

## *Age-related cortical thinning in schizophrenia*

Manabu Kubota<sup>a</sup>, Jun Miyata<sup>a</sup>, Hidefumi Yoshida<sup>b</sup>, Kazuyuki Hirao<sup>a</sup>, Hironobu Fujiwara<sup>a</sup>, Ryosaku Kawada<sup>a</sup>, Shinsuke Fujimoto<sup>a</sup>, Yusuke Tanaka<sup>a</sup>, Akihiko Sasamoto<sup>a</sup>, Nobukatsu Sawamoto<sup>b</sup>, Hidenao Fukuyama<sup>b</sup>, and Toshiya Murai<sup>a</sup>

<sup>a</sup>Department of Neuropsychiatry, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

<sup>b</sup>Human Brain Research Center, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

Please address correspondence to:

Manabu Kubota, M.D.

Department of Neuropsychiatry, Graduate School of Medicine, Kyoto University

54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

Tel: +81-75-751-3386, Fax: +81-75-751-3246

E-mail: kubotajp@kuhp.kyoto-u.ac.jp

## **Abstract**

Although the effects of aging on the neural correlates of schizophrenia have been researched for many years, no clear conclusion has been reached. While some studies have demonstrated progressive age-related gray matter reductions in schizophrenia, other studies have not found evidence of progression. Moreover, it remains unclear whether the influence of aging on global or regional cortical thickness differs between schizophrenia patients and healthy controls. This study aimed to confirm previous reports of reduced cortical thickness in schizophrenia, and to investigate the effects of age on global and regional cortical thickness. Eighty-three patients with schizophrenia (six first-episode patients and 77 chronic patients; age range = 18-55 years) and 90 age-, gender- and education-matched healthy controls (age range = 19-56 years) underwent structural magnetic resonance imaging (MRI) using a 3-Tesla scanner. Surface-based analysis was applied to assess cortical thickness in the whole brain. The patient group exhibited both global and regional cortical thinning in regions including the prefrontal and temporal cortices. The correlation between age and cortical thickness showed a similar pattern in patients and controls, both globally and regionally. These results suggest that the reduction of cortical thickness in schizophrenia might not be progressive over the course of the illness, indicating that pathological processes occur in a relatively limited period of time around the onset of illness.

**Keywords:** MRI, cortical thickness, surface-based analysis, FreeSurfer, aging, progression

## **1. Introduction**

Magnetic resonance imaging (MRI) studies have revealed anatomical alterations in multiple brain regions associated with schizophrenia. Global gray matter (GM) reductions in schizophrenia have been consistently reported (Gur et al., 1999; Lim et al., 1996; Sowell et al., 2000). In addition, regional GM reductions have been demonstrated by studies using region of interest (ROI) approaches (Shenton et al., 2001) and voxel-based morphometry techniques (Ashburner and Friston, 2000; Ellison-Wright et al., 2008; Honea et al., 2005), particularly in prefrontal and temporal regions.

Although some of these alterations are already exhibited prior to illness onset, whether or not these anatomical brain alterations are progressive remains unclear (Borgwardt et al., 2009; DeLisi 2008). Several longitudinal and cross-sectional studies have suggested progressive brain volume loss globally (Hulshoff Pol et al., 2002; Whitford et al., 2006) and regionally (Kasai et al., 2003; Mathalon et al., 2001; Whitford et al., 2006). Some studies, however, have reported negative findings regarding age-related global or regional progressive cortical loss (Bose et al., 2009; DeLisi and Hoff, 2005). Whitford et al. found progressive GM loss over the first few years of illness in first-episode schizophrenia, especially in the parietal and temporal cortices (Whitford et al., 2006), while Bose et al. reported that there was diminished GM volume loss with age in schizophrenia patients compared with controls, when correcting for differences in total brain volume (Bose et al., 2009).

Meanwhile, some recent studies have focused on reduced cortical thickness in schizophrenia (Goldman et al., 2009; Kuperberg et al., 2003; Nesvåg et al., 2008; Schultz et

al., 2010). Alterations of cortical thickness might reflect underlying pathological abnormalities such as reduced neuropil density, as revealed in postmortem studies of schizophrenia (Glantz et al., 2006). As such, directly examining changes in cortical thickness could help increase our understanding of the cause, mechanisms, and progression of the illness. However, only a few studies (Kuperberg et al., 2003; Nesvåg et al., 2008) have investigated the correlation between age and cortical thickness in patients with schizophrenia. These studies examined the effect of age on regional cortical thickness in schizophrenia, but an influence of aging on global cortical thickness has not been reported. To our knowledge, no study has simultaneously investigated global and regional cortical thickness in schizophrenia to determine whether it exhibits normal age-related changes, or represents a separate pathological process. Therefore, it remains unclear whether there is a progression of altered cortical thickness over the course of the illness.

The present study aimed to elucidate whether age-related global and regional cortical thickness changes in patients with schizophrenia differ from those in healthy controls, and to examine whether these changes are progressive or not.

It was predicted that global and regional cortical thickness would be reduced in schizophrenia. Surface-based analysis was applied to compare the pattern of the effects of aging on global and regional cortical thickness between patients with schizophrenia and healthy controls. In addition, we investigated whether or not the reduction of cortical thickness in schizophrenia would be progressive over the course of the illness.

## **2. Materials and methods**

## **2.1. Participants**

The schizophrenia group comprised 83 patients (six first-episode patients and 77 chronic patients; age range = 18-55 years) who were referred to the Department of Psychiatry at the Kyoto University Hospital. Each patient fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV (SCID). The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to assess the severity of clinical symptoms. All patients were receiving antipsychotic medication (typical [n=9], atypical [n=56], typical and atypical [n=18]). Haloperidol equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia (Inagaki and Inada, 2008; Lehman et al., 2004).

The comparison group comprised 90 healthy individuals (age range = 19-56 years) who were matched to the schizophrenia group with respect to age, gender, and education level. They were also evaluated using the SCID and had no history of psychiatric disease, and they had no first-degree relatives with a history of psychotic episodes. The patients and controls were all physically healthy at the time of scanning. None had a history of neurological injury or disease, severe medical diseases, or substance abuse that could affect brain function.

The estimated verbal and performance IQ (VIQ and PIQ) scores of each participant were obtained from vocabulary and block design subtests, respectively, in the Wechsler Adult Intelligence Scale-Revised, by transforming the scores corrected for age into T scores.

This study was approved by the Committee on Medical Ethics of Kyoto University and was carried out in accordance with The Code of Ethics of the World Medical Association.

Written informed consent was obtained from each participant after a complete description of the study.

## **2.2. MRI acquisition and pre-processing**

All participants underwent MRI scans on a 3-Tesla whole-body scanner equipped with an 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 4.38 ms; TR = 2000 ms; inversion time (TI) = 990 ms; FOV = 225 × 240 mm; matrix = 240 × 256; resolution = 0.9375 × 0.9375 × 1.0 mm<sup>3</sup>; and 208 total axial sections without intersection gaps.

For cortical thickness analysis in the whole brain, a surface-based approach was applied using FreeSurfer tools (version 4.5.0, <http://surfer.nmr.harvard.edu>; Dale et al., 1999; Fischl et al., 1999). The 3D-MPRAGE images were used to calculate thickness of the cerebral cortex throughout the cortical mantle. Briefly, the processing stream includes a Talairach transform of each subject's native brain, removal of non-brain tissue, and segmentation of gray matter/white matter (GM/WM) tissue. The cortical surface of each hemisphere was inflated to an average spherical surface to locate the pial surface and the GM/WM boundary. The entire cortex of each subject was visually inspected, and any topological defects were corrected manually, blind to subject identity. Cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. This method has been previously validated via histological as well as manual measurements in schizophrenia (Kuperberg et al., 2003).

Global mean cortical thickness for each subject was computed by averaging cortical thickness at each vertex, right and left hemispheres separately, and was used in the statistical analyses. The regional thickness value at each vertex for each subject was mapped to the surface of an average brain template (described at <http://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage>). The cortical map of each subject was smoothed with a Gaussian kernel of 10-mm full-width at half-maximum for the entire cortex analyses.

## **2.3. Statistical analyses**

### **2.3.1. Group comparison and regression analyses of global cortical thickness**

First, two independent sample t-tests were applied to examine group differences of demographic variables and global mean cortical thickness. Gender differences were examined using a chi-squared test. In the patient group, correlations between the mean cortical thickness and PANSS scores (positive, negative, and general psychopathology subscales), age of onset, and duration of illness (year), and medication were also examined. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The statistical significance level was set at  $p < 0.05$ .

Second, using SPSS, a multiple regression model was applied to detect the effects of age, and the age-diagnosis interaction on global mean cortical thickness. The global mean cortical thickness was analyzed separately for each hemisphere. Thus, the dependent variables were mean cortical thickness of the right and left hemispheres, while the independent variables were age, diagnosis (dummy parameterized, control = 1,

schizophrenia = 0), and their interactions.

### **2.3.2. Group comparison of regional cortical thickness**

The general linear model (GLM) was implemented at each vertex in the whole brain to identify brain regions in which schizophrenia patients showed significant differences in cortical thickness relative to controls, using FreeSurfer's `mri_glmfit` (described at [http://surfer.nmr.mgh.harvard.edu/fswiki/mri\\_glmfit](http://surfer.nmr.mgh.harvard.edu/fswiki/mri_glmfit)). In the patient group, the cortical regions showing correlations with PANSS scores (positive, negative, and general psychopathology subscales), age of onset, duration of illness, and medication were also examined. The effects of age and gender were regressed out in these models. All the analyses were performed for the right and left hemispheres separately. The threshold was set at  $p < 0.05$  (False Discovery Rate; [FDR]; Genovese et al., 2002) to resolve the problem of multiple comparisons.

### **2.3.3. Correlational analyses between regional cortical thickness and age**

First, vertex-wise GLM analyses were performed in the control and patient groups independently to explore the brain regions that showed significant correlations between cortical thickness and age both in controls and schizophrenia patients, using `mri_glmfit`. Second, the interaction between diagnosis and age was examined to examine the difference in age regression slopes between both groups, modeling another design that included both groups. All of these analyses were performed on the right and left hemispheres separately. The same threshold of  $p < 0.05$  (FDR) was applied.

Third, to investigate the regional aging effect in more detail, age regression slopes of



controls and patients were compared within regions exhibiting significant cortical thinning in the schizophrenia group. Contiguous regions exhibiting significant cortical thinning in the group comparison were selected as ROIs. ROIs were automatically mapped onto each subject, from which the mean thickness of each ROI was calculated. Two-tailed t-tests were applied to compare z-transformed correlation coefficients of age and regional mean cortical thickness within each ROI between the both groups. In addition, because regionally-specific effects of medication have been previously reported (Navari and Dazzan, 2009; Smieskova et al., 2009), possible correlations between cortical thickness and medication were further examined within each ROI. Data were analyzed using SPSS 15.0. Statistical significance was defined as  $p < 0.05$ .

#### **2.3.4 Effect of medication type**

To test the possible effects of medication type, we divided the patients into three subgroups (typical = patients taking typical antipsychotics; atypical = patients taking atypical antipsychotics; and combined = patients taking combined therapy with both typical and atypical antipsychotics).

To examine effect of medication type on global cortical thickness, an analysis of covariance (ANCOVA) was applied within each hemisphere. In addition to age and gender, the haloperidol equivalent dosage was included as a nuisance covariate in the model, to examine the effect of medication type separately from dose effect.

To examine the effect of medication type on regional cortical thickness, we performed between-subgroup comparisons using vertex-wise GLM analyses throughout the whole brain.

In addition, an ANCOVA was applied to examine the effect of medication type in each ROI that showed significant cortical thinning in patients compared with healthy controls. Age, gender, and the haloperidol equivalent dosage were also included as nuisance covariates in these analyses.

### **3. Results**

#### **3.1. Demographic data**

Demographic and clinical data are shown in Table 1. The estimated VIQ and PIQ were significantly lower in the patient group (patients' data were available for 77 subjects) than the control group. There was no significant difference in education level or gender between both groups.

#### **3.2. Group comparison and regression analyses of global mean cortical thickness**

For the global mean cortical thickness, the patient group showed a significant reduction in both hemispheres (Table 2a).

In the patient group, significant correlations were found between cortical thickness and the age of onset, and between cortical thickness and duration of illness. That is, a higher age of onset and longer duration of illness were associated with lower cortical thickness. However, in both hemispheres cortical thickness was not correlated with scores on the positive, negative, and general psychopathology subscales of the PANSS, or with medication (Table 2b).

The regression analyses revealed significant main effects of age ( $p < 0.001$  for both

hemispheres) and diagnosis ( $p < 0.001$  for both hemispheres), but no significant interaction between them.

A scatter plot of mean cortical thickness against age is shown in Fig. 1. The regression line of patients with schizophrenia was almost parallel to that of normal subjects for both hemispheres.

To examine patients in the chronic stage only, a supplementary investigation of the effects of age, and the age-diagnosis interaction on global mean cortical thickness was performed by eliminating the six first-episode patients from our sample. We found that the results did not change significantly when chronic stage patients were examined alone.

Because highly significant correlations were found between cortical thickness and duration of illness in the patient group, further analyses were performed to examine the effects of illness on cortical thickness in more detail. Since duration of illness was highly correlated with age ( $r = 0.713$ ,  $p < 0.001$ ), step-wise regression analyses were performed, with global cortical thickness of the right and left hemisphere as dependent variables, and duration of illness and age as independent variables. In this model, only age remained significant ( $p < 0.001$  for both hemispheres).

### **3.3. Group comparison of regional cortical thickness**

The patient group exhibited reduced cortical thickness compared with the control group in several regions, including frontal, temporal, parietal, and limbic structures in both hemispheres (Fig. 2). Highly significant differences were found in bilateral rostral middle frontal areas, bilateral superior frontal areas, the right insula, right isthmus, right precuneus,

right superior temporal, and right middle temporal area. The results revealed no regions in which the patient group exhibited a greater cortical thickness than the control group. In the patient group, regional cortical thickness did not correlate with scores on the positive, negative, or general psychopathology subscales of PANSS, age of onset, duration of illness, and medication.

### **3.4. Correlational analyses between regional cortical thickness and age**

Cortical thickness in widespread regions including the frontal, temporal, parietal and occipital areas was found to be negatively correlated with age in the control group, and a similar pattern was detected in the patient group (Fig. 3a, 3b). Highly significant correlations were shown in the frontal and temporal regions in both groups. There was no effect of an interaction between diagnosis and age on thickness in the vertex-wise GLM analysis.

Eight regions of significant cortical thinning in schizophrenia found in the group analysis were selected as ROIs (Fig. 2, Table 3). Results from the comparison of correlation coefficients of mean thickness and age in each ROI are shown as scatter plots in Fig. 4. The age regression slopes within all these ROIs did not significantly differ between groups (p value range = 0.215 – 0.960).

Significant correlations were found between cortical thickness and medication in the ROIs in the right superior frontal (SF;  $r=-0.304$ ,  $p=0.005$ ) and left SF ( $r=-0.234$ ,  $p=0.033$ ) cortices. The other six ROIs did not show any significant correlations.

### **3.5 Effect of medication type**

No significant differences in cortical thickness were found among medication type subgroups in an ANCOVA examining global cortical thickness, in vertex-wise GLM analyses, or in an ANCOVA examining regional cortical thickness within each ROI.

## **4. Discussion**

The effect of aging on regional cortical thickness in schizophrenia has been examined in a small number of previous studies (Kuperberg et al., 2003; Nesvåg et al., 2008), but the effect of aging on global cortical thickness in schizophrenia is currently not clear. Moreover, whether the alteration in cortical thickness associated with the disorder is progressive or not remains an open question.

To our knowledge, this is the first study to examine the effects of aging on both global and regional cortical thickness simultaneously in detail in schizophrenia, and to investigate whether the cortical thickness reduction associated with the disease is progressive or not.

The group comparison of global cortical thickness revealed reduced global cortical thickness in patients with schizophrenia. Our results indicated a global GM volume reduction in schizophrenia, similar to that shown previously (Gur et al., 1999; Lim et al., 1996; Sowell et al., 2000). Our examination revealed that a variety of specific regions were affected in terms of thickness in patients with schizophrenia, including the prefrontal and temporal cortices. This finding is consistent with previous volumetric and cortical thickness studies (Ellison-Wright et al., 2008; Kuperberg et al., 2003, Nesvåg et al., 2008), and suggests that GM volume reduction might reflect pathological abnormalities that cause

reduced cortical thickness in schizophrenia.

The correlation between age and cortical thickness was a major finding of this study. The effect of age on cortical thickness was found to be similar in patients compared with controls, both globally and regionally. Moreover, the results of our step-wise analyses indicated that age contributed to the variance in global cortical thickness more than the duration of illness in schizophrenia patients.

Although our results appear inconsistent with previous volumetric studies focusing on progressive GM loss (Hulshoff Pol et al., 2002; Mathalon et al., 2001), more recent studies have suggested that substantial progressive global and regional alterations are not exhibited over the entire course of the illness, but are most prominent in a relatively early stage of the illness (Bose et al., 2009; Sun et al., 2009; Takahashi et al., 2010; Whitford et al., 2006). One possible explanation for this inconsistency is that educational levels in the studies by Hulshoff Pol et al. (2002) and Mathalon et al. (2001) were lower in the patient group than in controls. Differences in education level may affect cortical thickness, directly or latently. In addition, it is possible that the absence of an interaction between diagnosis and age was due to the inclusion of only six first-episode patients in this study. A number of recent neuroimaging studies have provided evidence for brain alterations in individuals at a high risk of psychosis, and during the early phases of schizophrenia (Haller et al., 2009; Jung et al., 2009; Smieskova et al., 2010; Wood et al., 2008). Although one previous study suggested that cortical thickness asymmetry might be more sensitive for the early detection of illness (Haller et al., 2009), most of these studies have reported reduced cortical thickness and GM volume in the prefrontal, anterior cingulate, and temporal regions. The

pattern of cortical thinning shown by the schizophrenia group in our study was largely similar to that in previous studies, but the thinning was more widespread than that found in individuals at a high risk of psychosis (Jung et al., 2009). Taken together with previous studies, our findings indicate that pathological alterations in cortical thickness might occur at a relatively early phase of the illness, and that changes might be within the normal range in later phases.

Previous studies reported a possible correlation between symptom severity and altered GM volume (Hulshoff Pol and Kahn 2008; Mathalon et al., 2001). The lack of a correlation with symptom severity in the present results may have been due to the inclusion of patients with mild symptoms.

Among the eight ROIs, weak but significant negative correlations between dosage and cortical thickness were found within the right and left SF cortices. Although previous studies reported inconsistent findings regarding the effect of medication on cortical thickness or volume, this negative correlation is consistent with other studies reporting associations between antipsychotic medication and regional gray matter volume reductions within the frontal lobe (Navari and Dazzan, 2009; Smieskova et al., 2009). Because of the cross-sectional, correlational design of the current study, it is difficult to determine whether antipsychotic medication caused cortical thinning, or whether patients with lower cortical thickness in these regions require a larger amount of medication. As such, a longitudinal study will be necessary to investigate the effects of medication on cortical thickness.

We did not find any differences in cortical thickness among medication type subgroups (typical, atypical, or combined), globally or regionally, suggesting that the effects of

antipsychotics on cortical thickness do not differ among these medication types. However, larger studies will be needed to further investigate the effects of antipsychotic types in future, because the sample sizes of the typical group ( $n=9$ ) and combined group ( $n=18$ ) in the current study are smaller than is desirable for interpreting such differences.

Several limitations involved in the present study should be considered. First, since the study design was cross-sectional rather than longitudinal, the effects of aging should be interpreted with caution. Although our results provide some useful suggestions, a cross-sectional design does not allow decisive conclusions to be drawn regarding disease-related cortical thinning and the progression of cortical thinning over the course of the illness. Second, because different types of antipsychotic drugs might have different effects on cortical structure (Navari and Dazzan, 2009; Salimi et al., 2009), the possible effects of medication cannot be entirely excluded in this study. Third, all of the patients included in our study exhibited mild and stable symptoms, which might be associated with relatively small changes in cortical thickness. Finally, in this study we used FreeSurfer tools to perform analyses on cortical thickness. Because the use of different image analysis techniques (Fusar-Poli et al., 2010) might have caused heterogeneity between previous studies of cortical thickness in schizophrenia patients, the findings of this study should be confirmed using other image analysis techniques. Future research will be required to test the generalizability of these results.

In conclusion, the present study revealed that schizophrenia was associated with reduced global and regional cortical thickness, and a similar correlation between age and thickness was found in patients with schizophrenia and healthy controls. These results suggest that a



reduction of cortical thickness in schizophrenia may occur within a relatively early period of the illness, and might reflect pathological processes in a relatively limited period around illness onset rather than progressing over the course of the illness.

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**Figure legends.**

**Fig. 1**

Scatter plots and regression slopes of global mean cortical thickness with age in both groups.

**Fig. 2**

Statistical maps corrected for age and gender showing reduced cortical thickness in patients with schizophrenia relative to controls. Maps are shown for right and left hemispheres in lateral and medial views respectively, and significant regions are shown in red.  $P < 0.05$  (False Discovery Rate [FDR])

Yellow arrows and fonts indicate regions of interest (ROIs) in the ROI analyses.

Abbreviations, r = right, l = left, RMF = rostral middle frontal, SF = superior frontal, ST = superior temporal, MT = middle temporal, Isth = isthmus, Precun = precuneus. Anatomical terms are used according to the Desikan template (Desikan et al., 2006).

**Fig. 3**

Statistical maps showing the regions of cortical thickness negatively correlated with age in (a) the control group and (b) the patient group. Maps are shown for right and left hemispheres in lateral and medial views respectively, and significant regions are shown in blue.  $P < 0.05$  (False Discovery Rate [FDR])



**Fig. 4**

Scatter plots and regression slopes of regional mean cortical thickness with age in each region of interest (ROI).

Abbreviations, r = right, l = left, RMF = rostral middle frontal, SF = superior frontal, ST = superior temporal, MT = middle temporal, Isth = isthmus, Precun = precuneus. Anatomical terms are used according to the Desikan template (Desikan et al., 2006).

**Table 1** Demographic, clinical, and neuropsychological characteristics of subjects

	Control group (n=90)		Patient group (n=83)		Statistics	
	Mean	S.D.	Mean	S.D.	t	p
Age (years)	34.3	10.9	35.7	10.1	-0.91	N.S. <sup>b</sup>
Gender (male/female)	39/51		44/39			N.S. <sup>c</sup>
Handedness (right/left)	87/3		79/4			
Education (years)	14.0	2.3	13.4	2.2	1.59	N.S. <sup>b</sup>
Estimated VIQ (Vocabulary) <sup>a</sup>	112.2	15.2	98.8	17.8	5.18	p<0.001
Estimated PIQ (block design) <sup>a</sup>	116.6	15.0	103.3	17.3	5.32	p<0.001
PANSS positive			14.1	5.5		
PANSS negative			16.7	6.1		
PANSS general			31.6	9.2		
PANSS total			62.4	17.3		
Age of onset			24.8	7.4		
Duration of illness (years)			11.0	9.2		
Medication (mg/day, haloperidol equivalent)			10.6	6.8		

Abbreviations, VIQ = verbal IQ; PIQ = performance IQ; PANSS = Positive and Negative Syndrome Scale (Kay et al., 1987).

<sup>a</sup> Patients' data were available for 77 subjects

<sup>b</sup> Two-tailed t tests,  $\alpha = 0.05$

<sup>c</sup> Two-tailed chi-squared test,  $\alpha = 0.05$

**Table 2a** Statistics of mean cortical thickness within each hemisphere

	Cortical thickness		Cortical thickness			
	(mm)		(mm)			
	Control group (n=90)		Patient group (n=83)		Statistics	
	Mean	S.D.	Mean	S.D.	t	p
Right hemisphere	2.55	0.09	2.48	0.11	4.28	p<0.001
Left hemisphere	2.54	0.09	2.49	0.10	3.92	p<0.001

**Table 2b** Correlational analyses of mean cortical thickness in the patient group

	Cortical thickness (Right hemisphere)		Cortical thickness (Left hemisphere)	
	Pearson's r	p	Pearson's r	p
PANSS positive	-0.080	N.S.	-0.154	N.S.
PANSS negative	0.095	N.S.	0.100	N.S.
PANSS general	0.028	N.S.	-0.011	N.S.
Age of onset	-0.260	p=0.018	-0.224	p=0.042
Duration of illness (year)	-0.372	p=0.001	-0.348	p=0.001
Medication (mg/day, haloperidol equivalent)	-0.166	N.S.	-0.186	N.S.

Abbreviations, PANSS = Positive and Negative Syndrome Scale (Kay et al., 1987).

**Table 3** Statistics within each region of interest (ROI), selected from significant cortical thinning regions in schizophrenia in the group analysis

Region of interest (ROI)	Cortical thickness		Cortical thickness		Statistics	
	(mm)		(mm)			
	Control group		Patient group			
	(n=90)		(n=83)			
	Mean	S.D.	Mean	S.D.	t	p
Right rostral middle frontal	2.51	0.17	2.36	0.16	5.76	p<0.001
Right superior frontal	3.05	0.17	2.87	0.19	6.42	p<0.001
Right insula	2.77	0.15	2.62	0.14	6.59	p<0.001
Right isthmus/precuneus	2.75	0.16	2.58	0.16	6.65	p<0.001
Right superior/middle temporal	2.85	0.22	2.68	0.23	5.06	p<0.001
Left rostral middle frontal	2.43	0.10	2.37	0.12	3.76	p<0.001
Left superior frontal	3.02	0.17	2.87	0.19	5.90	p<0.001
Left superior/rostral middle frontal	2.76	0.17	2.62	0.16	5.36	p<0.001

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## **Contributors**

The authors Manabu Kubota and Toshiya Murai designed the study and wrote the protocol. Manabu Kubota managed the literature searches and analyses. Manabu Kubota, Jun Miyata, Kazuyuki Hirao, Hironobu Fujiwara, Ryosaku Kawada, Shinsuke Fujimoto, Yusuke Tanaka and Akihiko Sasamoto undertook the analysis and interpretation of clinical and psychological data. Manabu Kubota performed data processing and statistical analyses, under technical supervision by Hidenao Fukuyama, Nobukatsu Sawamoto, Hidefumi Yoshida, and Jun Miyata. Manabu Kubota wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

**Conflict of interest**

All authors declare that they have no conflicts of interest.

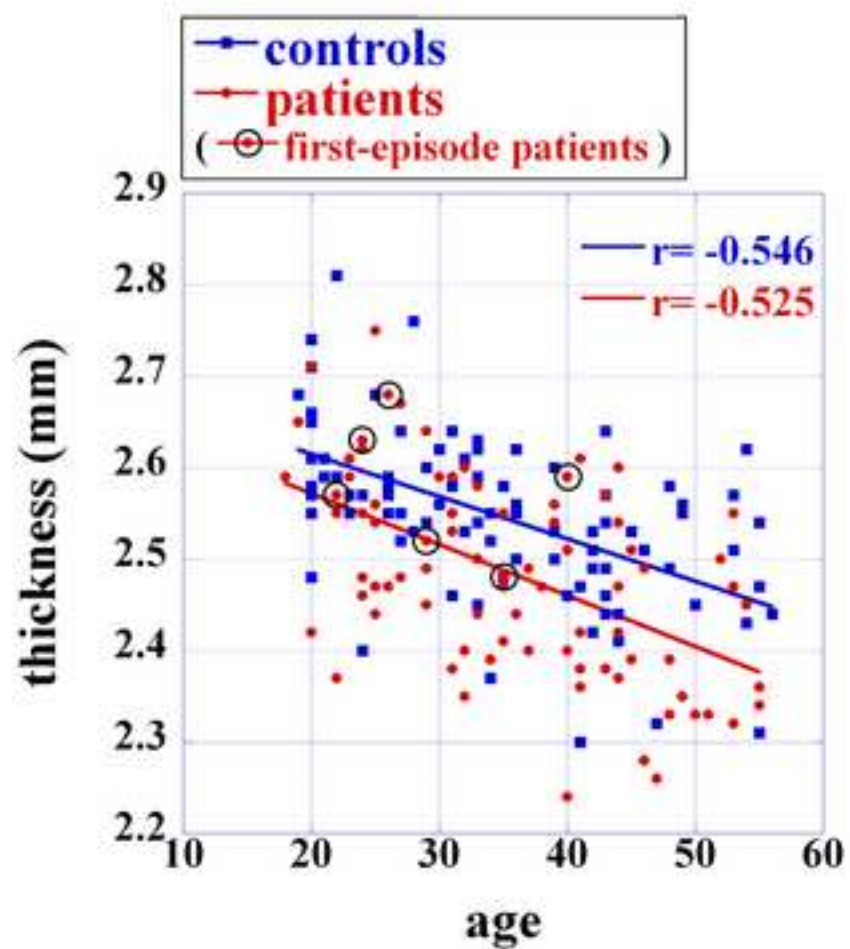


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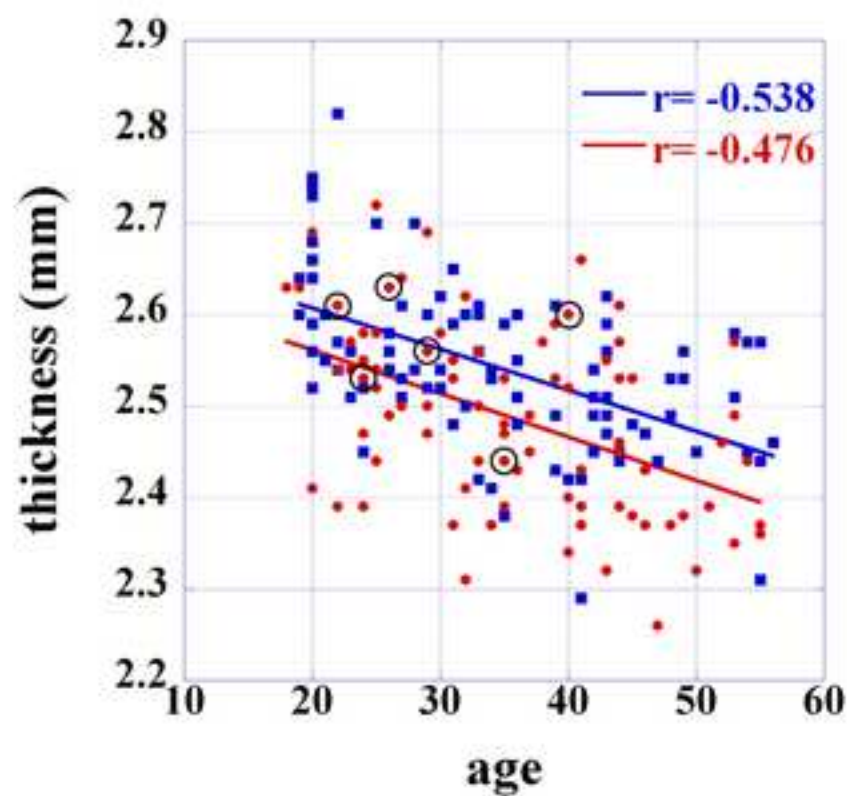
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Figure1

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Right hemisphere



Left hemisphere

Figure2

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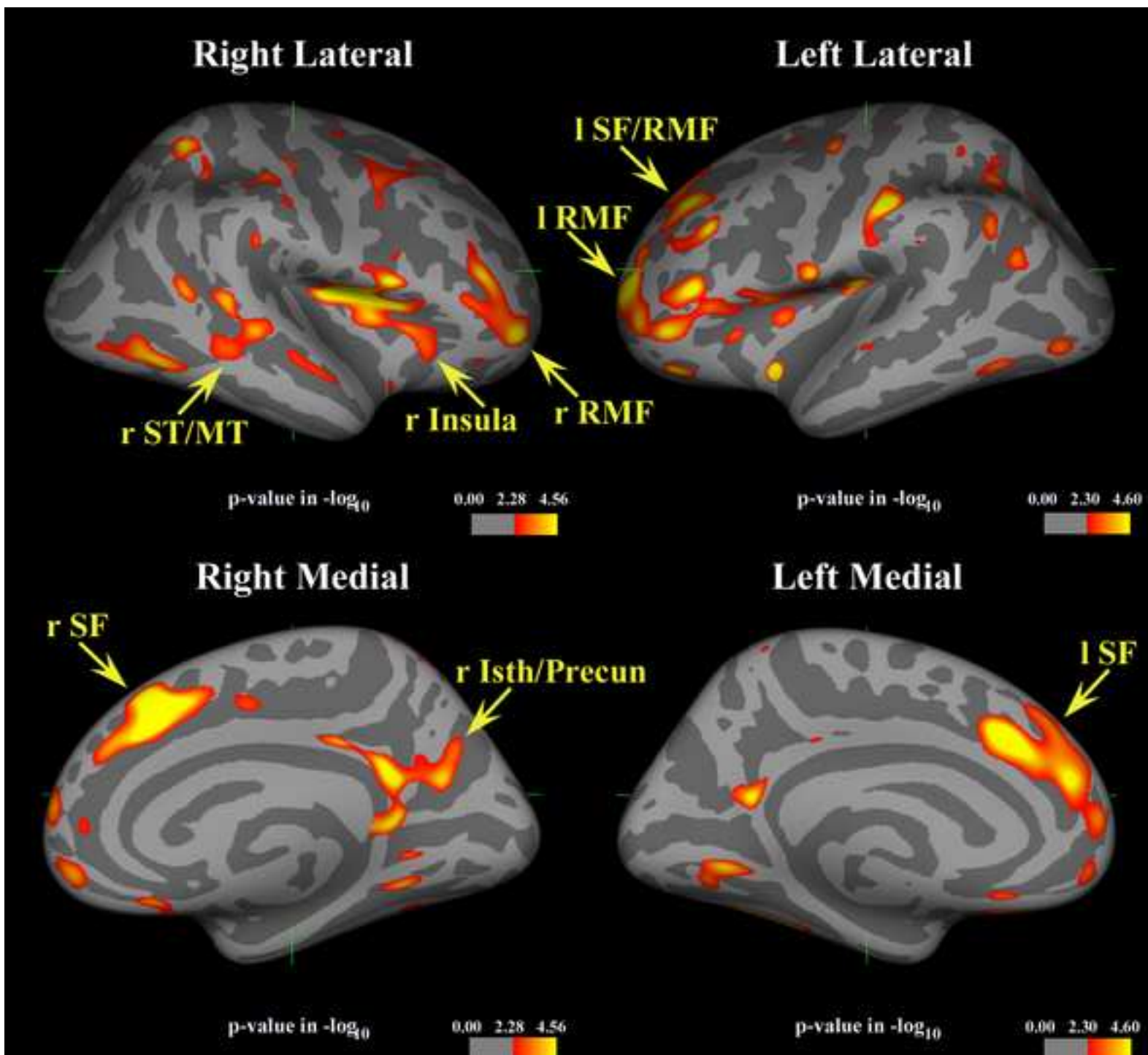


Figure3a

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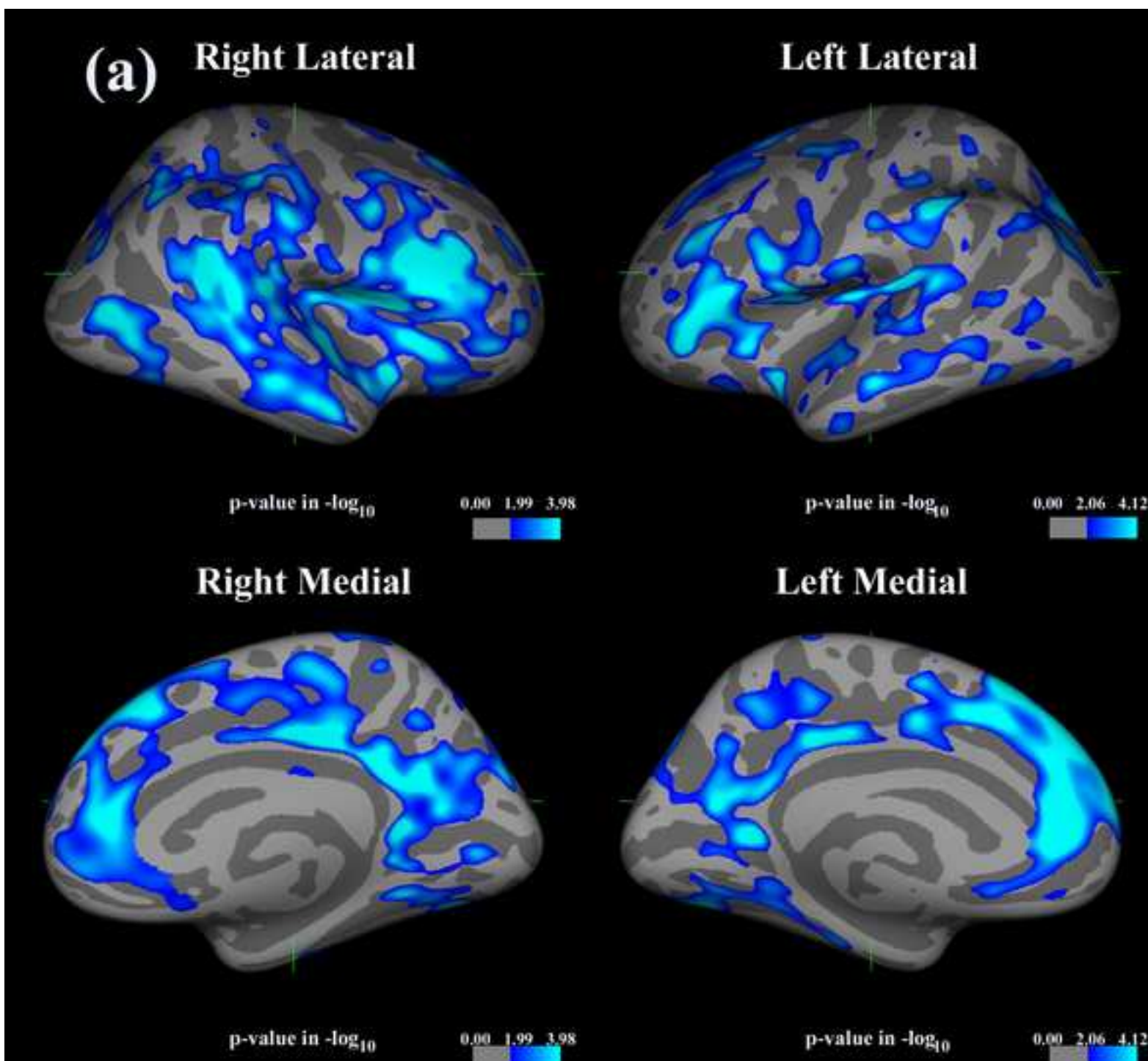




Figure3b  
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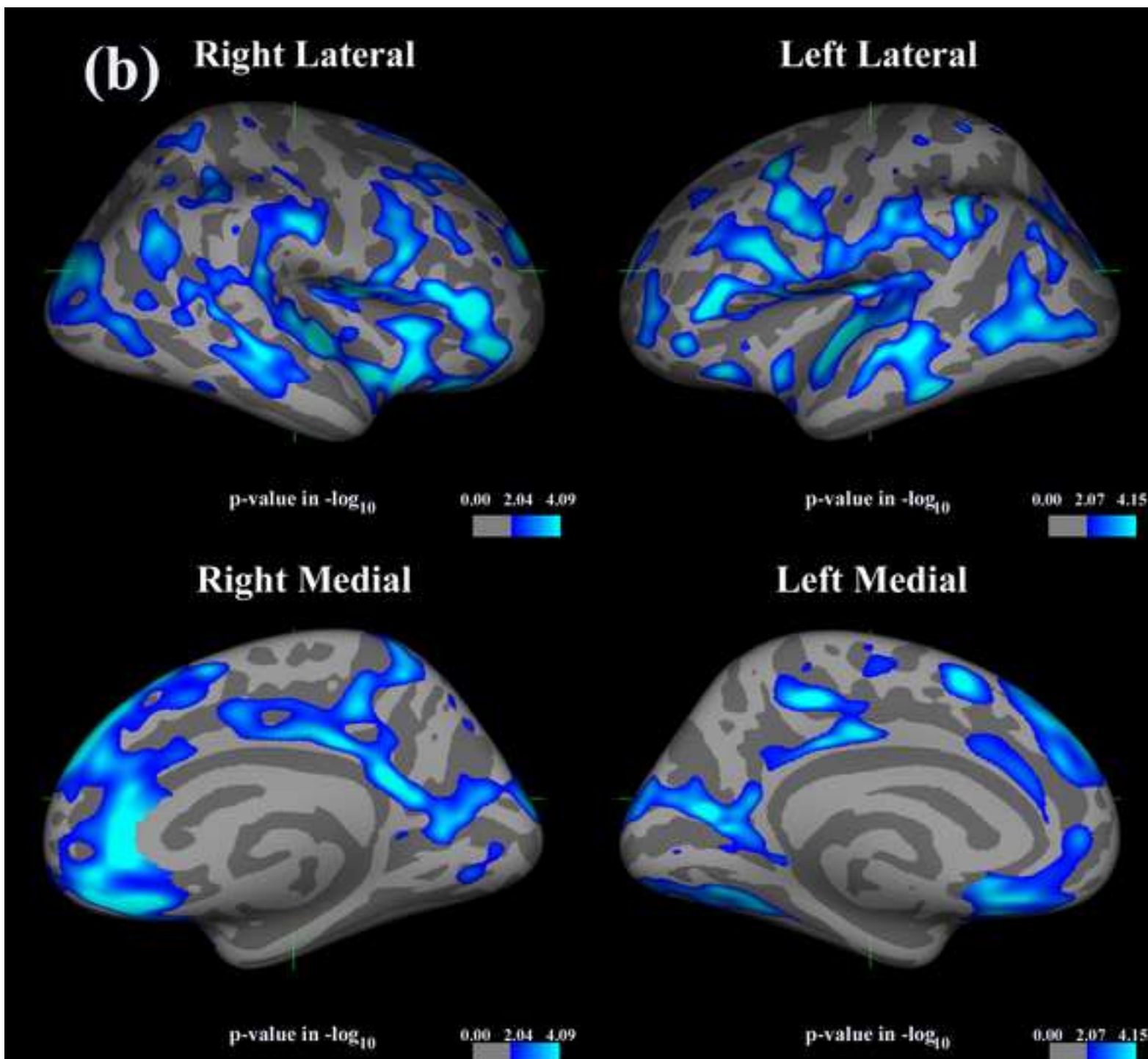


Figure4

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