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Abnormal asymmetries in subcortical brain volume in schizophrenia

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Subcortical structures, which include the basal ganglia and parts of the limbic system, have key roles in learning, motor control and emotion, but also contribute to higher-order executive functions. Prior studies have reported volumetric alterations in subcortical regions in schizophrenia. Reported results have sometimes been heterogeneous, and few large-scale investigations have been conducted. Moreover, few large-scale studies have assessed asymmetries of subcortical volumes in schizophrenia. Here, as a work completely independent of a study performed by the ENIGMA consortium, we conducted a large-scale multisite study of subcortical volumetric differences between patients with schizophrenia and controls. We also explored the laterality of subcortical regions to identify characteristic similarities and differences between them. T1-weighted images from 1680 healthy individuals and 884 patients with schizophrenia, obtained with 15 imaging protocols at 11 sites, were processed with FreeSurfer. Group differences were calculated for each protocol and meta-analyzed. Compared with controls, patients with schizophrenia demonstrated smaller bilateral hippocampus, amygdala, thalamus and accumbens volumes as well as intracranial volume, but larger bilateral caudate, putamen, pallidum and lateral ventricle volumes. We replicated the rank order of effect sizes for subcortical volumetric changes in schizophrenia reported by the ENIGMA consortium. Further, we revealed leftward asymmetry for thalamus, lateral ventricle, caudate and putamen volumes, and rightward asymmetry for amygdala and hippocampal volumes in both controls and patients with schizophrenia. Also, we demonstrated a schizophrenia-specific leftward asymmetry for pallidum volume. These findings suggest the possibility of aberrant laterality in neural pathways and connectivity patterns related to the pallidum in schizophrenia.

INTRODUCTION

Patients with schizophrenia have volumetric abnormalities in both cortical and subcortical brain regions, which are closely related to characteristic symptoms and behaviors.[1,2] Patients with schizophrenia demonstrate both positive and negative symptoms as well as cognitive impairment, and many of these characteristic symptoms have been related to structural brain alterations and disrupted interregional connections.[3] Subcortical structures, which include the basal ganglia and parts of the limbic system, are integrally involved in learning and memory, as well as many primitive functions such as motor control, attention and emotion.[4,5] Further, they also have important roles in higher-order executive functions including inhibitory control and working

memory through their structural and functional connectivity with prefrontal cortices.[6,7]

Prior studies have revealed volumetric alterations in the subcortical regions in schizophrenia. For example, many studies report bilateral hippocampal volume reductions in patients with schizophrenia.[8–10] Likewise, on average, individuals with schizophrenia demonstrate lower volumes in the left,[8] right[11] or both thalamic regions,[12–14] and decreased left thalamic volume has even been reported in individuals experiencing first-episode psychosis.[14] On the other hand, results of prior studies on basal ganglia volume in schizophrenia have been somewhat heterogeneous. Stegmayer et al.[15] reported decreased gray matter density in the right ventral striatum in patients with schizophrenia having

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severe emotional dysregulation, while Ha et al.[16] showed increased gray matter concentrations in the right striatum in schizophrenia. Perhaps owing to differences in antipsychotic medications or duration of illness, the right putamen volume has been reported as being increased in schizophrenia in one study,[8] while another study demonstrated decreased gray matter volume in the left putamen in recurrently ill patients with schizophrenia.[14] Thus, individual studies may reach different conclusions, suggesting added value of multi-cohort meta-analyses.

Brain lateralization is considered highly related to human psychological and behavioral characteristics.[17] Initially, it was widely believed that the left hemisphere supported language and logical thinking, while the right hemisphere was involved to a greater extent in creativity and intuition.[18] In recent years, anatomical and functional brain lateralization has been assessed using brain-mapping approaches,[17] and various investigations have revealed the lateralization of subcortical regional volumes in healthy subjects. For example, rightward asymmetry has been commonly reported for the hippocampus[19–22] and amygdala.[20–22] In contrast, results on lateralization of regional volumes for the thalamus,[21,23] lateral ventricles,[24,25] caudate nuclei,[26–31] putamen,[30,31] globus pallidus[30,31] and nucleus accumbens[21] are so far controversial and non-conclusive.

Altered structural lateralization in schizophrenia has recently been investigated. Many studies have shown differences in hemispheric asymmetries of cortical volume between patients with schizophrenia and controls.[32] In addition, changes in subcortical structural asymmetry in schizophrenia have also been demonstrated. For example, exaggerated rightward asymmetry of the thalamus,[13] similar but exaggerated rightward asymmetry of the hippocampus[19] and reduced rightward asymmetry of the amygdala[21] have been reported. However, few comprehensive studies have been conducted and little is known on the lateralization of subcortical structures in schizophrenia.

Conventional meta-analyses have been used to assess the overall evidence for structural alterations in schizophrenia.[12,33–35] However, this method has some disadvantages. Studies included in a conventional meta-analysis have varying designs, and often have different populations, conditions and analysis methods.[36] Thus, the overall effects may be weakened.

Multi-centered large-scale research is very important for elucidating the neural basis of psychiatric disorders such as schizophrenia, as some single studies may have only small effects, or the confidence interval on the magnitude of the effects may be wide in smaller cohorts. In this context, the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium was organized by neuroscience and genetics researchers from worldwide, to work together on imaging genetics research for psychiatric disorders. Several reports have already been published by the consortium.[37–43] Recently, van Erp et al.[44] published an original article about the analysis of brain morphology in schizophrenia. They identified subcortical regional volumes that are different between patients with schizophrenia and controls, across 15 cohorts, and ordered them by effect sizes. Patients with schizophrenia showed smaller-than-normal volumes in the hippocampus, amygdala, thalamus and accumbens as well as smaller-than-normal intracranial volume (ICV). On the other hand, these patients showed larger-than-normal pallidum and lateral ventricle volumes.

In our current study, as a research project by a Japanese consortium, the COCORO (Cognitive Genetics Collaborative Research Organization), we conducted a multisite large-scale cross-sectional investigation of subcortical regional volumetric differences between patients with schizophrenia and healthy subjects by using meta-analytic methods similar to those of the van Erp et al.[44] study. As a new line of work, we also separately assessed group differences in each hemispheric regional volume. Further, we explored the asymmetry of subcortical regional volumes both in healthy subjects and in patients with schizophrenia, and investigated possible alterations of subcortical asymmetry in schizophrenia. The first aim of our study was to investigate whether the results of the work by van Erp et al. could be replicated. The second aim was to elucidate characteristic similarities and differences in subcortical volumetric lateralization between patients with schizophrenia and healthy individuals.

MATERIALS AND METHODS

Sample subjects and imaging

A total of 3208 individuals took part in the current large-scale cross-sectional cohort project—the overall cohort consisted of 2091 healthy controls and 1117 patients with schizophrenia from 11 sites in COCORO. Participants did not overlap between the van Erp et al.[44] study and our current study. Subject inclusion and exclusion criteria by site are described in Supplementary Method 1. Written informed consent was obtained from each subject before participation. This procedure was approved by each local institutional review board. Each participating site conducted magnetic resonance imaging (MRI) scanning and obtained T1-weighted images with one or more scanner(s) and imaging protocol(s). A combination of one scanner and one imaging protocol was defined as one 'protocol', and 26 protocols were registered in the current study. Detailed imaging parameters for each protocol are shown in Supplementary Table 1. For accurate exploration of brain hemispheric characteristics including lateralization, we investigated the possibility of left–right errors derived from MRI data format conversion. The details are described in Supplementary Method 2.

Imaging processing, quality control and protocol selection

The procedures described in this section are summarized in Figure 1. In the first quality control step, original T1-weighted images were checked by visual inspection. We excluded images with insufficient brain coverage (field-of-view problem), those with low signal-to-noise ratios or any artifacts (for example, motion artifacts and magnetic susceptibility artifacts) and those with any abnormal organic findings (for example, large cerebellar cysts and cavum septum pellucidum). Through this process, 306 healthy subjects and 167 patients with schizophrenia were excluded. Next, T1-weighted imaging data that had passed the first quality control step were processed with FreeSurfer software version 5.3 (http://surfer.nmr.mgh.harvard.edu), as described previously.[44] Through this procedure, we obtained images of subcortical segmentation and regional volumes (for the bilateral lateral ventricles, thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, accumbens and the ICV). Fourteen healthy controls and three patients with schizophrenia were rejected owing to the failure of FreeSurfer processing. After that, two independent researchers visually inspected each segmentation image to exclude images with poor parcellation. One patient with schizophrenia was excluded by this approach. A total of 14 healthy controls and four patients with schizophrenia were excluded in the second quality control step (the quality control of FreeSurfer analysis). After the two quality control steps (inspection of original MRI data and screening for successful FreeSurfer processing), 1771 healthy subjects and 946 patients with schizophrenia
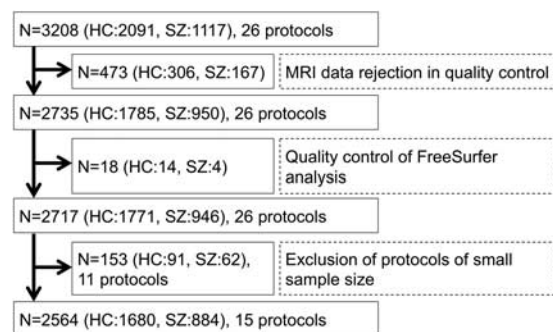

Figure 1. Flow chart of protocol selection into the current meta-analytic study. HC, healthy control; MRI, magnetic resonance imaging; SZ, schizophrenia.

Table 1. Basic characteristics of the included protocols

Protocol name	HC					SZ					Vendor	MFS
				Age					Age			
	N	Male	Female	Mean	s.d.	N	Male	Female	Mean	s.d.		
01. Osaka_A	404	187	217	35.4	12.6	136	80	56	36.4	12.6	GE	1.5 T
02. Tokyo_A	233	143	90	34.4	11.5	102	57	45	33.3	9.5	GE	1.5 T
03. Osaka_B	237	131	106	31.4	13.2	79	35	44	33.1	12.0	GE	3.0 T
04. Toyama_A	118	63	55	25.9	6.3	117	60	57	26.7	6.3	Siemens	1.5 T
05. Kyoto	111	63	48	31.9	10.6	85	45	40	35.9	9.2	Siemens	3.0 T
06. Hokkaido	35	15	20	48.3	12.0	117	43	74	35.1	12.4	Siemens	1.5 T
07. Tokyo_B	83	57	26	28.7	5.5	45	30	15	31.2	9.0	GE	3.0 T
08. Yamaguchi	91	18	73	49.5	16.1	28	5	23	55.5	8.0	Siemens	1.5 T
09. Nagoya_A	68	38	30	37.7	9.8	43	26	17	43.6	10.6	Siemens	3.0 T
10. Kyushu_A	78	36	42	33.2	11.9	31	9	22	39.4	9.5	Philips	3.0 T
11. Kanazawa-med	53	32	21	35.9	11.7	34	14	20	35.9	9.5	Siemens	3.0 T
12. UOEH	54	36	18	36.6	12.0	15	6	9	28.0	13.4	GE	3.0 T
13. Yaesu_A	47	17	30	38.8	9.0	11	6	5	38.4	4.2	Philips	3.0 T
14. Tokyo_C	41	25	16	28.8	7.5	15	8	7	30.5	12.7	GE	3.0 T
15. Kyushu_B	27	11	16	34.6	13.8	26	14	12	35.5	11.0	Philips	3.0 T
Total	1680	872	808	34.5	12.7	884	438	446	34.8	11.7		

Abbreviations: HC, healthy control; MFS, magnetic field strength; SZ, schizophrenia.

remained for possible analysis in the study (available data remained as shown in Supplementary Table 2). Among potential candidates, protocols with less than 50 total participants and those with less than 10 participants in either diagnostic group were excluded before the following meta-analysis, to minimize undue effects of very small groups. Finally, 1680 healthy individuals and 884 patients with schizophrenia from 15 protocols remained for inclusion (Table 1).

The mean and standard deviation of age across protocols for healthy controls were 34.5 ± 12.7 and for patients were 34.8 ± 11.7 years. As for sex ratio, 52% of the controls and 50% of the patients were male. Supplementary Figures 1a–q and 2a–q demonstrate regional volume histograms by site in healthy subjects and in patients with schizophrenia, respectively. Subgroup sample sizes of the van Erp *et al.* study[44] and the current study are compared in Supplementary Table 3.

Alterations of subcortical regional volumes in schizophrenia

All linear regression analyses were conducted using SPSS version 19.0.0 (SPSS, Chicago, IL, USA), and all meta-analyses were performed using Review Manager version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and Metasoft software.[45] For definition of statistical significance, we set the type-I error rate (*P*-value) at 0.05. Moreover, a Bonferroni correction was applied to the statistical results to reduce type-I errors generated by multiple comparisons. First, means and standard deviations of subcortical regional volumes and ICV were calculated for each protocol for each diagnostic group. Second, we examined group differences in regional volumes within each protocol. Group differences in subcortical regional volumes were investigated using a univariate linear regression analysis including sex, age and ICV as nuisance covariates. For group differences in ICV, only sex and age were included as nuisance covariates in the regression analysis. Finally, we performed meta-analysis of group differences in each regional volume. The group differences and standard errors for each protocol were entered into a random-effect model meta-analysis, and overall group differences and standard errors were obtained. For each brain region, Cohen's *d* effect sizes were calculated from the overall group contrast. The analytical methods used in the van Erp *et al.* study from the ENIGMA Schizophrenia Working Group (ENIGMA-SZ) were followed in this analysis.[44]

Laterality of subcortical regional volumes

To assess laterality for each regional volume, we used a laterality index (LI), defined as the ratio [(left − right)/(left+right)]; this is commonly used to evaluate brain structural asymmetry.[19,30,46] LIs can range from − 1 to 1 and a positive LI means a leftward asymmetry.

First, the means and standard deviations of LIs of subcortical regional volumes were calculated for each protocol for each diagnostic group. One-sample tests were conducted to evaluate whether mean LIs were significantly different from zero. Second, we performed a separate meta-analysis for LIs in each group. Mean LIs and standard errors in each protocol were entered into a random-effect model meta-analysis, and overall mean LIs in each group were obtained. LIs have similar characteristics to effect sizes; that is, both of them are referenced and indexed to zero (thus, LIs themselves can be meta-analyzed). For each group and each brain region, Cohen's *d* effect sizes for LIs were calculated from the overall average.

Third, group differences in LIs within each protocol were examined using a univariate linear regression, which included sex and age as nuisance covariates, as LIs may not distribute normally. Fourth, we performed a meta-analysis of group differences in LIs. Group differences in LIs and standard errors in each protocol were included into a random-effect model meta-analysis, and overall group differences in LIs were obtained. Cohen's *d* effect sizes for differences in LIs between groups were calculated from the overall group contrast. Using a similar method as used in the van Erp *et al.*[44] study, we also conducted a power analysis to estimate the sample sizes required to detect the given effect sizes at a power of 0.80 and a one-tailed significance level of 0.05, with G*Power version 3.1.9.2.[47]

Finally, as an additional analysis, we performed a meta-analysis of group differences in LIs using FMRIB's Integrated Registration and Segmentation Tool (FIRST) in the FMRIB Software Library (FSL) version 5.0.8 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST), as LIs for subcortical volumes calculated with FreeSurfer can be different from those calculated using FSL.[48] Of the 2564 participants (1680 healthy controls and 884 patients with schizophrenia) included in the main analyses, 29 subjects (18 controls and 11 patients) failed to be processed with FSL. After that, each segmentation image was visually checked for exclusion of poor parcellation. Fifty-eight subjects (35 controls and 23 patients) were excluded by this approach. Thus, a total of 2477 participants (1627 controls and 850 patients) were entered into the additional analysis.

RESULTS

Alterations of subcortical regional volumes in schizophrenia

Means and standard deviations of regional volumes for each protocol for each diagnostic group can be found in Supplementary Table 4. Group differences in regional volumes within each protocol were examined and listed in Supplementary Table 5. We performed a meta-analysis of group differences in
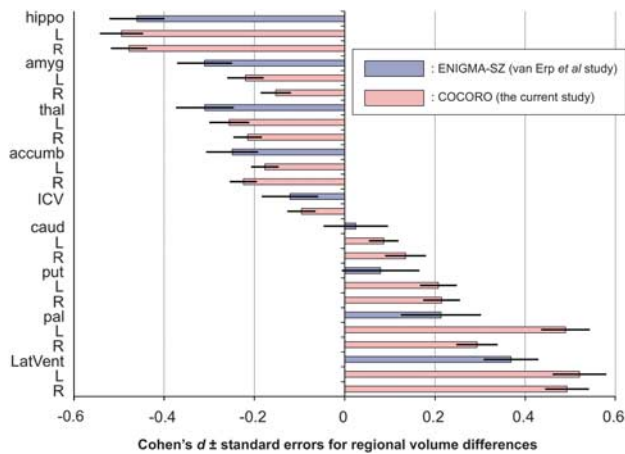
Figure 2. Meta-analytic overall effect sizes (Cohen's *d*) ± standard errors for subcortical regional volume differences between patients with schizophrenia and healthy controls. Results of the van Erp *et al.* study from ENIGMA-SZ (blue-colored bars) and those of the current study from COCORO (pink-colored bars) are merged. Between-group differences in subcortical volumes adjusted for age, sex and intracranial volume, as well as differences in intracranial volume adjusted for age and sex, were included into the meta-analysis and overall differences were obtained. The corresponding forest plots are described in Supplementary Figures 3a–q. An overall effect size was calculated as the ratio of the overall difference to the pooled standard deviation. A positive effect size means that patients with schizophrenia had larger volumes than healthy controls. accumb, accumbens; amyg, amygdala; caud, caudate; COCORO, Cognitive Genetics Collaborative Research Organization; ENIGMA, Enhancing Neuro Imaging Genetics through Meta-Analysis; ENIGMA-SZ, ENIGMA Schizophrenia Working Group; hippo, hippocampus; ICV, intracranial volume; L, left; LatVent, lateral ventricle; pal, pallidum; put, putamen; R, right; thal, thalamus.

regional volumes. Compared with controls, patients with schizophrenia demonstrated significantly smaller bilateral hippocampus, amygdala, thalamus and accumbens volumes as well as smaller ICVs; however, patients exhibited larger bilateral caudate, putamen, pallidum and lateral ventricle volumes (Supplementary Table 6). The largest decreasing patient–control effect size was found for left hippocampal volume ($d = -0.49$, $P = 7.2 \times 10^{-25}$) and the largest increase was seen for left lateral ventricle volume ($d = 0.52$, $P = 2.1 \times 10^{-18}$). Each of these brain structures studied, excluding the left caudate volume ($d = 0.09$, $P = 8.5 \times 10^{-3}$) and right caudate volume ($d = 0.13$, $P = 3.0 \times 10^{-3}$), had significant group differences even at a conservative Bonferroni-corrected threshold of $P < 2.9 \times 10^{-3}$ (0.05/17). Results for left and right hemispheric volumes of each region demonstrated similar tendencies. The effect sizes and standard errors for subcortical regional volume differences are depicted in Figure 2, where the results of the van Erp *et al.*[44] study from ENIGMA-SZ and those of the current study from COCORO are merged. The I^2 index, which represented the heterogeneity of effect sizes, varied from zero to moderate (range: 0–56%). Group differences for each protocol are provided in Supplementary Figures 3a–q.

Laterality of subcortical regional volumes
Means and standard deviations of LIs of regional volumes for each protocol for each group are listed in Supplementary Table 7. We performed a meta-analysis of LIs in each group (Figure 3 and Supplementary Table 8). Healthy controls and patients with schizophrenia showed significantly positive LIs in the thalamus ($d = 1.32$, $d = 1.26$, respectively), lateral ventricles ($d = 0.59$, $d = 0.62$, respectively), caudate ($d = 0.57$, $d = 0.53$, respectively)
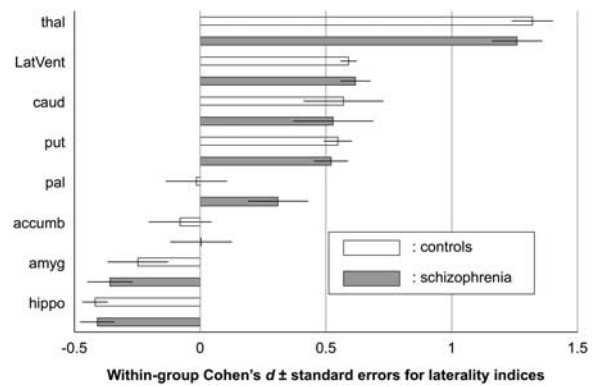

Figure 3. Within-group meta-analytic overall effect sizes (Cohen's *d*) ± standard errors for laterality indices (LIs) of subcortical regional volumes in healthy controls (white bars) and in patients with schizophrenia (gray bars). An LI was defined as the ratio [(left − right)/(left+right)]. In each group, mean LIs and their standard errors were entered into the meta-analysis and an overall mean was obtained. The corresponding forest plots are described in Supplementary Figures 4a–h and 5a–h. An overall effect size for LIs was calculated as the ratio of the overall mean LIs to the overall standard deviation. A positive effect size demonstrates a leftward asymmetry. accumb, accumbens; amyg, amygdala; caud, caudate; hippo, hippocampus; LatVent, lateral ventricle; pal, pallidum; put, putamen; thal, thalamus.

and putamen ($d = 0.55$, $d = 0.52$, respectively), as well as significantly negative LIs in the hippocampus ($d = -0.42$, $d = -0.41$, respectively) and amygdala ($d = -0.25$, $d = -0.36$, respectively). LIs of these regions in both groups survived a Bonferroni correction with a threshold of $P < 6.3 \times 10^{-3}$ (0.05/8), except that of the amygdala in healthy subjects. LIs of the nucleus accumbens in both groups were not significantly different from zero ($d = -0.08$, $d = 0.00$, respectively). The LI of the globus pallidus in controls did not differ from zero ($d = -0.02$, $P = 0.90$), while in patients with schizophrenia it was positive with a trend towards significance ($d = 0.31$, $P = 1.0 \times 10^{-2}$). LIs for each protocol in controls and in patients with schizophrenia are provided in Supplementary Figures 4a–h and 5a–h, respectively.

Group differences in LIs within each protocol were examined (Supplementary Table 9). We performed a meta-analysis of group differences in LIs (Supplementary Figure 6 and Supplementary Table 10). The LI of the globus pallidus in patients with schizophrenia was significantly higher than in the healthy controls (mean difference = 0.021, $d = 0.30$, $P = 2.8 \times 10^{-11}$). However, LIs of the other regions were not significantly different between groups. Group differences in LIs for each protocol are provided in Supplementary Figures 7a–h. According to a power analysis, the estimated sample sizes required for each group to reach a power of 0.80 ($P < 0.05$, one-tailed) across regions ranged from 141 to 1 016 462.

As an additional analysis, we performed a meta-analysis of group differences in LIs using FSL (Supplementary Figure 8). The LI of the globus pallidus in patients with schizophrenia was significantly higher than in the healthy controls (mean difference = 0.009, $d = 0.20$, $P = 1.3 \times 10^{-8}$). For the other regions, LIs were not significantly different between groups.

DISCUSSION

In the current study, we showed smaller-than-normal volumes in the bilateral hippocampi, amygdala, accumbens and ICV, and larger-than-normal volumes in the bilateral caudate, putamen, pallidum and lateral ventricle in patients with schizophrenia.

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Supplementary Table 11 demonstrates sample sizes and results on subcortical volume alterations in schizophrenia both in previous studies and in the current study. We successfully replicated the previous study from the ENIGMA consortium[44] and another large-scale meta-analytic study conducted by Haijma et al.,[35] both of which showed smaller-than-normal volumes in the hippocampus, amygdala, thalamus and nucleus accumbens and ICV, as well as larger-than-normal volumes in the globus pallidus and lateral ventricles. In addition, as demonstrated in Figure 2, the rank order of effect sizes for group differences in the current study was similar to that in the van Erp et al.[44] study. Our results revealing larger-than-normal volumes of the caudate and putamen in patients with schizophrenia were not in line with the two previous studies. This discrepancy might partly be because the samples included in the current study were relatively ethnically homogeneous, namely, most of the participants were Japanese people. The discrepancy might also be owing to the use of a single pipeline for preparation before the statistical analysis of the MRI data, which included quality control and preprocessing with FreeSurfer. In contrast to the two above-mentioned studies, our results of enlarged caudate and putamen volumes in patients with schizophrenia were consistent with a number of previous studies. For example, Hokama et al.[49] reported enlarged volumes of the globus pallidus, putamen and caudate. Moreover, Glahn et al.[50] reported enlarged volumes in the bilateral putamen and right head of the caudate. Another study reported an association between caudate volume and working memory, as well as putamen volume and verbal learning, vigilance and executive function in schizophrenia.[51] Mamah et al.[52] reported increased volume in the bilateral caudate and putamen and a positive correlation between attention/vigilance performance with caudate and putamen volume in schizophrenia. Finally, a review by Brandt and Bonelli[53] demonstrated a decreased caudate volume in first-episode schizophrenia and increased caudate and putamen volume in chronic schizophrenia. Further research is needed to elucidate volumetric alterations of caudate and putamen in schizophrenia.

The current study revealed asymmetry in several subcortical structures. First, healthy controls demonstrated leftward asymmetry in the lateral ventricles, thalamus, caudate and putamen, while rightward asymmetry was found in the hippocampus and amygdala. For hippocampus and amygdala volumes, our results are consistent with previous studies,[19–22] one of which was a meta-analytic review.[20] Although our results are discordant with those of some previous studies on volumetric lateralization for the thalamus,[23] caudate[27–30] and putamen,[31,46] the current study is in accordance with other previous reports on volumetric lateralization of the lateral ventricle,[24] putamen,[27,30] globus pallidus[31] and nucleus accumbens.[21] Except for Pedraza et al.,[20] these previous studies had at most 150 participants, and may have been driven by sampling bias. Further, scanner differences (for example, vendor, model and magnetic field strength) and image processing biases may have also possibly influenced findings across the studies. Meta-analytic methods, such as the ones used in this study, could overcome such drawbacks.

Second, with the exception of the globus pallidus, volumetric asymmetries in the subcortical regions were not significantly different between controls and patients with schizophrenia. The current study is consistent with a prior study demonstrating similar patterns of rightward hippocampal asymmetry in both schizophrenia and control groups.[19] However, it should be noted that our results are discordant with some previous reports. Csernansky et al.[13] showed increased rightward asymmetry of the thalamus in patients with schizophrenia compared with healthy controls. Moreover, Qiu et al.[21] revealed rightward amygdala asymmetry in controls and a reduction of this asymmetry in patients with schizophrenia. We assume that the differences in results across studies can be ascribed to scanner differences,

imaging processing biases, different sample sizes and various ethnicities. Collectively, to our knowledge, our results are the first to comprehensively characterize laterality of brain subcortical regional volumes in schizophrenia.

Third, we revealed significant alterations of hemispheric asymmetry for globus pallidus volume in patients with schizophrenia when compared with controls. For this region, healthy subjects showed no asymmetry, while patients with schizophrenia demonstrated leftward asymmetry. Few previous studies have addressed globus pallidus volume laterality or made a direct comparison of left- and right-side volumes, although, contradictory to our results, some previous studies have reported enlarged globus pallidus volumes only on the right side in schizophrenia.[52,54] van Erp et al.[44] demonstrated a bilaterally increased volume of the globus pallidus in schizophrenia with similar effect sizes for both left and right regions, while not investigating the volume lateralization of this region. We presume no lateralization differences between groups in their data set. Of note, our results were likely not owing to a technical pitfall or instability of the current imaging analysis technology, because the additional analysis using FSL found similar results to the main analysis using FreeSurfer. Thus, schizophrenia–control differences in the lateralization of globus pallidus volume could be robust.

There are several reports of left globus pallidus abnormalities in schizophrenia using imaging modalities other than structural MRI. A positron emission tomography study showed significantly higher blood flow in the left globus pallidus in never-medicated patients with schizophrenia than in controls.[55] Another positron emission tomography study revealed a correlation between the severity of negative symptoms and increased left external globus pallidus activation in schizophrenia.[56] A functional MRI study showed that patients with schizophrenia demonstrated greater activation during procedural learning in the left globus pallidus.[57] Further, some previous investigations have shown altered connectivity involving the globus pallidus in schizophrenia. A resting-state functional MRI study revealed significantly aberrant interhemispheric connections in the globus pallidus, as well as a negative correlation with bilateral connections of the pallidum and duration of illness in schizophrenia.[58] Finally, a diffusion tensor imaging study showed that patients with schizophrenia have lower-than-normal fractional anisotropy values in the bilateral globus pallidus, implying aberrant microstructures of the globus pallidus.[59]

The basal ganglia have important roles in motor function and the reward system,[60,61] and the globus pallidus externus is in the central position among the loop circuits of the basal ganglia.[62] It has long been known that the basal ganglia use modulatory systems to regulate cerebral cortical activity via a projection to the thalamus.[63] A recent mouse study described a direct GABAergic (gamma-aminobutyric acidergic) projection from the globus pallidus externus to the frontal cortex, which is exclusively ipsilateral and sensitive to antipsychotic drugs.[64] These results imply the existence of altered structural and functional connectivity, especially ipsilateral connectivity, between basal ganglia and frontal cortices in schizophrenia. In patients with schizophrenia, altered GABAergic interneuron function resulting in dysfunction of the dorsolateral prefrontal cortex,[65] which is closely associated with impairments in executive functioning such as working memory,[66] may occur ipsilaterally. Thus, it is suggested that there may be aberrant laterality in neural pathways and connectivity patterns related to the globus pallidus in schizophrenia. Further research is required to elucidate this hypothesis.

A few limitations to the current study should be noted. First, possible effects of medically prescribed drugs on subcortical regional volumes in patients with schizophrenia cannot be overlooked. Although few studies reported associations between limbic volumes and antipsychotic medications,[67] several studies have demonstrated increased basal ganglia volume after

treatment with neuroleptics (especially typical neuroleptics).[68,69] A review by Ebdrup et al.,[70] however, revealed that typical neuroleptics do not increase the volume of the basal ganglia, while atypical neuroleptics do. A recent meta-analytic study revealed no significant longitudinal differences in caudate volume related to antipsychotic treatment in patients with schizophrenia.[71] Thus, results regarding medication-induced changes in subcortical regional volumes in schizophrenia remain controversial and heterogeneous. Second, the results of any meta-analysis must be interpreted cautiously, because of possible confounds such as a statistical paradox.[72] The sample sizes of this study were unequal; therefore, the current meta-analytic results may be unstable. Third, we did not investigate correlations between subcortical region volumes and clinical characteristics. Only the Osaka site was able to provide such detailed clinical characteristics. The ENIGMA consortium has already launched a research project studying such associations. The Osaka site supplied its own data set of T1-weighted images and clinical information to this ENIGMA project. The results of their study are expected to be published in the near future.

In conclusion, we demonstrated reduced bilateral hippocampus, amygdala, thalamus, accumbens and ICVs, but enlarged bilateral caudate, putamen, pallidum and lateral ventricle volumes in schizophrenia. The rank order of effect sizes for subcortical regional volumetric differences between patients with schizophrenia and healthy subjects reported by van Erp et al.[44] was successfully replicated and confirmed. Further, we revealed leftward asymmetry for thalamus, lateral ventricle, caudate and putamen volumes, and rightward asymmetry for amygdala and hippocampal volumes both in controls and in patients with schizophrenia. Also, we demonstrated schizophrenia-specific leftward asymmetry in globus pallidus volume. These findings suggest the possibility of aberrant laterality in neural pathways and connectivity patterns related to the pallidum in schizophrenia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

RH supervised the entire project. NOk, MFuk, KK and RH designed the study. NOk, MFuk, DK, HYamam, KO, YY, MFuj, YoshiyW, NY, HF, MI, SI, TN, HN, NH, JM, SK, TT, HYamas, KM, TO, TI, YK, RY, YoshifW, MS, MT, NOz, KK and RH contributed to data collection. NOk, Fuk, FY, DK, KN and RH analyzed the data. NOk, MFuk, FY, DK, HYamam, KO, YY, MFuj, YoshiyW, NY, KN, DPH, TGMvE, HF, MI, SI, TN, HN, NH, JM, SK, TT, HYamas, KM, TO, TI, YK, RY, YoshifW, MS, JAT, MT, PMT, NOz, KK and RH interpreted the results. NOk, MFuk and RH wrote the manuscript.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)