (35). Dilated PVS can be a T1 elongation factor and can compensate for the iron deposition effect, even if it is difficult to detect on MRI due to its small size (36).

A monotonous decline in T1 relaxation time was observed in the nucleus accumbens in this study. Previous studies suggested that $R2^*$ values in the ventral striatum increase with aging as a result of iron accumulation (26,37), as observed by T1 shortening. Although it is not easy to correlate specific brain structure changes with specific brain functions due to the heterogeneity of these structures, Steiger et al. demonstrated that higher iron levels within the ventral striatum predicts memory

performance (37). The nucleus accumbens is a part of the limbic circuit and is involved in both motivation (38) and memory functions (37), which tend to decrease with aging. Accumulation of iron causes cell damage resulting in functional impairment (39).

Conversely, iron concentration in the thalamus is the lowest of all the deep GM structures (6,12,31). The thalamus contains myelin as laminar structures separating the thalamic sub-nuclei. In this study, the T1 value in the thalamus declined in the first half of the lifespan, and began to increase after the minimum T1 value, between age of 30 and 50. A similar correlation between T1 and aging has been reported (32). In addition, iron content in the thalamus decreases with ages over 30 years old (6). Due to the lower iron concentration, axonal disintegration and cell loss are expected to contribute to age-related microstructural changes, similar to those occurring in the WM. VBA failed to reveal a significant increase in T1 values in the posterior part of thalamus. As iron accumulation in the thalamus is relatively large in the pulvinar (40), it is plausible that T1 elongation by myelin degeneration with aging (41,42) was partially offset by iron accumulation in this area.

Age-related T1 elevation was also significant in the internal capsule and deep WM in the VBA in this study. As previously reported, even in WM without any abnormal intensity on T2-weighted images, quantitative parameters such as T1 relaxation time,

magnetization transfer, and fractional anisotropy change (26). Although pathological confirmation is difficult to obtain, WM demyelination and axonal loss are common in aging brains, and these changes can cause T1 elongation. This result is consistent with the former studies (10,26).

Quantification of T1 relaxation time has mainly focused on WM and enabled the detection of subtle changes that cannot be detected with conventional MR imaging (9). Deep GM structures are also affected in patients with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Parkinson's syndrome (43-45). Neurodegenerative diseases often affect older subjects, therefore, our results contribute to the comprehension of normal age-related changes and the necessity of investigating T1 relaxation time in pathological states.

Volume changes in the aging brain have been widely investigated. Cortical GM volume consistently decreases with aging, whereas WM volume increases up to around 40 years of age and decreases thereafter (46-48). Volume decline with aging is also reported in the thalamus, putamen, caudate, and nucleus accumbens (49-51). However, this study found different changes in T1 values in these deep GM structures, which may help shed light on the mechanisms of aging.

There are some limitations to this study. The first is the age distribution of the

subjects, in that subjects younger than twenty years old were not enrolled in this study. Due to the lack of a young age group, dynamic decreases of T1 relaxation times in the first and second decades, as reported in previous studies, could not be evaluated (14,19,22). Secondly, the number of subject in this study was not sufficient to enable the detection of significant age-related changes in the putamen and caudate head. Furthermore, this study was a cross-sectional study. A 7-year follow up of seventeen subjects in a previous study detected longitudinal changes in T1 relaxation time in deep GM while cortical GM T1 values showed significant decreases (52). However, in the future, a longitudinal study with a larger number of subjects may reveal significant correlations between age and T1 values in deep GM.

In conclusion, here we have reported a correlation between T1 relaxation time and aging, that differs by location, in deep GM. T1 relaxation time in the ventral striatum tended to shorten monotonically in association with aging, while T1 values in the thalamus, globus pallidus, and substantia nigra decreased in the first half of the age range and investigated and increased in the latter half. These findings will contribute to the improved interpretation of future studies in patient populations.

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TABLE 1. Mean T1 values for each ROI compared with previous studies

	This study	Marques et al.	Wright et al.	Lu et al.	Gelman et al.
Putamen	1056 ± 33	1130 ± 70	1332 ± 68	1102 ± 40	1763 ± 60
Thalamus	981 ± 25	1080 ± 70		986 ± 33	1218 ± 40
Globus pallidus	885 ± 31	970 ± 70			1043 ± 37
Substantia nigra	925 ± 28				1147 ± 50
Caudate	1183 ± 30	1250 ± 70	1395 ± 49	1258 ± 55	1483 ± 42
Nucleus accumbens	1216 ± 36				
Corpus callosum	725 ± 24	780 ± 40			
White matter	783 ± 29	810 ± 30	840 ± 50	760 ± 50	847 ± 43

TABLE 2. Results of regression analyses

	R^2 (linear)	P (linear)	R^2 (Quadratic)	P (Quadratic)
Putamen	0.0045	0.577	0.118	0.0149
Thalamus	0.0836	0.0152	0.255	<0.0001*
Globus pallidus	0.0114	0.378	0.243	<0.0001*
Substantia nigra	0.0304	0.148	0.216	0.0003*
Caudate head	0.113	0.0044	0.116	0.0158
Nucleus accumbens	0.137	0.0016*	0.122	0.0126
gCC	0.18	0.0003*	0.20	0.0006*
Frontal WM	0.13	0.002*	0.27	<0.0001*

Variance (R^2) and P -values of linear and quadratic regression analysis. * $P < 0.0031$ was the threshold for statistical significance following Bonferroni's correction.

Figure legends.

FIGURE 1: ROIs used for analysis. The mask image used for (a) voxel-based analysis, and (b) manual drawn ROIs on the population averaged T1 map.

ROIs indicate the caudate head, putamen, globus pallidus, thalamus, nucleus accumbens, and substantia nigra.

FIGURE 2: VBA result for regression analysis of T1 values with age.

Significant positive correlations were seen in the bilateral thalami, the deep white matter, and the internal capsule (a). Significant negative correlations were seen in the ventral-inferior putamen, nucleus accumbens, amygdala, and temporal white matter (b). The statistical parametric maps are superimposed on a normalized T1 map of a single subject. A $P < 0.05$ after false discovery rate correction at cluster level ($P < 0.005$ uncorrected at voxel level) was regarded significant.

FIGURE 3: Results of ROI analyses. Scatter plots represent the relationship between T1 relaxation time and age. Only significant regression lines are shown as solid lines. Shaded area shows 95% confidence interval for the regression analyses.

Fig. 1

a.



b.

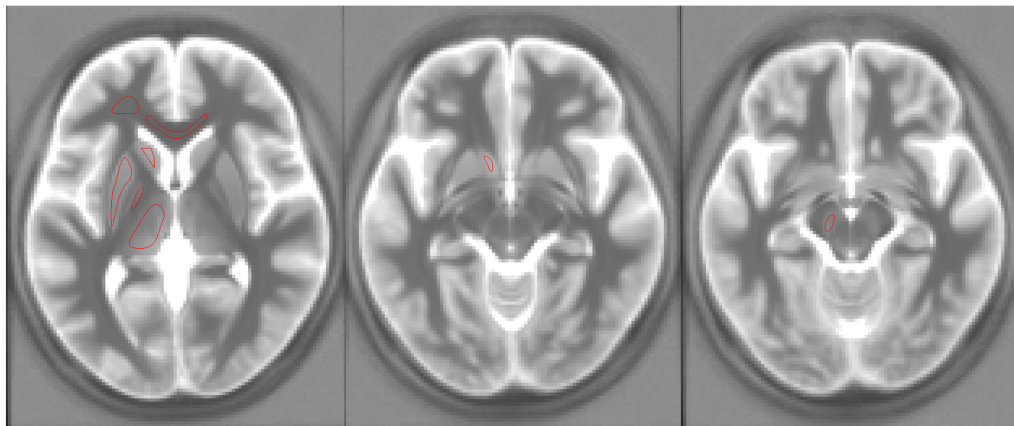


Fig. 2

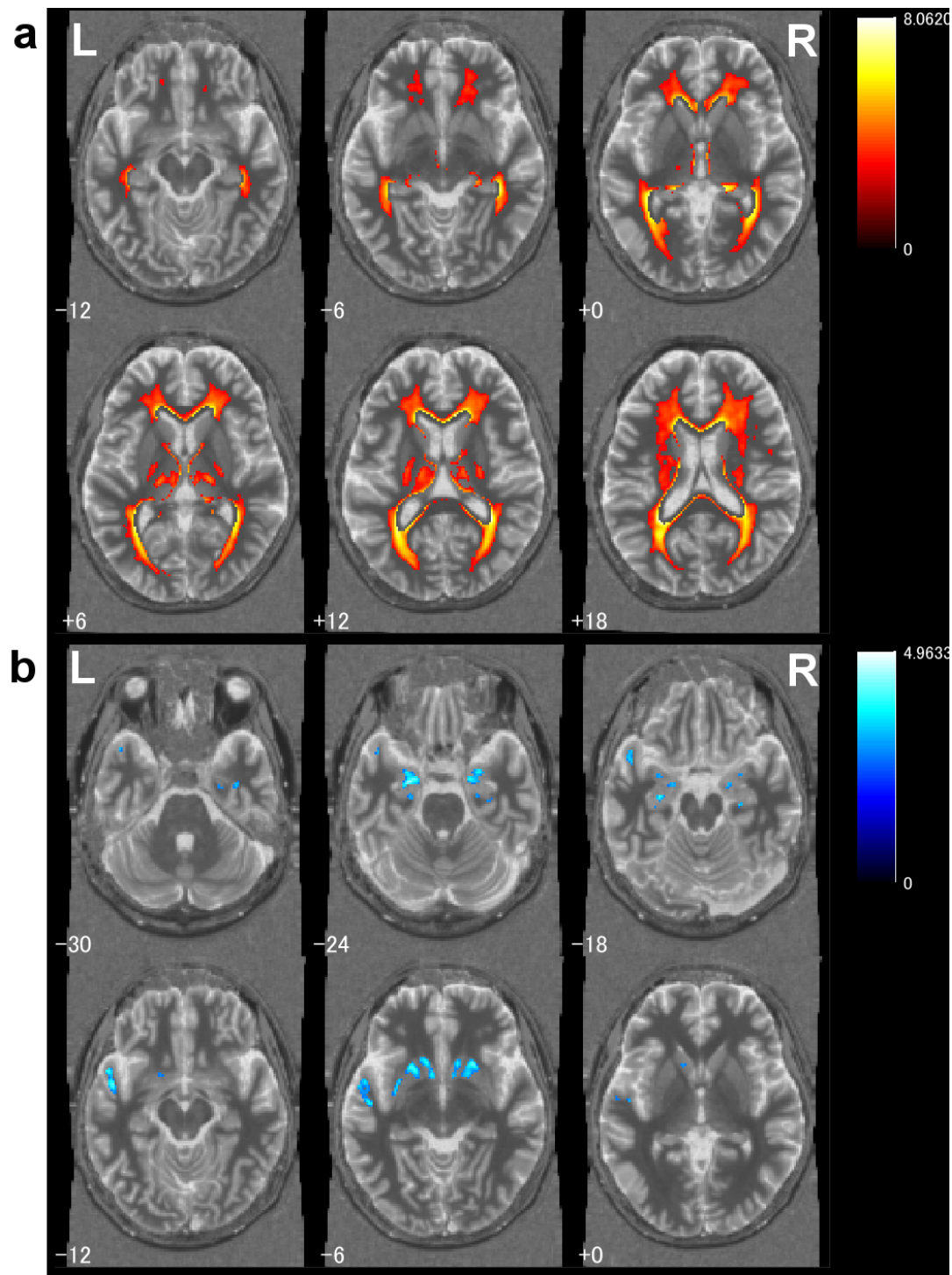


Fig. 3

