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An overlapping pattern of cerebral cortical thinning is associated with both positive symptoms and aggression in schizophrenia via the ENIGMA consortium

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For more details regarding the ENIGMA Schizophrenia Working Group (ENIGMA-SZ), see http://enigma.ini.usc.edu/ongoing/enigma-schizophrenia-working-group/

Running Title: ENIGMA-SZ - Positive Symptoms and Aggression

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Abstract

Background. *Positive symptoms are a useful predictor of aggression in schizophrenia. Although a similar pattern of abnormal brain structures related to both positive symptoms and aggression has been reported, this observation has not yet been confirmed in a single sample.*

Method. To study the association between positive symptoms and aggression in schizophrenia on a neurobiological level, a prospective meta-analytic approach was employed to analyze harmonized structural neuroimaging data from 10 research centers worldwide. We analyzed brain MRI scans from 902 individuals with a primary diagnosis of schizophrenia and 952 healthy controls.

Results. The result identified a widespread cortical thickness reduction in schizophrenia compared to their controls. Two separate meta-regression analyses revealed that a common pattern of cerebral cortical thinning within the left lateral temporal lobe and right midcingulate cortex was significantly associated with both positive symptoms and aggression.

Conclusion. These findings suggested that positive symptoms such as formal thought disorder and auditory misperception, combined with cognitive impairments reflecting difficulties in

deploying an adaptive control towards perceived threats, could escalate the likelihood of aggression in schizophrenia.

Introduction

If men define situations as real, they are real in their consequences.

Thomas and Thomas

The Thomas theorem (Thomas & Thomas 1928) states that our perception influences the way we act. Individuals with schizophrenia usually suffer from a distorted perception of reality and tend to perceive threat in a situation that healthy individuals perceive as non-threatening, possibly leading to an immediate sequel of aggression and violence. Escalated aggression in schizophrenia engenders numerous critical concerns, including (a) It appears as a critical public health concern and a potential threat to caregivers and mental health professionals especially during an acute phase of psychosis with the presence of positive symptoms (Hodgins *et al.* 2007; Hoptman 2015). (b) Aggressive and violent behaviors evinced by individuals with schizophrenia often aggravate stigmatization of the disorder (Stuart 2003; Torrey 2011), which in turn reduce the tendency of affected patients to seek adequate help (Clement *et al.* 2015). (c) Aggressive individuals with schizophrenia increase their chances of institutional admissions and prolonged hospitalization (Wehring & Carpenter 2011). All these

concerns eventually contribute to poor treatment outcomes and prognosis.

Evidence from birth cohorts (Arseneault *et al.* 2000; Brennan *et al.* 2000; Wallace *et al.* 2004), meta-analyses (Douglas *et al.* 2009; Fazel *et al.* 2009; Large & Nielssen 2011; Dack *et al.* 2013) and epidemiological studies (Swanson *et al.* 2006) have demonstrated that psychotic symptoms increase the risk of aggression and violence. Nolan and colleagues (2003) documented with a semi-structured interview that 11 out of 55 assaults in schizophrenia inpatients were directly related to positive psychotic symptoms. Supporting these findings, a subset of positive psychotic symptoms, categorized as the threat/control-override (TCO) symptoms including persecutory delusion and hallucinations of imposing thoughts or voices to harm others, was further proposed as a useful predictor of aggression and violence in schizophrenia (Link *et al.* 1998; Bjørkly 2002). Indeed, Song and Min (2009) revealed that anger was mediating the association between aggressive expressions and positive symptoms. Such a strong negative emotion is usually provoked by a potential proximal threat to perceivers. In a healthy sample, aggressive behaviors were positively associated with psychotic-like experiences mediated by perceived threats (Fanning *et al.* 2011). Altogether, these studies suggest that aggression in schizophrenia arises from a strong negative affect

associated with threats possibly due to a misperception triggered by positive symptoms (Coid *et al.* 2013). Although aggression has been linked to positive symptoms in behavioral studies (Cheung *et al.* 1997), one important missing link is whether there is a common neural basis that can explain the close tie between positive symptoms and aggression in schizophrenia. Therefore, an enhanced understanding of neural abnormalities associated with aggression, particularly an impulsive and aggressive response towards threat in schizophrenia, is indispensable for the development of more preventive and effective intervention strategies.

Although violence is sometimes considered as a separate concept from aggression, most social psychologists considered violence as a subset of aggression (Sturmey *et al.* 2017). For our study, therefore, we considered aggression as a board concept of overt social interaction eliciting damage while violence is an extremely physical form of aggression. In other words, being aggressive does not necessarily mean to be violent but being violent would be necessarily considered as being aggressive. Dysfunctional aggression has long been recognized as a maladaptive behavioral expression emanating from an anomalous frontolimbic socio-emotional information processing network (Davidson *et al.* 2000; Siever 2008; Coccaro *et al.* 2016). Failures in regulating negative emotion may channel provocation

into aggression. Recent studies and reviews further acknowledge the role of consequence evaluation (i.e. evaluating rewards or benefits of the action) and decision making in elicited aggression (Blake & Grafman 2004; Blair 2016). Individuals with intermittent explosive disorder (IED), a pathologically aggressive population, showed reduced gray matter volume in the orbitofrontal cortex, ventral medial prefrontal cortex, anterior cingulate cortex, amygdala, insula and uncus compared to their healthy or non-aggressive psychiatric counterparts (Coccaro *et al.* 2016). In a healthy adolescent population, cortical thickness alterations within the middle frontal cortex, anterior cingulate cortex, lateral temporal lobe including superior, middle and inferior temporal gyri were associated with measures of aggression (Yang *et al.* 2017). These structural brain studies provided further evidence that aberrance in middle frontal and lateral temporal regions possibly contributed to impulsive aggression due to impeded socioemotional information integration and poor decision making (Shackman *et al.* 2011; Vogt 2016). In contrast to a large body of literature on brain abnormalities associated with aggression in general, studies on structural changes associated with aggressive behavior in schizophrenia remain scarce and their results vary (Soyka 2011; Weiss 2012; Hoptman 2015; Fjellvang *et al.* 2018). The few studies available generally agree that structural abnormalities in a frontotemporal network seem to differentiate between violent and non-violent

schizophrenia patients (Sandyk 1993; Hoptman *et al.* 2005; Narayan *et al.* 2007; Hoptman 2015; Fjellvang *et al.* 2018).

Widespread cortical and subcortical structural abnormalities associated with positive symptoms were documented in youths and adults with schizophrenia (Gur *et al.* 1998; Narr *et al.* 2005; Ross *et al.* 2006; Satterthwaite *et al.* 2016) while some cortical abnormalities were associated with positive symptoms. In a medication free community sample, youths with high psychosis spectrum symptoms showed that global gray matter volume reduction began at an early stage of symptom manifestation (Satterthwaite *et al.* 2016). Particularly, this study identified regional volume loss in the medial temporal lobe, ventromedial and orbital frontal cortex, posterior cingulate, and dorsolateral prefrontal cortex. Individuals with either clinical or non-clinical auditory verbal hallucinations had thinner cortices within the pars orbitalis, paracentral lobule, fusiform gyrus and inferior temporal gyrus compared to the healthy controls (Van Lutterveld *et al.* 2014). Other studies demonstrated that the severity of auditory hallucination was associated with grey matter volume of the bilateral superior temporal gyri, supramarginal gyrus, as well as middle/inferior right prefrontal gyri (Gaser *et al.* 2004; Modinos *et al.* 2013). Furthermore, the structural abnormalities in the lateral temporal lobe,

anterior cingulate cortex and precuneus were associated with severity of formal thought disorder in schizophrenia (Horn *et al.* 2009). In individuals with delusional disorder, grey matter reduction compared to healthy subjects was observed in the medial frontal/anterior cingulate cortex and bilateral insula (Vicens *et al.* 2016).

Taken together, positive symptoms in schizophrenia are associated with structural brain abnormalities in the prefrontal cortex, cingulate cortex and lateral temporal lobe as well as the insula. Importantly, these findings indicate that there might be a common pattern of structural brain abnormalities linked to both positive symptoms and aggression. Here, we employed a *prospective meta-analytic approach* to investigate whether there is an overlapping pattern of brain structural changes in schizophrenia that is associated with both positive symptoms and aggression in two separate meta-regression through pooling over summary statistics computed at each research site within the framework of the ENIMGA Consortium Schizophrenia Working Group (ENIGMA-SZ; working group website: http://enigma.ini.usc.edu/ongoing/enigma-schizophrenia-working-group/). Based on the aforementioned literature, we predicted that an overlapping pattern of structural changes within the ventromedial prefrontal cortex, anterior cingulate cortex, midcingulate cortex,

lateral temporal lobe and insula is associated with both positive symptoms and aggression.

METHODS

Samples

A total of 902 individuals with a primary diagnosis of schizophrenia or psychosis (hereinafter "cases") and 952 healthy controls (hereinafter "controls") was included in the current analysis, pooling from 10 datasets with MRI scans of the brain and clinical data as part of the ENIGMA-SZ. All participating sites obtained local approval from their institution review boards and ethics committees, and all study participants provided written informed consent. Please note that initial call of data for the present study successfully gathered 16 datasets with different scales for measuring symptoms severity for schizophrenia, including the Positive and Negative Symptom Scales (N = 11), Scale for the Assessment of Positive Symptoms (N = 4), and Brief Psychotic Symptom Scale (N = 1). Due to inability of extracting and validating a harmonized aggression symptom score from different scales, only datasets using the Positive and Negative

Symptom Scale (PANSS) were included for the current analysis. Furthermore, we excluded a dataset containing only patient data. Accordingly, the final dataset included 10 study sites worldwide (please refer to Table 1 and Table S1 for details).

Positive Symptoms and Aggression Measurements

Positive symptoms were accessed through PANSS (Kay *et al.* 1987). We used a composite score derived from the sum of the first six items (P1 to P6) as an indicator of the severity of positive symptoms while aggression was indexed by the sum of the item P7-Hostility and item G14-Poor Impulse Control. The P7 and G14, together with P4-Excitement and G8-Uncooperativeness, contributed to a common factor, named as the excitement/hostility factor, in a 5-factor model of PANSS (van der Gaag *et al.* 2006). Especially, P7 measures verbal and nonverbal expressions of anger and resentment while this description fits the definition of impulsive aggression construct.

Image Acquisition and Processing

Each site acquired high-resolution (at least 1x1x1 mm voxel size) T_1-weighted structural brain scans locally. All imaging data was processed using the standardized ENIGMA analysis pipeline (see http://enigma.ini.usc.edu/protocols/imaging-protocols/ for details) to harmonize analysis and quality control processes across multiple sites (Thompson *et al.* 2014). The images were analyzed using the fully automated and validated segmentation on FreeSurfer (Fischl *et al.* 2002). Segmentations of 68 (34 per each hemisphere) cortical gray matter regions of interest (ROIs) were created based on the Desikan-Killiany atlas (Desikan *et al.* 2006). Segmented regions were visually inspected and statistically evaluated through histogram plots for outliers.

Prospective Meta-Analyses and Meta-Regression

Analyses were conducted in R, version 3.4.1 (R Core Team 2003). The outcome measures were standardized mean difference (SMD) between cases and controls from each of the 68 cortical regions of interest (ROIs). SMDs were computed by "compute.es" package (Del Re 2013) at each site using the Hedges' *g* metric that corrected for biased upwards for sites with a smaller sample size. The intercept in the models represented the estimation of the average effect size

of group differences (i.e. cases vs. control). Effects sizes of SMDs per each individual ROI were analyzed using this brain structural modality with meta-regression models using the "*rma"* function from the "*Metafor*" package (Viechtbauer 2010) and a Restricted-Maximal Likelihood method. This function fits the meta-analytic mixed-effects regression model with regressors and covariates.

$$SMD = \beta_0 + \beta_{c1} * SEX + \beta_{c2} * AGE \quad (1)$$

We then conducted two primary meta-regression models to study association of positive symptoms and aggression with the SMDs of cortical thickness and surface areas in each ROI:

$$SMD = \beta_0 + \beta_1 * Positive\ Symptoms + \beta_{c1} * SEX + \beta_{c2} * AGE \quad (2)$$

$$SMD = \beta_0 + \beta_1 * Aggression + \beta_{c1} * SEX + \beta_{c2} * AGE \quad (3)$$

In these models, all βs are standardized. β_0 represents the intercept: the effect sizes of the difference between cases and controls while β_1 is the standard coefficient of our main outcomes. We set sex and age of the participants as the covariates (β_{c1} and β_{c2}) of the models.

All *p* values were corrected for multiple testing using false discovery rate (FDR) with a Benjamini-Hochberg procedure limited at 5% (i.e., $p_{FDR} < 0.05$) for 68 ROIs (Benjamini & Hochberg 1995). In addition, we calculated heterogeneity scores (I^2) for each ROI. I^2 indicates the percent of the total variance in effect size explained by heterogeneity alone. Thus, lower values of I^2 represent lower variance in the effect size estimation across study sites.

RESULTS

Demographics and Clinical Characteristics

The demographic and clinical characteristics of 1,854 subjects (902 cases and 952 healthy controls) are summarized in Table 1 for each site. Weighted mean age across individuals with schizophrenia was 34.94 (Range: 22.16 to 44.46). Within the schizophrenia group, 27.71% of the subjects (Range: 0% to 52.08%) were female and their duration of illness was 12.87 years (Range: 0.51 to 19.41). The mean score of positive symptoms (i.e., sum of P1 to P6) was 14.54 (Range: 10.09 to 18.83) and the mean score of aggression symptom (i.e., sum of P7 and G14)

was 3.19 (Range: 2.68 to 4.77). Weighted mean age across healthy controls was 32.70 (Range: 22.41 to 43.60) and 44.67% of participants (Range: 0 to 62.50%) were female.

[Insert Table 1 here]

Meta-Analysis: Cortical Differences Between Cases and Controls

No regional difference in surface areas between cases and controls was documented. However, we observed cortical thinning in the case group compared to their healthy controls. ROI analysis revealed significant cortical thinning ($ps_{FDR} < 0.05$) in the lateral orbitofrontal cortex bilaterally, left medial orbitofrontal, bilateral pars opercularis, bilateral pars orbitalis, bilateral pars triangularis, bilateral precuneus, bilateral rostral middle frontal gyrus, left superior frontal gyrus, right caudal middle frontal gyrus and right posterior cingulate gyrus. Most brain regions have a low-to-median level of unexplained variances (I^2: 10 to 40%). This means that after controlling for sex and age, group differences (diagnosis of schizophrenia) can explain around 60 to 90% of variances of the differences. Details are displayed in Table 2.

[Insert Table 2 here]

Meta-Regression: Association between Symptoms and Structural Changes

Since no significant differences of cortical surface areas were found between the schizophrenia patients and the healthy control group, its association with symptoms was not examined. We examined whether positive symptoms and aggression were significantly associated with the difference of cortical thickness in each ROI in two separate meta-regression models. For positive symptoms (see Figure 1a and Table 3a), significant (ps_{FDR} < 0.05) associations between symptom severity and SMDs were documented within the bilateral medial orbitofrontal gyrus (MOFG; left $\beta_1 = 0.064$, right $\beta_1 = 0.89$), right caudal anterior cingulate cortex (cACC; $\beta_1 = 0.09$), left inferior (ITG; $\beta_1 = 0.075$) and middle temporal gyrus (MTG; $\beta_1 = 0.091$). For aggression (see Figure 1b and Table 3b), significant ($ps_{FDR} < 0.05$) associations between symptom severity and SMDs were observed within the bilateral rACC (left $\beta_1 = 0.287$, $\beta_1 = 0.229$), right insula ($\beta_1 = 0.237$) right cACC ($\beta_1 = 0.266$), left ITG ($\beta_1 = 0.22$), and left MTG ($\beta_1 = 0.23$). By comparing two association patterns, we found that both positive and aggression symptoms were associated with differences of cortical thickness

between schizophrenia and their healthy controls within the right midcingulate cortex (MCC), left MTG, and ITG. The heterogeneity indices showed that with group differences (diagnosis of schizophrenia), age, sex, and symptom severity, the meta-regression models explained most variances (> 90%) except medial orbitofrontal gyrus (unexplained variances: 51.76%) in the positive symptom meta-regression model and insula (unexplained variances: 24.36%) in the aggression meta-regression model.

[Insert Figure 1 & Table 3 Here]

DISCUSSION

With a prospective meta-analytic approach, we investigated structural neural integrity in a large sample of individuals with schizophrenia compared to healthy controls. Reduced cortical thickness, but not surface area, was observed in our sample within the lateral and medial orbitofrontal cortex, inferior frontal gyrus, cingulate cortex, lateral temporal lobe, and insula. These results replicate previous findings (Fornito *et al.* 2009; Schultz *et al.* 2010; Nenadic *et*

al. 2015; Satterthwaite *et al.* 2016; van Erp *et al.* 2018). More importantly, within these regions with thinning, the right MCC, left MTG and ITG were positively associated with both positive symptoms and aggression, indicating that the severity of these symptoms is associated with these differences in cortical thickness between schizophrenia patients and their healthy controls.

Language, Sources of Threats and the Lateral Temporal Lobe

The lateral temporal lobe is implicated in language and semantic memory processing (Levy *et al.* 2004) as well as multimodal sensory integration (Mesulam 1998). Brain damage in this region leads to impairments of auditory perception and language abilities (Catani *et al.* 2012). Structural abnormalities within the lateral temporal lobe have been associated with positive symptoms, especially auditory hallucination, in schizophrenia patients (Kuperberg *et al.* 2003; Onitsuka *et al.* 2004; Kuroki *et al.* 2006; Allen *et al.* 2012). Furthermore, a recent meta-analysis pooling over fMRI studies provided convergent evidence that superior temporal gyrus (STG) and MTG were linked to disorganized and incoherent speech (i.e., thought disorder; Wensing *et al.* 2017). These studies implicate that the lateral temporal lobe is critical for impairments

in formal thought processes and auditory misperception in schizophrenia. Similarly, IED individuals have lower gray matter volume not only in frontolimbic regions but also in the ITG and STG, compared to non-IED patients with a similar psychiatric profile and healthy controls (Coccaro *et al.* 2016). Another study focusing on white matter reported that IED was associated with lower white matter integrity in the superior longitudinal fasciculus that has a role in executive functions, visuospatial working memory, and language (Lee *et al.* 2016). Behaviorally, lower verbal abilities in adolescent boys with serious conduct problems predicted later life violence (Manninen *et al.* 2013). In a population-based longitudinal study, children with poor language abilities showed more physical aggression (Girard *et al.* 2014). Consistent with our findings, this data suggests that language abilities associated with the lateral temporal lobe might play a key role in both aggression and positive symptoms. One can speculate that the lateral temporal lobe abnormalities in schizophrenia become a potential trigger for aggression because of impaired cognitive abilities – which, in turn, will negatively influence coping strategies and perceived threats due to positive symptoms like auditory misperceptions. Failures in utilizing language as an effective method to resolve conflicts further increases the likelihood of overreacting or even aggressive responses in a non-threatening situation.

Cingulate Cortex, Auditory Hallucination and Cognitive Control

Thinner cortices in schizophrenia were associated with both positive symptoms and aggression in the right midcingulate cortex (MCC). The cingulate cortex is part of the limbic system and densely connected to the prefrontal cortex (Devinsky *et al.* 1995). The cingulate cortices are implicated in functions including emotion regulation, motivation, conflict monitoring, error detecting and cognitive control. In a review, Etkin *et al.* (2011) proposed that the rostral anterior cingulate cortex (ACC) together with dorsomedial prefrontal cortex (dmPFC) are involved in emotion regulation while the MCC together with supplementary motor area (SMA) and pre-SMA are involved in reappraisal and expression. A thinner MCC may be associated with impairment in information integration and generating adaptive responses (Shackman *et al.* 2011; Hoffstaedter *et al.* 2013, 2014). For example, violent schizophrenia patients demonstrated ACC hyperactivations compared to their non-violent or healthy counterparts when viewing negative pictures (Tikàsz *et al.* 2016). Aberrant activities of cingulate cortex and structural changes are often reported to be linked to emotion-related negative symptoms (Bersani *et al.* 2014) while other studies discovered the auditory

hallucinations were associated with ACC (Gleghorn *et al.* 1990; Noga *et al.* 1995). Particularly, a study had showed that the caudal ACC (i.e., midcingulate cortex) was recruited only when the healthy subjects heard either a real or hallucinated stimulus but not imagination (Szechtman *et al.* 1998). It is noteworthy that structural abnormalities within the cingulate cortex are not specific to auditory hallucination in schizophrenia. IED individuals also displayed reduced gray matter volume within the cingulate cortex (Coccaro *et al.* 2016). The transdiagnostic structural abnormalities suggest that the cingulate cortex serves more general cognitive control processes including emotion regulation, self-regulation, socioemotional information integration and decision making. Thinner midcingulate cortices in schizophrenia may lead to confusion in evaluating a non-threatening situation (e.g., positive symptoms) and impairment in controlling inappropriate responses (e.g., aggression) (Shackman *et al.* 2011; Vogt 2016).

From Misperception to Aggression in Schizophrenia

Previous studies showed that TCO symptoms increase the risk of violent behaviors in schizophrenia (Fanning *et al.* 2011). A certain degree of variation in aggressive traits of

schizophrenia patients can be explained by positive symptoms, suggesting an at least partially shared neurobiological basis between aggression and positive symptoms. Our results demonstrated that there is an overlapping pattern of thinner cortical thickness associated with both positive symptoms and aggression. Impaired structural integrity of the lateral temporal lobe may lead to auditory misperception in schizophrenia. The impaired midcingulate cortex may, in turn, not be able to suppress or channel such perceived threats, increasing the likelihood of aggressive expressions. This could offer a neurobiological explanation for why a subset of positive symptoms (i.e., TCO symptoms) may be a useful predictor of aggression. However, an important question whether both positive symptoms and aggression are moderated by a common cognitive factor or aggression is moderated or mediated by positive symptoms remains unanswered. Future studies should address this question and also focus on a specific assessment of TCO symptoms.

Surprisingly, we did not observe any structural abnormalities within prefrontal regions associated with aggression. These regions were deemed to be an important hub for a top-down “brake” of initiated responses and proposed in many neural models of human aggression (Davidson *et al.* 2000; Blair 2010, 2016; Coccaro *et al.* 2011). This could be due to

reduced power since our aggression score was only indexed by two items in the PANSS. Especially the use of the item “poor impulse control” may bias our findings towards reactive aggression (i.e., impulsive aggressive response to immediate threat) and against proactive aggression (i.e., being aggressive instrumentally in order to obtain a desirable outcome). Please note that although reactive aggression is comparatively well studied, little is known about the neural correlates of proactive aggression (Wrangham 2018). At least regarding structural brain anomalies, a clear difference between reactive and proactive aggression has not been found so far (Yang et al. 2017). Still, indirect evidence links proactive aggression to prefrontal regions. For example, a study found that applying non-invasive brain simulation to the right dorsolateral prefrontal cortex reduced proactive aggressive behavior in male participants (Dambacher et al. 2015). The General Aggression Model (Anderson & Bushman 2002; Allen et al. 2018) proposed that a reappraisal process is critical in a thoughtful outcome (even an aggressive one). Given that proactive aggression requires higher level of cognitive abilities such as self-regulation and reappraisal, abnormalities in ventral medial prefrontal cortex (Etkin et al. 2011) may play a role too. Shifting the focus towards proactive aggression may indeed lead towards a characterization of anomalies within prefrontal regions. Furthermore, measuring and observing aggression and/or impulsivity is certainly a challenge

for research, as respective studies hardly measure acts of aggression per se, but rely usually rather on proxy measures, such as rating scales, etc. In the present study, the differences in cortical thickness within the ventral medial prefrontal cortex were only moderated by positive symptoms.

Heterogeneity of Aggression and Clinical Manifestations in Schizophrenia

Aggression in schizophrenia is a multifaceted construct attributed to various factors (Blake & Grafman 2004; Volavka & Citrome 2008, 2011; Hoptman 2015), including personal dispositions (e.g., personality, genetics and epigenetics), life-history (e.g., childhood adversities, exposure to violence, and socioeconomic status), clinical manifestations (e.g., schizophrenia symptomatology and comorbidity with substance misuse disorders or others) and treatment (e.g., cumulative antipsychotic dosage). In particular, comorbidity, such as substance abuse (Fazel *et al.* 2009) in schizophrenia increases the risk of violence by more than 2-fold (Arseneault *et al.* 2000). The current study design did not allow us to clarify the developmental trajectory of aggression in schizophrenia. The differences of cortical thickness in schizophrenia associated with both positive symptoms and aggression might indicate that

these regions are the critical hubs that are severely influenced by these abovementioned factors. Particularly, regions like the medial orbitofrontal gyrus and insula showed relatively higher unexplained variances after addressing sex, age and symptom severity. Future studies could examine whether other factors, such as dosage of antipsychotic drugs or a history of substance abuse, could explained these variances. Similar to aggression, schizophrenia is often described as a heterogenous disorder while individual with schizophrenia may present clinical presentations differently (Tsuang *et al.* 1990). Data collection across the globe may even aggravate the heterogeneity issue. As mentioned above, clinical manifestations could contribute to expression of aggression. Therefore, future studies could investigate the effect of diagnostic heterogeneity on aggression.

Limitations of Generalization and Methodological Considerations

This study encounters several limitations related to generalization. First, our operationalization of aggression through using only 2 items (i.e., hostility and poor impulse control) from the PANSS might bias our findings. The concept of aggression may not be fully covered by only using these two items. Future study could employ a comprehensive scale like

Buss-Perry Aggression Questionnaire (Buss & Perry 1992) to measure aggression. Second, the current symptom scores relied on observation from medical clinicians. A multi-perspective measurement, adding self-reports and reports from close friends or relatives, could offer a more complete profile of the participants. Another issue is that the current study does not have actual measurement of clinical characteristics of healthy controls. In the analysis, healthy controls were assumed to have no manifestation of any positive symptoms and aggression. However, it is likely that some healthy subjects would have subclinical positive symptoms or elevated aggressive traits. However, with a large sample in this study the majority of healthy participants should score 0 in most of the symptom items, while only a very small portion of them could be reasonably expected score high in some of them. Thus, the results should not be biased significantly, as outliers within the healthy population should average out. due to the small sample size. Though, we acknowledge the lack of available scores for healthy controls as a limitation of this study.

This study also encounters some methodological considerations. First, confounding variables like the FreeSurfer version and working environment might affect the results of parcellation although other published studies within the Schizophrenia Working Group using a similar

dataset did not document effect of FreeSurfer version and working environment on the structural difference across study sties (van Erp *et al.* 2016). Second, similar to retrospective meta-analyses, our approach is limited by the availability of information. Although the brain imaging protocol was synchronized, availability of clinical information still varies. Missing data like duration of illness and information on actual and past medication impaired the power of the current analyses. However, the effect sizes in our models after controlling sex and age as well as the symptom severity could be explained by a relative low heterogeneity alone, indicating lower variance in the effect size estimation across sites in different brain ROIs. Third, we should interpret these results with caution since the biological nature of cortical thickness is still unclear, but it is considered to reflect the integrity of cortical neurons. Since the organization of the cortical thickness network showed vigorous small-world properties (He *et al.* 2007), a thinner cortex may indicate a poorer neuronal connectivity. Finally, meta-regression analyses must be interpreted with caveats because of possible confounds such as Yule-Simpson's Paradox (Goltz 2010). However, it is still useful for hypothesis generation for future studies.

Conclusions

An overlapping pattern of thinner cortical thickness in the left lateral temporal lobe and right midcingulate cortex between schizophrenia and their healthy controls was moderated by both positive symptoms and aggression, providing neurobiological evidence to elucidate the link between these symptoms. Our findings suggested that a portion of aggressive behaviors in schizophrenia can be explained by loss of tissue integrity in regions related to positive symptoms such as formal thought disorder and auditory misperception, and cognitive impairments reflecting the difficulties to deploy an adaptive reaction towards perceived threats. Follow-up studies are necessary to address issues such as heterogeneity and medication effect.

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Conflicts of interest:

All authors have no conflict of interest related to this study.

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Figures and Tables

Figure 1. Moderation Effects on Regional Cortical Thinning Controlled for Sex and Age. The right color bar represents the standardized beta coefficients on the cortical thinning between the control group compared to case group. Those beta coefficients with an FDR adjusted *p* value higher than 0.06 was set to 0 for a clearer visual inspection. The surface brain is visualized by PySurfer (version 0.9.0; https://pysurfer.github.io/index.html). The color figure can refer to the online version of this paper.

Table 1. Demographics and clinical profiles of the case and control group (*N* = 1,854)

Table 2. Full meta-analytic results for thickness of brain regions of interests for cases vs controls comparison controlling for age and sex. Only significant regions are displayed.

Table 3. Effects of moderators controlling for sex and age on significant cortical thinning in individuals with schizophrenia compared to their healthy controls.

Supplementary Tables

Table S1. Site details and patient composition.