Psychological Medicine

cambridge.org/psm

Original Article

See the Appendix for additional affiliations of authors, grouped by each research site. For more details regarding the ENIGMA Schizophrenia Working Group (ENIGMA-SZ), see http://enigma.ini.usc.edu/ongoing/enigma-schizophrenia-working-group/.

*Affiliation information for all authors can be found in the appendix at the end of the article.

Cite this article: Wong TY *et al* (2019). An overlapping pattern of cerebral cortical thinning is associated with both positive symptoms and aggression in schizophrenia via the ENIGMA consortium. *Psychological Medicine* 1–12. https://doi.org/10.1017/S0033291719002149

Received: 27 November 2018
Revised: 12 July 2019
Accepted: 1 August 2019

Key words:
Aggression; cerebral cortical thinning; hostility; impulse control; positive symptoms; prospective meta-analysis; schizophrenia

Author for correspondence:
Ting Yat Wong, E-mail: twong@ukaachen.de, tywong.one@gmail.com

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

Ting Yat Wong[1,2], Joaquim Radua, Edith Pomarol-Clotet, Raymond Salvador, Anton Albajes-Eizagirre, Aleix Solanes, Erick J. Canales-Rodriguez, Amalia Guerrero-Pedraza, Salvador Sarro, Tilo Kircher, Igor Nenadic, Axel Krug, Dominik Grotegerd, Udo Dannlowski, Stefan Borgwardt, Anita Riecher-Rössler, Andre Schmidt, Christina Andreou, Christian G. Huber, Jessica Turner, Vince Calhoun, Wenhao Jiang, Sarah Clark, Esther Walton, Gianfranco Spalletta, Nerisa Banaj, Fabrizio Piras, Valentina Ciullo, Daniela Vecchio, Irina Lebedeva, Alexander S. Tomyshev, Vasily Kaleda, Tatyana Klushnik, Geraldo Busatto Filho, Marcus Vinicius Zanetti, Mauricio Henriques Serpa, Pedro Gomes Penteado Rosa, Ryota Hashimoto, Masaki Fukunaga, Anja Richter, Bernd Krämer, Oliver Gruber, Aristotle N. Voineskos, Erin W. Dickie, David Tomecek, Antonin Skoch, Filip Spaniel, Cyril Hoschl, Alessandro Bertolino, Aurora Bonvino, Annabella Di Giorgio, Laurena Holleran, Simone Ciufolini, Tiago Reis Marques, Paola Dazzan, Robin Murray, Jelle Lamsma, Wiepke Cahn, Neeltje van Haren, Ana M. Díaz-Zuluaga, Julián A. Pineda-Zapata, Cristian Vargas, Carlos López-Jaramillo, Theo G. M. van Erp, Ruben C. Gur[2] and Thomas Nickl-Jockschat[1,3]*

[1]Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital Aachen, RWTH Aachen University, Aachen, Germany; [2]Department of Psychiatry, Brain and Behavioral Laboratory, University of Pennsylvania, Philadelphia, PA, USA and [3]Department of Psychiatry, Iowa Neuroscience Institute, Carver College of Medicine, University of Iowa, Iowa City, IA, USA

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 reduced cortical gray matter thickness 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 toward 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 and 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 and 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 and 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 *et al.* (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 toward 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 (Allen and Anderson, 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 and 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 gray 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, less gray matter 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 ENIGMA 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

https://doi.org/10.1017/S0033291719002149

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 institutional 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 the 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 one dataset containing only patient data. Accordingly, the final dataset included 10 study sites worldwide (please refer to Table 1 and online Supplementary 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–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 $1 \times 1 \times 1$ mm voxel size) T_1-weighted structural brain scans locally. All imaging data were 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 upward 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 *v.* control). Effects sizes of SMDs per each 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:

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

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

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

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

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 and 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 1854 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: 22.16–44.46). Within the schizophrenia group, 27.71% of the subjects (range: 0–52.08%) were female and their duration of illness was 12.87 years (range: 0.51–19.41). The mean score of positive symptoms (i.e. sum of P1–P6) was 14.54 (range: 10.09–18.83) and the mean score of aggression symptom (i.e. sum of P7 and G14) was 3.19 (range: 2.68–4.77). Weighted mean age across healthy controls was 32.70 (range: 22.41–43.60) and 44.67% of participants (range: 0–62.50%) were female.

Meta-analysis: cortical differences between cases and controls

No regional difference in surface areas between cases and controls was found. 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,

https://doi.org/10.1017/S0033291719002149

Table 1. Demographics and clinical profiles of the case and control group ($N = 1854$)

Schizophrenia							
Site[a]	*N*	Age	Female %	Diagnosis[b]	DOI[c]	Aggression[d]	PS score[e]
01. FIDMAG	124	40.25	22.78	100% SZ	16.12	3.18	15.36
02. GAP	88	27.44	29.84	63.3% SZ, 31.7% SZAD	NA	2.74	13.28
03. COBRE	72	37.20	18.06	100% SZ	15.48	2.65	13.78
04. CAMH	144	43.95	40.68	100% SZ	19.17	2.46	12.80
05. FSL	172	39.34	31.98	100% SZ	15.04	4.77	18.83
06. RSCZ	46	22.16	34.62	93.5% Ps, 6.5% SZAD	13.17	2.28	10.09
07. ESNA	12	26.62	25.68	100% Ps	NA	3.92	18.00
08. UNIBA	53	33.36	46.82	100% SZ	13.42	3.92	14.02
09. ESO	31	30.63	52.08	58.1% Ps, 41.9% SZ	0.51	2.86	12.81
10. UMCU	160	26.79	22.84	83.1% SZ, 16.9% SZAD	3.70	2.68	13.42
Total *N*	902						
Weighted mean		34.94	27.71	–	12.87	3.19	14.54
Healthy controls							
Site	*N*	Age	Female %	Diagnosis	DOI	Aggression	PS score
01. FIDMAG	122	38.00	55.74	–	–	–	–
02. GAP	88	25.91	62.50	–	–	–	–
03. COBRE	70	35.70	28.57	–	–	–	–
04. CAMH	146	43.60	47.26	–	–	–	–
05. FSL	116	37.48	37.07	–	–	–	–
06. RSCZ	54	22.41	0	–	–	–	–
07. ESNA	69	27.26	34.78	–	–	–	–
08. UNIBA	131	27.28	49.62	–	–	–	–
09. ESO	48	28.38	52.08	–	–	–	–
10. UMCU	108	27.52	52.23	–	–	–	–
Total *N*	952						
Weighted mean		32.70	44.67	–	–	–	–

[a]FIDMAG, FIDMAG Sisters Hospitallers Research Foundation, Spain; GAP, Genetics and Psychosis First-Episode Study, UK; COBRE, Center for Biomedical Research Excellence, USA; CAMH, The Centre for Addiction and Mental Health, Canada; FSL, Fondazione Santa Lucia, Italy; RSCZ, Mental Health Research Center, Russia; ESNA, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil; UNIBA, University of Bari 'Aldo Moro', Italy; ESO, National Institute of Mental Health, Czech Republic; UMCU, University Medical Center Utrecht, the Netherlands.
[b]SZ, schizophrenia; SZAD, schizoaffective disorder; Ps, psychosis.
[c]DOI, duration of illness (years).
[d]Aggression is calculated by the sum of the PANSS item P7 for hostility and G14 for poor impulse control.
[e]PS (positive symptom) score is calculated by the sum of the first 6 PANSS items for positive symptoms (P1–P6).

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: 10–40%). This means that after controlling for sex and age, group differences (diagnosis of schizophrenia) can explain around 60–90% of variances of the differences. Details are displayed in Table 2.

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 Fig. 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 Fig. 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

https://doi.org/10.1017/S0033291719002149

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

Hemisphere	ROIs (Desikan–Killiany atlas)	Hedges' *g*	S.E.	95% CI	p_{FDR}	I^2
Left	Lateral orbitofrontal gyrus	−1.124	0.316	−1.744 to −0.504	<0.001	29.83
	Medial orbitofrontal gyrus	−1.22	0.357	−1.921 to −0.520	0.008	46.26
	Pars opercularis	−0.78	0.274	−1.317 to −0.243	0.020	4.40
	Pars orbitalis	−1.101	0.326	−1.740 to −0.462	0.008	34.27
	Pars triangularis	−1.258	0.268	−1.784 to −0.732	<0.001	<0.001
	Precuneus	−1.081	0.362	−1.790 to −0.372	0.017	43.40
	Rostral anterior cingulate cortex	−0.817	0.29	−1.385 to −0.249	0.023	12.44
	Superior frontal gyrus	−1.107	0.37	−1.833 to −0.381	0.017	43.04
Right	Caudal middle frontal gyrus	−0.893	0.304	−1.488 to −0.297	0.017	23.54
	Lateral orbitofrontal gyrus	−1.361	0.35	−2.046 to −0.676	<0.001	38.72
	Pars opercularis	−1.493	0.319	−2.118 to −0.868	<0.001	31.14
	Pars orbitalis	−0.959	0.268	−1.485 to −0.433	<0.001	<0.001
	Pars triangularis	−1.399	0.294	−1.976 to −0.822	<0.001	9.10
	Posterior cingulate cortex	−0.759	0.268	−1.285 to −0.234	0.023	<0.001
	Precuneus	−0.889	0.348	−1.572 to −0.206	0.047	43.18
	Rostral anterior cingulate cortex	−1.415	0.305	−2.013 to −0.817	<0.001	16.30

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.

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 increase 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

https://doi.org/10.1017/S0033291719002149

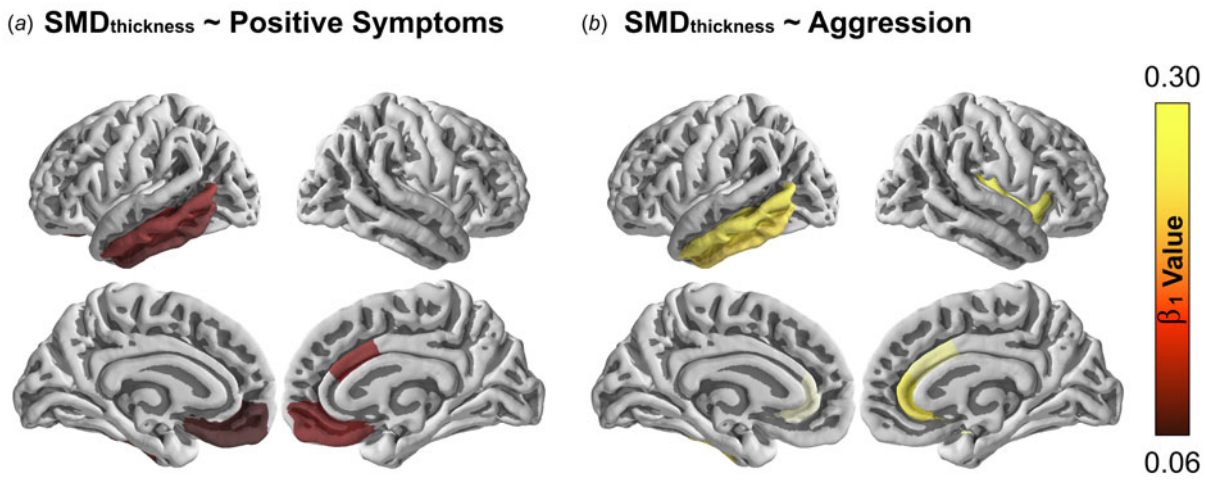

Fig. 1. Moderation effects on regional cortical thinning controlled for sex and age. The right color bar represents the standardized beta coefficients on the cortical thinning between the control group compared to the case group. Those beta coefficients with an FDR adjusted *p* value higher than 0.05 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 3. Effects of moderators controlling for sex and age on significant cortical thinning in individuals with schizophrenia compared to their healthy controls

Hemisphere	ROIs (Desikan–Killiany atlas)	β_1	S.E.	p_{FDR}	I^2
(a) $SMD_{thickness} = \beta_0 + \beta_1 \times$positive symptoms					
Left	Inferior temporal gyrus	0.075	0.023	0.017	10.04
	Medial orbitofrontal gyrus	0.064	0.021	0.041	<0.001
	Middle temporal gyrus	0.091	0.021	<0.001	<0.001
Right	Caudal anterior cingulate cortex	0.090	0.021	<0.001	<0.001
	Medial orbitofrontal gyrus	0.089	0.021	<0.001	51.76
(b) $SMD_{thickness} = \beta_0 + \beta_1 \times$aggression					
Left	Inferior temporal gyrus	0.220	0.057	<0.001	<0.001
	Middle temporal gyrus	0.230	0.061	<0.001	5.30
	Rostral anterior cingulate cortex	0.287	0.057	<0.001	<0.001
Right	Caudal anterior cingulate cortex	0.266	0.057	<0.001	<0.001
	Rostral anterior cingulate cortex	0.229	0.06	<0.001	4.95
	Insula	0.237	0.073	0.011	24.36

(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 shown 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

https://doi.org/10.1017/S0033291719002149

(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 toward reactive aggression (i.e. impulsive aggressive response to an immediate threat) and against proactive aggression (i.e. being aggressive instrumentally 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 stimulation to the right dorsolateral prefrontal cortex reduced proactive aggressive behavior in male participants (Dambacher *et al.*, 2015). The General Aggression Model (Anderson and 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 a higher level of cognitive abilities such as self-regulation and reappraisal, abnormalities in the ventral medial prefrontal cortex (Etkin *et al.*, 2011) may play a role too. Shifting the focus toward proactive aggression may indeed lead toward 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 usually rely 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 and Grafman, 2004; Volavka and 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 in 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 explain these variances. Similar to aggression, schizophrenia is often described as a heterogeneous disorder while individual with schizophrenia may present clinical presentations differently (Tsuang *et al.*, 1990). Data collected across the globe also enhance heterogeneity. 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 two 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 and 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 complete profile of the participants. Another issue is that the current study does not have an 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

https://doi.org/10.1017/S0033291719002149

although other published studies within the Schizophrenia Working Group using a similar dataset did not document the effect of FreeSurfer version and working environment on the structural difference across study sites (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, the 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 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 toward perceived threats. Follow-up studies are necessary to address issues such as heterogeneity and medication effect.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719002149.

Acknowledgement. ENIGMA was supported in part by a Consortium grant (U54 EB020403) from the NIH Institutes contributing to the Big Data to Knowledge (BD2K) Initiative, including the NIBIB and NIMH. This study is also supported by Deutsche Forschungsgemeinschaft (DFG, International Research Training Group IRTG2150). Acknowledgments for the various participating data contributors are listed in the Appendix.

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

References

Allen JJ and Anderson CA (2017) Aggression and Violence: Definitions and Distinctions. In Sturmey P. (Ed.), *The Wiley Handbook of Violence and Aggression*. Chichester, West Sussex, UK: John Wiley & Sons, Ltd, pp. 1–14.

Allen JJ, Anderson CA and Bushman BJ (2018) The general aggression model. *Current Opinion in Psychology* **19**, 75–80.

Allen P, Modinos G, Hubl D, Shields G, Cachia A, Jardri R, Thomas P, Woodward T, Shotbolt P, Plaze M and Hoffman R (2012) Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. *Schizophrenia Bulletin* **38**, 695–703.

Anderson CA and Bushman BJ (2002) Human aggression. *Annual Review of Psychology* **53**, 27–51.

Arseneault L, Moffitt TE, Caspi A, Taylor PJ and Silva PA (2000) Mental disorders and violence in a total birth cohort: results from the Dunedin study. *Archives of General Psychiatry* **57**, 979–986.

Benjamini Y and Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society* **57**, 289–300.

Bersani FS, Minichino A, Fojanesi M, Gallo M, Maglio G, Valeriani G, Biondi M and Fitzgerald PB (2014) Cingulate cortex in schizophrenia: its relation with negative symptoms and psychotic onset. A review study. *European Review for Medical and Pharmacological Sciences* **18**, 3354–3367.

Bjørkly S (2002) Psychotic symptoms and violence toward others – A literature review of some preliminary findings: part 1. Delusions. *Aggression and Violent Behavior* **7**, 617–631.

Blair RJR (2010) Psychopathy, frustration, and reactive aggression: the role of ventromedial prefrontal cortex. *British Journal of Psychology* **101**, 383–399.

Blair RJR (2016) The neurobiology of impulsive aggression. *Journal of Child and Adolescent Psychopharmacology* **26**, 4–9.

Blake P and Grafman J (2004) *The neurobiology of aggression. Lancet* **364**, 12–13.

Brennan PA, Mednick SA and Hodgins S (2000) Major mental disorders and criminal violence in a Danish birth cohort. *Archives of General Psychiatry* **57**, 494.

Buss AH and Perry M (1992) The aggression questionnaire. *Journal of Personality* **63**, 452–459.

Catani M, Dell'Acqua F, Bizzi A, Forkel SJ, Williams SC, Simmons A, Murphy DG and Thiebaut de Schotten M (2012) Beyond cortical localization in clinico-anatomical correlation. *Cortex* **48**, 1262–1287.

Cheung P, Schweitzer I, Crowley K and Tuckwell V (1997) Aggressive behaviour in schizophrenia: role of state versus trait factors. *Psychiatry Research* **72**, 41–50.

Clement S, Schauman O, Graham T, Maggioni F, Evans-Lacko S, Bezborodovs N, Morgan C, Rüsch N, Brown JSL and Thornicroft G (2015) What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychological Medicine* **45**, 11–27.

Coccaro EF, Sripada CS, Yanowitch RN and Phan KL (2011) Corticolimbic function in impulsive aggressive behavior. *Biological Psychiatry* **69**, 1153–1159.

Coccaro EF, Fitzgerald DA, Lee R, McCloskey M and Phan KL (2016) Frontolimbic morphometric abnormalities in intermittent explosive disorder and aggression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* **1**, 32–38.

Coid JW, Ullrich S, Kallis C, Keers R, Barker D, Cowden F and Stamps R (2013) The relationship between delusions and violence: findings from the East London first episode psychosis study. *JAMA Psychiatry* **70**, 465–471.

Dack C, Ross J, Papadopoulos C, Stewart D and Bowers L (2013) A review and meta-analysis of the patient factors associated with psychiatric in-patient aggression. *Acta Psychiatrica Scandinavica* **127**, 255–268.

Dambacher F, Schuhmann T, Lobbestael J, Arntz A, Brugman S and Sack AT (2015) Reducing proactive aggression through non-invasive brain stimulation. *Social Cognitive and Affective Neuroscience* **10**, 1303–1309.

Davidson RJ, Putnam KM and Larson CL (2000) Dysfunction in the neural circuitry of emotion regulation – A possible prelude to violence. *Science* **289**, 591–594.

Del Re AC (2013) compute.es: Compute Effect Sizes. R package. 0.2-2.

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS and Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* **31**, 968–980.

Devinsky O, Morrell MJ and Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. *Brain* **118**, 279–306.

Douglas KS, Guy LS and Hart SD (2009) Psychosis as a risk factor for violence to others: a meta-analysis. *Psychological Bulletin* **135**, 679–706.

Etkin A, Egner T and Kalisch R (2011) Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences* **15**, 85–93.

Fanning JR, Berman ME, Mohn RS and McCloskey MS (2011) Perceived threat mediates the relationship between psychosis proneness and aggressive behavior. *Psychiatry Research* **186**, 210–218.

Fazel S, Gulati G, Linsell L, Geddes JR and Grann M (2009) Schizophrenia and violence: systematic review and meta-analysis. *PLoS Medicine* **6**, e1000120.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, Van Der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B and Dale AM (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341–355.

Fjellvang M, Grøning L and Haukvik UK (2018) Imaging violence in schizophrenia: a systematic review and critical discussion of the MRI literature. *Frontiers in Psychiatry* **9**, 333.

Fornito A, Yücel M, Dean B, Wood SJ and Pantelis C (2009) Anatomical abnormalities of the anterior cingulate cortex in schizophrenia: bridging the gap between neuroimaging and neuropathology. *Schizophrenia Bulletin* **35**, 973–993.

Gaser C, Nenadic I, Volz HP, Büchel C and Sauer H (2004) Neuroanatomy of 'hearing voices': a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cerebral Cortex* **14**, 91–96.

Girard LC, Pingault JB, Falissard B, Boivin M, Dionne G and Tremblay RE (2014) Physical aggression and language ability from 17 to 72 months: cross-lagged effects in a population sample. *PLoS ONE* **9**, e112185.

Gleghorn JM, Garnett ES, Nahmias C, Brown GM, Kaplan RD, Szechtman H, Szechtman B, Franco S, Dermer SW and Cook P (1990) Regional brain metabolism during auditory hallucinations in chronic schizophrenia. *British Journal of Psychiatry* **157**, 562–570.

Goltz HH (2010) Yule–Simpson's paradox in research. *Practical Assessment, Research & Evaluation* **15**, 1–9.

Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W and Gur RC (1998) A follow-up magnetic resonance imaging study of schizophrenia: relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Archives of General Psychiatry* **55**, 145–152.

He Y, Chen ZJ and Evans AC (2007) Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cerebral Cortex* **17**, 2407–2419.

Hodgins S, Alderton J, Cree A, Aboud A and Mak T (2007) Aggressive behaviour, victimisation and crime among severely mentally ill patients requiring hospitalisation. *British Journal of Psychiatry* **191**, 343–350.

Hoffstaedter F, Grefkes C, Zilles K and Eickhoff SB (2013) The 'what' and 'when' of self-initiated movements. *Cerebral Cortex* **23**, 520–530.

Hoffstaedter F, Grefkes C, Caspers S, Roski C, Palomero-Gallagher N, Laird AR, Fox PT and Eickhoff SB (2014) The role of anterior midcingulate cortex in cognitive motor control: evidence from functional connectivity analyses. *Human Brain Mapping* **35**, 2741–2753.

Hoptman MJ (2015) Impulsivity and aggression in schizophrenia: a neural circuitry perspective with implications for treatment. *CNS Spectrums* **20**, 280–286.

Hoptman MJ, Volavka J, Weiss EM, Czobor P, Szeszko PR, Gerig G, Chakos M, Blocher J, Citrome LL, Lindenmayer JP, Sheitman B, Lieberman JA and Bilder RM (2005) Quantitative MRI measures of orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. *Psychiatry Research – Neuroimaging* **140**, 133–145.

Horn H, Federspiel A, Wirth M, Müller TJ, Wiest R, Wang J-J and Strik W (2009) Structural and metabolic changes in language areas linked to formal thought disorder. *The British Journal of Psychiatry* **194**, 130–138.

Kay SR, Fiszbein A and Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SCR, van der Kouwe AJW, Salat DH, Dale AM and Fischl B (2003) Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry* **60**, 878–888.

Kuroki N, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Ersner-Hershfield H, Yurgelun-Todd D, Kikinis R, Jolesz FA and McCarley RW (2006) Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. *American Journal of Psychiatry* **163**, 2103–2110.

Large MM and Nielssen O (2011) Violence in first-episode psychosis: a systematic review and meta-analysis. *Schizophrenia Research* **125**, 209–220.

Lee R, Arfanakis K, Evia AM, Fanning J, Keedy S and Coccaro EF (2016) White matter integrity reductions in intermittent explosive disorder. *Neuropsychopharmacology* **41**, 2697–2703.

Levy DA, Bayley PJ and Squire LR (2004) The anatomy of semantic knowledge: medial vs. lateral temporal lobe. *Proceedings of the National Academy of Sciences* **101**, 6710–6715.

Link BG, Stueve A and Phelan J (1998) Psychotic symptoms and violent behaviors: probing the components of 'threat/control-override' symptoms. *Social Psychiatry and Psychiatric Epidemiology* **33**, S55–S60.

Manninen M, Lindgren M, Huttunen M, Ebeling H, Moilanen I, Kalska H, Suvisaari J and Therman S (2013) Low verbal ability predicts later violence in adolescent boys with serious conduct problems. *Nordic Journal of Psychiatry* **67**, 289–297.

Mesulam M-M (1998) From sensation to cognition. *Brain* **121**, 1013–1052.

Modinos G, Costafreda SG, Van Tol MJ, McGuire PK, Aleman A and Allen P (2013) Neuroanatomy of auditory verbal hallucinations in schizophrenia: a quantitative meta-analysis of voxel-based morphometry studies. *Cortex* **49**, 1046–1055.

Narayan VM, Narr KL, Kumari V, Woods RP, Thompson PM, Toga AW and Sharma T (2007) Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. *American Journal of Psychiatry* **164**, 1418–1427.

Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR, Robinson D, Sevy S, Gunduz-Bruce H, Wang YP, DeLuca H and Thompson PM (2005) Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cerebral Cortex* **15**, 708–719.

Nenadic I, Yotter RA, Sauer H and Gaser C (2015) Patterns of cortical thinning in different subgroups of schizophrenia. *British Journal of Psychiatry* **206**, 479–483.

Noga JT, Aylward E, Barta PE and Pearlson GD (1995) Cingulate gyrus in schizophrenic patients and normal volunteers. *Psychiatry Research: Neuroimaging* **61**, 201–208.

Nolan KA, Czobor P, Roy BB, Platt MM, Shope CB, Citrome LL and Volavka J (2003) Characteristics of assaultive behaviour among psychiatric inpatients. *Psychiatric Services* **54**, 1012–1016.

Onitsuka T, Shenton ME, Salisbury DF, Dickey CC, Kasai K, Toner SK, Frumin M, Kikinis R, Jolesz FA and McCarley RW (2004) Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *American Journal of Psychiatry* **161**, 1603–1611.

R Core Team (2003) *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing.

Ross CA, Margolis RL, Reading SAJ, Pletnikov M and Coyle JT (2006) Neurobiology of schizophrenia. *Neuron* **52**, 139–153.

Sandyk R (1993) Aggressive behavior in schizophrenia: relationship to age of onset and cortical atrophy. *International Journal of Neuroscience* **68**, 1–10.

Satterthwaite TD, Wolf DH, Calkins ME, Vandekar SN, Erus G, Ruparel K, Roalf DR, Linn KA, Elliott MA, Moore TM, Hakonarson H, Shinohara RT, Davatzikos C, Gur RC and Gur RE (2016) Structural brain abnormalities in youth with psychosis spectrum symptoms. *JAMA Psychiatry* **73**, 515.

Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Schachtzabel C, Reichenbach JR, Sauer H and Schlösser RGM (2010) Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. *Psychiatry Research – Neuroimaging* **182**, 134–140.

Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ and Davidson RJ (2011) The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience* **12**, 154–167.

Siever LJ (2008) Neurobiology of aggression and violence. *American Journal of Psychiatry* **165**, 429–442.

Song H and Min SK (2009) Aggressive behavior model in schizophrenic patients. *Psychiatry Research* **167**, 58–65.

Soyka M (2011) Neurobiology of aggression and violence in schizophrenia. *Schizophrenia Bulletin* **37**, 913–920.

Stuart H (2003) Violence and mental illness: an overview. *World Psychiatry* **2**, 121–124.

Swanson JW, Swartz MS, Van Dorn RA, Elbogen EB, Wagner HR, Rosenheck RA, Stroup TS, McEvoy JP and Lieberman JA (2006)

A national study of violent behavior in persons with schizophrenia. *Archives of General Psychiatry* **63**, 490–499.

Szechtman H, Woody E, Bowers KS and Nahmias C (1998) Where the imaginal appears real: a positron emission tomography study of auditory hallucinations. *Proceedings of the National Academy of Sciences* **95**, 1956–1960.

Thomas WI and Thomas DS (1928) *The Child in America: Behavior Problems and Programs*. New York: A. A. Knopf.

Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, Toro R, Jahanshad N, Schumann G, Franke B, Wright MJ, Martin NG, Agartz I, Alda M, Alhusaini S, Almasy L, Almeida J, Alpert K, Andreasen NC, Andreassen OA, Apostolova LG, Appel K, Armstrong NJ, Aribisala B, Bastin ME, Bauer M, Bearden CE, Bergmann Ø, Binder EB, Blangero J, Bockholt HJ, Bøen E, Bois C, Boomsma DI, Booth T, Bowman IJ, Bralten J, Brouwer RM, Brunner HG, Brohawn DG, Buckner RL, Buitelaar J, Bulayeva K, Bustillo JR, Calhoun VD, Cannon DM, Cantor RM, Carless MA, Caseras X, Cavalleri GL, Chakravarty MM, Chang KD, Ching CRK, Christoforou A, Cichon S, Clark VP, Conrod P, Coppola G, Crespo-Facorro B, Curran JE, Czisch M, Deary IJ, de Geus EJC, den Braber A, Delvecchio G, Depondt C, de Haan L, de Zubicaray GI, Dima D, Dimitrova R, Djurovic S, Dong H, Donohoe G, Duggirala R, Dyer TD, Ehrlich S, Ekman CJ, Elvsåshagen T, Emsell L, Erk S, Espeseth T, Fagerness J, Fears S, Fedko I, Fernández G, Fisher SE, Foroud T, Fox PT, Francks C, Frangou S, Frey EM, Frodl T, Frouin V, Garavan H, Giddaluru S, Glahn DC, Godlewska B, Goldstein RZ, Gollub RL, Grabe HJ, Grimm O, Gruber O, Guadalupe T, Gur RE, Gur RC, Göring HHH, Hagenaars S, Hajek T, Hall GB, Hall J, Hardy J, Hartman CA, Hass J, Hatton SN, Haukvik UK, Hegenscheid K, Heinz A, Hickie IB, Ho BC, Hoehn D, Hoekstra PJ, Hollinshead M, Holmes AJ, Homuth G, Hoogman M, Hong LE, Hosten N, Hottenga JJ, Hulshoff Pol HE, Hwang KS, Jack CR, Jenkinson M, Johnston C, Jönsson EG, Kahn RS, Kasperaviciute D, Kelly S, Kim S, Kochunov P, Koenders L, Krämer B, Kwok JBJ, Lagopoulos J, Laje G, Landen M, Landman BA, Lauriello J, Lawrie SM, Lee PH, Le Hellard S, Lemaître H, Leonardo CD, Li C, Liberg B, Liewald DC, Liu X, Lopez LM, Loth E, Lourdusamy A, Luciano M, Macciardi F, Machielsen MWJ, MacQueen GM, Malt UF, Mandl R, Manoach DS, Martinot JL, Matarin M, Mather KA, Mattheisen M, Mattingsdal M, Meyer-Lindenberg A, McDonald C, McIntosh AM, McMahon FJ, McMahon KL, Meisenzahl E, Melle I, Milaneschi Y, Mohnke S, Montgomery GW, Morris DW, Moses EK, Mueller BA, Muñoz Maniega S, Mühleisen TW, Müller-Myhsok B, Mwangi B, Nauck M, Nho K, Nichols TE, Nilsson L, Nugent AC, Nyberg L, Olvera RL, Oosterlaan J, Ophoff RA, Pandolfo M, Papalampropoulou-Tsiridou M, Papmeyer M, Paus T, Pausova Z, Pearlson GD, Penninx BW, Peterson CP, Pfennig A, Phillips M, Pike GB, Poline JB, Potkin SG, Pütz B, Ramasamy A, Rasmussen J, Rietschel M, Rijpkema M, Risacher SL, Roffman JL, Roiz-Santiañez R, Romanczuk-Seiferth N, Rose EJ, Royle NA, Rujescu D, Ryten M, Sachdev PS, Salami A, Satterthwaite TD, Savitz J, Saykin AJ, Scanlon C, Schmaal L, Schnack HG, Schork AJ, Schulz SC, Schür R, Seidman L, Shen L, Shoemaker JM, Simmons A, Sisodiya SM, Smith C, Smoller JW, Soares JC, Sponheim SR, Sprooten E, Starr JM, Steen VM, Strakowski S, Strike L, Sussmann J, Sämann PG, Teumer A, Toga AW, Tordesillas-Gutierrez D, Trabzuni D, Trost S, Turner J, Van den Heuvel M, van der Wee NJ, van Eijk K, van Erp TGM, van Haren NEM, van 't Ent D, van Tol MJ, Valdés Hernández MC, Veltman DJ, Versace A, Völzke H, Walker R, Walter H, Wang L, Wardlaw JM, Weale ME, Weiner MW, Wen W, Westlye LT, Whalley HC, Whelan CD, White T, Winkler AM, Wittfeld K, Woldehawariat G, Wolf C, Zilles D, Zwiers MP, Thalamuthu A, Schofield PR, Freimer NB, Lawrence NS, Drevets W, Alzheimer's Disease Neuroimaging Initiative, EPIGEN Consortium, IMAGEN Consortium, Saguenay Youth Study (SYS) Group (2014) The ENIGMA consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging and Behavior* **8**, 153–182.

Tikàsz A, Potvin S, Lungu O, Joyal CC, Hodgins S, Mendrek A and Dumais A (2016) Anterior cingulate hyperactivations during negative emotion processing among men with schizophrenia and a history of violent behavior. *Neuropsychiatric Disease and Treatment* **12**, 1397–1410.

Torrey EF (2011) Stigma and violence: isn't it time to connect the dots? *Schizophrenia Bulletin* **37**, 892–896.

Tsuang MT, Lyons MJ and Faraone SV (1990) Heterogeneity of schizophrenia. Conceptual models and analytic strategies. *British Journal of Psychiatry* **156**, 17–26.

van der Gaag M, Hoffman T, Remijsen M, Hijman R, de Haan L, van Meijel B, van Harten PN, Valmaggia L, de Hert M, Cuijpers A and Wiersma D (2006) The five-factor model of the positive and negative syndrome scale II: a ten-fold cross-validation of a revised model. *Schizophrenia Research* **85**, 280–287.

van Erp TGM, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, Agartz I, Westlye LT, Haukvik UK, Dale AM, Melle I, Hartberg CB, Gruber O, Kraemer B, Zilles D, Donohoe G, Kelly S, McDonald C, Morris DW, Cannon DM, Corvin A, Machielsen MWJ, Koenders L, de Haan L, Veltman DJ, Satterthwaite TD, Wolf DH, Gur RC, Gur RE, Potkin SG, Mathalon DH, Mueller BA, Preda A, Macciardi F, Ehrlich S, Walton E, Hass J, Calhoun VD, Bockholt HJ, Sponheim SR, Shoemaker JM, van Haren NEM, Pol HEH, Ophoff RA, Kahn RS, Roiz-Santiañez R, Crespo-Facorro B, Wang L, Alpert KI, Jönsson EG, Dimitrova R, Bois C, Whalley HC, McIntosh AM, Lawrie SM, Hashimoto R, Thompson PM and Turner JA (2016) Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry* **21**, 547–553.

van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, Pearlson GD, Yao N, Fukunaga M, Hashimoto R, Okada N, Yamamori H, Bustillo JR, Clark VP, Agartz I, Mueller BA, Cahn W, de Zwarte SMC, Hulshoff Pol HE, Kahn RS, Ophoff RA, van Haren NEM, Andreassen OA, Dale AM, Doan NT, Gurholt TP, Hartberg CB, Haukvik UK, Jørgensen KN, Lagerberg TV, Melle I, Westlye LT, Gruber O, Kraemer B, Richter A, Zilles D, Calhoun VD, Crespo-Facorro B, Roiz-Santiañez R, Tordesillas-Gutiérrez D, Loughland C, Carr VJ, Catts S, Cropley VL, Fullerton JM, Green MJ, Henskens FA, Jablensky A, Lenroot RK, Mowry BJ, Michie PT, Pantelis C, Quidé Y, Schall U, Scott RJ, Cairns MJ, Seal M, Tooney PA, Rasser PE, Cooper G, Shannon Weickert C, Weickert TW, Morris DW, Hong E, Kochunov P, Beard LM, Gur RE, Gur RC, Satterthwaite TD, Wolf DH, Belger A, Brown GG, Ford JM, Macciardi F, Mathalon DH, O'Leary DS, Potkin SG, Preda A, Voyvodic J, Lim KO, McEwen S, Yang F, Tan Y, Tan S, Wang Z, Fan F, Chen J, Xiang H, Tang S, Guo H, Wan P, Wei D, Bockholt HJ, Ehrlich S, Wolthusen RPF, King MD, Shoemaker JM, Sponheim SR, *et al.* (2018) Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium. *Biological Psychiatry* **84**, 644–654.

Van Lutterveld R, Van Den Heuvel MP, Diederen KMJ, De Weijer AD, Begemann MJH, Brouwer RM, Daalman K, Blom JD, Kahn RS and Sommer IE (2014) Cortical thickness in individuals with non-clinical and clinical psychotic symptoms. *Brain* **137**, 2664–2669.

Vicens V, Radua J, Salvador R, Anguera-Camós M, Canales-Rodríguez EJ, Sarró S, Maristany T, McKenna PJ and Pomarol-Clotet E (2016) Structural and functional brain changes in delusional disorder. *British Journal of Psychiatry* **208**, 153–159.

Viechtbauer W (2010) Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* **36**, 1–48.

Vogt BA (2016) Midcingulate cortex: structure, connections, homologies, functions and diseases. *Journal of Chemical Neuroanatomy* **74**, 28–46.

Volavka J and Citrome L (2008) Heterogeneity of violence in schizophrenia and implications for long-term treatment. *International Journal of Clinical Practice* **62**, 1237–1245.

Volavka J and Citrome L (2011) Pathways to aggression in schizophrenia affect results of treatment. *Schizophrenia Bulletin* **37**, 921–929.

Wallace C, Mullen PE and Burgess P (2004) Criminal offending in schizophrenia over a 25-year period marked by deinstitutionalization and increasing prevalence of comorbid substance use disorders. *American Journal of Psychiatry* **161**, 716–727.

https://doi.org/10.1017/S0033291719002149

Wehring HJ and Carpenter WT (2011) Violence and schizophrenia. *Schizophrenia Bulletin* **37**, 877–878.

Weiss EM (2012) Neuroimaging and neurocognitive correlates of aggression and violence in schizophrenia. *Scientifica* **2012**, 1–12.

Wensing T, Cieslik EC, Müller VI, Hoffstaedter F, Eickhoff SB and Nickl-Jockschat T (2017) Neural correlates of formal thought disorder: an activation likelihood estimation meta-analysis. *Human Brain Mapping* **38**, 4946–4965.

Wrangham RW (2018) Two types of aggression in human evolution. *Proceedings of the National Academy of Sciences* **115**, 245–253.

Yang Y, Joshi SH, Jahanshad N, Thompson PM and Baker LA (2017) Neural correlates of proactive and reactive aggression in adolescent twins. *Aggressive Behavior* **43**, 230–240.

Appendix

ENIGMA Schizophrenia Working Group: authors' affiliations and their acknowledgment

Joaquim Radua[1,2,3,4,5], Edith Pomarol-Clotet[1,2], Raymond Salvador[1,2], Anton Albajes-Eizagirre[1,2], Aleix Solanes[1,3], Erick J. Canales-Rodriguez[1,2,6,7], Amalia Guerrero-Pedraza[8] and Salvador Sarro[1,2]

[1]FIDMAG Germanes Hospitalàries, Sant Boi de Llobregat, Barcelona, Spain

[2]Mental Health Research Networking Center (CIBERSAM), Madrid, Spain

[3]Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[4]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[5]Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[6]Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

[7]Signal Processing Lab (LTS5), École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

[8]Benito Menni Complex Assistencial en Salut Mental, Sant Boi de Llobregat, Spain

Acknowledgment: This work was supported by the Catalan Government (2017-SGR-1271 to FIDMAG) and several grants from the Plan Nacional de I+D+i 2008–2011 and 2013–2016, and the Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, 'Investing in your future'): Miguel Servet Research Contracts (MS14/00041 to JR, CPII13/00018 to RS and CPii16/00018 to EP-C) and Research Project Grants (PI14/01151 to RS, PI14/01148 to EP-C, PI14/00292 and CP14/00041 to JR, and PI15/00277 to EC-R).

Tilo Kircher[1], Igor Nenadic[1], Axel Krug[1], Dominik Grotegerd[2] and Udo Dannlowski[2]

[1]University of Marburg, Department of Psychiatry and Psychotherapy, Marburg, Germany

[2]University of Münster, Department of Psychiatry, Marburg, Germany

Acknowledgment: This work was funded by the German Research Foundation (DFG, grant FOR2107 KI 588/14-1, KI 588/14-2, KI 588/17-1 to TK; grant KR 3822/7-1, KR 3822/7-2 to AK, grant NE 2254/1-2 to IN; grant DA1151/5-1, DA1151/5-2 to UD; SFB-TRR58, Projects C09 and Z02 to UD) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/012/17 to UD).

Stefan Borgwardt[1], Anita Riecher-Rössler[1], Andre Schmidt[1], Christina Andreou[1] and Christian Huber[1]

[1]Department of Psychiatry (UPK), University of Basel, Basel, Switzerland

Acknowledgment: We would like to thank the UPK Forschungsförderungsfonds for grant support.

Jessica Turner[1], Vince Calhoun[2,3], Wenhao Jiang[1], Sarah Clark[1] and Esther Walton[4]

[1]Department of Psychology, Georgia State University, Atlanta, Georgia, USA

[2]The Mind Research Network, Albuquerque, NM, USA

[3]Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM, USA

[4]Department of Psychology, University of Bath, Bath, UK

Acknowledgment: The imaging data and phenotypic information were collected and shared by the Mind Research Network and the University of New Mexico funded by a National Institute of Health Center of Biomedical Research Excellence (COBRE) grant 1P20RR021938-01A2.

Gianfranco Spalletta[1,2], Nerisa Banaj[1], Fabrizio Piras[1], Valentina Ciullo[1,3] and Daniela Vecchio[1]

[1]Laboratory of Neuropsychiatry, Department of Clinical and Behavioral Neurology, IRCCS Santa Lucia Foundation, Rome, Italy

[2]Division of Neuropsychiatry, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA

[3]Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Italy

Acknowledgment: This work was supported by the Italian Ministry of Health grants RC 12-13-14-15-16-17-18-19/A.

Irina Lebedeva[1], Alexander S. Tomyshev[1], Vasily Kaleda[1] and Tatyana Klushnik[1]

[1]Mental Health Research Center, Moscow, Russia

Geraldo Busatto Filho[1], Marcus Vinicius Zanetti[1,2], Mauricio Henriques Serpa[1] and Pedro Gomes Penteado Rosa[1]

[1]Laboratory of Psychiatric Neuroimaging (LIM-21), Departamento e Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

[2]Instituto de Ensino e Pesquisa, Hospital Sírio-Libanês, Sao Paulo, SP, Brazil

Ryota Hashimoto[1,2] and Masaki Fukunaga[3]

[1]Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan

[2]Osaka University, Osaka, Japan

[3]Division of Cerebral Integration, National Institute for Physiological Sciences, Aichi, Japan

Anja Richter[1,2], Bernd Krämer[1] and Oliver Gruber[1]

[1]Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, University Hospital Heidelberg, 69115 Heidelberg, Germany

[2]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Aristotle N. Voineskos[1,2] and Erin W. Dickie[1,2]

[1]Addiction and Mental Health, Toronto, Canada

[2]Department of Psychiatry, University of Toronto, Toronto, Canada

Acknowledgment: The CAMH datasets were collected and shared with support from the CAMH Foundation, Canadian Institutes of Health Research, the Ontario Mental Health Foundation and the Brain and Behavior Research Foundation.

David Tomecek[1,2,3], Antonin Skoch[1,4], Filip Spaniel[1], Cyril Hoschl[1]

[1]National Institute of Mental Health, Klecany, Czech Republic

[2]Institute of Computer Science, Czech Academy of Sciences, Czech Technical University in Prague, Prague, Czech Republic

[3]Faculty of Electrical Engineering, Czech Technical University in Prague, Prague, Czech Republic

[4]MR Unit, Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Acknowledgment: The National Institute of Mental Health, Klecany, Czech Republic was supported by project no. LO1611 with funding from the MEYS under the NPU I program.

Alessandro Bertolino[1], Aurora Bonvino[1] and Annabella Di Giorgio[2]

[1]Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Italy

[2]Section of Clinical Neuroscience, Department of Experimental and Clinical Medicine, Università Politecnica delle Marche, Ancona, Italy

Laurena Holleran[1]

[1]Neuroimaging and Cognitive Genomics Group, NUI Galway, Ireland

Simone Ciufolini[1], Tiago Reis Marques[1], Paola Dazzan[1] and Robin Murray[1]

[1]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Jelle Lamsma[1,2], Wiepke Cahn[1,3] and Neeltje van Haren[1,4]

[1]Department of Psychiatry, University Medical Centre Utrecht, Utrecht, The Netherlands

https://doi.org/10.1017/S0033291719002149

[2]Department of Psychiatry, University of Oxford, Oxford, UK
[3]Utrecht Mental Health Institute, Utrecht, The Netherlands
[4]Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

Ana M. Díaz-Zuluaga[1], Julián A. Pineda-Zapata[2], Cristian Vargas[1] and Carlos López-Jaramillo[1,3]

[1]Research Group of Psychiatry GIPSI, Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia
[2]Research Group, Instituto de Alta Tecnología Médica (IATM), Medellín, Antioquia, Colombia
[3]Mood Disorders Program, Hospital Universitario San Vicente Fundación, Medellín, Colombia

Theo G. M. van Erp[1,2]

[1]Clinical Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, University of California, Irvine, California, USA
[2]Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, CA 92697, USA

Acknowledgement: TGMvE is supported by the ENIGMA's NIH Big Data to Knowledge (BD2K) initiative U54 EB020403, and the ENIGMA Sex Differences Initiative R01 MH116147.

https://doi.org/10.1017/S0033291719002149