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Gray matter volume reductions in patients with schizophrenia: A replication study across two cultural backgrounds

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ABSTRACT

Structural gray matter (GM) volume reductions in patients with schizophrenia have rarely been replicated across two different sites, the impact of culture and clinical characteristics remains unresolved. Hence, we assessed GM volume reductions in patients with schizophrenia using 3 T magnetic resonace imaging to replicate results across two independent and culturally different backgrounds (Germany, Japan), and to investigate the impact of brain volume reductions on clinical characteristics. In total, 163 German (80 patients) and 203 Japanese (83 patients) participants were included in the analysis. Voxel-based morphometry (VBM) was used to investigate structural differences between the groups and across the two sites, comparing local GM volumes. Clinical variables were used to analyze effects unrelated to the socio-cultural background. Across both data sets, widespread GM reductions in frontal and temporal cortical parts were found between patients and controls, indicating strong effects of diagnosis and only small effects of site. The investigation of clinical characteristics revealed the strongest effects for chlorpromazine equivalents on GM volume reductions primarily in the Japanese sample. Although the effects of site are small, several brain regions do not overlap between the two groups. Thus, GM may be affected differently at the two sites in patients with schizophrenia.

1. Introduction

Schizophrenia is one of the most severe mental illnesses with an often debilitating course of the disease (Boonstra et al., 2012), the prevalence is about 0.5–1% of the population. It is known that schizophrenia has a biological basis with multifactorial causes including epigenetic and genetic aspects, which is mirrored by a large number of previously identified risk gene loci for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Genetic phenotypes seem to cause a biological vulnerability in form of neurodevelopmental alterations that facilitate the transformation from high-risk to full-blown psychotic states in case of major life events (Perrin et al., 2010). The genetic predisposition seems to express itself before the onset of the disease in high-risk patients (Pettersson-Yeo et al., 2013).

Rapid methodological developments in neuroimaging have allowed increasing preciseness in registering morphological brain changes in schizophrenia (Cahn et al., 2009; Fujiwara et al., 2007a,b; Gur et al., 1998; Koelkebeck et al., 2013; Yamada et al., 2007). Changes in gray, but also in white, matter in patients with neuropsychiatric disorders can be attributed to abnormalities in brain development or to atrophic processes. In patients with schizophrenia, reductions of cortical gray matter (GM) in the prefrontal cortex, insula and thalamus seem to progress after the onset of the disease (Ananth et al., 2002; Ho et al., 2003; Mitelman et al., 2007). Other studies found volume reductions in the anterior cingulate cortex, temporal cortex, parahippocampus, fusiform gyrus, insula and lingual gyrus (Davatzikos et al., 2005; Sheng et al., 2013; Yamasue et al., 2004). In men, these reductions have been

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Table 1
Clinical and social characteristics of patients with schizophrenia (SC) and healthy controls (HC) in means and standard deviations. Abbreviations: PANSS = Positive and Negative Syndrome Scale: pos = positive subscale; neg = negative subscale; CPZ = chlorpromazine equivalent doses; DUI = duration of illness. [a]$n = 43$. [b]For the assessment of educational level, in Germany only education until university or vocational training was asked for, while in Japan graduate training was included.

Measure	SC / Japan ($n = 83$)	HC / Japan ($n = 120$)	SC / Germany ($n = 80$)	HC / Germany ($n = 83$)	Comparison patients Japan/Germany (significance)
Age (years)	37.36 (9.230) Range: 20–56	32.19 (11.144) Range: 19–62	29.25 (7.617), Range: 18–51	30.58 (8.632) Range: 19–53	Japan vs. Germany:t (364) = 4.318, $p < 0.001$ SC: t (161) −6.108, $p < 0.001$ HC: n.s.
Sex	42♂, 41 ♀	68♂, 52 ♀	47♂, 33 ♀	54♂, 29 ♀	n.s.
DUI (months)	156.3781 (101.28860) Range: 3–420	–	63.917 (86.49409) Range: 1–276	–	t (161) = −6.802, $p < 0.001$
CPZ	584.5807 (452.38974) Range: 50–2374.24	–	828.2542 (718.30863) Range: 0–3833.30	–	n.s.
PANSS (pos)	14.3415 (4.62871) Range: 7–27	–	13.3054 (4.66935) Range: 0–125	–	n.s.
PANSS (neg)	15.6707 (5.30314) Range: 7–29	–	17.816 (5.36994) Range: 9–32	–	t (161) = 2.440, $p = 0.016$
PANSS general	31.8340 (8.16836) Range: 20–64	–	29.9759 (9.44558) [a] Range: 0–50	–	n.s.
Handedness (right/left)	74:4 (other: 3) ($n = 81$)	102:5 (other: 7) ($n = 114$)	73:7	76:7	n.s.
School years[b]	13.80 (2.053) ($n = 76$) Range: 9–18	14.92 (2.730) ($n = 114$) Range: 9–24	11.91 (1.552) 9–15	12.10 (1.385) Range: 9–13	Japan: t (188) = −3.043, $p = 0.003$ Germany: n.s.

found to add up to 2–6% volume loss as compared to healthy controls (Gur et al., 1999; Haijma et al., 2013). GM reductions have also been related to cognitive dysfunction, less so to psychopathology (Gur et al., 1999; Ho et al., 2011). Illness duration has also been found to correlate negatively to GM volumes (Haijma et al., 2013). Volume reductions in prefrontal and temporal regions and the cingulate gyrus have been found in patients with prodromal symptoms; additionally, in the course of the illness, reductions in GM in parahippocampal, orbitofrontal and cerebellar cortices as well as the cingulate gyri have been shown (Pantelis et al., 2003). These changes seem to be specific to patients with schizophrenia, e.g. in comparison with those with bipolar disorder (Schlaepfer et al., 1994). However, other studies showed only very moderate volume reduction, e.g. in the cingulate gyrus in at-risk mental states (Nakamura et al., 2013).

Schizophrenia has long been identified to have very similar characteristics across different countries, cultures and climate zones (Pfeiffer, 1967). Psychopathology, e.g. delusional contents, has been shown to be subject to cultural influences (Koelkebeck and Wilhelm, 2014), which might relate to specific neurodevelopmental circuits that mediate certain functions in the brain (Pearlson, 2000). Brain functions, e.g. those related to social-cognitive or language abilities, have shown to be strongly dependent on the socio-cultural background of an individual (Hoeft et al., 2007; Koelkebeck et al., 2011; Siok et al., 2008). Little is known about how much impact the environment (e.g. social interaction styles, language education, attitudes, etc.) has on the neuroplasticity in neurodevelopmental disorders. Studies on groups of patients with mental disorders and healthy controls reported cultural influences on cognitive processing and the correlated neural networks (see Han and Northoff, 2008; Koelkebeck et al., 2017). In one of the first studies to directly investigate samples of patients with schizophrenia in four different ethnicities, Gong et al. (2015), who studied Chinese, Japanese, African-Caribbean and White Caucasian patients with schizophrenia vs. healthy controls, found a consistent pattern of right anterior insula volume reductions independent of ethnicity in patients. In another study with differing ethnicities in the United Kingdom, no GM volume loss differences were found across African-Caribbean and Black African patients as compared t o White Caucasian patients (Morgan et al., 2010). Disease progress, medication (Torres et al., 2016), age (Cropley et al., 2017) and comorbid cannabis use (Rais et al., 2008) have been discussed as possible variables that influence brain morphology other than the socio-cultural background.

In the study presented here, we investigated brain volumes with a focus on GM in a European and an Asian group of patients with schizophrenia compared to healthy controls. We wanted to replicate previous findings of GM volume reductions in schizophrenia in a large sample of patients. We were also interested in the comparison of two patient groups with different socio-cultural backgrounds. We hypothesized that both groups shared certain brain areas regarding GM volume reductions, but would also show differences, e.g. in brain regions that are related to social cognition or language processing, as has been shown in functional imaging studies. We also controlled for clinical variables that might influence GM volume loss in schizophrenia.

2. Methods

2.1. Subjects

In this study, a large sample of patients with schizophrenia was investigated from two study sites: Japan (Kyoto University, Department of Neuropsychiatry) and Germany (University of Muenster, Department of Psychiatry and Psychotherapy). Structural imaging data were taken from data sets acquired in the course of ten years (2005–2015). All participants were recruited as a part of single-center cross-sectional investigation projects at the respective sites. Healthy controls were matched by age, gender and education. The data set included a total of 401 participants (190 patients, 211 healthy controls). From Germany, 180 data sets (94 patients with schizophrenia and 86 healthy controls) were included. From Japan, 221 data sets (96 patients with schizophrenia and 125 healthy controls) were included. All patients were diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder according to interviews performed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I First et al., 1996) by experienced interviewers. The samples included in- and outpatients and were mainly recruited from patients treated in the participating center at the time of the respective study. Healthy controls were assessed locally via advertisements and personal contacts, and matched to the patient groups with regard to age, gender and education. All participants cleared the usual exclusion criteria, including severe neurological or internal medical disorders, any other current mental disorder, acute drug or alcohol abuse or dependence.

The final German sample, after removing double entries ($n = 13$) and participants with gross anatomical abnormalities (> 2 SD

according to check data homogeneity; $n = 4$), consisted of 163 participants (80 patients with schizophrenia and 83 healthy controls).

The final Japanese sample was comprised of 203 participants (83 patients with schizophrenia and 120 healthy controls) (for details see Table 1). For this final sample, double entries ($n = 11$), participants with gross anatomical abnormalities ($n = 5$) as well as corrupted data sets ($n = 6$) were removed. Moreover, one healthy participant was excluded due to a post-hoc psychiatric diagnosis ($n = 1$). For some of the participants, several of these criteria lead to their data exclusion.

2.2. Assessment

Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS Kay et al., 1987). In one of the German subsets with 35 patients, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS Andreasen, 1984a,b) were used to assess psychopathology. For comparison of the data, the method by van Erp et al. (2014) was used to transform SANS/SAPS to PANSS data. Clinical data which were assessed for all sites included chlorpromazine equivalents (CPZ) and duration of illness (DUI). Handedness was measured with the Neurological Soft Signs (NSS Schroder et al., 1991) and the Edinburgh Handedness Scale (Oldfield, 1971). Years of education were additionally assessed. Clinical and social characteristics of the sample are compiled in Table 1. Ethical approval for all studies was granted by the local ethics committees, i.e. the Ethics Committee of the University of Muenster and the Westphalian State Chamber of Physicians as well as the Committee on Medical Ethics of Kyoto University. All patients gave their informed consent. The study was conducted in accordance with the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/; last access to all referred HP: 2019-08-30).

2.3. Neuroimaging procedures

In Germany, the magnetic resonance images were acquired on a Philips 3 T scanner (Gyroscan Intera 3T, Philips Medical Systems, Best, The Netherlands) (repetition time (TR) = 7.5 ms, echo time (TE) = 3.4 ms, field of view (FOV) = 256 × 204 mm, in-plane-matrix = 256 × 204, 160 slices à 1 mm, reconstructed voxel size 0.5 mm isotrop). In Japan, all scans were performed on a Siemens 3 T scanner (Trio, Siemens, Erlangen, Germany) (TR = 2000 ms; TE = 4.38 ms; FOV = 225 × 240 mm, matrix = 240 × 256; resolution 0.9375 × 0.9375 × 1.0 mm^3, inversion time = 990 ms).

2.4. Statistical analyses

The Computational Anatomy Toolbox (CAT12 r1184) (http://dbm.neuro.uni-jena.de/cat/) for Statistical Parametrical Mapping (SPM) 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) was used for preprocessing all structural images using default parameters. Images were bias-corrected, tissue-classified, and normalized to Montreal Neurological Institute (MNI) space using linear (12-parameter affine) and nonlinear transformations within a unified model including high-dimensional Diffeomorphic Registration Algorithm (DARTEL, http://www.neurometrika.org/node/34 Ashburner, 2007) normalization. As mentioned above, homogeneity of GM images was checked using the covariance structure of each image with all other images, as implemented in the check data quality function. The modulated GM images were smoothed with a Gaussian kernel of 8 mm Full-Width Half-Maximum (FWHM).

Following the pre-processing, group statistics were then calculated using SPM12. As a first step, we calculated a General Linear Model (GLM) approach, using group (patients and healthy controls) and site (Germany and Japan) as between-subjects variables. Age and gender as well as intracranial volumes (ICV), which are known to have an impact on GM volumes (Taki et al., 2011), were used as regressors in all analyses. The threshold was peak-level Family Wise Error (FWE)-corrected ($p < 0.05$) for the effect of group. For the sake of brevity, due to strongly significant effects, we used an extent cluster threshold of $k = 100$. For the effect of group x site, the threshold was $p < 0.001$ uncorrected with an extent threshold cluster of 50 voxels. After that, we performed a correlative analysis using PANSS positive and negative scores, duration of illness and chlorpromazine equivalents as variables of interest, and included these factors as regressors. This was performed separately for the Japanese and the German patient samples. Results are presented with a threshold of $p < 0.001$, uncorrected, with an extent threshold cluster of 50 voxels.

Finally, to replicate findings of GM reductions, we performed a whole-brain analysis to identify brain areas with a general GM volume reduction in German patients with schizophrenia. With these results, an anatomical mask was generated. The mask encompassed all areas with a significant GM volume reduction identified in the German patients. Consecutively, a Region of interest (ROI) approach was applied (Dannlowski et al., 2014, 2015a,b), restricting the analyses to the respective brain areas identified. Note that voxels surviving $p < 0.001$ in both samples independently in fact survive a combined threshold of $p < 0.001^2 = 0.000001$.

Clinical results were processed with the Superior Performing Software System (SPSS 24, IBM, http://www.spss.com.hk/software/statistics/). For anatomical labeling, the Automatic Anatomical Labeling (aal) brain atlas was used (Neurofunctional Imaging Group, http://www.gin.cnrs.fr/en/tools/aal-aal2/).

3. Results

3.1. Socio-demographic and clinical data

Socio-demographic and clinical data that were available for both groups are presented in Table 1. They differed as follows: on average, patients from Japan were older with a longer duration of illness. Moreover, their negative symptoms were lower than those in the German sample. For both sites, level of education was significantly higher in the healthy control group. Gender, handedness, chlorpromazine equivalents and positive symptomatology were not significantly different across samples.

3.2. GM volume analyses

3.2.1. Effect of group

As described above, we used a GLM approach with group and site as between-subjects variables. Fig. 1 and Table 2 present the results of this analysis, indicating the main effect of group. Overall, we found reduced GM volumes in both patient groups with schizophrenia in frontal and temporal brain regions, cingulate cortex, insula, hippocampus and precuneus.

3.2.2. Effect of site

The next step was to investigate the interaction effect of group x site. The results are shown in Fig. 2 and Table 3. GM reductions in patients with schizophrenia related to site included the anterior cingulate cortex and the gyrus fusiformis. However, these effects survived only a less stringent threshold ($p < 0.001$, uncorrected, extent threshold cluster 50 voxels), but not a corrected level of significance.

3.2.3. Replication

As we wanted to replicate the GM volume reductions across both study sites, we used an ROI analysis approach to analyze which GM volume reductions were equally reduced and overlapping in both samples. The results can be found in Fig. 3 and Table 4. Areas of overlap included frontal brain regions, but also thalamus, hippocampus and anterior cingulate cortex.

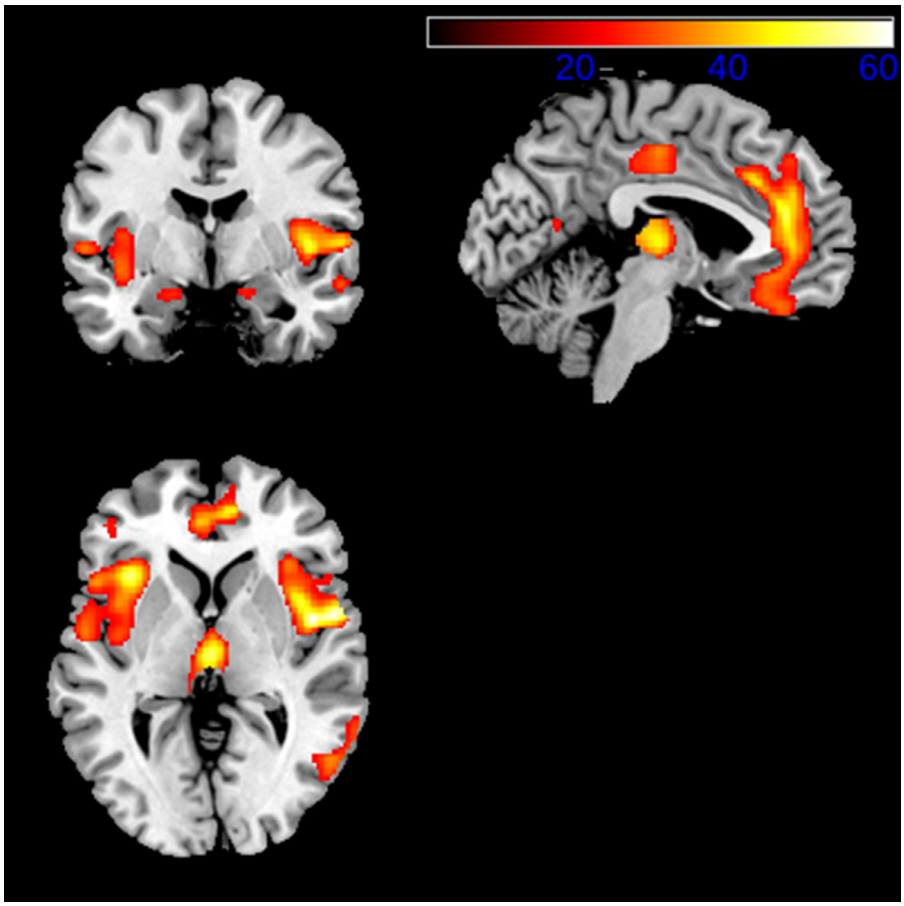

Fig. 1. Voxel-based morphometric results for group comparisons of individuals with schizophrenia and healthy controls using the combined sample. Main effect of group. Full factorial design (FWE, $p < 0.05$, extent threshold cluster 100 voxels, *F*-scores are presented); axial, coronal and sagittal slices depict decreased GM volume in patients with schizophrenia in comparison with healthy controls.

3.2.4. *Effects of clinical data*

As we assumed that the effects of site might be explained by differences in clinical characteristics or treatment approaches and by the socio-cultural background, we included DUI, PANSS scores and CPZ into the analyses of patients. All clinical variables and their differences in both sites are presented in Table 5. Effects differed between the Japanese and the German group. PANSS values had no impact on the patients in the German sample, while DUI and CPZ affected GM volumes in a positive and negative direction. In the Japanese sample, the strongest effects were seen regarding CPZ, with a negative correlation of medication and GM volumes.

4. Discussion

To investigate the impact of the socio-cultural background in schizophrenia on brain volumes, we analyzed GM volume reductions in a large sample of 163 patients with schizophrenia and 203 healthy controls from Germany and Japan. In this large sample, we were able to show consistent areas of GM volume reductions in patients from both investigation sites comprising fronto-temporal brain regions, the cingulate cortex, hippocampus and insula. These results replicate previous findings that showed consistent patterns of GM volume reductions in patients with schizophrenia (Glahn et al., 2008; Koelkebeck et al.,

Table 2
Voxel-based morphometric results for group comparisons of individuals with schizophrenia and healthy controls using the combined sample. Main effect of group. Full factorial design (FWE, $p < 0.05$, extent threshold cluster 100 voxels); decreased GM volume in patients with schizophrenia in comparison with healthy controls.

Region	Hemisphere	MNI at peak X	Y	Z	F (1359)	Z-score	Cluster size (k)
Insula	R	45	0	2	60.74	7.39	3807
Anterior cingulate cortex	L/R	2	28	32	57.34	7.19	7328
Thalamus	L	0	−15	4	54.25	7.01	1263
Insula	L	−34	20	3	52.99	6.93	2976
Superior temporal sulcus	R	58	−8	−12	40.44	6.08	418
Middle cingulate cortex	L	2	−24	44	39.10	5.98	1241
Middle temporal gyrus	R	56	−62	−2	38.06	5.90	1024
Middle orbitofrontal cortex	L	−27	34	−15	35.88	5.73	277
Middle frontal cortex	R	28	28	44	35.53	5.70	792
Hippocampus	R	15	−10	−16	34.45	5.61	636
Middle frontal cortex	L	−24	32	38	33.02	5.50	180
Hippocampus	L	−28	−30	−9	30.92	5.32	292
Inferior frontal gyrus, pars triangularis	L	−44	40	8	29.61	5.20	221
Precuneus	R	4	−60	18	29.34	5.18	179
Hippocampus, Amygdala	L	−16	−6	−18	28.85	5.14	184
Inferior orbitofrontal cortex	R	30	36	−16	25.67	4.84	118

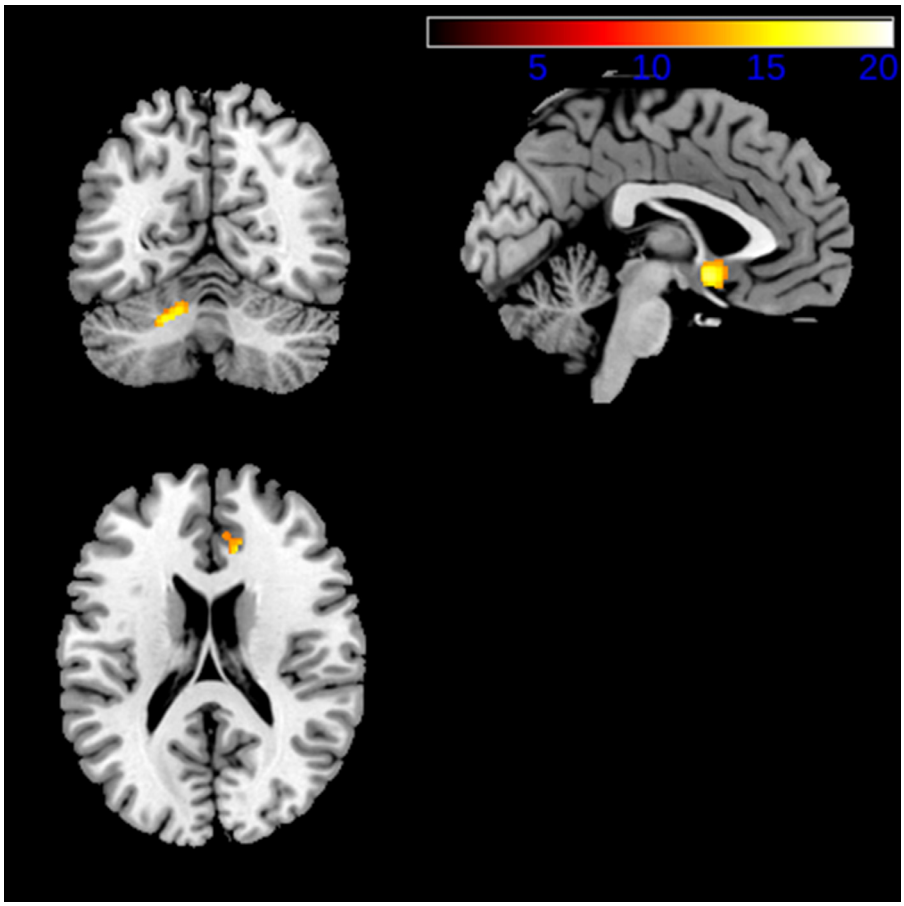

Fig. 2. Voxel-based morphometric results for group comparisons of individuals with schizophrenia and healthy controls using the combined sample. Effect of group x site. Full factorial design ($p < 0.001$, uncorrected, extent threshold cluster 50 voxels, F-scores are presented); axial, coronal and sagittal slices depict decreased GM volume in patients with schizophrenia in comparison with healthy controls.

2013).

Moreover, we investigated the influence of culture on GM reductions but found very few cortical regions which survived on a more lenient threshold, for example the cingulate cortex and the cerebellum. Both the caudate nucleus and the cingulate cortex have been implicated in bilingual word recognition (Hsieh et al., 2017), while the cerebellum was found to be activated in motion recognition in a Chinese sample (Han et al., 2011). Cerebellar volume reduction has been reported previously after the onset of schizophrenia (Borgwardt et al., 2008; Pantelis et al., 2003). Other research groups found increased volume in the cerebellum (Sheng et al., 2013). Apparently, some of the brain regions implicated here might be prone to socio-cultural influences.

As the volume of these brain regions might have been impacted by culture, but might also have been subject to differences in other factors across the investigation sites, we used illness duration, medication and psychopathology scores in the sample of patients as possible variables of influence. Here, we also found an overall weak effect of clinical variables, mainly a reducing effect on GM volumes by medication in the Japanese sample. Although the antipsychotic medication was not significantly different at the two sites, it might have impacted in this patient sample more strongly, as studies have found that specific polymorphisms might induce differential pharmacokinetic and -dynamic properties of antipsychotic medication in Asian individuals (Han and Pae, 2013). Antipsychotic medication seems to have an impact on GM volumes, some studies reported beneficial effects of treatment with antipsychotics on frontal brain areas (Goghari et al., 2013), but other studies also found a correlation between higher doses as well as long-term treatment and lower GM volumes (Ho et al., 2011). In a meta-analysis, unmedicated patients presented reductions in the thalamus and the caudate nucleus only (Haijma et al., 2013). It is also possible that other effects, which we did not or could not control for, play a role. In that regard, genetic architecture might be relevant in the group differences outlined here. GWAS and risk gene studies have indicated that with certain SNPs, risk alleles have different directions of effects in samples of different cultural backgrounds, as shown for example in Caucasian vs. Han Chinese (Zhang et al., 2018). Also, specific susceptibility genes have been identified for Japanese samples (Kanazawa et al., 2017). Moreover, as environmental factors have repeatedly been shown to affect brain structure in schizophrenia, factors associated with the disease, like cannabis use (Frissen et al., 2018; Hartberg et al., 2018; Quinn et al., 2018) and urban upbringing (Besteher et al., 2017; Haddad et al., 2015), might have had an impact

Table 3
Voxel-based morphometric results for group comparisons of individuals with schizophrenia and healthy controls using the combined sample. Effect of group x site. Full factorial design ($p < 0.001$, uncorrected, extent threshold cluster 50 voxels); decreased GM volume in patients with schizophrenia in comparison with healthy controls.

Region	Hemisphere	X	Y	Z	F (1359)	Z-score	Cluster size (k)
Caudate nucleus/ olfactory nerve	L	0	6	−10	20.23	4.28	274
Cerebellum	L	−15	−64	−28	19.25	4.17	276
Inferior temporal gyrus	R	36	0	−44	15.91	3.77	98
Cingulate gyrus	R	12	32	20	15.70	3.75	99

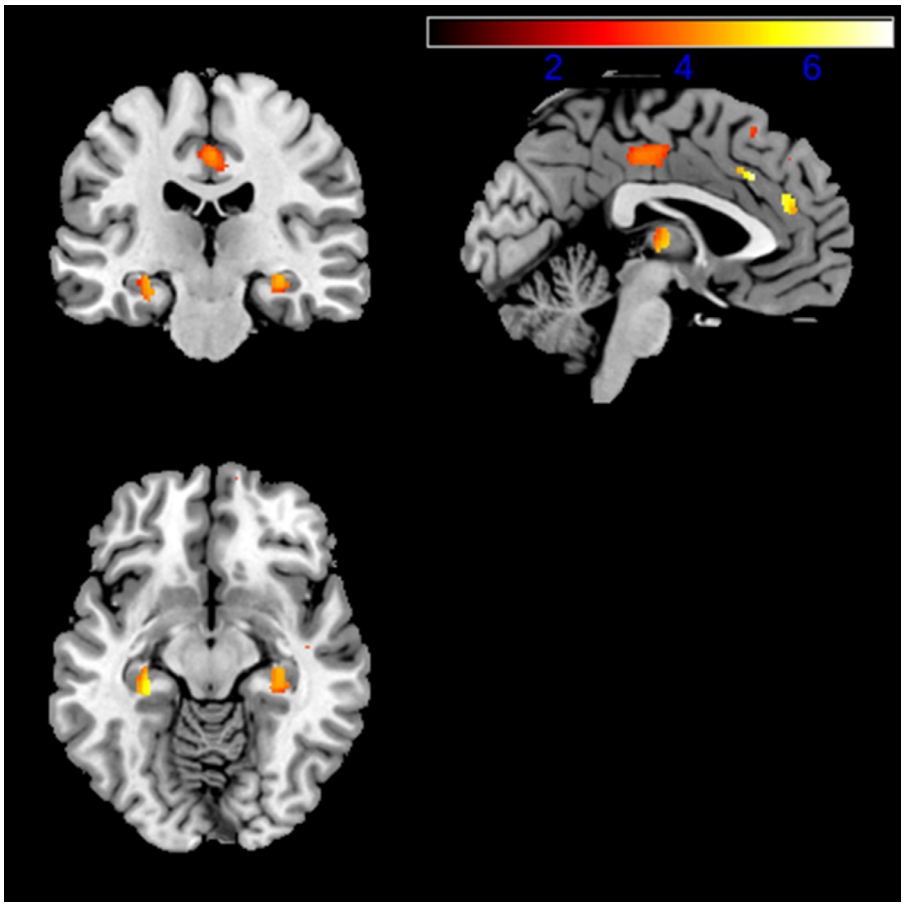

Fig. 3. Voxel-based morphometric results for group comparisons. ROI analysis indicating areas of overlap between the German and the Japanese patient samples, using the contrast healthy > patient group in the German sample as a mask ($p < 0.001$, uncorrected, extent threshold cluster 50 voxels, *T*-values are presented); axial, coronal and sagittal slices depict decreased GM volume in patients with schizophrenia in comparison with healthy controls.

on the results presented here. In East Asia, for example, the rate of cannabis use is lower than in European countries (Lee and Kwon, 2016). However, as the effects are visible only on a lenient threshold, conclusions have to be drawn with care and findings need to be replicated in larger samples assessing the respective variables of interest.

Our results, with only very small effects of culture on cortical GM volumes in schizophrenia, strengthen the findings of previous research that did not show differences in GM volume reductions in indivuals from different cultures (Gong et al., 2015). These results underline the notion that schizophrenia has a very strong biological background, and its effects of brain alterations are only marginally influenced by sociocultural circumstances such as country of residence or origin. However, while we did not find an interaction effect of group x site, there were fewer brain regions overlapping between the groups than both groups showed in a combined analysis. The results of the pooled sample might be due to stronger effect sizes. At the same time, it cannot be ruled out that site might have, by differing degrees, a brain-altering effect in those brain regions that did not show an overlap between the groups.

There are some limitations to this study. We are well aware of the difficulties arising from the use of two scanner sites in terms of different machines and protocols. As the research question and our consecutive analyses have been performed post-hoc, procedures could not be

Table 4
Voxel-based morphometric results for group comparisons. ROI analysis indicating areas of overlap between the German and the Japanese samples, using the contrast healthy > patient group in the German sample as a mask ($p < 0.001$, uncorrected, extent threshold cluster 50 voxels); GM volume in patients with schizophrenia in comparison with healthy controls.

Region	Hemisphere	MNI at peak X	Y	Z	T	Z-score	Cluster size (k)
R	Middle cingulate cortex	2	27	34	7.13	6.72	139
L	Hippocampus	−26	−32	−8	6.35	6.05	265
L	Anterior cingulate cortex	−2	39	22	6.06	5.80	52
R	Medial superior frontal cortex	12	48	−2	5.71	5.48	55
R	Rolandic operculum	45	2	2	5.67	5.46	436
R	Hippocampus	27	−32	−4	5.64	5.42	203
R	Medial orbitofrontal cortex	16	60	−4	5.37	5.18	104
L	Insula	−33	22	2	5.06	4.90	265
L	Thalamus	0	−10	8	4.90	4.75	176
L	Medial frontal superior cortex	8	48	14	4.72	4.58	79
R	Middle cingulate cortex	0	−24	45	4.26	4.16	489
R	Middle frontal cortex	27	51	16	4.05	3.96	138
R	Middle temporal cortex	52	−64	−3	4.03	3.95	260
L	Medial frontal superior cortex	0	24	60	3.99	3.81	82
R	Precuneus	4	−58	15	3.49	3.44	55

Table 5
Effects of clinical variables in patient groups. All effects including (+) the variable and with the variable removed (−) for the Japanese and the German patient groups. $p < 0.001$, uncorrected, extent threshold cluster of 50 voxels. Abbreviations: PANSS = Positive and Negative Syndrome Scale - pos = positive subscale; neg = negative subscale; CPZ = chlorpromazine equivalents; DUI = duration of illness.

Variable	Region	Hemisphere	MNI at peak X	Y	Z	T	Z-score	Cluster size (k)
Japanese patients with schizophrenia								
PANSS pos. +	–	–	–	–	–	–	–	–
PANSS pos. −	R	Superior temporal gyrus	62	−21	0	3.66	3.50	56
	L	Superior temporal gyrus	−40	−9	−10	3.59	3.43	51
	L	Inferior frontal operculum	−44	8	0	3.51	3.37	53
PANSS neg +	L	Superior temporal gyrus	−36	−14	−9	3.91	3.72	125
	L	Precuneus	−10	−52	12	3.84	3.65	84
	L	Superior temporal pole	−57	9	−21	3.75	3.58	92
PANSS neg −	L	Hippocampus	−21	−30	−8	4.19	3.96	80
	R	Parahippocampal gyrus	24	−42	−9	4.04	3.84	79
CPZ +	R	Cerebellum	10	−54	−22	4.78	4.45	2212
CPZ−	L	Anterior cingulate	−0	34	4	4.73	4.41	816
	R	Rolandic operculum	−45	−2	2	4.30	4.05	496
	L	Middle cingulate gyrus	2	−26	42	3.97	3.77	476
	L	Thalamus	−14	−26	12	3.91	3.72	297
	L	Middle frontal gyrus	−22	54	16	3.79	3.62	58
	L	Rolandic operculum	−46	−28	16	3.61	3.45	59
	L	Inferior temporal gyrus	−40	−46	−18	3.51	3.37	61
DUI +	R	Superior temporal pole	50	21	−20	4.02	3.81	321
	L	Cuneus	−18	−74	28	3.99	3.78	248
	R	Calcarine sulcus	22	−56	15	3.63	3.48	79
DUI −	–	–	–	–	–	–	–	–
German patients with schizophrenia								
PANSS pos. +	–	–	–	–	–	–	–	–
PANSS pos. −	–	–	–	–	–	–	–	–
PANSS neg +	–	–	–	–	–	–	–	–
PANSS neg −	–	–	–	–	–	–	–	–
CPZ +	L	Postcentral gyrus	−50	−10	30	4.32	4.06	833
	L	Inferior occipital cortex	−40	−63	−8	4.11	3.88	94
	L	Cerebellum	−33	−60	−52	3.68	3.51	95
CPZ−	L	Cerebellum	−33	−86	−22	4.04	3.82	65
	L	Inferior frontal gyrus triangularis	−51	21	10	4.00	3.79	102
DUI +	L	Superior Frontal medial cortex	−4	66	8	3.63	3.47	62
	L	Putamen	−24	12	4	3.59	3.44	54
DUI −	R	Postcentral cortex	24	−38	66	3.55	3.40	80

synchronized. A study by Stonnington et al. (2008) in Alzheimer's disease, however, was able to show that the effects of scanner site on the investigated morphological data were negligible compared to the impact of the disorder on the same data. Similar results were produced by a multi-site study with children and two different kinds of scanners (Pardoe et al., 2008). Moreover, even though Gong et al. (2015) scanned participants across four different scanner sites, their study still yielded uniform results in a single brain region. Finally, not all participants were right-handed and samples across the sites were not matched regarding handedness, which might pose a confounding factor.

We investigated GM volume reductions in schizophrenia on two sites with a large sample of patients with schizophrenia and healthy controls with different cultural and genetic backgrounds. We replicated earlier findings of GM reductions in patients with schizophrenia, which significantly overlapped in both sites. We moreover identified a small effect of culture (investigation site) and clinical variables such as chlorpromazine equivalents. We conclude that cultural effects on GM volume reductions in schizophrenia are small, emphasizing the biological basis of the disorder.

CRediT authorship contribution statement

Katja Koelkebeck: Conceptualization, Investigation, Methodology, Formal analysis, Data curation, Writing - original draft, Visualization, Writing - review & editing. **Udo Dannlowski:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Patricia Ohrmann:** Investigation, Writing - review & editing. **Thomas Suslow:** Investigation, Writing - review & editing. **Toshiya Murai:** Conceptualization, Investigation, Writing - review & editing. **Jochen Bauer:** Investigation, Writing - review & editing. **Anya Pedersen:** . **Noriko Matsukawa:** Conceptualization, Investigation, Writing - review & editing. **Shuraku Son:** Investigation, Writing - review & editing. **Theresa Haidl:** Investigation, Writing - review & editing. **Jun Miyata:** Conceptualization, Investigation, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

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