Psychological Medicine (2017), **47**, 401–413. © Cambridge University Press 2016
doi:10.1017/S0033291716002683

REVIEW ARTICLE

Common pattern of gray-matter abnormalities in drug-naive and medicated first-episode schizophrenia: a multimodal meta-analysis

C. Shah[1,2], W. Zhang[2], Y. Xiao[2], L. Yao[2], Y. Zhao[2], X. Gao[2], L. Liu[2], J. Liu[2], S. Li[2], B. Tao[2], Z. Yan[1], Y. Fu[1], Q. Gong[2] and S. Lui[1,2]*

[1] *Radiology Department, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China*
[2] *Department of Radiology, Huaxi MR Research Center (HMRRC), the Center for Medical Imaging, West China Hospital of Sichuan University, Chengdu, Sichuan, China*

Studies of schizophrenia at drug-naive state and on antipsychotic medication have reported a number of regions of gray-matter (GM) abnormalities but the reports have been inconsistent. The aim of this study was to conduct multimodal meta-analysis to compare the cross-sectional voxel-based morphometry studies of brain GM in antipsychotic-naive first-episode schizophrenia (AN-FES) and those with antipsychotic treatment within 1 year (AT-FES) to determine the similarities and differences in these groups. We conducted two separate meta-analyses containing 24 studies with a sample size of 801 patients and 957 healthy controls. A multimodal meta-analysis method was used to compare the findings between AN-FES and AT-FES. Meta-regression analyses were done to determine the influence of different variables including age, duration of illness, and positive and negative symptom scores. Finally, jack-knife analyses were done to test the robustness of the results. AN-FES and AT-FES showed common patterns of GM abnormalities in frontal (gyrus rectus), superior temporal, left hippocampal and insular cortex. GM in the left supramarginal gyrus and left middle temporal gyrus were found to be increased in AN-FES but decreased in AT-FES, whereas left median cingulate/paracingulate gyri and right hippocampus GM was decreased in AN-FES but increased in AT-FES. Findings suggest that both AN-FES and AT-FES share frontal, temporal and insular regions as common anatomical regions to be affected indicating these to be the primary regions of GM abnormalities in both groups.

Received 5 May 2016; Revised 14 September 2016; Accepted 15 September 2016; First published online 25 October 2016

Key words: Antipsychotics, first-episode schizophrenia, gray matter, meta-analysis, magnetic resonance imaging, naive.

Introduction

Schizophrenia is complex clinical syndrome with abnormalities of thinking, emotion, behavior and social functioning. Neuroimaging studies have shown gray matter (GM) abnormalities involving almost all brain regions with evidence suggesting that these changes are due to progressive changes affecting both brain anatomy and function (Vita *et al.* 2012; Anticevic *et al.* 2015; Zhang *et al.* 2015) as well as acute effects of antipsychotic treatments (Chakos *et al.* 1994; Keshavan *et al.* 1998; Kubicki *et al.* 2002; Dazzan *et al.* 2005; Girgis *et al.* 2006; Kasparek *et al.* 2007; Crespo-Facorro *et al.* 2008; Chua *et al.* 2009; Deng *et al.* 2009; Lui *et al.* 2010; Lei *et al.* 2015; Zhang *et al.* 2015). While many studies showed neuroanatomical alterations, results of imaging studies in treated and untreated first-episode cases have been inconsistent. A longitudinal study of first-episode schizophrenia (FES) ($n = 813$ patients) by Vita *et al.* (2012) found progressive loss of cerebral GM volume especially in frontal, temporal and parietal lobes and left Heschl gyrus over 3 years. Another study by Andreasen *et al.* (2011) ($n = 202$) reported significant decreases in multiple GM (total cerebral, frontal, thalamus) and white-matter regions (total cerebral, frontal, temporal, parietal) over 15 years, and a corresponding increase in cerebrospinal fluid (lateral ventricles and frontal, temporal and parietal sulci), suggesting a neuroprogressive component in schizophrenia. However, evidence from the meta-analysis of longitudinal studies of schizophrenia may be affected by the fact that most reported longitudinal studies are those with positive results rather than negative results, which therefore increases the likelihood of false-positive rates. Furthermore, the observed changes in longitudinal studies could be the effect of illness duration and treatment. Additionally, there is a high probability that such studies can suffer from cohort effects, for

* Address for correspondence: Professor S. Lui, Radiology Department of the Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, China; Department of Radiology, Huaxi MR Research Center (HMRRC), West China Hospital of Sichuan University, Chengdu, Sichuan, China.
(Email: lusuwcums@tom.com)

example, sometimes the environment to which a given cohort is exposed in the latter part of the growth cycle may differ substantially from that which obtained when the sample was taken first (Labarre, 1993).

As several studies have now examined brain anatomy in first-episode patients and in recently treated first-episode patients, a meta-analysis of these findings may provide a broader characterization of brain anatomic alterations early in the course of schizophrenia. Haijma *et al.* (2013) and van Erp *et al.* (2014) presented meta-analysis on brain volume measurements using harmonized methods comparing patients with controls providing important clues regarding effect size estimates for sub cortical and intracranial brain volume differences between individuals with schizophrenia and healthy controls. Interestingly, neither of these studies used whole brain analysis or directly compared the drug-naive state and with effects seen during the early course of the treatment. Therefore, lack of direct comparison between different stages of schizophrenia, i.e. at drug-naive state (AN-FES) and during the early course of antipsychotic treatment (AT-FES), offers us an opportunity to conduct an analysis of cross-sectional studies and determine the areas of GM abnormalities which might represent as the primary anomaly and also to determine whether these anomalies are stable in both groups, as confounding effects such as chronicity and long term medication can be minimized (Joyal *et al.* 2003; Spinks *et al.* 2005; Upadhyaya *et al.* 2007).

Thus, using an anisotropic effect-size-based algorithm-signed differential mapping (AE-SDM) method as the primary tool, we conducted two separate meta-analyses (one with drug-naive subjects and the other with early course of illness patients on antipsychotic medication) to identify the predominant GM alterations in these groups, and then we compared the findings of two meta-analyses to identify common and distinct regions of GM abnormalities.

Method and materials

Search strategy

Literature search was carried out using PubMed, Medline (http://www.ncbi.nlm.nih.gov/pubmed) and Schizophrenia Research databases (http://www.journals.elsevier.com/schizophrenia-research) to identify FES studies using a voxel-based morphometry (VBM) method and comparison of GM (whole brain) between FES and healthy controls between the years 2001 and 2015. Earlier development of VBM-type approaches and data unavailability were the reasons for including the studies after 2000. Key words such as 'first episode schizophrenia' crossed with 'neuroleptics', 'antipsychotic agents', 'antipsychotics' AND 'antipsychotic naive' OR 'drug naive' AND 'grey matter' OR 'gray matter' OR 'GM' AND 'voxel based morphometry' OR 'morphometric' OR 'VBM' AND 'magnetic resonance imaging or MRI' were used. We evaluated all the articles with full texts and screened references for each article to identify other qualified articles as well. All the studies obtained were from peer-reviewed journals and were written in the English language.

Inclusion criteria

We included papers only if they met the following criteria: (*a*) research findings reported in an original paper; (*b*) study used voxel-wise whole-brain analysis [excluding papers using region of interest (ROI) analysis]; and (*c*) coordinates of GM differences were reported in standard stereotactic space; (*d*) diagnosis was established according to the Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria. For studies containing multiple independent patient samples, group coordinates were treated as separate studies (i.e. same sample were recorded for the different time points). In cases where coordinates were not reported in published papers, corresponding authors were contacted for details. Abstracts from professional meetings and case studies were not included. First-episode patients were defined here as patients who had confirmed diagnosis of schizophrenia spectrum illness including schizophreniform or brief psychotic disorder. In addition, average duration of illness was no longer than 10 months in both groups. The AN-FES group was comprised of patients who received no antipsychotic treatment before their scan and the AT-FES group was defined as patients receiving antipsychotic treatment for an average duration of 3 months with maximum treatment for 282 days and minimum of 7 days. VBM methods were required to provide methodological consistency and whole-brain analysis (Wright *et al.* 1995), testing for group differences on a voxel-by-voxel basis (Salgado-Pineda *et al.* 2003). Additionally, we only included data from the largest sample in instances where the same or similar samples were used in different papers. We followed PRISMA guidelines (Fujiwara *et al.* 2007) as a quality control procedure for the selection of the articles as in previous studies (Bora *et al.* 2011; Radua *et al.* 2012*b*).

Recorded variables in the database

The following data were extracted from the selected studies: sample size, gender (percentage), mean age, duration of illness (months), Positive and Negative Syndrome scale (PANSS-P, PANSS-N), software package, MRI acquisition, diagnostic criteria, smoothing kernel and year of publication (Supplementary Tables S1 and S2).

https://doi.org/10.1017/S0033291716002683 Published online by Cambridge University Press

Meta-analytical method and statistical analysis

First, we conducted separate meta-analyses consisting of AN-FES and AT-FES. We used ES-SDM (version 4.21, http://www.sdmproject.com) as our fundamental meta-analytical software, which is a statistical technique that has been used previously for meta-analysis of group differences in brain activity or structure (Zhao *et al.* 2014). Then, we adopted 'Multimodal meta-analysis method' to make a distinct comparison of structural changes between AN-FES and AT-FES. Given that, the theory of multimodal analysis used in the software is based on coordinates of group differences in each meta-analysis (Radua *et al.* 2012*b*), we examined regions based on location of significant peak effects from studies showing alterations in one or both of the above studies. In short, SDM's criterion is to select reported peak coordinates thereby preventing biases resulting from methods using liberal thresholds and ROI methods in neuroimaging studies by ensuring only regions with statistical significance at the global brain level are considered in the meta-analysis. Its principal advantage is that the re-created maps are signed (i.e. they account for both positive and negative differences between patients and controls), thus avoiding the bias towards those brain regions with more inter-study heterogeneity. The method has been applied previously in psychiatric studies (Radua *et al.* 2014; Lesh *et al.* 2015), and methodological details are available elsewhere (Radua & Mataix-Cols, 2009).

Meta-regression and covariate analyses were used to look for potential confounding variables (Radua *et al.* 2012*b*). We examined potential effects of age, sex, duration of illness, PANSS-P and PANSS-N by means of simple regression. In order to minimize the detection of spurious relationships we decreased the probability threshold to 0.0005, required abnormalities to be detected both in the slope and in one of the extreme of regressor and discarded findings in the regions other than those detected in the main analysis (Radua & Mataix-Cols, 2009). We also inspected the regression plots to discard effects driven by too few studies (Radua *et al.* 2012*a*). Additionally, we combined the cohorts (from AN-FES and AT-FES) in the regression analyses to examine the effects of age, duration of illness and symptom ratings. The between-studies heterogeneity of individual clusters (mean of the brain regions reported from the original papers) was examined using a random-effect model with Q statistics (χ^2 distribution converted to z values and tested with a permutation approach ($p < 0.005$, peak height $z = 1$, cluster extent = 10 voxels) and examined the possibility of publication bias for brain regions showing conjoint alteration of GM using Egger's test (Shepherd *et al.* 2012). Furthermore, we conducted subgroup analysis of those studies using 1.5-T scanners, studies with slice thickness $\leqslant 1.5$ mm, and studies using SPM (Supplementary Tables S7 and S8). In addition, to assess the robustness of results, we conducted jack-knife analyses (Radua *et al.* 2011). In addition, we also conducted a sub-analysis in order to avoid the influence the double counting of control groups (short duration of psychosis *v.* controls and long duration of psychosis *v.* controls) (Guo *et al.* 2013).

Results

Systematic search results

The selection procedure is illustrated in PRISMA flow chart (Fig. 1). Twenty-four original studies (Supplementary Tables S1 and S2) that met the inclusion criteria and were published between 2002 and February 2015 were analyzed and included in the final database. It should be noted that three papers from Guo *et al.* (2013, 2014, 2015) were included in this study as they were taken from three different institutions. The net sample consisted of 801 patients and 957 controls, out of which 13 studies with 14 combinations (total number of patients 449, mean age 25.16 years; total number of controls 473, mean age 25.32 years) from antipsychotic-naive studies and 11 studies (total number of patients 352, mean age 22.24 years; total number of controls 484, mean age 23.20 years) from studies of patients who were being treated with antipsychotics.

Meta-analysis results

On comparison with the healthy controls, meta-analysis of AN-FES studies showed a GM increase in (1) left inferior parietal gyri and (2) left paracentral lobule and a decrease in (1) bilateral insula, (2) right superior frontal gyrus and (3) left fusiform gyrus (Supplementary Table S3 and Fig. S1). By contrast, AT-FES, compared to healthy controls, showed increased GM in (1) right middle occipital gyrus, and (2) right superior frontal gyrus and decreased GM in (1) left anterior cingulate/paracingulate gyri, (2) left middle temporal gyrus, (3) right post-central gyrus, and (4) left inferior temporal gyrus (Supplementary Table S4 and Fig. S2). Jack-knife sensitivity analysis suggested that all the results were highly reliable (Supplementary Tables S5 and S6).

Multimodal analysis results

Comparison between AN-FES and AT-FES, left superior temporal gyrus, right anterior cingulate/paracingulate gyrus, right insula, right gyrus rectus and left hippocampus showed decrease GM in both studies. Left paracentral lobule was the only structure to show GM increase in both groups. GM in the left

https://doi.org/10.1017/S0033291716002683 Published online by Cambridge University Press

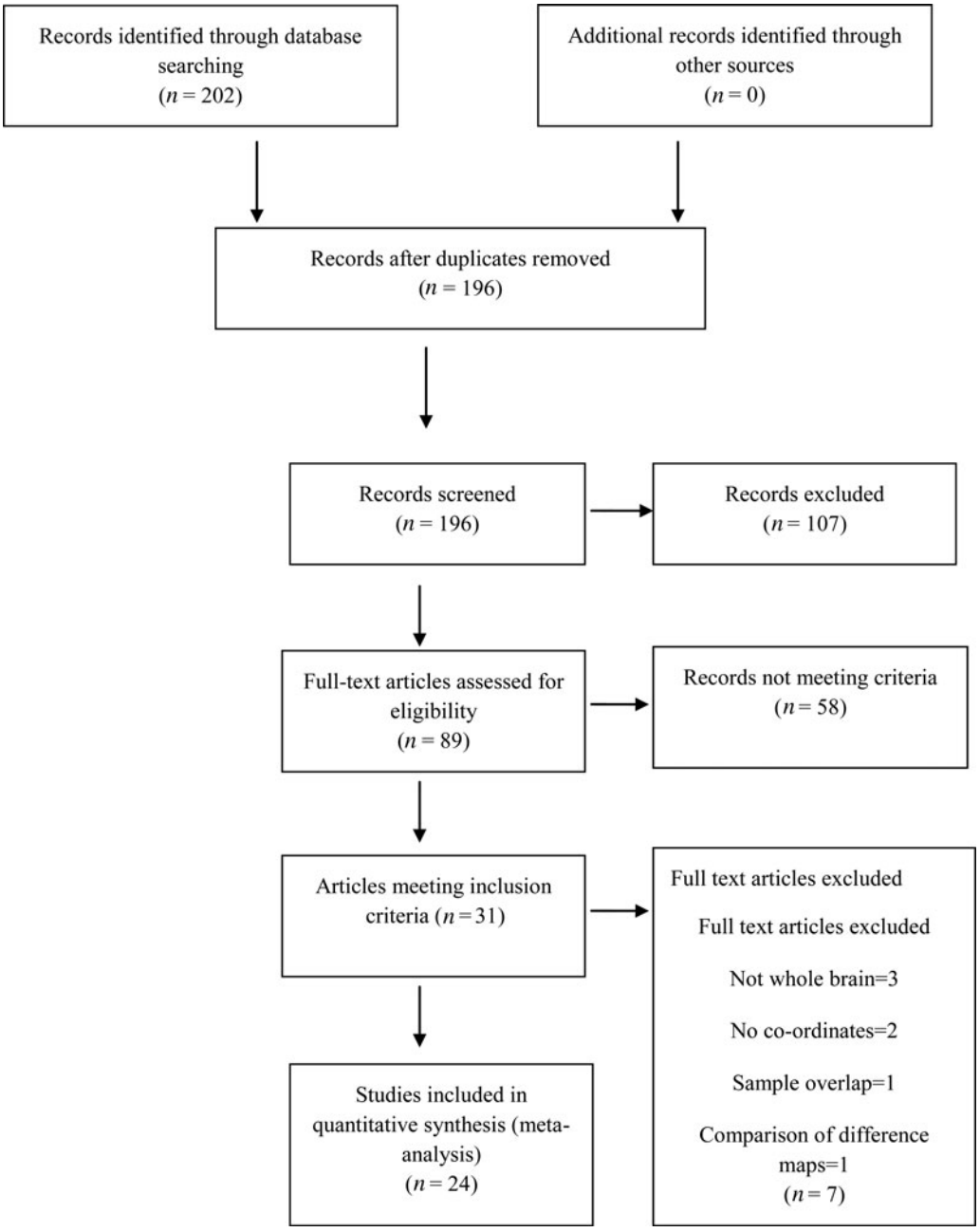

Fig. 1. PRISMA guidelines showing the selection process of the articles.

supramarginal gyrus and left middle temporal gyrus was increased in AN- FES but decreased in AT-FES. Comparisons also showed decreased GM in left median cingulate and paracingulate gyri and right hippocampus in AN-FES but this was increased in AT-FES (Table 1 and Fig. 2).

Meta-regression analysis results

The following variables (age, duration of illness, male patients, PANSS-P and PANSS-N) were explored by regression analysis. Meta-regression of GM in AT-FES showed left anterior cingulate gyrus was negatively correlated with age (Fig. 3). No significant association was found between GM changes and duration of illness, male patients, PANSS-P or PANSS-N. Furthermore, meta-regression of combined cohorts showed no association between GM changes and duration of illness, age or symptom ratings.

Subgroup analysis results

For subgroup meta-analyses of the studies with AN-FES applying slice thickness $\leqslant 1.5$ mm ($n = 10$) and using

https://doi.org/10.1017/S0033291716002683 Published online by Cambridge University Press

Table 1. *Results of multimodal analysis of AN-FES and AT-FES*

Description	MNI coordinate	Cluster breakdown	Voxels	SDM-Z	*p*
(*a*) Gray-matter (GM) decrease in both AN-FES and AT-FES					
Left superior temporal gyrus	−44, −8, −8	Left superior temporal gyrus, BA 21, 22, 38, 41, 42, 48 [1191] Left insula, BA 38, 45, 47, 48 [847] Left Rolandic operculum, BA 6, 22, 41, 42, 48 [656] Left temporal pole, superior temporal gyrus, BA 21, 28, 34, 36, 38, 48 [428] Left middle temporal gyrus, BA 20, 21, 22, 48 [283] Left post-central gyrus, BA 4, 6, 22, 42, 43, 48 [306] Left inferior frontal gyrus, opercular part, BA 6, 44, 48 [282] Left Heschl gyrus, BA 22, 48 [186] Left inferior frontal gyrus, orbital part, BA 38, 47 [154] Left inferior frontal gyrus, triangular part, BA 45, 47, 48 [108] Left precentral gyrus, BA 4, 6, 43, 48 [85] Left supramarginal gyrus, BA 42, 48 [63] Left lenticular nucleus, putamen, BA 48 [45] Left parahippocampal gyrus, BA 28, 36 [34] Left inferior temporal gyrus BA 20 [15]	5915	6.914	∼0
Right anterior cingulate/paracingulate gyri, BA 10	4, 44, 8	Left anterior cingulate/paracingulate gyri, BA 10, 11, 24, 25, 32 [900] Right anterior cingulate/paracingulate gyri, BA 11, 24, 25, 32 [637] Left superior frontal gyrus, medial, BA 9, 24, 32 [372] Right median cingulate/paracingulate gyri, BA 9, 23, 24, 32 [290] Right superior frontal gyrus, medial orbital, BA 10, 11 [259] Right superior frontal gyrus, medial, BA 9, 10, 32 [183] Left median cingulate/paracingulate gyri, BA 23, 24, 32 [228] Left superior frontal gyrus, medial orbital, BA 10, 11 [133] Left olfactory cortex, BA 11, 25 [28]	3518	3.958	∼0
Right insula, BA 48	38, −4, 10	Right superior temporal gyrus, BA 21, 38, 42, 48 [439] Right Rolandic operculum, BA 6, 22, 42, 48 [553] Right insula, BA 38, 47, 48 [418] Right inferior frontal gyrus, triangular part, BA 45, 47, 48 [277] Right inferior frontal gyrus, opercular part, BA 6, 38, 44, 45, 48 [162] Right middle temporal gyrus, BA 20, 21, 22 [118] Right Heschl gyrus, BA 48 [137] Right temporal pole, middle temporal gyrus, BA 21, 38 [174]	2868	3.225	∼0
Right gyrus rectus, BA 11	6, −50, −28	Right gyrus rectus BA 11 [15]	63	1.946	∼0
Left hippocampus, BA 20	−26, −16, −22	Left hippocampus, BA 20, 35 [34]	70	1.991	∼0

Table 1 (*cont.*)

Description	MNI coordinate	Cluster breakdown	Voxels	SDM-Z	*p*
(*b*) GM increase in AN-FES but decreased in AT-FES					
Left supramarginal gyrus, BA 48	−58, −26, 28	Left supramarginal gyrus, BA 2, 48 [31]	40	2.081	∼0
Left middle temporal gyrus, BA 21	−52, −46, 6	Left middle temporal gyrus, BA 21, 22 [28]	28	2.067	∼0
(*c*) GM decrease in AN-FES but increased in AT-FES					
Left median cingulate/ paracingulate gyri, BA 23	−2, −48, 34	Left precuneus BA 23 [76]	124	1.284	0.000000119
Right hippocampus, BA 20	34, −28, −6	Right hippocampus, BA 20, 37 [14]	25	1.857	∼0
(*d*) GM increase in both AN-FES and AT-FES					
Left paracentral lobule, BA 6	−12, −14, 66	Left paracentral lobule, BA 4, 6 [506] Left precentral gyrus, BA 6 [426] Left supplementary motor area, BA 4, 6 [240] Left superior frontal gyrus, dorsolateral, BA 6 [96] Right supplementary motor area, BA 4, 6 [94] Right paracentral lobule, BA 4 [70] Left post-central gyrus, BA 3, 4, 6 [39]	1792	3.227	∼0

AN-FES, Antipsychotic-naive first-episode schizophrenia; AT-FES, antipsychotic treatment within 1 year; MNI, Montreal Neurological Institute; SDM, signed differential mapping; BA, Brodmann area.

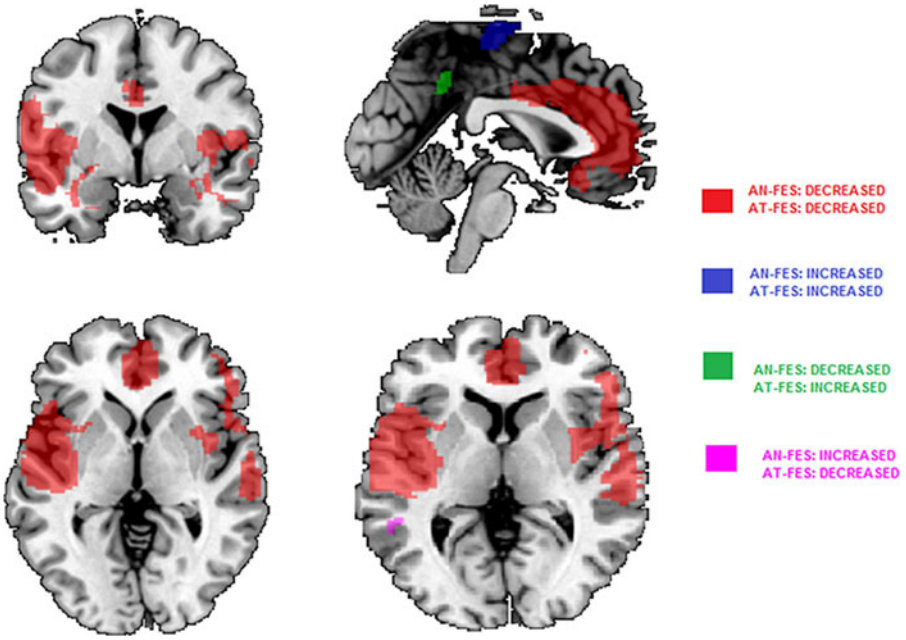

Fig. 2. Figure showing a direct comparison of studies between antipsychotic-naive first-episode schizophrenia (AN-FES) and antipsychotic treatment within 1 year (AT-FES). Red represents areas with decreased GM in both groups including right anterior cingulate/paracingulate gyrus, right insula, left superior temporal gyrus and left hippocampus. Blue represents increased gray matter (GM) in both groups, which includes left paracentral lobule. Green represents areas with increased GM in AN-FES but decreased in AT-FES and includes left supramarginal gyrus and left middle temporal gyrus. Violet represents areas with decreased GM in AN-FES but increased in AT-FES and includes right lingual gyrus, right hippocampus, left percuneus and left cerebellum.

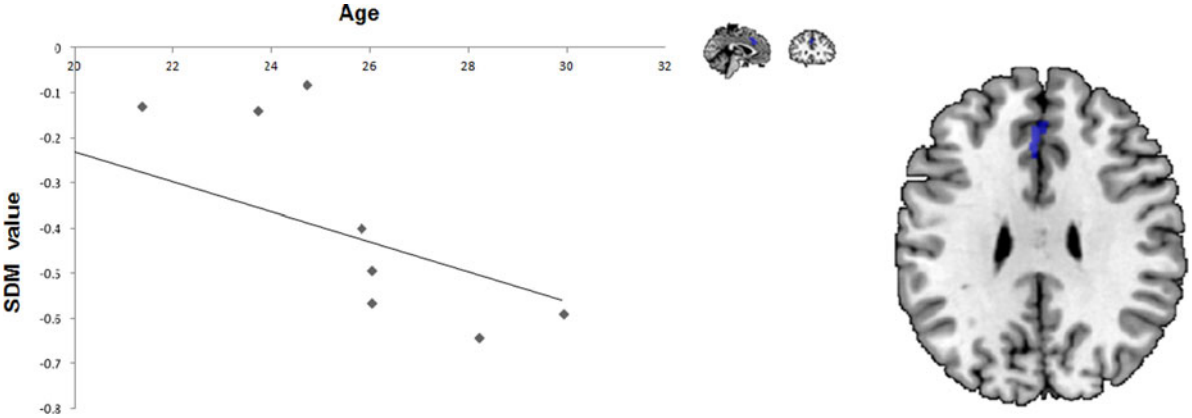

Fig. 3. Regression analysis (left anterior cingulate). Scatter plot displaying within-group relationships between gray matter and age in first-episode schizophrenic patients on antipsychotic medication in the anterior cingulate gyrus (BA 24; Montreal Neurological Institute coordinates: −2, 30, and 30). The patient group exhibited a significant negative correlation ($R^2 = 0.3532$) between gray matter and age.

SPM software ($n = 11$), the results remained largely unchanged (Supplementary Table S7A–C). Similarly, meta-analysis of studies with AT-FES remained largely unchanged as well (Supplementary Table S8A–C). In addition, the sub-analysis results after excluding the controls each time from Guo *et al.* (2013) remained largely the same (Supplementary Table S10A, B).

Results for heterogeneity and publication bias

Analysis of heterogeneity revealed that number of regions with altered GM in AN-FES (left fusiform gyrus, left insula and right insula), and in AT-FES (right superior temporal gyrus, left middle frontal gyrus, right inferior frontal gyrus, left precentral

https://doi.org/10.1017/S0033291716002683 Published online by Cambridge University Press

gyrus, left middle temporal gyrus) had significant statistical heterogeneity among studies ($p < 0.005$, Supplementary Table S9A, B). For the studies with antipsychotic-naive subjects, analysis of publication bias showed a non-significant Egger test for left insula ($p = 0.078$), left fusiform gyrus (0.467), but significant heterogeneity for left inferior parietal gyrus ($p = 0.02$), left paracentral lobule ($p = 0.001$), right insula ($p = 0.048$), right superior frontal gyrus ($p = 0.008$). Moreover, studies with antipsychotic-medicated subjects showed non-significant Egger tests for right inferior occipital gyrus ($p = 0.278$), right middle temporal gyrus ($p = 0.053$), right superior frontal gyrus ($p = 0.334$), but significant heterogeneity for left anterior cingulate/paracingulate gyri ($p = 0.006$), right post-central gyrus ($p = 0.024$) and left inferior temporal gyrus ($p = 0.009$) in the regional homogeneity meta-analysis.

Discussion

In this meta-analysis we investigated the cross-sectional GM changes in FES determining the abnormal GM areas that are true for both the drug-naive state as well as for patients with antipsychotic medication (within 1 year). A systematic literature search yielded a large database of 24 studies consisting of both FES patients at drug-naive state as well as medicated subjects.

First, separate analysis was conducted between drug-naive patients with controls and medicated patients with controls, respectively. We then applied multimodal approach by combining the studies thus replicating the structural similarities and differences of GM between these studies. Substantial findings of this analysis are that both (AN-FES and AT-FES) highlighted similar patterns of GM abnormality. Especially, GM in the right anterior cingulate/paracingulate gyrus, left superior temporal gyrus, left hippocampus, right gyrus rectus and right insula was observed to be reduced in both groups (Table 1 and Fig. 2). Both groups also showed larger GM in the paracentral lobule (Table 1). Regression analysis showed that increase in age was associated with decrease in GM in the left anterior cingulate gyrus (Fig. 3).

GM abnormalities in frontal, temporal, and insular lobes are most consistently documented and have already been demonstrated by significant number of studies (Ellison-Wright *et al.* 2008; Olabi *et al.* 2011; Radua *et al.* 2012*a*; Vita *et al.* 2012), and are specific to schizophrenia (Honea *et al.* 2005; Kuroki *et al.* 2006). Frontal lobe structures, especially anterior cingulate/paracingulate, which is an integral part of the limbic system are commonly reported in functional studies of schizophrenia and are thought to be involved in many specific functions such as error detection, task anticipation as well as attention (Weissman *et al.* 2005) and have also been demonstrated by ROI studies (Suzuki *et al.* 2002; Yamasue *et al.* 2004). In fact, Costain and colleagues in their study of familial schizophrenia found significant GM reductions in the anterior cingulate gyrus on both affected individuals and their unaffected first-degree relatives compared to their unaffected second-degree relatives suggesting these changes are primarily due to genetic risk and not illness type (Costain *et al.* 2010). Superior temporal gyrus and hippocampus play an important role in cognition and cognitive impairment in schizophrenia, which is associated with loss of superior temporal gyrus and hippocampus volumes (Bechara *et al.* 1995; Szeszko *et al.* 2002; Antonova *et al.* 2005). Apart from individual differences, these structures together may also represent part of fronto-temporal dysconnectivity, which is thought to be the basis of the disorder (Fletcher *et al.* 1999). Insula, a paralimbic structure is considered as a gateway between somatosensory cortex and limbic structures (Duggal *et al.* 2005) and reduction of GM in this region has been reported in previous FES study as well (Ellison-Wright *et al.* 2008). Additionally, this decrease in GM has been also associated with reduced salience network connectivity during information processing, suggesting disturbance to the system which effects changes between contextually relevant functional brain states (White *et al.* 2010).

Possible reasons of identifying a common pattern of GM abnormality in fronto-temporal and insular regions must be due to the fact that these abnormalities, which are present even prior to the onset of disease, might not be responsible for the GM alteration in the early course treatment with antipsychotics (Weinberger, 1997). In fact, Gur *et al.* (2000) in their cross-sectional study with schizophrenia subjects ($n = 29$ antipsychotic-naive and $n = 41$ previously treated), compared with healthy controls concluded that GM reduction in the prefrontal cortex showed that the changes observed in their study was not the byproduct of antipsychotics. Another possible reason for identifying this common pattern is that antipsychotics are likely to act on the functions (Lui *et al.* 2010) rather than structural architecture (Leung *et al.* 2011) with short duration of treatment in FES. In fact, our previous study (Lui *et al.* 2009) with AN-FES patients ($n = 68$) found no association between structural and functional changes in FES patients, thus, indicating that the GM changes involved in fronto-temporal and insular regions which are consistent in FES are not likely to be state- related changes.

Furthermore, we also noted that such GM abnormalities were not correlated with duration of illness or PANSS scores. This is consistent with our previous

https://doi.org/10.1017/S0033291716002683 Published online by Cambridge University Press

studies showing that the GM deficits in schizophrenia are stable at early course of illness (Xiao *et al.* 2015; Zhang *et al.* 2015), but may be progressive in the later course of illness (Zhang *et al.* 2015). However, we noted that meta-regression of GM in AT-FES showed left anterior cingulate gyrus to be inversely correlated with age ($R^2 = 0.3532$, Fig. 3). This may be due to the fact that the anterior cingulate gyrus might be vulnerable with increasing age (Bose *et al.* 2009) and that normal aging is associated with changes in GM and in cerebral vasculatures especially in anterior cingulate regions (Martin *et al.* 1991; Meltzer *et al.* 2000; Resnick *et al.* 2003; Grieve *et al.* 2005).

However, progressive changes of GM have been also observed in longitudinal studies (Andreasen *et al.* 2011; Vita *et al.* 2012). In particular, Vita *et al.* (2012) in their meta-analysis ($n = 813$) demonstrated a significant pattern of progressive loss of whole cerebral GM volume involving the frontal, temporal and parietal lobes indicating an underlying pathological process to be more active during the early stages of the disease, which is moderated by type of pharmacological treatment received. However, factors such as duration of illness, age, severity of illness should also be taken into consideration (Tanskanen *et al.* 2010). Moreover, disruptions of neurodevelopment or neural plasticity might also be one of the causes for the progressive brain deficits in schizophrenia (Ho *et al.* 2003). Owing to the fact that our study was deprived of these confounding factors, it therefore assumes that the changes observed are true to both AN-FES and AT-FES groups.

It should also be noted that, besides the common pattern of GM alterations before and after treatment, we also observed small regions with different changes of GM between AN-FES and AT-FES. Right hippocampus and left median cingulate/paracingulate gyri, that were decreased in naive patients were found to be increased in medicated patients. This small change might be due to the neuroprotective effect of antipsychotics especially second-generation antipsychotics either by stimulating neurogenesis (Halim *et al.* 2004) or increasing the expression of neurotrophic factors (Angelucci *et al.* 2005) or interacting with *N*-methyl-D-aspartate glutamate receptors (Millan, 2005). Indeed, 68% of the patients included in this study were receiving second-generation antipsychotics and 10% were receiving typical antipsychotics. However, regression analysis (to evaluate the effect of antipsychotic dose) did not yield any association between GM abnormality and antipsychotic dose. GM in the supramarginal gyrus and left middle temporal gyrus were increased in AN-FES but decreased in AT-FES. This minor reduction of GM after treatment may be attributed to a direct neurotoxic effect secondary to oxidative stress and/or excitotoxic phenomena (Vita *et al.* 2015). Apart from the reasons above, these differences may also be due to the different samples between AN-FES and AT-FES among others.

Several limitations should be noted in this study. First, the emphasis of this study was to see the regions that were similar in both groups rather than to see the effect of antipsychotics. However, we acknowledge that the influence of antipsychotics could not be ruled out. Then, considering the high prevalence of substance abuse in the first phase of schizophrenia and despite most of the studies reported to be drug free, it could, however, not be confirmed individually, which might again influence the results of the present study. Moreover, our voxel-wise meta-analysis is based on the coordinates from published studies instead of using raw statistical brain maps, which limits its accuracy (Lui *et al.* 2010). Additionally, because of limited available data we could not access the effects of intelligence quotient (IQ). Although, four of the studies from AN-FES (Chua *et al.* 2007; Prasad *et al.* 2007; Witthaus *et al.* 2009; Nenadic *et al.* 2015) reported IQ, none of them noted how this influenced the findings. Among the AT-FES group (Kubicki *et al.* 2002; Whitford *et al.* 2006; Douaud *et al.* 2007; Yoshihara *et al.* 2008), only Yoshihara *et al.* (2008) reported a minimal effect of IQ with respect to the regional brain changes. Moreover, although we did not detect any influence on GM due to patient population via regression analysis, the possibility of systematic difference between AN-FES and AT-FES could not be totally discarded. However, upon comparison, no significant difference in proportion of the scanner and analysis methods (i.e. VBM 2/5/8, Dartel) were observed. Similarly, subgroup analysis revealed that in studies applying a slice thickness $\leqslant 1.5$ mm, only studies using SPM software and studies using the 1.5 T MRI system remained largely unchanged. Finally, it should also be noted that although we tried to obtain the T-Maps which could have assisted in increasing the accuracy of the analysis, we were unable to do so as we did not receive any response from the authors.

Conclusion

Our study reveals that GM abnormalities in frontal, temporal and insular regions are the fundamental regions of pathological GM changes in FES. This common pattern of GM changes in FES patients with and without antipsychotics suggests the anatomical deficits involved in most of the fronto-temporal and limbic regions are likely to be the core regions of GM abnormalities at the early course of illness and can be assumed as biomarkers for FES subjects. Further studies with larger numbers of subjects would provide crucial information in understanding the changes within

https://doi.org/10.1017/S0033291716002683 Published online by Cambridge University Press

the core regions of GM abnormalities, which may help in understanding the disease pathology and in developing newer approaches in the assessment of schizophrenia in the future.

Supplementary material

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0033291716002683

Acknowledgements

This research was partially supported by the, the National Natural Science Foundation of China (grant nos. 81222018, 81371527), Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT, grant no. IRT1272) of China. We sincerely thank Dr Chua Siew for providing additional information about his study.

Declaration of Interest

None declared.

References

Andreasen NC, Nopoulos P, Magnotta V, Pierson R, Ziebell S, Ho BC (2011). Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. *Biological Psychiatry* **70**, 672–679.

Angelucci F, Aloe L, Iannitelli A, Gruber SH, Mathe AA (2005). Effect of chronic olanzapine treatment on nerve growth factor and brain-derived neurotrophic factor in the rat brain. *European Neuropsychopharmacology* **15**, 311–317.

Anticevic A, Hu X, Xiao Y, Hu J, Li F, Bi F, Cole MW, Savic A, Yang GJ, Repovs G, Murray JD, Wang XJ, Huang X, Lui S, Krystal JH, Gong Q (2015). Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. *Journal of Neuroscience* **35**, 267–286.

Antonova E, Kumari V, Morris R, Halari R, Anilkumar A, Mehrotra R, Sharma T (2005). The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. *Biological Psychiatry* **58**, 457–467.

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* **269**, 1115–1118.

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, Yucel M, Velakoulis D, Pantelis C (2011). Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia Research* **127**, 46–57.

Bose SK, Mackinnon T, Mehta MA, Turkheimer FE, Howes OD, Selvaraj S, Kempton MJ, Grasby PM (2009). The effect of ageing on grey and white matter reductions in schizophrenia. *Schizophrenia Research* **112**, 7–13.

Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogerts B, Wu H, Kinon B, Ashtari M (1994). Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *American Journal of Psychiatry* **151**, 1430–1436.

Chua SE, Cheung C, Cheung V, Tsang JT, Chen EY, Wong JC, Cheung JP, Yip L, Tai KS, Suckling J, McAlonan GM (2007). Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia. *Schizophrenia Research* **89**, 12–21.

Chua SE, Deng Y, Chen EY, Law CW, Chiu CP, Cheung C, Wong JC, Lienenkaemper N, Cheung V, Suckling J, McAlonan GM (2009). Early striatal hypertrophy in first-episode psychosis within 3 weeks of initiating antipsychotic drug treatment. *Psychological Medicine* **39**, 793–800.

Costain G, Ho A, Crawley AP, Mikulis DJ, Brzustowicz LM, Chow EW, Bassett AS (2010). Reduced gray matter in the anterior cingulate gyrus in familial schizophrenia: a preliminary report. *Schizophrenia Research* **122**, 81–84.

Crespo-Facorro B, Roiz-Santianez R, Perez-Iglesias R, Pelayo-Teran JM, Rodriguez-Sanchez JM, Tordesillas-Gutierrez D, Ramirez M, Martinez O, Gutierrez A, de Lucas EM, Vazquez-Barquero JL (2008). Effect of antipsychotic drugs on brain morphometry. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **32**, 1936–1943.

Dazzan P, Morgan KD, Orr K, Hutchinson G, Chitnis X, Suckling J, Fearon P, McGuire PK, Mallett RM, Jones PB, Leff J, Murray RM (2005). Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. *Neuropsychopharmacology* **30**, 765–774.

Deng MY, McAlonan GM, Cheung C, Chiu CP, Law CW, Cheung V, Sham PC, Chen EY, Chua SE (2009). A naturalistic study of grey matter volume increase after early treatment in anti-psychotic naive, newly diagnosed schizophrenia. *Psychopharmacology* (*Berlin*) **206**, 437–446.

Douaud G, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J, James S, Voets N, Watkins K, Matthews PM, James A (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain* **130**, 2375–2386.

Duggal HS, Muddasani S, Keshavan MS (2005). Insular volumes in first-episode schizophrenia: gender effect. *Schizophrenia Research* **73**, 113–120.

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E (2008). The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *American Journal of Psychiatry* **165**, 1015–1023.

Fletcher P, McKenna PJ, Friston KJ, Frith CD, Dolan RJ (1999). Abnormal cingulate modulation of fronto-temporal connectivity in schizophrenia. *Neuroimage* **9**, 337–342.

Fujiwara H, Hirao K, Namiki C, Yamada M, Shimizu M, Fukuyama H, Hayashi T, Murai T (2007). Anterior cingulate pathology and social cognition in schizophrenia: a

study of gray matter, white matter and sulcal morphometry. *Neuroimage* **36**, 1236–1245.

Girgis RR, Diwadkar VA, Nutche JJ, Sweeney JA, Keshavan MS, Hardan AY (2006). Risperidone in first-episode psychosis: a longitudinal, exploratory voxel-based morphometric study. *Schizophrenia Research* **82**, 89–94.

Grieve SM, Clark CR, Williams LM, Peduto AJ, Gordon E (2005). Preservation of limbic and paralimbic structures in aging. *Human Brain Mapping* **25**, 391–401.

Guo W, Liu F, Liu J, Yu L, Zhang J, Zhang Z, Xiao C, Zhai J, Zhao J (2015). Abnormal causal connectivity by structural deficits in first-episode, drug-naive schizophrenia at rest. *Schizophrenia Bulletin* **41**, 57–65.

Guo X, Li J, Wang J, Fan X, Hu M, Shen Y, Chen H, Zhao J (2014). Hippocampal and orbital inferior frontal gray matter volume abnormalities and cognitive deficit in treatment-naive, first-episode patients with schizophrenia. *Schizophrenia Research* **152**, 339–343.

Guo X, Li J, Wei Q, Fan X, Kennedy DN, Shen Y, Chen H, Zhao J (2013). Duration of untreated psychosis is associated with temporal and occipitotemporal gray matter volume decrease in treatment naive schizophrenia. *PLoS ONE* **8**, e83679.

Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, Bilker WB, Gur RC (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry* **57**, 761–768.

Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS (2013). Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin* **39**, 1129–1138.

Halim ND, Weickert CS, McClintock BW, Weinberger DR, Lipska BK (2004). Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. *Neuropsychopharmacology* **29**, 1063–1069.

Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M (2003). Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Archives of General Psychiatry* **60**, 585–594.

Honea R, Crow TJ, Passingham D, Mackay CE (2005). Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *American Journal of Psychiatry* **162**, 2233–2245.

Joyal CC, Laakso MP, Tiihonen J, Syvalahti E, Vilkman H, Laakso A, Alakare B, Rakkolainen V, Salokangas RK, Hietala J (2003). The amygdala and schizophrenia: a volumetric magnetic resonance imaging study in first-episode, neuroleptic-naive patients. *Biological Psychiatry* **54**, 1302–1304.

Kasparek T, Prikryl R, Mikl M, Schwarz D, Ceskova E, Krupa P (2007). Prefrontal but not temporal grey matter changes in males with first-episode schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **31**, 151–157.

Keshavan MS, Haas GL, Kahn CE, Aguilar E, Dick EL, Schooler NR, Sweeney JA, Pettegrew JW (1998). Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *Journal of Psychiatric Research* **32**, 161–167.

Kubicki M, Shenton ME, Salisbury DF, Hirayasu Y, Kasai K, Kikinis R, Jolesz FA, McCarley RW (2002). Voxel-based morphometric analysis of gray matter in first episode schizophrenia. *Neuroimage* **17**, 1711–1719.

Kuroki N, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Ersner-Hershfield H, Yurgelun-Todd D, Kikinis R, Jolesz FA, 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.

Labarre R (1993). Cohort effects: a possible limitation to the interpretation of longitudinal studies. *American Journal of Human Biology*. **5**, 305–310.

Lei W, Deng W, Li M, He Z, Han Y, Huang C, Ma X, Wang Q, Guo W, Li Y, Jiang L, Gong Q, Hu X, Zhang N, Li T (2015). Gray matter volume alterations in first-episode drug-naive patients with deficit and nondeficit schizophrenia. *Psychiatry Research* **234**, 219–226.

Lesh TA, Tanase C, Geib BR, Niendam TA, Yoon JH, Minzenberg MJ, Ragland JD, Solomon M, Carter CS (2015). A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry* **72**, 226–234.

Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q, Chua S, McAlonan G (2011). Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. *Schizophrenia Bulletin* **37**, 199–211.

Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H, Zhang T, Li X, Li D, Zou L, Tang H, Zhou XJ, Mechelli A, Collier DA, Sweeney JA, Li T, Gong Q (2009). Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. *American Journal of Psychiatry* **166**, 196–205.

Lui S, Li T, Deng W, Jiang L, Wu Q, Tang H, Yue Q, Huang X, Chan RC, Collier DA, Meda SA, Pearlson G, Mechelli A, Sweeney JA, Gong Q (2010). Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by 'resting state' functional magnetic resonance imaging. *Archives of General Psychiatry* **67**, 783–792.

Martin AJ, Friston KJ, Colebatch JG, Frackowiak RS (1991). Decreases in regional cerebral blood flow with normal aging. *Journal of Cerebral Blood Flow Metabolism* **11**, 684–689.

Meltzer CC, Cantwell MN, Greer PJ, Ben-Eliezer D, Smith G, Frank G, Kaye WH, Houck PR, Price JC (2000). Does cerebral blood flow decline in healthy aging? A PET study with partial-volume correction. *Journal of Nuclear Medicine* **41**, 1842–1848.

Millan MJ (2005). N-Methyl-D-aspartate receptors as a target for improved antipsychotic agents: novel insights and clinical perspectives. *Psychopharmacology* (*Berl*) **179**, 30–53.

Nenadic I, Dietzek M, Schonfeld N, Lorenz C, Gussew A, Reichenbach JR, Sauer H, Gaser C, Smesny S (2015). Brain structure in people at ultra-high risk of psychosis, patients

with first-episode schizophrenia, and healthy controls: a VBM study. *Schizophrenia Research* **161**, 169–176.

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM (2011). Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biological Psychiatry* **70**, 88–96.

Prasad KM, Shirts BH, Yolken RH, Keshavan MS, Nimgaonkar VL (2007). Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. *Molecular Psychiatry* **12**, 105–113.

Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK, Fusar-Poli P (2012*a*). Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neuroscience and Biobehavioral Reviews* **36**, 2325–2333.

Radua J, Grau M, van den Heuvel OA, Thiebaut de Schotten M, Stein DJ, Canales-Rodriguez EJ, Catani M, Mataix-Cols D (2014). Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder. *Neuropsychopharmacology* **39**, 1547–1557.

Radua J, Mataix-Cols D (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry* **195**, 393–402.

Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, Surguladze S (2012*b*). A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry* **27**, 605–611.

Radua J, Via E, Catani M, Mataix-Cols D (2011). Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls. *Psychological Medicine* **41**, 1539–1550.

Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *Journal of Neuroscience* **23**, 3295–3301.

Salgado-Pineda P, Baeza I, Perez-Gomez M, Vendrell P, Junque C, Bargallo N, Bernardo M (2003). Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. *Neuroimage* **19**, 365–375.

Shepherd AM, Matheson SL, Laurens KR, Carr VJ, Green MJ (2012). Systematic meta-analysis of insula volume in schizophrenia. *Biological Psychiatry* **72**, 775–784.

Spinks R, Nopoulos P, Ward J, Fuller R, Magnotta VA, Andreasen NC (2005). Globus pallidus volume is related to symptom severity in neuroleptic naive patients with schizophrenia. *Schizophrenia Research* **73**, 229–233.

Suzuki M, Nohara S, Hagino H, Kurokawa K, Yotsutsuji T, Kawasaki Y, Takahashi T, Matsui M, Watanabe N, Seto H, Kurachi M (2002). Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. *Schizophrenia Research* **55**, 41–54.

Szeszko PR, Strous RD, Goldman RS, Ashtari M, Knuth KH, Lieberman JA, Bilder RM (2002). Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia. *American Journal of Psychiatry* **159**, 217–226.

Tanskanen P, Ridler K, Murray GK, Haapea M, Veijola JM, Jaaskelainen E, Miettunen J, Jones PB, Bullmore ET, Isohanni MK (2010). Morphometric brain abnormalities in schizophrenia in a population-based sample: relationship to duration of illness. *Schizophrenia Bulletin* **36**, 766–777.

Upadhyaya AR, El-Sheikh R, MacMaster FP, Diwadkar VA, Keshavan MS (2007). Pituitary volume in neuroleptic-naive schizophrenia: a structural MRI study. *Schizophrenia Research* **90**, 266–273.

van Erp TG, Greve DN, Rasmussen J, Turner J, Calhoun VD, Young S, Mueller B, Brown GG, McCarthy G, Glover GH, Lim KO, Bustillo JR, Belger A, McEwen S, Voyvodic J, Mathalon DH, Keator D, Preda A, Nguyen D, Ford JM, Potkin SG, Fbirn (2014). A multi-scanner study of subcortical brain volume abnormalities in schizophrenia. *Psychiatry Research* **222**, 10–16.

Vita A, De Peri L, Deste G, Barlati S, Sacchetti E (2015). The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. *Biological Psychiatry* **78**, 403–412.

Vita A, De Peri L, Deste G, Sacchetti E (2012). Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Translational Psychiatry* **2**, e190.

Weinberger DR (1997). The biological basis of schizophrenia: new directions. *Journal of Clinical Psychiatry* **58**(Suppl.) **10**, 22–27.

Weissman DH, Gopalakrishnan A, Hazlett CJ, Woldorff MG (2005). Dorsal anterior cingulate cortex resolves conflict from distracting stimuli by boosting attention toward relevant events. *Cerebral Cortex* **15**, 229–237.

White TP, Joseph V, Francis ST, Liddle PF (2010). Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophrenia Research* **123**, 105–115.

Whitford TJ, Grieve SM, Farrow TF, Gomes L, Brennan J, Harris AW, Gordon E, Williams LM (2006). Progressive grey matter atrophy over the first 2–3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. *Neuroimage* **32**, 511–519.

Witthaus H, Kaufmann C, Bohner G, Ozgurdal S, Gudlowski Y, Gallinat J, Ruhrmann S, Brune M, Heinz A, Klingebiel R, Juckel G (2009). Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. *Psychiatry Research* **173**, 163–169.

Wright IC, McGuire PK, Poline JB, Travere JM, Murray RM, Frith CD, Frackowiak RS, Friston KJ (1995). A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *Neuroimage* **2**, 244–252.

Xiao Y, Lui S, Deng W, Yao L, Zhang W, Li S, Wu M, Xie T, He Y, Huang X, Hu J, Bi F, Li T, Gong Q (2015). Altered cortical thickness related to clinical severity but not the untreated disease duration in schizophrenia. *Schizophrenia Bulletin* **41**, 201–210.

Yamasue H, Iwanami A, Hirayasu Y, Yamada H, Abe O, Kuroki N, Fukuda R, Tsujii K, Aoki S, Ohtomo K, Kato N, Kasai K (2004). Localized volume reduction in prefrontal, temporolimbic, and paralimbic regions in schizophrenia: an MRI parcellation study. *Psychiatry Research* **131**, 195–207.

Yoshihara Y, Sugihara G, Matsumoto H, Suckling J, Nishimura K, Toyoda T, Isoda H, Tsuchiya KJ, Takebayashi K, Suzuki K, Sakahara H, Nakamura K, Mori N, Takei N (2008). Voxel-based structural magnetic resonance imaging (MRI) study of patients with early onset schizophrenia. *Annals of General Psychiatry* **7**, 25.

Zhang W, Deng W, Yao L, Xiao Y, Li F, Liu J, Sweeney JA, Lui S, Gong Q (2015). Brain structural abnormalities in a Group of never-medicated patients with long-term schizophrenia. *American Journal of Psychiatry* **172**, 995–1003.

Zhao YJ, Du MY, Huang XQ, Lui S, Chen ZQ, Liu J, Luo Y, Wang XL, Kemp GJ, Gong QY (2014). Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. *Psychological Medicine* **44**, 2927–2937.