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Inferior frontal gyrus gray matter volume is associated with aggressive behavior in schizophrenia spectrum disorders

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ABSTRACT

We aimed to assess potential gray matter (GM) alterations for aggressive patterns of behavior in a sample of in- and outpatients with schizophrenia spectrum disorders. Eighty-four patients previously participating in brain volumetric studies were included. Aggression was assessed using the Modified Overt Aggression Scales (MOAS) based upon review of clinical records of the hospital register. Multiple regression analyses for total MOAS and each MOAS subscale separately were conducted correcting for age, sex, history of addiction, chlorpromazine equivalents, illness duration, and total intracranial volume. Significant effects were reported in two cases; the total MOAS scores and MOAS verbal aggression scores were associated with GM volume in left inferior frontal gyrus. From the demographic/clinical characteristics, only the number of episodes correlated with the subscales and the total MOAS scores. Our results highlight the role of GM volume in left inferior frontal gyri in patients with history of aggression. This evidence ties in well with previous data reporting involvement of these regions in response control and semantic networks.

1. Introduction

Enhanced prevalence of aggressive behavior has been reported for patients with schizophrenia spectrum disorders (Fazel et al., 2009a; Swanson et al., 2006). Yet, the nature of aggression in schizophrenia is unknown. Researchers have captured different aspects of aggression with heterogeneous methodological instruments in different patient samples (Candini et al., 2017; Huber et al., 2014; Sanghani et al., 2017). However, aggression in psychosis may occur for various reasons, such as premorbid personality or psychotic symptoms (Volavka and Citrome, 2008). Moreover, such patterns of behavior may frequently precede the onset of psychotic disorders as well (Hodgins, 2017). Consequently, the relationship between psychotic symptoms and violence remains poorly understood. Evidence suggests that it is a particular subgroup of psychotic symptoms that may be linked to risk of violence (Foley et al., 2007; Berman et al., 2010; Haddock et al., 2013; Coid et al., 2016). Of particular interest may be persecutory delusions (Freeman et al., 2007; Schoretsanitis et al., 2016); such psychopathology patterns may correlate with enhanced levels of agitation (Link et al., 1998). It has been assumed that these symptoms may account for violent behaviors in individuals with schizophrenia (Link et al., 1998); nevertheless, evidence supporting this hypothesis has been conflicting hitherto (Appelbaum et al., 2000; Foley et al., 2007; Haddock et al., 2013; Hodgins et al., 2009; Krakowski and Czobor, 2004).

Regardless of the underlying mechanism, different potentially mediating factors for aggressive behavior have been also investigated. A Swedish nationwide register study reported exposure to violence as the most important risk factor for violent criminality in patients with psychotic disorders (Sariaslan et al., 2016), an association also demonstrated in a cohort of male in- and outpatients (Oakley et al., 2016). Moreover, aggressive behavior has been consistently associated with comorbid substance abuse or dependence (Fazel et al., 2009b; Large and Nielssen, 2011; Walsh et al., 2002; Witt et al., 2013). The

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prevalence of aggression also seems to be higher in schizophrenia patients receiving no mental health services or psychopharmacological treatment (Fazel et al., 2014; Munkner et al., 2003; Witt et al., 2013). Another predictor of aggressive behavior in schizophrenia disorders includes personality traits such as impulsivity or comorbid personality disorders (Crocker et al., 2005; Krakowski and Czobor, 2004). Further risk factors comprise male sex, younger age and lower socioeconomic status (Large and Nielssen, 2011; Pinna et al., 2016). The aforementioned parameters seem to essentially capture the clinical and demographic correlates of aggression in schizophrenia.

Brain imaging techniques could potentially identify the neural correlates of aggressive behavior in schizophrenia. A series of recent comprehensive reviews emphasizes on the limbic system and frontal lobe for aggressive behavior in schizophrenia, but also highlights shortcomings and future challenges (Fjellvang et al., 2018; Leclerc et al., 2018; Widmayer et al., 2018). Apart from frontal regions, Leclerc and associates included the striatum in their neuroanatomical model of aggression in schizophrenia considering the role of striatum in arousal control (Leclerc et al., 2018). However, attempts to detect structural brain correlates of aggression in schizophrenia are essentially perplexed with neuroanatomical abnormalities accompanying the natural course of the disorder (Gur et al., 1998). Additionally, brain volumes might be influenced by short- and long-term treatment with antipsychotics (Glenthoj et al., 2007; Ho et al., 2011). Apart from the inherent challenges, the literature on structural alterations related to aggressive behavior in schizophrenia remains limited and methodologically heterogeneous. Moreover, applied neuroimaging techniques were frequently restricted to specific regions of interest. For example, an early study detected reduced amygdala volumes in offenders with schizophrenia when compared with healthy individuals (Wong et al., 1997). This finding could not be replicated in a small sample of men with schizophrenia and violent history, where researchers observed reduction of hippocampus as well as whole brain volumes when compared to non-violent individuals with schizophrenia (Barkataki et al., 2006). A subsequent investigation of the same sample yielded interesting findings; parallel to the previously reported association of violence with reduced hippocampus volume researchers also observed an orbitofrontal cortex gray matter reduction for patients with schizophrenia and history of violence (Kumari et al., 2009). Likewise, a study following a similar design observed a gray matter volume reduction in cerebellum bilaterally and Broadmann areas 39 and 40 in schizophrenia patients with history of serious offending such as murder compared to patients without (Puri et al., 2008). Likewise, gray matter volume reduction in the hippocampus and parahippocampal gyrus was demonstrated in murderers with schizophrenia, but alterations in parahippocampal areas were also detected in murderers without schizophrenia (Yang et al., 2010). Applying diffusion tensor imaging techniques Hoptman and associates concluded that history of aggression in schizophrenia may be related to inferior frontal white matter microstructure alterations (Hoptman et al., 2002). Further, they reported a positive correlation between gray matter volumes in left orbitofrontal cortex and scores for an aggression scales covering the time period of a double-blind antipsychotic treatment trial (Hoptman et al., 2005). The same research group demonstrated that larger caudate volumes were linked to more severe incidents of aggression in the past in patients with schizophrenia spectrum disorders (Hoptman et al., 2006).

Although results tended to implicate limbic system and frontal regions, the samples remained small and failed to identify consistent brain alterations in patients with schizophrenia and aggressive behavior. Given the major clinical importance of aggressive behavior in psychotic disorders, the aim of this work was to seek for the structural brain correlates of aggression in patients with psychotic disorders. Therefore, we investigated the relationship between whole brain gray matter volume as derived from voxel-based morphometry and history of aggressive behavior in a group of in- and outpatients with schizophrenia spectrum disorders. In light of the previous evidence we hypothesized alterations in the limbic system and frontal regions to be associated with aggressive behavioral patterns in the past as assessed with an aggression-specific rating scale applied to the clinical records of the patients.

2. Materials and methods

2.1. Study design

Sample selection was conducted based on a two-phase process. First, we included all patients who previously participated in two structural neuroimaging studies at the University Hospital of Bern (Stegmayer et al., 2014a; Viher et al., 2018). All studies had been approved by the ethics committee of Canton of Bern and were in alignment with the Declaration of Helsinki. Written informed consent was provided by all participants, who did not receive financial compensation. Subsequently, clinical records from the register of the University Hospital of Psychiatry, Bern were identified. The University Hospital of Psychiatry in Bern is the largest mental health provider in the region and the majority of the included patients have been continuously treated in this clinic. In one case records were missing and patient's data were discarded. One patient had participated in two studies and, thus, we kept the most recent report. In the second phase, clinical records consisting of psychiatric history, charts, patient monitoring forms, medical and nursing notes as well as reports of mandatory measures from previous and current (for inpatients) hospitalizations were reviewed. For outpatients, available information for previous inpatient treatments were also considered. The Modified Overt Aggression Scale (MOAS) (Kay et al., 1988) was applied retrospectively by one rater (GS) to assess aggressive behavior. MOAS contains four subscales evaluating different types of aggression such as verbal aggression, aggression against property, autoaggression and physical aggression. The total MOAS score is computed by assigning a different weight to each subscale score and the lowest weight is attributed to verbal aggression. Previous reports had provided support for MOAS scores being a reliable state-marker (Foley et al., 2007; Krakowski and Czobor, 2014). As participants were in- and outpatients and the application of MOAS covered the whole history of patients, thus, the MOAS scores were not a function of the inpatient treatment duration (see supplementary).

2.2. Participants

The final sample included 84 women and men, aged 19-65 with schizophrenia spectrum disorders according to DSM-IV criteria, who were recruited at the inpatient and outpatient departments of the University Hospital of Psychiatry, Bern for participation in two different neuroimaging studies. All participants were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971). Moreover, all included patients have been treated at least once as inpatients and the majority of them had participated in the imaging studies during inpatient treatment. General exclusion criteria included substance dependence other than nicotine in the last 12 months; subjects could still have had dependence before the past 12 months or ongoing substance abuse without qualifying for current dependence; history of idiopathic parkinsonism, multiple sclerosis or stroke; history of severe head trauma with concurrent loss of consciousness. All participants were interviewed with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients were further interviewed with the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Except from six patients, all other patients were on antipsychotic medication. The mean chlorpromazine equivalents dose (CPZ) was 423.32 ± 340.7 mg per day (Table 1). The CPZ equivalents were estimated as described by Woods (2003) (Woods, 2003). A list with antipsychotic medications is provided in supplementary file. Twelve patients (14.29%) received clozapine. Unmedicated patients had been stable without medication at the time point of assessment or

Table 1
Demographic, and clinical data ($n = 84$).

	Mean	SD
Women (%)	30 (35.7)	
Age (years)	36.7	11.3
Education (years)	13.3	3.6
Number of psychotic episodes	5.6	6.5
Duration of illness	10.9	10.8
Schizophrenia (%)	59 (70.2)	
Brief Psychotic Disorder (%)	20 (23.8)	
Schizoaffective Disorder (%)	5 (6)	
History of Addiction (%)	26 (31)	
Cannabis	5 (19.2)	
Alcohol	10 (38.5)	
More than one substances	11 (42.3)	
CPZ	423.3	340.7
PANSS total	65.9	18.6
PANSS positive	16.5	6.6
PANSS negative	16.9	6.3
PANSS positive factor	13.2	16.4
PANSS negative factor	16.4	7.5
PANSS disorganization factor	22.6	7.8
PANSS excitement factor	15.1	5.1
PANSS emotional distress factor	14.3	5.5
MOAS total (weighted)	14.1	12.7
- Verbal aggression	1.8	1.6
- Aggression against properties	1.3	1.5
- Autoaggression	1.8	1.8
- Physical aggression	1.1	1.5
Gray matter volume (ml)	714.1	111.0
Total intracranial volume (ml)	1795.7	239.8

CPZ: chlorpromazine equivalents; MOAS: Modified Overt Aggression Scale; PANSS: Positive And Negative Syndrome Scale; SD: standard deviation

categorically rejected treatment. Patients' mean PANSS scores were 16.46 ± 6.61 for the positive subscale, 16.89 ± 6.35 for the negative subscale, and 65.93 ± 18.56 for the total score. Additionally, we computed the five PANSS factors according to van der Gaag et al including positive, negative, disorganization, excitement and emotional distress factors (van der Gaag et al., 2006). We explored the correlations between PANSS subscales as well as PANSS factors with MOAS subscales. All statistic tests were performed with SPSS 22 (IBM Corporation, New York, USA).

2.3. Neuroimaging

Structural brain data derived from previous imaging studies employing a 3D-T1-weighted (Modified Driven Equilibrium Fourier Transform Pulse Sequence; MDEFT) (Deichmann et al., 2004) sequence in a 3-T scanner (Siemens Magnetom Trio; Siemens Medical Solutions, Erlangen, Germany). This provided 176 sagittal slices with 256 ´ 256 matrix points with a field of view (FOV) of 256 × 256, yielding a nominal isotopic resolution of 1mm^3. Further scan parameters were 7.92 ms repetition time (TR), 2.48 ms echo time (TE) and a flip angle of 16° (FA).

Data was processed using SPM12 (Wellcome Trust Center for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm) based on standard procedures of voxel based morphometry as implemented in SPM12 (Ashburner and Friston, 2000). Data processing included normalization, segmentation into tissue classes, modulation and smoothing with 8 mm full-width at half maximum (FWHM) kernel (Honea et al., 2005). In particular, segmentation was implemented using on a "modified gaussian mixture model based on an established algorithm, where each voxel is assigned a probability value reflecting the likelihood of belonging to one of the three tissue classes, celebral spinal fluid, gray and white matter (Ashburner & Friston, 2005). The normalization was based on the previously performed segmentation (Ashburner & Friston, 2005). After preprocessing steps the voxel dimensions were equivalent to 2 × 2 × 2 mm^3. Further details of the neuroimaging data preprocessing can be found in a previous paper (Stegmayer et al., 2016). Normalized, modulated and smoothed images of gray matter were used in further analyses.

2.4. Statistical analysis

The non-parametrical Spearman's rank correlation (r) was used for correlations between MOAS scores and demographical variables. To correct for the multiple comparisons as we investigated MOAS total and subscales, we performed a Bonferroni correction using a p value 0.05 divided by five (MOAS total and four subscales), which led to an adjusted p-value of 0.01. We performed multiple regression analyses for total MOAS scores and each MOAS subscale separately corrected for the following co-variates: age, sex, history of addiction, chlorpromazine equivalents, illness duration and total intracranial volume (TIV). These factors have been previously reported as predictors of aggressive behavior in schizophrenia (Kuroki et al., 2017; Witt et al., 2013). In case of TIV a previous review described alterations for whole brain volumes in patients with schizophrenia regardless of history of violence compared to healthy controls (Widmayer et al., 2018). History of addiction was used as a dummy variable (0 = no, 1 = yes). For the multiple regression analyses we applied a statistical threshold of $p < 0.001$ (uncorrected). Finally, imaging results are depicted at a cluster-level threshold of $p < 0.05$ and a cluster size of 16 voxels as determined by AFNI's 3dClustSim (version 19.1.18). Images were produced using SPM12 (Welcome Trust Center for Neuroimaging, London). Broadmann areas were identified based upon MNI correlates using the Yale BioImage Suite Package (Lacardie et al., 2008).

3. Results

Demographic and clinical data are given in Table 1.

3.1. MOAS and demographic characteristics

The MOAS total scores showed a skewed distribution (Fig. 1); sixteen patients did not have any history of aggression. Age, years of education and chlorpromazine equivalents did not show any correlation with MOAS total or subscales scores. The number of episodes correlated with all MOAS subscales ($r = 0.38$, $p < 0.001$ for verbal aggression, $r = 0.38$, $p < 0.001$ for aggression against property, $r = 0.27$, $p < 0.001$ for auto-aggression and $r = 0.37$, $p < 0.001$ for physical aggression) as well as total MOAS scales ($r = 0.43$, $p < 0.001$). No differences for MOAS scores were observed between women and men.

3.2. MOAS and clinical characteristics

No correlations were reported between MOAS total scores and PANSS total, positive and negative subscales scores (Fig. 2).

The MOAS total scores did not correlate with any of the 5 PANSS factor scores (van der Gaag et al., 2006) or the item P6 of the PANSS, which assesses paranoid delusions. Patients with history of drug addiction had higher scores for all MOAS subscales and total MOAS compared to patients without drug addiction history ($p < 0.001$ for all subscales and total scores except from MOAS against property, where $p = 0.001$, Mann-Whitney-*U* test in all cases).

3.3. MOAS and gray matter volume

The total MOAS scores were associated with gray matter volume in left inferior frontal gyrus (Brodmann area 44; pars opercularis) (Table 2). This association appeared at a threshold of $p < 0.001$ and $k > 50$ voxels, corrected for age, sex, history of addiction, CPZ equivalents, illness duration and TIV (Fig. 3). In contrast, the MOAS verbal aggression scores were associated with gray matter volume in left inferior frontal gyrus (Brodmann area 45; pars triangularis) (Fig. 4). The

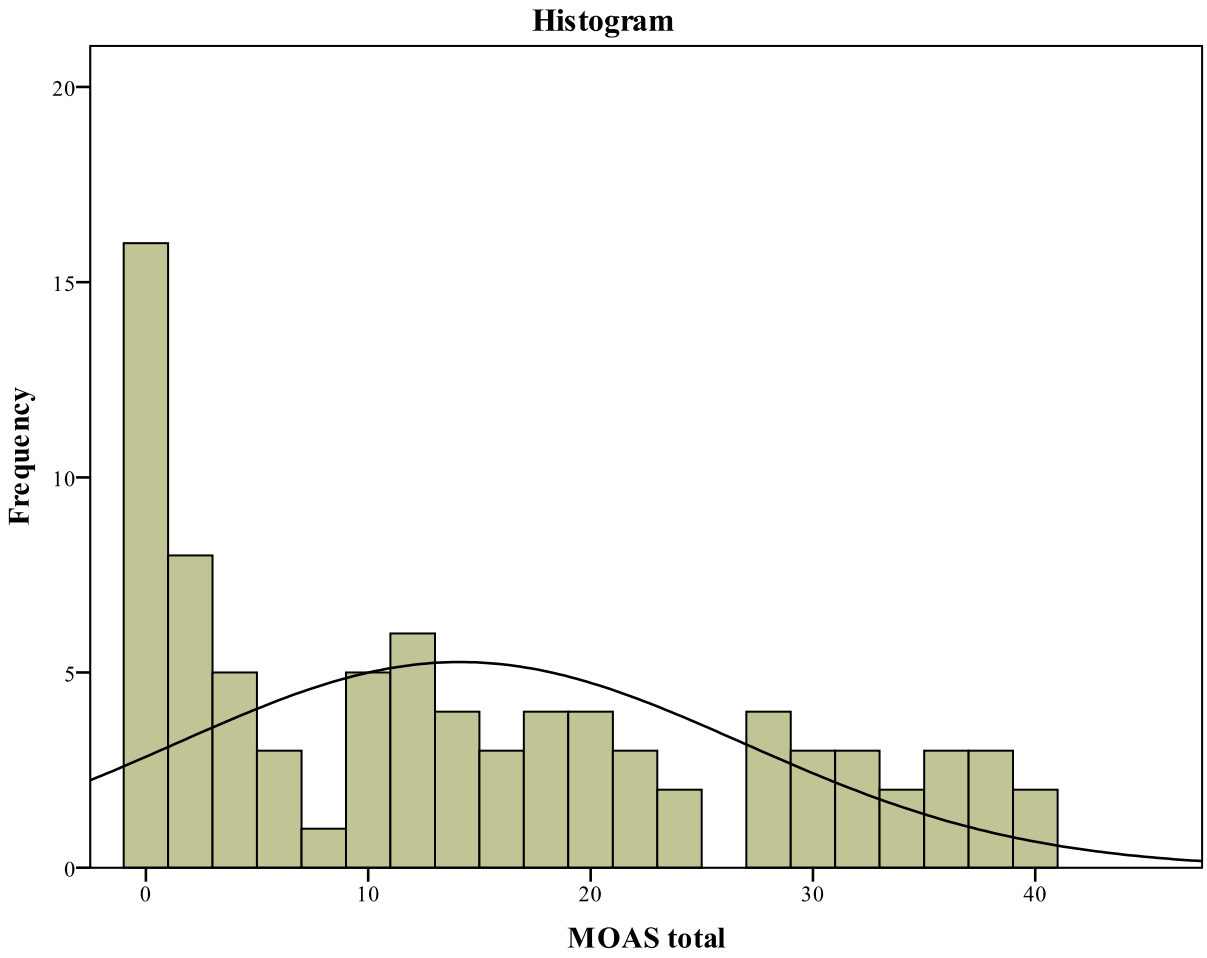

Fig. 1. Frequency distribution for MOAS total scores

other MOAS subscales were not associated with gray matter volume.

4. Discussion

Our study aimed to assess the relationship between gray matter volume alterations and history of aggression in schizophrenia patients. Our results highlighted the role of frontal lobe structures adding on previous evidence (Fjellvang et al., 2018; Leclerc et al., 2018; Widmayer et al., 2018). In fact, decreased gray matter volumes in orbitofrontal as well as ventrolateral prefrontal cortex have been reported in aggressive patients with schizophrenia compared to non-aggressive patients or healthy individuals (Hoptman et al., 2014, 2005; Kumari et al., 2009; Narayan et al., 2007). Further, older review articles clearly postulate a key role of frontal lobe in the emergence of violence and aggression in individuals with and without psychiatric disorders (Coccaro et al., 2011; Davidson et al., 2000; Rosell and Siever, 2015).

Correlations were detected in two instances; between total MOAS scores and gray matter volume in the left inferior frontal gyrus and between the MOAS verbal aggression scores and gray matter volume in the left inferior frontal gyrus as well. In particular, after controlling for age, sex, history of addiction, CPZ equivalents, duration of illness, and TIV, gray matter volume reduction was observed in left inferior frontal gyrus (IFG) related to total (weighted) scores of MOAS, which reflects four subtypes of aggression. Among subtypes, the gray matter volume alterations in left IFG were also related to the verbal aggression subscales. Due to the implication of IFG in information integration there are several aspects to address (Kohn et al., 2014). The link between IFG alterations and aggressive behavior may pertain to emotional dysregulation (Leclerc et al, 2018). Previously, a large longitudinal study indicated a relationship between angry affect-linked delusions and violence in patients from acute psychiatric facilities (Ullrich et al., 2014). Negative emotions may underlie aggression in patients suffering from voices, which they considered malevolent (Berman et al., 2010). Our group had demonstrated gray matter alterations in several clusters including IFG bilaterally for patients with severe emotional dysregulation (Stegmayer et al., 2014b). Moreover, evidence has previously reported implication of the left IFG in behavioral inhibition in healthy individuals (Boehler et al., 2010; Swick et al., 2008). Therefore, the left hemisphere may participate in mechanisms controlling response inhibition. However, since these findings were mainly driven by the correlation between the verbal aggression and left IFG gray matter volumes, it is worth to consider this evidence in light of the left IFG implication in speech production and understanding and therefore communication (Burton, 2009; Marangolo et al., 2013; Tops and Boksem, 2011). Patients with left IFG alterations may have communication deficits and they thereby may be susceptible to a verbal communication breakdown (Cantisani et al., 2018). These deficits may be understood with reference to semantic network alterations as previously reported for patients with formal thought disorder (Cavelti et al., 2018; Horn et al., 2012; Stegmayer et al., 2017a). In the context of communication problems, we may also regard the connectivity alterations involving left IFG during processing of metaphoric gestures for patients with schizophrenia (Straube et al., 2014). Regarding implication of the semantic network, we may also consider altered activation patterns for left ventrolateral prefrontal cortex, which includes the IFG, during a theory of mind task when comparing violent versus non-violent men with schizophrenia (Schiffer et al., 2017). Finally, we also need to take into account the poorer verbal fluency and verbal IQ in

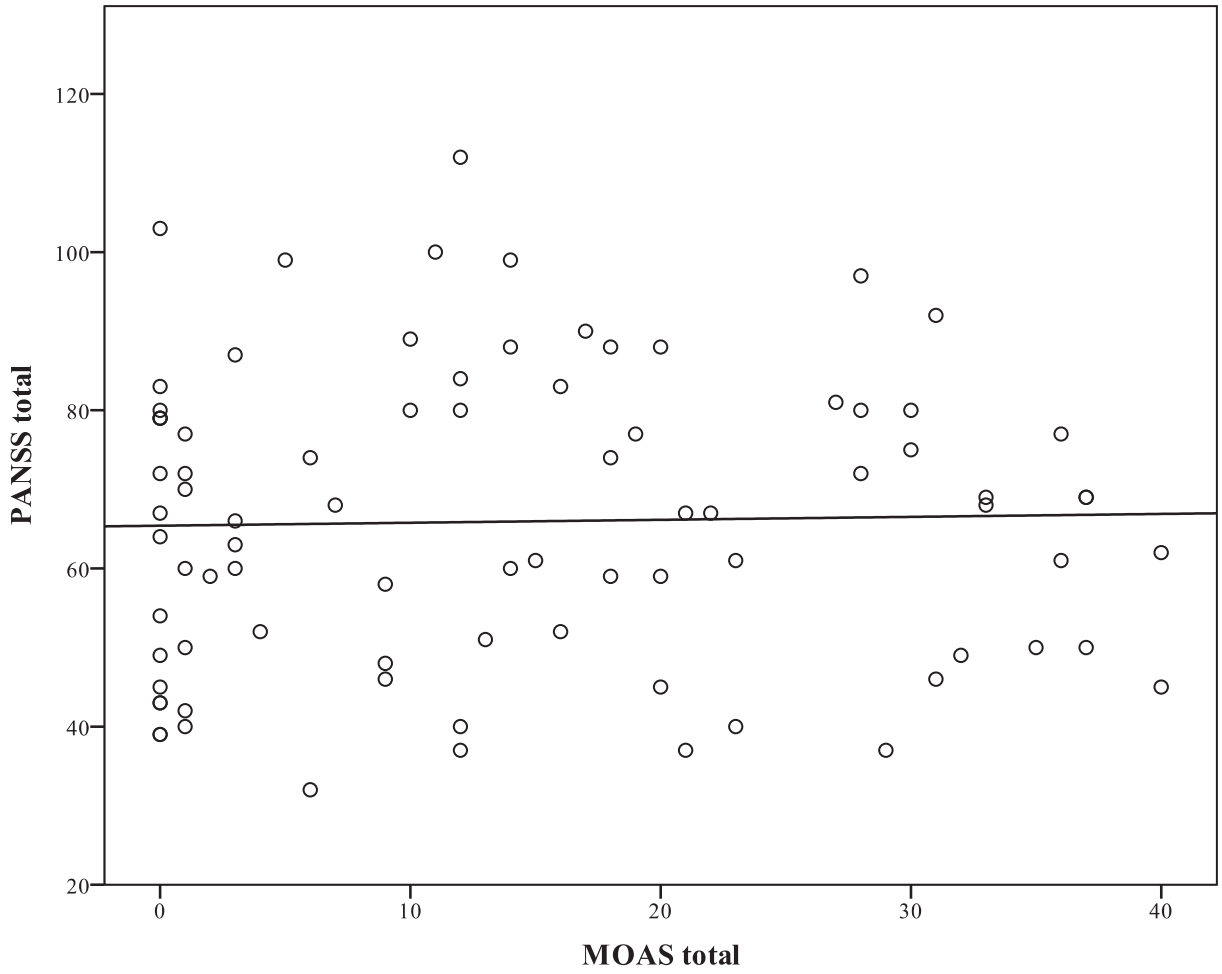

Fig. 2. Scatter plot of PANSS total and MOAS total scores

violent individuals with schizophrenia compared to healthy controls (Sedgwick et al., 2017). Collectively, disturbed behavioral inhibition combined with interpersonal communication difficulties may plausibly account for aggressive behaviors in patients with schizophrenia. Nevertheless, a meta-analysis of volumetric data demonstrated that left IFG alterations are present in the half of patients with schizophrenia (Honea et al., 2005). Therefore, our finding is moderately specific regarding aggressive patterns of behavior in patients with schizophrenia given that PANSS total scores did not predict MOAS scores in alignment with previous meta-analyses (Fazel et al., 2009a; Witt et al., 2013). Moreover, when considering structural alterations, one should bear in mind that these changes are not always related to functional alterations and vice-versa.

Our findings are in partial alignment with our initial hypothesis; we expected significant alterations in the frontal regions to be associated with aggressive behaviors. Existent literature remains scarce and our evidence provides further support for the hypothesis that despite methodological heterogeneity and related limitations frontal structural changes are of clinical relevance. Across reported regions, decreased gray matter volumes in inferior frontal region have been described in a sample of patients with schizophrenia preceded by conduct disorder patients with co-morbid conduct disorder (Schiffer et al., 2013); in the same sample a positive association between lifetime tendency towards aggressive behavior and gray matter volume in hypothalamus was observed (Schiffer et al., 2013). Based on that, we had also expected alterations in limbic areas for aggression in schizophrenia. A potential mechanism would have included paranoid symptoms (Pinkham et al., 2015; Stegmayer et al., 2014b; Stegmayer et al., 2017b) leading to behavioral consequences (Schoretsanitis et al., 2016). However, no correlations between limbic system structures and MOAS scores were detected. A reason for that may be that acute (or new) onset of aggressive behaviors in schizophrenia might be related to limbic system alterations, which were not captured by our retrospective analysis rather reflecting chronic changes.

Table 2
Regions with significant group differences in gray matter volume. The values given are the stereotactic (MNI) coordinates and the T values of each anatomical region. SPM maps were thresholded at $p < 0.001$ (uncorrected, voxel-level); minimum cluster size threshold of 16 voxels.

Contrast	Region Brodmann area	Anatomical region	MNI (mm) X	y	z	Statistical effects Cluster size (No. of voxels)	Peak T value
MOAS total	BA44	L pars opercularis (inferior frontal gyrus)	-42	16	14	54	4,44
MOAS verbal aggression	BA45	L pars triangularis (inferior frontal gyrus)	-42	26	6	85	3,73

BA: Brodmann area, MNI: Montreal Neurological Institute, MOAS: modified overt aggression scales

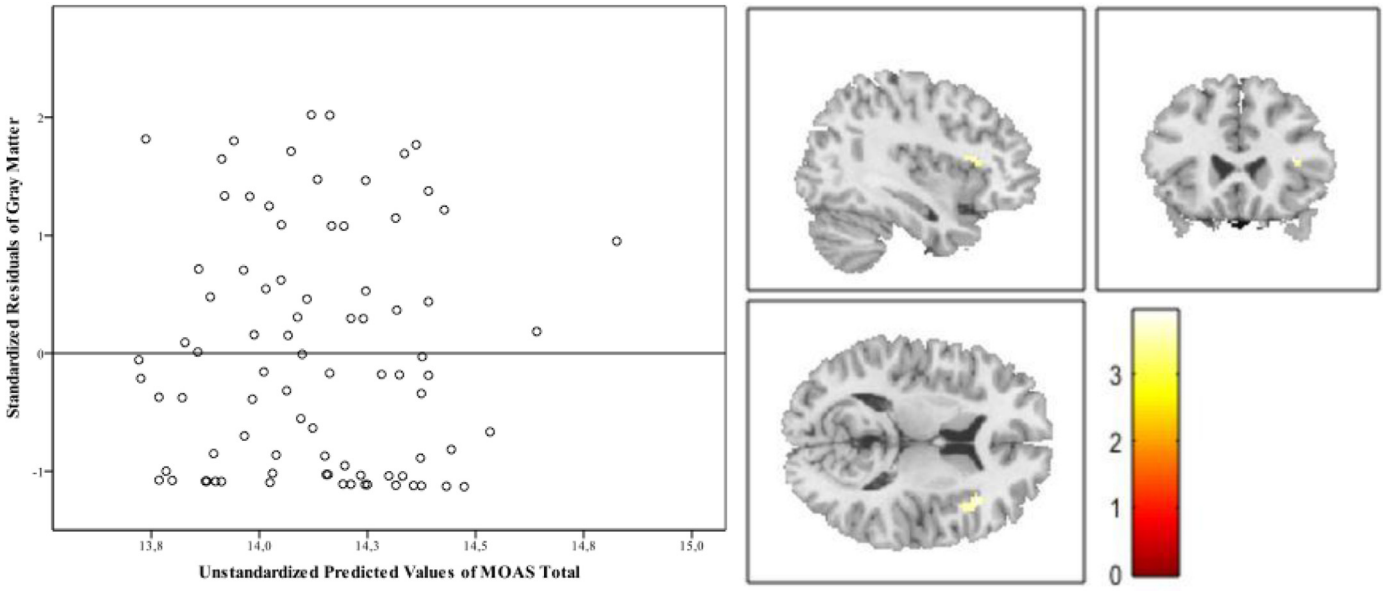

Fig. 3. Association of total MOAS scores with gray matter volume in left inferior frontal gyrus controlling for age, sex, history of addiction, CPZ equivalents, duration of illness and TIV. In the scatterplot standardized residuals of gray matter volume (GM) are plotted against unstandardized predicted values of MOAS total.

Adding on previous research, we included several additional co-variates to control for various confounds such as age, sex, addiction history and illness duration, which have previously reported to exert a crucial effect on aggressive behavior or brain structure. Therefore, the reported results are not contaminated by the effects of these potential confounds. Moreover, the application of MOAS does not cover a restricted observation period, but extends to an essential part of the psychiatric history of our patients. This is possible through the fact that the vast majority of the included individuals have been continuously treated in our hospital. Additionally, an exploratory Spearman correlation with a corrected p-value for multiple comparisons did not report significant associations between illness duration and MOAS total or subscales (see Supplementary). Neither did we detect differences when comparing illness duration between patients with high and low MOAS total scores using the median MOAS total as cut-off (see Supplementary), nor did we detect bivariate correlation between MOAS and PANSS. Therefore, the structural findings are less likely to be mediated by current psychopathology. A possible shortcoming of the study may derive from the effects of antipsychotic treatment on gray matter volume. Although chlorpromazine equivalents have been included as co-variate in the analysis, the pharmacological class and the duration of antipsychotic treatment may also determine the sort of gray matter alterations (Navari and Dazzan, 2009). For instance, clozapine has been prescribed to target aggression in schizophrenia patients. Nevertheless, in an exploratory non-parametrical analysis no differences for MOAS total and subscales were detected between clozapine-medicated patients and patients receiving other treatment, so that we decided not to include clozapine-based treatment as a co-variate in our

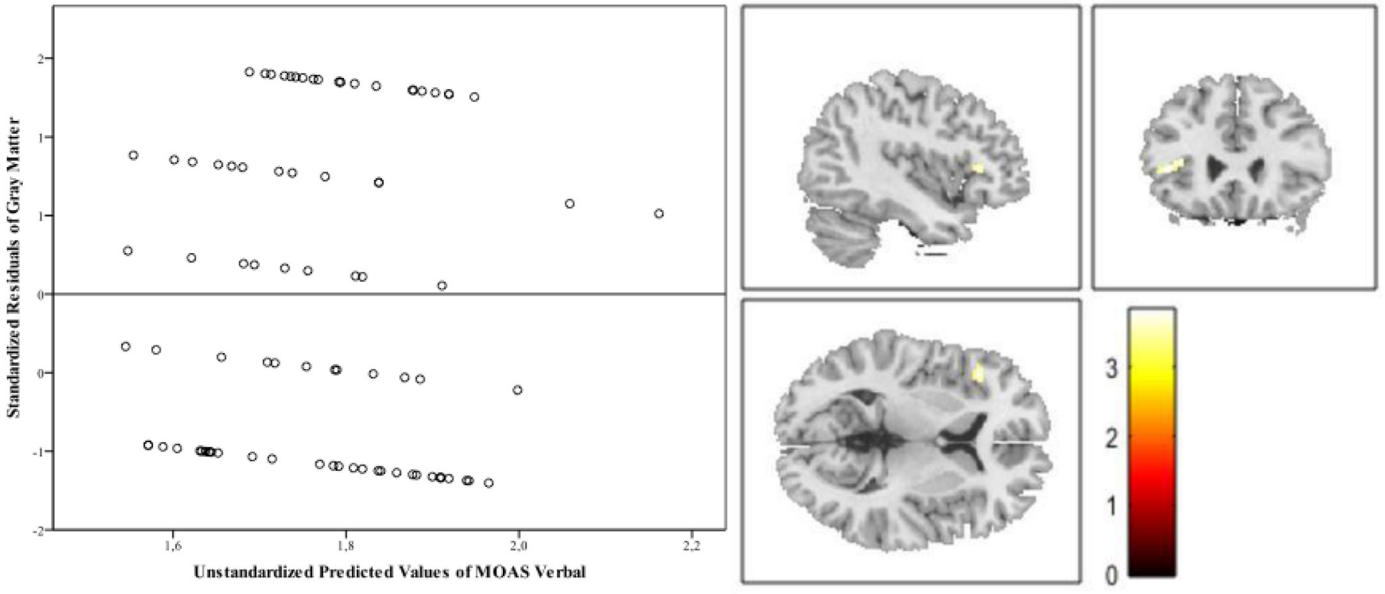

Fig. 4. Association of MOAS verbal scores with gray matter volume in left inferior frontal gyrus controlling for age, sex, history of addiction, CPZ equivalents, duration of illness and TIV. In the scatterplot standardized residuals of gray matter volume (GM) are plotted against unstandardized predicted values of MOAS verbal scales scores.

analysis. Assessment of additional parameters such as verbal intelligence or word fluency would have provided further insight; unfortunately this type of data was not available. Further, we entered history of addiction as a binary parameter in the analysis rather than performing subgroup comparisons. Moreover, the retrospective application of MOAS by reviewing clinical records cannot exclude the possibility of missing information, in particular for patients treated exclusively as outpatients. Nevertheless, the University Hospital of Psychiatry in Bern is the major mental health provider in the region, and therefore this possibility is minimal, since the majority of the included patients are exclusively referred to our clinic for inpatient and outpatient services. Moreover, the use of MOAS result in limited precision when grasping the seriousness, the pattern and the specific patterns of violent behaviors. Our study focused on the gray matter volume measures; despite the considerable size of our sample few associations between MOAS scores and gray matter alterations were observed. We may hypothesize that aggressive behavior is more a trait marker, so that volumetric measures of brain alterations may be less suitable to capture the related pathways. Consequently, there may be more place for imaging correlates of state markers in future studies addressing aggression in schizophrenia. The understanding of aggression in schizophrenia, whether as state- or trait marker, will essentially stimulate the debate regarding dimensional conceptualization of psychopathological constructs and support the unravelling of symptom clusters out of the wide heterogeneity of schizophrenia manifestations.

5. Conclusion

Our study demonstrates an important role for gray matter volume in the left inferior frontal gyrus in schizophrenia patients with history of aggression. This volumetric data can be interpreted in light of previous findings implicating the region in response control and semantic networks. In other words, aggression may relate to behavioral control problems or communication deficits. In depth assessment of further contributing factors in future studies will aid elucidating the neurobiology of aggressive behavior in schizophrenia.

Author contributions

Drs. Schoretsanitis, Stegmayer, Razavi, Federspiel, Müller, Horn, Wiest, Strik and Walther participated in the research design of the study. Dr Schoretsanitis and Walther performed the initial statistical analyses and wrote the first article draft. All the authors contributed to the interpretation of data and approved the final manuscript.

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Declaration of Competing Interest

Authors declare no conflicts of interest for this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.06.003.

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