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A preliminary study of cortical morphology in schizophrenia patients with a history of violence

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ABSTRACT

Clinical studies of patients with schizophrenia and a history of violence are challenging both from an ethical and practical perspective, and the neurobiological underpinnings remain largely unknown. We here present a comprehensive account of the brain cortical characteristics associated with violence in schizophrenia. We obtained 3T MRI scans and thorough clinical characterization of schizophrenia patients with a history of violence (murder, attempted murder, criminal assault, SCZ-V, $n = 11$), schizophrenia patients with no history of violence (SCZ-NV, $n = 17$), and healthy controls (HC, $n = 19$). Cortical thickness, area, and folding were analyzed vertex-wise across the cortical mantle (FreeSurfer). SCZ-V had significantly increased cortical folding in the visual and orbitofrontal cortex, and reduced cortical thickness within the precentral-, parietal-, temporal-, and fusiform cortex compared to SCZ-NV, as well as widespread regional thinning and increased folding compared to HC. There were no group differences in cortical area. A major limitation is the small subject sample. If replicated, the results from this pilot study suggest cortical abnormalities in areas involved in sensory processing, emotion recognition, and reward to be of importance to the neurobiology of violence in schizophrenia.

1. Introduction

Epidemiological studies have shown an association between schizophrenia and violent or aggressive actions (Fazel et al., 2009; Fleischman et al., 2014). The risk is particularly elevated in young age and in the presence of substance abuse, childhood trauma, and previous acts of violence (Hodgins and Klein, 2017; Oakley et al., 2016). The increased risk for violent behavior in schizophrenia remains after controlling for known environmental risk factors (Fazel et al., 2009; Fleischman et al., 2014) which suggests that neurobiological factors are also of importance.

Magnetic resonance imaging (MRI) allows for the creation of accurate representations of the cortical surface. MRI-studies have shown abnormalities in the cerebral cortex in patients with schizophrenia, in particular cortical thinning in frontotemporal regions, cortical folding abnormalities and volume reductions (Haukvik et al., 2013; Nesvag et al., 2014; Rimol et al., 2012). Neuroimaging studies of aggression and violence in schizophrenia have shown hippocampal and amygdala volume reductions in violent offenders with schizophrenia (Barkataki et al., 2006; Yang et al., 2010), and an association between aggression, impulsivity and volumes of the orbitofrontal- and anterior cingulate cortex (Hoptman et al., 2014, 2005). A recent meta-analysis reported reduced whole brain gray matter related to aggression in schizophrenia (Widmayer et al., 2018). Cortical neuroimaging studies of aggression and violence in schizophrenia have shown reduced gray matter volume in the right parahippocampal gyrus in murderers with schizophrenia (Yang et al., 2010), greater gray matter volumes in the left cuneus/precuneus and the inferior parietal cortex in patients with both schizophrenia and conduct disorder (Schiffer et al., 2013), and lower gray matter volume in the inferior and middle temporal gyrus, fusiform

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gyrus and the right insula in a forensic schizophrenia sample (see Fjellvang et al., 2018 for review). The only previous study of cortical thickness in patients with schizophrenia and a history of violence found cortical thinning in sensory motor areas compared to schizophrenia patients without a history of violence (Narayan et al., 2007).

The cerebral cortex is a layer of primarily neuronal and glial cell bodies that cover the outer portion of the cerebrum. Cortical volume is a product of cortical thickness and area, which both are thought to be influenced by independent biological mechanisms (Rakic, 2009). The cerebral convolution of the cortex (the cortical gyrification) starts during the embryonic stage and continues through the early years of neurodevelopment and may be considered a marker of early neurodevelopment (Schaer et al., 2008). As such, the cortical folding, area, and thickness represent distinct neurobiological trajectories that could be differently associated with violent behavior.

The aim of this study was to give a complete MRI-based characterization of cortical morphology (i.e. folding, volume, thickness, and area) in schizophrenia patients with a history of violence (SCZ-V). We hypothesized that the SCZ-V group would show specific cortical morphology changes compared to patients with schizophrenia without any known history of violence (SCZ-NV), i.e. cortical thinning, cortical area reductions, and cortical folding abnormalities. This is to the best of our knowledge the first comprehensive study of the cortical morphology associated with violence in schizophrenia.

2. Methods

2.1. Subject sample

The subject sample consisted of patients with a DSM-IV diagnosis of schizophrenia (DSM-IV 295.3 (paranoid) or 295.9 (undifferentiated)) who previously had a history of severe violence (murder, attempted murder, or violent assault) ($n = 11$) from the high security forensic psychiatry unit at Østfold Hospital Norway (SCZ-V), and age and sex matched schizophrenia patients ($n = 17$) without a history of violence (SCZ-NV), and healthy controls (HC $n = 19$) from the on-going multi-centre Thematically Organized Psychosis (TOP) Study at the University of Oslo and collaborator hospitals in Oslo, Norway.

The patients in the SCZ-V group were recruited from the populations of two forensic security wards of a psychiatric hospital in Norway. The patients in the SCZ-NV group were included from four major psychiatric hospitals and their out-patient clinics that together cover most of the population in Oslo. The medical files and PANSS-scores at inclusion time have been examined to ensure no previous or current violence (i.e. murder, attempted murder, or criminal assault). The healthy control subjects were randomly selected from the national population register. Inclusion criteria were age between 18 and 65 years; no head trauma leading to loss of consciousness; and absence of previous or current somatic illness that might affect brain morphology.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and was conducted in accordance with the Helsinki declaration. After complete description of the study to the subjects, written informed consent was obtained from all participating subjects.

2.2. Clinical assessment

All patients underwent thorough clinical investigation by specially trained psychologists and physicians. Clinical diagnoses were assessed using the Structured Clinical Interview for DSM-IV axis 1 disorders (SCID-I) module A-E (Spitzer et al., 1992). Psychosocial function was assessed with the Global Assessment of Function (GAF) scale, split version. Affective state was assessed with the Young Mania Rating Scale (YMRS), and the Calgary Depression Scale for Schizophrenia (CDSS), and current psychotic symptoms were rated by the use of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). G.B.S and U.K.H performed the clinical inclusion of the schizophrenia patients with a history of violence at the forensic security ward to minimize the risk of violent episodes during study procedures. The nurses at the forensic psychiatry ward and occasionally the treating psychologists or psychiatrists were present during the patient inclusion. To reduce stress for participants in the SCZ-V group, DSM-IV diagnoses were obtained from their medical records and forensic reports. For all participants, current IQ was measured with the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007) by specially trained project psychologists. Years of education was estimated as the number of completed years of formal schooling.

Defined Daily Dosages of antipsychotic medication use was calculated using the guidelines from the WHO (https://www.whocc.no/atc_ddd_index/).

Healthy controls were screened for symptoms of severe mental illness through interviews by trained clinical psychologists and examined with the Primary Care Evaluation of Mental disorders (PRIME-MD). The TOP-study that the SCZ-NV and healthy control sample were drawn from has previously been described in detail elsewhere (Haukvik et al., 2015; Simonsen et al., 2011).

2.3. MRI acquisition and post-processing

Patients in the SCZ-V group were followed to the Oslo University Hospital to be scanned in the same MRI scanner as participants in the SCZ-NV and healthy control groups. Discreet but adequate security measures were taken, and there were no incidents of violent behaviour or attempted escapes during the study procedures. Inclusion in the study involved travel of approximately 200 km in cars, with the patients being out of their wards up to a total of 5 h.

T1-weighted 3D Fast Spoiled Gradient Echo (FSPGR) volumes were aquired with a 3T GE MRI scanner with the following scanning parameters: TR/TE/TI = 7.8 ms/min Full/450 ms, flip angle = 12°, FOV = 256×256 mm^2, slice thickness = 1.2 mm, acquisition matrix = 256×192, reconstruction matrix = 256×256. There was no major scanner upgrade during the study period, and patients and controls were scanned interchangeably to avoid the influence of scanner drift on results. A neuroradiologist evaluated all scans, and subjects with scans showing minor brain pathology were excluded from the study. Two patients in the SCZ-V group had to interrupt their scanning sessions due to claustrophobia within the scanner and were not included in the study (leaving a total of $n = 11$ persons in this group).

The FreeSurfer software (version 5.3.0) (http://surfer.nmr.mgh.harvard.edu/) was used for cortical reconstruction (Fischl, 2012). In this study, all subjects were processed on the same Ubuntu Linux version (3.2.0-29-generic) and with the same version of FreeSurfer (Linux-centos4_x86_64-stable-pub-v5.3.0). The processing procedures have been described in detail elsewhere (Haukvik et al., 2014, 2012). Briefly, this method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of the cortical surfaces. *Cortical thickness* is calculated as the least distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). *Cortical area* is the areal expansion or compression for each triangle in a common spherical atlas, when mapped nonlinearly to the individual subject space. Cortical folding, or *the local gyrification index* (lGI) is calculated by first creating an outer envelope that wraps the pial surface. Second, lGI is computed for each vertex on the pial surface as the ratio of the area of a circular region on the enveloping surface and the area of a corresponding region on the pial surface. The resulting cortical maps quantify the amount of cortex buried within the sulcal folds in the surrounding region (see Schaer et al., 2008 for details).

That is, for all the cortical analyses, we did not limit the cortical analyses to fit the predefined cortical parcellations embedded in the FS software. Moreover, the maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting sub-millimeter differences between groups (Fischl and Dale, 2000). The reliability of the automatic volume measurements has been validated against manual tracing, and the agreement between automatically obtained volumes and manual tracings was comparable to the agreement between manual tracings (Fischl et al., 2002). All scans were visually inspected, and if necessary, edited by trained research assistants following standard procedures (McCarthy et al., 2015).

2.4. Statistics

All statistical analyses were performed by the use of the statistical package SPSS version 24 (IBM, SPSS Inc., Armonk, New York, USA). Demographic and clinical variables were evaluated by analysis of variance (ANOVA), independent samples T-test, and Chi-Square analysis between diagnostic groups. All statistical tests were two-tailed.

Analyses of cortical area, thickness, and folding estimates were performed using FreeSurfer (McCarthy et al., 2015). For each whole-surface analysis, we used a general linear model with diagnostic group as the predictor variable and age and sex as covariates at each vertex across the entire cortex. The groups were contrasted pairwise (i.e. SCZ-V vs SCZ-NV, SCZ-V vs HC, and SCZ-NV vs HC) in the vertex-wise cortical analyses We used a smoothing kernel of 10 mm for the analyses of area and thickness. We did not smooth the surface maps in the lGI analysis. To adjust for multiple comparisons, parametric cluster-wise correction for multiple comparisons was performed with the Monte Carlo simulation tool in FreeSurfer. The initial cluster forming threshold was set to $p < 0.05$ and clusters with an empirical $p < 0.05$ were considered significant. The results of the statistical analyses are presented as statistical maps covering the entire cortical surface.

Follow-up analyses of the effects of clinical and demographic factors that were statistically differed between the groups were conducted with linear regression models for each of the significant clusters/contrasts with the cluster as the dependent variable, and diagnostic group, age and sex as covariates for each of the factors of interest separately.

3. Results

3.1. Clinical and demographic variables

The SCZ-V group had lower WASI-IQ scores and fewer years of education compared to SCZ-NV and healthy controls. While the two patient groups did not significantly differ in age at illness onset, the SCZ-V group had a significantly lower age at first admission. The healthy controls had lower drug use than either patient group. There were no significant group differences in the other clinical and demographic variables (Table 1). With regard to medication use there was no significant difference in daily defined dosages of antipsychotic medication use between the two patient groups. Hence medication use was left out of the statistical analysis of this pilot cohort. For completeness: the primary antipsychotic medication was: SCZ-V: Paliperidone ($n = 1$), Clozapine ($n = 3$), Aripiprazole ($n = 2$), Zuclopenthixol ($n = 3$), no antipsychotic medication ($n = 2$); SCZ-NV: Olanzapine ($n = 6$), Paliperidone ($n = 2$), Quetiapine ($n = 4$), Amisulpride ($n = 1$), Zuclopenthixol ($n = 1$), perphenazine ($n = 1$), Risperidone ($n = 1$), no antipsychotic medication ($n = 1$). Secondary antipsychotic use was: SCZ-V Paliperidone ($n = 1$), and for SCZ-NV: Paliperidone ($n = 1$), Quetiapine ($n = 1$), Aripiprazole ($n = 1$), Risperidone ($n = 1$), Clozapine ($n = 1$). In addition, antidepressants were used by two SCZ-V (Venlafaxine + Mirtazapine $n = 1$, Trimipramine $n = 1$) and four SCZ-NV (Venlafaxine $n = 2$, Escotalopram $n = 1$, Mianserin $n = 1$) patients, and anxiolytics by two patients in the SCZ-NV group (Buspirone $n = 1$, Oxazepam $n = 1$). Of the patients in the SCZ-NV group three used Lithium and two used other mood stabilizers (Lamotrigine $n = 1$, Valproate $n = 1$).

3.2. Cortical thickness, area, and gyrification

Compared to SCZ-NV, SCZ-V showed increased cortical folding in the visual (lateral occipital) cortex bilaterally and left lateral orbitofrontal cortex (Fig. 1 and Table 2). Compared to healthy controls, SCZ-V showed increased folding patterns in the lateral orbitofrontal-, inferior temporal-, inferior parietal-, supramarginal-, postcentral-, lingual-, and pericalcarine cortex (Fig. 1 and Table 2). SCZ-NV showed increased folding in the right fusiform cortex compared to HC, but decreased folding in the left rostral middle frontal cortex (Table 2)".

SCZ-V had reduced cortical thickness in the left precentral-, inferior parietal-, superior temporal- and the right fusiform cortex compared to SCZ-NV, and reduced thickness in the left fusiform- and right inferior parietal-, superior frontal-, and lingual cortex compared to healthy controls (Fig. 2 and Table 2). There were no significant differences in cortical thickness between SCZ-NV and healthy controls.

All the reported results were significant after Monte Carlo adjustment for multiple comparisons. There were no significant group differences in cortical area.

The follow-up analyses of clinical and demographic factors with significant group differences (i.e. age at illness onset, years of education, WASI, and DUDIT) showed no significant effects of age at onset. For IQ (as measured by WASI), there were no significant effects except for the left inferiorparietal lGI in SCZ-V vs HC, which also affected the case-control differences among the subjects with available WASI-scores (n smaller than original sample). Years of education affected the lGI in the left lateral occipital cortex in the SCZ-V vs SCZ-NV contrast and thickness in the left fusiform in the SCZ-V vs SCZ-NV contrast, but the group difference remained significant. DUDIT affected the lGI in the left lingual and supramarginal cortex in the SCZ-V vs HC contrast, and thickness in the right precentral cortex in the SCZ-V vs SCZ-NV contrast but the group differences in the precentral cortex and supramarginal cortex were not affected.

The reported results from the follow-up analyses were not adjusted for multiple comparisons (20 clusters x 4 variables). None of the variables had significant effects after multiple comparison control.

4. Discussion

The main findings in this pilot study were regional reduced cortical thickness and increased cortical folding in patients with a history of violence (SCZ-V), compared to patients without a history of violence (SCZ-NV) and healthy controls (HC). Bearing in mind the small subject sample, this is the first study to explore both cortical thickness, cortical folding and cortical surface area in schizophrenia patients with a history of violence, and the first study to report cortical folding abnormalities in this group.

We found increased cortical folding in the visual and orbitofrontal cortex in SCZ-V compared to SCZ-NV. The orbitofrontal cortex (OFC) has previously been linked to aggression and impulsivity in schizophrenia (Hoptman et al., 2014, 2005; Kumari et al., 2009) and is involved in the recognition of face and voice expressions, control and correction of reward- and punishment-related behavior and emotions (Rolls, 2004; Yankouskaya et al., 2017). Moreover, the OFC is connected to the entorhinal cortex (which projects sensory information to the hippocampus) as well as the cingulate cortex (Rolls, 2004), areas that also have been linked to violence and aggression in schizophrenia (Kumari et al., 2009, 2014; Yang et al., 2010). The visual cortex is of specific interest since schizophrenia patients have shown impaired visual processing also related to difficulties with recognizing faces and facial expressions (Chen and Ekstrom, 2015; Norton et al., 2009).

The cortical folding patterns are thought to reflect cortico-cortical connectivity, from van Essen's mechanical hypothesis of cortical folding which states that tension-based forces bring connected cortical regions closer together and by this form the sulcal and gyral patterns (Van Essen, 1997). As such, the increased cortical folding is

Table 1
Demographic and clinical characteristics.

	Schizophrenia $n = 17$		Violent Schizophrenia $n = 11$		Control subjects $n = 19$		Statistics p-value
	Number	*%*	*Number*	*%*	*Number*	*%*	*Chi-square*
Sex (m/f)	16/1	94/6	10/1	91/9	17/2	90/10	NS
	Mean (SD)	***Range***	***Mean (SD)***	***Range***	***Mean (SD)***	***Range***	***ANOVA***
Age (years)	34.3 (7.4)	24–47	33.2 (9.0)	19–49	33.2 (9.1)	19–46	NS
Years of education	12.4 (2.6)	8–19	10.4 (1.9)	9–15	13.7 (1.6)	12–17	**.001**
WASI IQ *(n = 15/8/13)*	101.2 (14.8)	76–123	94.4 (15.6)	76–118	111.9 (10.5)	100–138	**.018**
AUDIT (*n* = 16/8/18)	9.4 (7.8)	1–27	4.6 (8.2)	0–22	6.2 (3.9)	1–14	NS
DUDIT (*n* = 15/8/18)	9 (9.7)	0–26	8.5 (12.1)	0–29	0.6 (2.4)	0–10	**.009**
	Number	***%***	***Number***	***%***	***Number***	***%***	***Chi-square***
Cannabis, last 2 weeks (no/yes)	16/1	94/6	10/1	91/9			NS
Cannabis, last 2 years (no/yes)	8/9	47/53	3/6	33/67			NS
	Mean (SD)	***Range***	***Mean (SD)***	***Range***	***Mean (SD)***	***Range***	***ANOVA***
Alcohol last 2 weeks (units)	25 (91)	0–380	2 (5)	0–18			NS
Alcohol last 2 years (units)	1135 (2599)	0–10,944	538 (902)	0–2496			NS
CDSS	3.1 (3.4)	0–10	3.2 (3.1)	0–7			NS
GAF symptom	42.2 (10.3)	28–62	38.1 (9.7)	28–50			NS
GAF function	41.8 (9.3)	28–65	40 (11.1)	28–55			NS
PANSS positive	16.3 (6.1)	8–27	18.3 (8.3)	7–28			NS
PANSS negative	14.8 (5.1)	7–22	19.4 (7.2)	8–27			NS
PANSS general	28.9 (5.3)	20–40	35.0 (11.7)	18–49			NS
Age at psychosis onset	21.9 (6.1)	12–39	18.1 (5.5)	10–29			NS
Age at first psychosis admission	27.2 (7.6)	18–43	19.6 (6.1)	10–29			**.020**
Medication (DDD) (n = scz/vscz)							
Antipsychotics *n* = 17/11	1.6 (1.1)	0.0–4.0	1.2 (0.7)	0.0–2.0			NS

Abbreviations: m/f, male/ female; SD, standard deviation; YMRS, Young Mania Rating Scale; CDSS, Calgary Depression Scale; GAF, Global Assessment of Function split version; PANSS, Positive And Negative Syndrome Scale; DDD, Defined Daily Dosage; ns, not significant; na ,not applicable; scz; schizophrenia; vscz, violent schizophrenia; AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test; WASI, Wechsler Abbreviated Scale of Intelligence.

hypothesized to reflect cortical dysconnectivity (Matsuda and Ohi, 2018). Previous studies have reported both increased (Zuliani et al., 2018) and decreased (Nesvag et al., 2014; Palaniyappan and Liddle, 2012) cortical folding in schizophrenia. In line with our results, Schultz et al. reported increased cortical folding in the visual cortex of schizophrenia patients compared to healthy controls by the use of the same Freesurfer lGI vertex-wise method (Schultz et al., 2013). Occipital hypergyria has also been reported in persons at risk of psychosis (Sasabayashi et al., 2017). Moreover, in a large study of over 700 incarcerated males, Miskovich et al. found an association between increased cortical folding in the visual areas of the occipital lobe and higher scores on the factor 1 (the interpersonal in contrast to the impulsive factor 2) of the psychopath checklist (PCL) (Miskovich et al., 2018). Since the cortical folding patterns reflect early neurodevelopment (Cachia et al., 2016), our results could suggest that abnormal neurodevelopment is of importance to the neurobiology of violence in schizophrenia. The possible association between impaired visual processing and aggression and violence among schizophrenia patients should be investigated in future studies.

We found thinner cortices in SCZ-V compared to SCZ-NV in several regions, including precentral-, inferior parietal-, superior temporal-, and the fusiform cortex. One previous study has examined the cortical thickness in SCZ-V compared to SCZ-NV in a subject cohort of the same size as ours (Narayan et al., 2007). They found thinner cortices in sensory-motor areas, which does not overlap with our findings, despite the fact that both studies performed a whole brain surface analysis in FreeSurfer. While Narayan et al. (Narayan et al., 2007) used an uncorrected two-tailed alpha level of $p < 0.05$ to determine the threshold for statistical significance, we used cluster-wise Monte Carlo correction for multiple comparison control, which could explain why we did not find thickness differences between SCZ-V and SCZ-NV in the sensory-motor areas. However, the different significance thresholds cannot explain why Narayan et al. did not find significant differences between SCZ-V and SCZ-NV in the same regions as we did (the fusiform, inferior parietal, superior temporal, and precentral cortex). Another, possibility for this discrepancy is the use a 3T scanner with better resolution in our study, or that the limited sample sizes with potential for false positives (Eklund et al., 2016; Greve and Fischl, 2018) and subject cohort bias, could account for the different findings.

On the other hand, a recent MRI-study (Kuroki et al., 2017) of gray matter volumes in a sample of schizophrenia patients with a history of severe violence from a forensic ward, similar to the subject sample in the present study, found reduced volume in several brain regions. Notably, one of the regions was the fusiform gyrus, where we also found reduced thickness in SCZ-V. The fusiform gyrus is thought to serve an important role in the ventral stream of visual processing (Kuroki et al., 2017). SCZ-V also had reduced cortical thickness in other areas that are suggested to play a role in the ability to interpret facial expressions, i.e. emotion recognition, like the left inferior parietal cortex and the left superior temporal cortex (Radua et al., 2010). Both SCZ groups showed cortical thinning in regions where previous studies of non-overlapping subject samples from our group (Haukvik et al., 2014; Nesvag et al., 2008; Rimol et al., 2010, 2012) and others, including a large-scale multi-site ENIGMA study (van Erp et al., 2018) have reported differences between SCZ and HC. Taken together, the results from both analyzes of cortical folding and cortical thinning point towards changes in the visual cortex and the ability of facial expression recognition to be of importance to schizophrenia patients with a history of violence, and thus putatively to violence.

Because of the limited sample size, we could not divide the SCZ-V group according to premeditated or impulsive/reactive violence category which may have different neurobiological underpinnings (Anderson and Kiehl, 2014). Previously, Kuroki et al. have studied premeditated and impulsive violence in schizophrenia and reported more widespread cortical volume reductions among the group with premeditated violence, while the group with affective violence had only reduced volume of the right inferior temporal lobe (Kuroki et al., 2017). Moreover, two studies of violent offenders with psychopathic traits, but without schizophrenia, showed that relative to non-psychopaths, psychopaths had significantly thinner cortex in a number of regions, including the left insula and dorsal anterior cingulate cortex, the left and right precentral gyri, the left and right anterior temporal cortices, and the right inferior frontal gyrus (Howner et al., 2012; Ly et al., 2012), which is somewhat overlapping with our findings of cortical thinning in

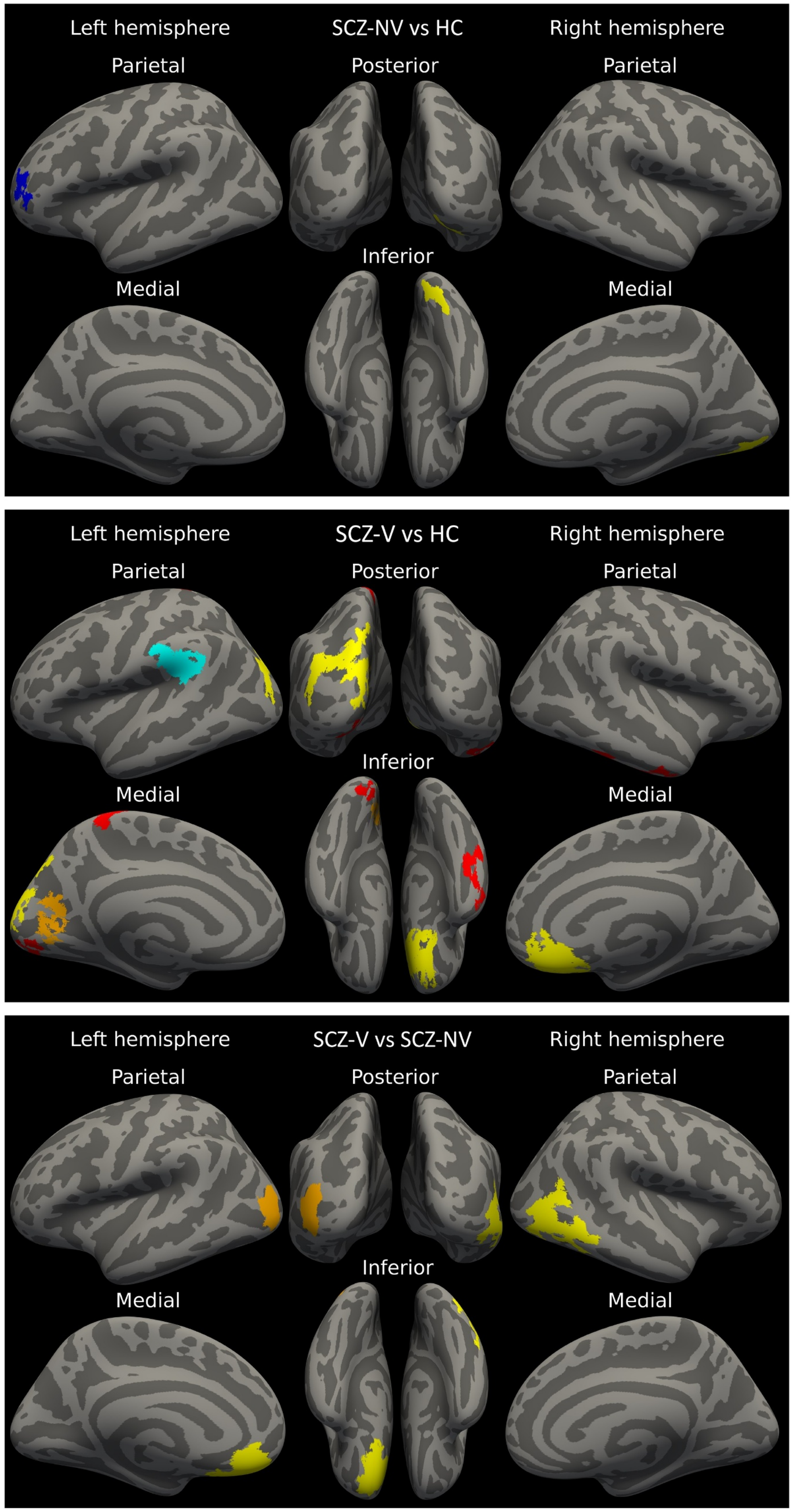

Fig. 1. Regional cortical folding differences. The colored areas represent significantly increased cortical folding in schizophrenia patients with a history of violence after Monte Carlo Simulation adjustment for multiple comparisons.
Upper panel: dark blue – left rostral middle frontal cortex; yellow – right fusiform cortex
Middle panel: orange – left lingual cortex; left yellow – inferioparietal cortex; left red -postcentral cortex and pericalcanerine cortex; turquoise – left supramarginal cortex; right yellow – lateral orbitofrontal cortex; right red – inferiortemporal cortex.

Table 2
Description of clusters with significant group differences in local gyrification index or cortical thickness in the left and right hemispheres.

Sample	Hemisphere	Cluster	Location of peak vertex (MNI)	Area (mm^2)	Clusterwise *P*-value
Gyrification					
SCZ-V vs SCZ-NV	Left	Lateraloccipital	−37.0, −80.8,4.3	1050.96	0.0002
		Lateralorbitofrontal	−14.9,47.0, −16.6	1465.64	0.0001
SCZ-V vs HC	Left	Inferiorparietal	−36.5, −84.1, 22.5	2245.07	0.0001
		Supramarginal	−48.6, −44.5,25.4	1033.16	0.0001
		Postcentral	−16.9, −39.4,72.0	524.45	0.0187
		Lingual	−4.8, −89.6, −8.6	541.78	0.0146
		Pericalcarine	−15.1, −80.6,8.9	872.23	0.0004
SCZ-NV vs HC	Left	Rostralmiddlefrontal	−38.0,40.6, 1.9	556.16	0.0129
SCZ-V vs SCZ-NV	Right	Lateraloccipital	44.9, −72.3, 4.0	1788.20	0.0001
SCZ-V vs HC	Right	Lateralorbitofrontal	19.5, 29.0 , −20.4	1781.24	0.0001
		Inferiortemporal	53.8, −17.2 , −35.1	731.34	0.0018
SCZ-NV vs HC	Right	Fusiform	29.1, −74.2 , −8.6 5	698.08	0.0025
Thickness					
SCZ-V vs SCZ-NV	Left	Fusiform	−43.2, −28.0, −21.1	1154.04	0.0020
SCZ-V vs HC	Left	Inferiorparietal	−36.6, −63.9, 41.1	1364.34	0.0004
		Superiorfrontal	−11.6,26.5,31.6	836.45	0.0221
		Lingual	−23.5, −59.4, −8.9	922.29	0.0110
SCZ-V vs SCZ-NV	Right	Precentral	40.1, 1.0, 15.9	1137.30	0.0030
		Inferiorparietal	44.9, −56.5,23.9	1068.64	0.0046
		Superiortemporal	44.6, −26.7, −5.7	762.88	0.0463
SCZ-V vs HC	Right	Fusiform	36.9, −41.2, −21.5	1098.92	0.0034

Abbreviations: MNI: coordinate system, SCZ-V: schizophrenia patients with history of violence, SCZ-NV: schizophrenia patients without history of violence, HC: healthy controls.

SCZ-V compared to either SCZ-NV or HC. Since subgroups of violent offenders may display different patterns of brain abnormalities, future studies should further address the cortical morphology of premeditated vs reactive violence in schizophrenia.

Many factors might confound neuroimaging studies, notably medication in psychiatric samples (Ho et al., 2003). Previous studies have shown that antipsychotic medication may affect brain volumes and morphology (Huhtaniska et al., 2017), although some studies find no effect (Roiz-Santianez et al., 2014). In our sample, the Defined Daily Dosages of antipsychotic medication use were not significantly different between the two patient groups (SCZ-V vs. SCZ-NV). Indeed, SCZ-V used on average lower doses than SCZ-NV, and it is therefore unlikely that the differences in cortical folding and thickness are caused by medication effects alone. Duration of antipsychotic medical treatment may also be a confounder in some brain structures (Ebdrup et al., 2013). Although the SCZ-NV group was slightly older than the SCZ-V group at age of first medical antipsychotic treatment, the difference was not statistically significant. However, considering that the age range of onset of psychotic symptoms were 10–30 for SCZ-V and 12–39 for SCZ-NV, and the age range of first medical treatment were 15–29 for SCZ-V and 18–39 for SCZ-NV, some individuals in both groups might have been un-medicated for 5–6 years. Untreated psychosis might have detrimental effect on the brain, both in terms of anatomy and cognition and functional outcome. (Lappin et al., 2006; Lieberman et al., 1993; Wang et al., 2016).

Despite the interesting results and rigorous statistical analyses, this study has notable limitations. As we have discussed in a recent paper, MRI studies of violence and aggression in schizophrenia face challenges regarding small subject samples and the risk for false positives (Eklund et al., 2016; Fjellvang et al., 2018; Greve and Fischl, 2018). A major limitation of the current study is the small sample size which reflects the difficulties with conducting research in this patient group, such as severe psychopathology, safety issues and the ability to consent. Hence, the included SCZ-V group represent a somewhat selective sample. Moreover, because of the small subject size we could not study how the different subtypes (premeditated, impulsive) of violence were associated with cortical morphology. The IQ variable was not available for all subjects and was not included in the main analysis, which is a limitation despite the fact that follow-up analyses showed no effect of IQ on the clusters with significant differences between groups. The collinearity between DUDIT-values and HC-status limits the interpretation of possible substance abuse effects on the HC versus SCZ-V or SCZ-NV contrasts, but DUDIT scores did not affect morphology differences between SCZ-V and SCZ-NV. Methodologically, the risk of false positives is reported to be inflated with the use of the parametric cluster-wise correction in Freesurfer (Greve and Fischl, 2018). As such, our positive results need replication. Another important factor, the time window between the violent act and MRI scanning varies and is not accounted for in the statistical analyses. Hence, the reported cortical patterns probably represent trait rather than state characteristics of violence in schizophrenia. The neurobiological underpinnings of the two may differ.

Bearing these notable limitations in mind, this study also has some major strengths. Clinical characterization was thorough and performed with validated structured interview instruments (e.g. PANSS, SCID-1). All the MRI-images were obtained on the same 3T MRI-scanner with no major upgrades during the duration of the study. We used validated state of the art imaging analysis software and performed rigorous statistical multiple comparison control. With a whole-brain analysis of 300 000 vertices across the cerebral cortex we did not restrict our study to a priori regions of interest, as the latter may be biased toward findings in brain regions that have previously been associated with violence in schizophrenia.

We report a pattern of altered cortical folding and cortical thinning in patients with schizophrenia and a history of violence in regions of importance to visual processing and recognition of faces and facial expressions compared to patients with schizophrenia and no history of violence. Given the limitations above, the results must be interpreted with caution. Small subject samples will continue to be an inherit limitation when conducting imaging-research in schizophrenia patients with a history of violence given the challenges with consent, safety, and severe psychopathology. To overcome this challenge, data from different cohort could be merged for meta- and mega-analyses, and replications are called for. In this context, we here present our results. Future studies should seek to replicate and investigate the functional implications of the observed abnormalities, and their association with premeditated, reactive and psychotic violence patterns.

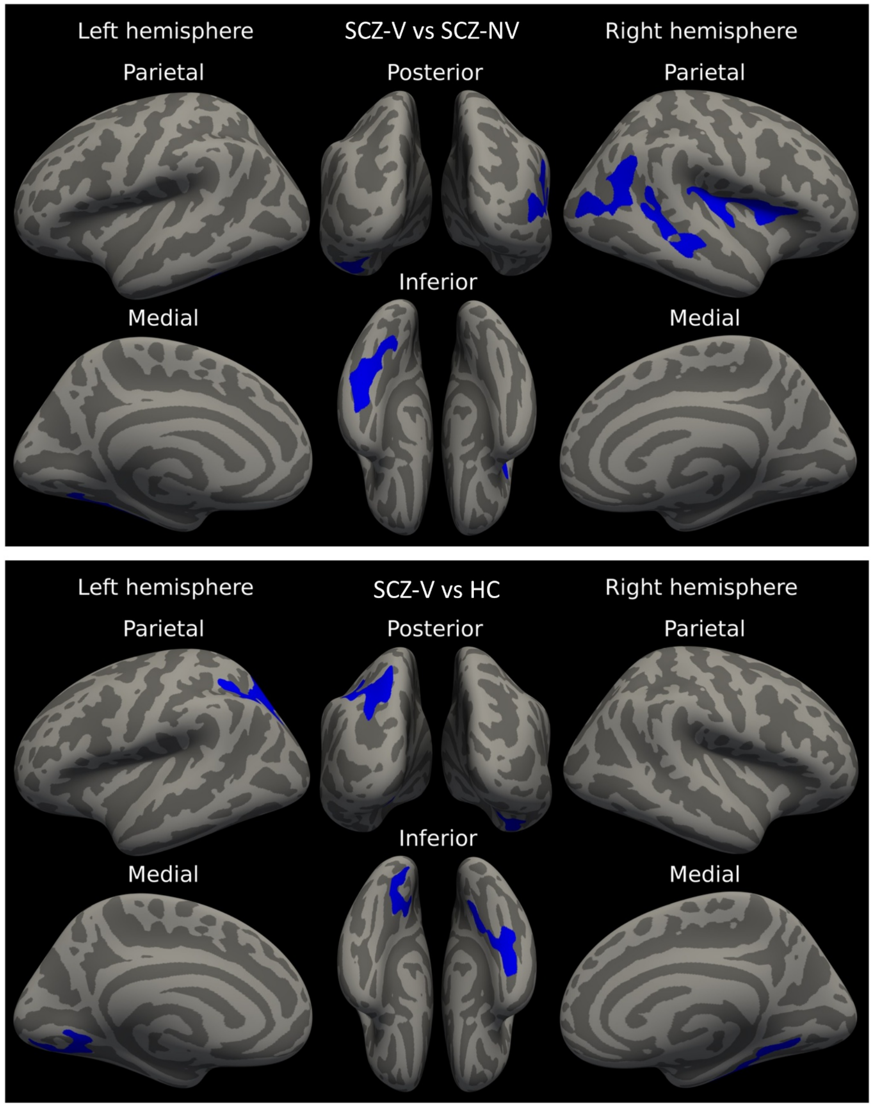

Fig. 2. Regional cortical thickness differences. The blue areas represent significant cortical thinning in schizophrenia patients with a history of violence after Monte Carlo Simulation adjustment for multiple comparisons.

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