



Mapping cortical surface features in treatment resistant schizophrenia with in vivo structural MRI

Erica F. Barry^{a,d,*}, Lucy D. Vanes^a, Derek S. Andrews^b, Krisna Patel^a, Charlotte M. Horne^{a,**}, Elias Mouchlianitis^a, Peter J. Hellyer^{a,c}, Sukhi S. Shergill^a

^a Cognition Schizophrenia and Imaging Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

^b Department of Forensic and Neurodevelopmental Sciences, Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

^c Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

^d Department of Clinical Sciences, Cornell University College of Veterinary Medicine, Ithaca, NY, USA

ARTICLE INFO

Keywords:

Schizophrenia
Treatment resistant
Cortical thickness
MRI
Cortical volume

ABSTRACT

Decreases in cortical volume (CV), thickness (CT) and surface area (SA) have been reported in individuals with schizophrenia by in vivo MRI studies. However, there are few studies that examine these cortical measures as potential biomarkers of treatment resistance (TR) and treatment response (NTR) in schizophrenia. This study used structural MRI to examine differences in CV, CT, and SA in 42 adults with schizophrenia (TR = 21, NTR = 21) and 23 healthy controls (HC) to test the hypothesis that individuals with TR schizophrenia have significantly greater reductions in these cortical measures compared to individuals with NTR schizophrenia. We found that individuals with TR schizophrenia showed significant reductions in CV and CT compared to individuals with NTR schizophrenia in right frontal and precentral regions, right parietal and occipital cortex, left temporal cortex and bilateral cingulate cortex. In line with previous literature, the temporal lobe and cingulate gyrus in both patient groups showed significant reductions of all three measures when compared to healthy controls. Taken together these results suggest that regional changes in CV and CT may index mechanisms specific to TR schizophrenia and potentially identify patients with TR schizophrenia for earlier treatment.

1. Introduction

Schizophrenia is a psychiatric disorder characterized by symptoms such as hallucinations, paranoia, and delusions. As such, schizophrenia is often associated with life-long disability, increased risk of mortality, significant social and economic cost due to long-term unemployment (Velligan et al., 2009). Delays in seeking and identifying effective treatment following the onset of schizophrenia is correlated with illness duration, loss of social and occupational function, and increase in treatment resistance (Elkis and Buckley, 2016; Harvey and Rosenthal, 2016). Contemporary first-line antipsychotic medications such as olanzapine, risperidone and haloperidol have shown significant efficacy in treating schizophrenia, predominantly through the blockade of dopaminergic (D₂) receptors (Bodén et al., 2017; Goghari et al., 2010; Jørgensen et al., 2016). Despite the widespread use of dopaminergic agents, approximately one third of patients with schizophrenia

demonstrate resistance to traditional anti-psychotic treatments, suggesting an alternative mechanism of action may underlie symptoms in these individuals (Elkis and Buckley, 2016; Harvey and Rosenthal, 2016; Nakajima et al., 2015). Clozapine remains the most viable treatment for such patients. However, clozapine is associated with severe side effects resulting in poor patient tolerance and adherence (Chakos et al., 2001).

Theories proposed to explain resistance to first line anti-psychotics include the continuum perspective, suggesting that treatment resistant schizophrenia (TR) is a more severe form of schizophrenia, and the heterogeneity theory, suggesting TR is a separate and categorically different form of illness underpinned by a different neuropathological mechanism (Howes and Kapur., 2017). Current evidence suggests that delays in seeking treatment is correlated with poor outcome, which may support a third neurodegenerative theory suggesting that TR can be induced and worsened by increased environmental insults and lack

* Corresponding author at: Cognition Schizophrenia and Imaging Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

** Corresponding author.

E-mail address: charlotte.horne@kcl.ac.uk (C.M. Horne).

<https://doi.org/10.1016/j.psychres.2019.02.028>

Received 21 November 2018; Received in revised form 12 February 2019; Accepted 12 February 2019

Available online 14 February 2019

0165-1781/ © 2019 Elsevier B.V. All rights reserved.

of effective treatment (Howes and Kapur, 2014; Szeszko et al., 2012; van Haren et al., 2008). However, a likely explanation of TR in patients with schizophrenia may include more than one of these aforementioned theories, which may overlap and predispose patients to a TR trajectory.

Understanding how these theoretical approaches to schizophrenia relate to the neurobiological mechanisms underlying TR is important to the development of novel treatment approaches to TR patients and improving diagnostic approaches to first episode psychosis. Differences in brain structure and function in TR patients relative to those who respond to first line dopaminergic agents (NTR) indicates the possibility of these measures being developed into imaging biomarkers to identify patients at risk of resistance to first-line treatment, and those suitable for earlier clozapine treatment. Investigation into neurobiological changes which are associated with aspects of schizophrenia that are specific to TR may be used reliably to identify TR and potentially clinically reduce risk associated with delays in efficient treatment.

Neuroimaging studies using high resolution MRI (Magnetic Resonance Imaging) demonstrate widespread differences in patients with schizophrenia in cortical grey matter volume (CV) (Anderson et al., 2015; Molina et al., 2010, 2008, 2005; Mouchlianitis et al., 2016; Zugman et al., 2013) cortical thickness (CT) (Heinrichs et al., 2017; Kuperberg et al., 2003; Narr et al., 2005; Nesvåg et al., 2008; Plitman et al., 2016; Rimol et al., 2010; Smiley et al., 2012; Sugihara et al., 2017) and surface area (SA) (Kong et al., 2015; van Haren et al., 2012; Xiao et al., 2015) compared to healthy controls (HC) (Maller et al., 2012; Quarantelli et al., 2014; Selemon and Goldman-Rakic, 1999). CV reductions in patients with schizophrenia are one of the most common findings in the condition, beginning with global grey matter reductions and associated increases in ventricular volume (Emami et al., 2016; Harvey et al., 1993; Honea et al., 2005; Kong et al., 2015; Shergill et al., 2001). Further studies have highlighted the importance of investigating CT and SA in addition to CV alone as each of these component measures has been shown to represent unique aspects of cortical architecture (Rakic, 1995) with different aetiologies, genetic determinants (Nesvåg et al., 2008; Panizzon et al., 2009) and neurodevelopmental trajectories (Ecker et al., 2014). CT has been shown to be influenced by a number of neuro-developmental factors including neuronal size, intra-neuronal neuropil, number of glial cells and blood vessels (Rakic, 1995). SA expansion has been attributed to the proliferation of cortical neuronal columns (Crespo-Facorro et al., 2000; Rakic, 1995). Thus, determining which of these measures procures CV differences in TR could contribute to understanding the underlying pathogenesis of TR and the effects that antipsychotics have on cortical morphology. However, in previous research few studies explored the relationship between cortical measures and treatment response directly.

Longitudinal assessment of CT and SA has demonstrated significant degeneration of frontal, temporal and parietal grey matter over time in patients with schizophrenia (van Haren et al., 2012). Furthermore, significant decreases in CT in the temporal lobe and in CV and CT of the dorso-lateral prefrontal cortex (dlPFC) have been noted in TR compared to NTR schizophrenia (Zugman et al., 2013). In addition, CT in the temporal lobe has been associated with treatment response and remission (Szeszko et al., 2012). Based on these reports, a link between temporal lobe CT and persistence of symptoms such as auditory hallucination or the failure of the mechanism identifying such hallucinations as internally generated has been proposed (Emami et al., 2016; Rimol et al., 2010; Shergill et al., 2001). Taken together, these results indicate that cortical surface measures in both the frontal and the temporal lobe may be an indicator of treatment resistance in schizophrenia patients. Therefore, this study aims to explore the differences in these cortical measures between TR and NTR patients and HC to establish whether there are specific cortical indicators of schizophrenia and different cortical indicators of TR.

In order to limit confounding variables in our patient groups, crucially, we controlled for potential influences on cortical measures such as age, medication dosage, age of illness onset and duration, and we

recruited only patients who are not treated with clozapine. These exclusion criteria allowed us to maintain the homogeneity of the population sample while continuing to meet the criteria for TR. To our knowledge this is the first study of cortical morphology to stratify a sample in this way. We test the hypotheses that (i) we will see a decrease in CV, CT and SA in all patients compared to HC, (ii) TR patients will exhibit CV, CT and SA reductions in the frontal and temporal lobes compared to NTR and (iii) the extent of these cortical changes will positively correlate with symptom scores in the TR group. By identifying differences in cortical structure between TR and NTR patient groups we aim to identify neuroanatomical features to further the understanding, identification and stratification of TR schizophrenia.

2. Methods

2.1. Subjects

We recruited 42 patients who satisfied ICD-10 1992 criteria for schizophrenia from the South London and Maudsley (SLaM) National Health Service (NHS) and 23 HC within the same range of age, sex, and socioeconomic status. The patient population was stratified into TR ($n = 21$) and NTR ($n = 21$) groups. The criteria for inclusion in the TR group included: at least two prior drug trials of 4–6 weeks duration with no clinical improvement and persistent psychotic symptoms as defined as a score of at least 4 (moderate) on at least two positive symptom items of the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1989), with a duration of over 5 years. Patients in the NTR group were defined by a score of 3 or less (stable for at least 6 months) on all items of the PANSS (Andreasen et al., 2005; Conley and Kelly, 2001). All patients were medicated on stable doses of first-generation antipsychotics at the time of testing and medication compliance was assessed via self-report, medical notes and by talking with the patient's care-coordinator. No patient had been on clozapine in the last 6 months in order to investigate treatment resistance in a more homogenous sample of patients as this second-generation antipsychotic targets different receptors within the brain. IQ was measured with the two-item Wechsler Abbreviated Scale of Intelligence, WASI (Wechsler, 2008). Chlorpromazine (CPZ) equivalent doses of medications were calculated using conversion tables (Bazire, 2016; Woods, 2003). Further demographics and clinical data are presented in Table 1.

2.2. Procedure

2.2.1. Magnetic resonance imaging

MRI was performed using a General Electric MR750 3T scanner. A T1-weighted spoiled gradient three-dimensional magnetization prepared rapid acquisition was used to acquire high-resolution structural images of the brain (repetition time, 7.312 ms; echo time, 3.016 ms; flip angle 11°; matrix size 256 × 256; field of view, 270) with 196 sagittal positions (at 1.2 × 1.05 × 1.05 mm resolution).

2.2.2. Cortical reconstruction with freesurfer

Cortical surface reconstruction of each subject's T1-weighted volumetric images was performed using FreeSurfer 5.2.0 (*freesurfer.net*). This resulted in a white matter and outer pial (i.e. grey matter) surface mesh for each subject (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000; Jovicich et al., 2006; Ségonne et al., 2004). All surfaces were visually inspected for errors in reconstruction in comparison to the underlying T1-weighted image in line with standardised QA protocols (Dale et al., 1999; Jovicich et al., 2006; Ségonne et al., 2004). Subjects whose cortical reconstructions were categorized as outliers by FreeSurfer's quality assurance tools (QA tools) were subsequently removed and are not described in this study (TR = 1, NTR = 1) (Dale et al., 1999). In addition to vertex-wise measures of CV, CT was estimated as the distance between corresponding vertices on the white matter and outer grey matter (i.e. pial) surface (Dale et al., 1999). Vertex-wise estimates

Table 1

Demographics and clinical data including the Wechsler abbreviated scale of intelligence (WASI), National Statistic for Socio-economic Classification (NS-SEC), Chlorpromazine equivalent (CPZ) and Positive and Negative Symptom Scale (PANSS) expressed in means (*M*) and standard deviations (*SD*).

	HC (<i>N</i> = 23)		NTR (<i>N</i> = 21)		TR (<i>N</i> = 21)		Group statistics	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	$\chi^2(2)$	<i>P</i>
Female(Male) (%)	26(74)		14(86)		14(86)		1.18	.555
Age	38.4	10.0	41.3	10.4	41.5	10.6	<i>F</i> (2,62)	<i>P</i>
WASI IQ	115.8	11.7	91.86	14.8	97.1	16.4	16.8	<0.001
NS-SEC	3.13	1.62	3.74	1.88	3.39	1.76	0.65	.525
Onset age (years)			27.7	6.2	26.0	7.7	<i>t</i> (42)	<i>P</i>
Illness duration (years)			14.1	10.1	15.5	8.8	0.46	.650
CPZ equivalents (mg)			280.3	147.1	383.5	236.5	1.88	.067
PANSS score								
Positive			10.7	2.1	20.5	3.1	12.10	<0.001
Negative			13.1	4.6	19.5	4.6	4.08	<0.001
General			23.6	5.1	34.9	9.2	4.91	<0.001
Total score			46.9	10.3	76.2	10.6	9.14	<0.001

of SA were also derived on the grey matter surface using a pycnophylactic or mass preserving interpolation method (Dale et al., 1999). Prior to any further statistical analysis each measure was smoothed using a 10 mm FWHM surface based Gaussian kernel.

2.2.3. Statistical analysis of cortical measures

To assess the relationship between vertex-wise measures of CV, CT, SA, and clinical measures of interest, we used a general linear model (GLM) based multiple regression approach with diagnostic group and sex as fixed-effect factors and age, IQ, total PANSS score, and medication dose as continuous co-variables:

$$Y_i = \beta_0 + \beta_1 \text{Group} + \beta_2 \text{Sex} + \beta_3 \text{Age} + \beta_4 \text{IQ} + \beta_5 \text{PANSS} + \beta_6 \text{Meds} + \varepsilon_i,$$

where ε_i is the residual error at vertex *i*. Between group differences were estimated from the corresponding coefficient β_1 , normalised by the corresponding standard error. Corrections for multiple comparisons across the whole brain were performed using random field theory (RFT) based cluster analysis using a cluster-based significance threshold of $p < 0.05$ (2-tailed) (Hayasaka et al., 2004; Winkler et al., 2012; Worsley et al., 2004). Differences in global measures of CV, CT, and SA between HC, TR, and NTR patient groups were assayed with a one-way ANOVA and followed up with pairwise independent samples *t*-tests (2-tailed).

3. Results

We observed no significant differences in age, IQ, medication dose, age of illness onset, and illness duration between patient groups ($p < 0.05$) but found a significant difference in IQ in patients compared to HC (Table 1).

3.1. Global measures

A one-way ANOVA was conducted to find the effect of group on CV, CT, and SA. A significant decrease was observed when comparing HC, TR, and NTR groups in a linear trend indicating HC > NTR > TR, on global mean CV ($F(2,62) = 6.22$, $p = .003$), CT ($F(2,62) = 3.38$, $p = 0.04$), and near significant in SA measures ($F(2,62) = 3.03$, $p = 0.056$) (Fig. 1). These differences could not be explained by group differences in total intracranial volume (ICV) ($F(2,62) = 1.47$, $p = 0.237$) (Fig. 1). A post hoc comparison revealed:

- Significant CV reductions ($p = 0.005$, Bonferroni corrected) in TR ($M = 4.89 \times 10^5$, $SD = 4.78 \times 10^4$) and NTR patients ($M = 5.01 \times 10^5$, $SD = 7.45 \times 10^4$) compared to HC ($M = 5.54 \times 10^5$, $SD = 4.76 \times 10^4$) (Fig. 1)
- Significant reduction in mean CT ($p = 0.046$, Bonferroni corrected) in TR patients ($M = 2.79$, $SD = 0.22$) and but not NTR

patients ($M = 2.83$, $SD = 0.26$) compared to HC ($M = 2.93$, $SD = 0.08$) (Fig. 1).

- No significant decrease in mean SA in NTR ($M = 9.87 \times 10^4$, $SD = 1.03 \times 10^4$) or TR patients ($M = 9.72 \times 10^4$, $SD = 7.21 \times 10^3$) compared to HC ($M = 1.04 \times 10^5$, $SD = 0.924 \times 10^3$) (Fig. 1).

3.2. Differences in cortical volume, cortical thickness and cortical surface area associated with schizophrenia

Vertex-wise analyses showed significant decreases in CV in the patient group compared to HC in seven clusters centred on the right insula ($t = -4.07$, $p < 0.001$), left insula ($t = -3.31$, $p < 0.001$), left inferior temporal ($t = -5.51$, $p < 0.001$) right lateral occipital ($t = -4.54$, $p < 0.001$), left precuneus ($t = -4.00$, $p < 0.001$), right middle temporal gyrus ($t = -3.16$, $p < 0.05$) and right precuneus ($t = -4.04$, $p < 0.05$) (Table 2). We observed decreases in CT in patients with schizophrenia compared to HC in two clusters centred on the right superior temporal gyrus (STG) ($t = -3.48$, $p < 0.001$) and left inferior temporal gyrus ($t = -3.61$, $p < 0.05$) (Table 2). There were significant decreases in SA in patients compared to HC in five clusters centred on the left precuneus ($t = -4.00$, $p < 0.001$), right precentral gyrus ($t = -3.33$, $p < 0.001$), left inferior temporal gyrus ($t = -5.01$, $p < 0.05$), right STG ($t = -3.84$, $p < 0.05$), and right medial orbital frontal cortex ($t = -3.59$, $p < 0.05$) (Table 2), (Fig. 2).

Mean cluster values across groups are visualised in Fig. 3. There were no significant correlations between PANSS symptom scores and measures of CV, CT and SA in significant cortical clusters.

3.3. Differences in cortical volume, cortical thickness and cortical surface area associated with treatment resistance

Significant decreases in CV were found in TR patients compared to NTR patients in one cluster incorporating the right frontal and precentral regions ($t = -4.43$, $p < 0.05$). Similarly, significant decreases in CT were also found in TR patients compared to NTR patients in four clusters including the right parietal and occipital regions ($t = -2.92$, $p < 0.001$), left temporal regions ($t = -3.65$, $p < 0.05$), right isthmus cingulate regions ($t = -4.11$, $p < 0.05$), and left isthmus cingulate regions ($t = -3.65$, $p < 0.05$) (Table 3). In contrast, an increase in SA in TR patients compared to NTR patients was observed in one cluster incorporating the right postcentral gyrus and superior parietal cortex ($t = 3.47$, $p < 0.05$) (Table 3, Fig. 3). There were no significant correlations between significant cortical clusters and PANSS scores in the TR patient group. However, a group trend showing a negative correlation between negative symptoms and cortical measures in the NTR patient

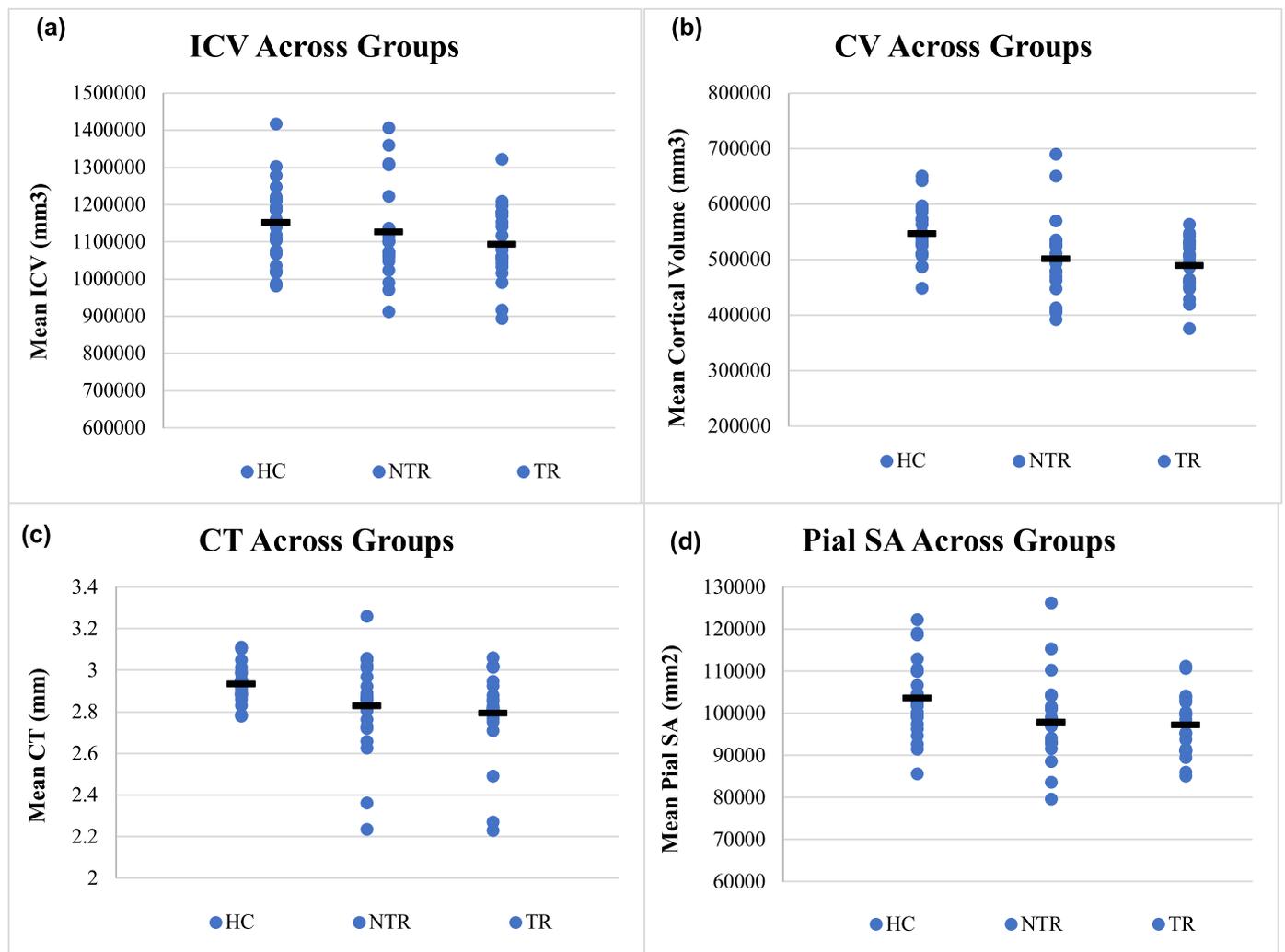


Fig. 1. Trends in mean global measures across groups. Measures include estimated intracranial volume (ICV), mean cortical volume (CV), mean cortical thickness (CT), and mean pial surface area (SA) across groups patients with schizophrenia.

group was observed.

4. Discussion

In this study we examined differences in measures of cortical morphology between two groups of patients with TR and NTR schizophrenia, and HC. In order to demonstrate differences in cortical measures specific to schizophrenia we compared the entire patient group

with HC on all cortical measures and found significant reductions in measures of CV, CT, and SA in patients with schizophrenia compared to HC. Examination of independent patient groups (TR vs NTR) revealed that individuals with TR schizophrenia were found to have more severe reductions in CV and CT across areas of the temporal and frontal lobes, in line with previous reports in this population. However, these results also showed an increase in SA in the superior parietal and postcentral gyrus, contrary to previous research (Kong et al., 2015;

Table 2

Clusters of significance (RFT, $p < 0.05$) between treatment resistant (Treatment Resistant) and non-treatment resistant (NTreatment Resistant) patients with schizophrenia. Brodmann Area (BA), left(L), right(R), ‘Vertices’ indicates the number of vertices within the cluster, tmax represents the maximum t statistic within the cluster at the $x y z$ Talairach coordinates reported, pcluster is the cluster corrected P value for significance reporting.

Measure	Cluster	Region Labels	Hemisphere	BA (tmax)	Vertices	Talairach	tmax	pcluster
Cortical Thickness TR > NTR	1	Inferior parietal cortex, lateral occipital cortex, middle temporal gyrus	R	39	4462	46 -56 31	-2.92	6.11×10^{-3}
	2	Isthmus-cingulate cortex, precuneus cortex	R	30	2774	23 -58 13	-4.11	2.67×10^{-2}
	3	Banks superior temporal sulcus, middle temporal gyrus, superior temporal gyrus	L	22	2956	-62 -18 0	-3.65	2.99×10^{-2}
	4	Isthmus-cingulate cortex, lingual gyrus, precuneus cortex	L	19	2663	-20 -48 -1	-3.65	3.91×10^{-2}
Cortical Volume TR > NTR	1	Caudal middle frontal gyrus, precentral gyrus	R	6	2773	42 -2 29	-4.43	4.10×10^{-2}
Cortical Surface Area TR > NTR	1	Postcentral gyrus, superior parietal cortex	R	40	2726	31 -41 55	3.47	1.75×10^{-2}

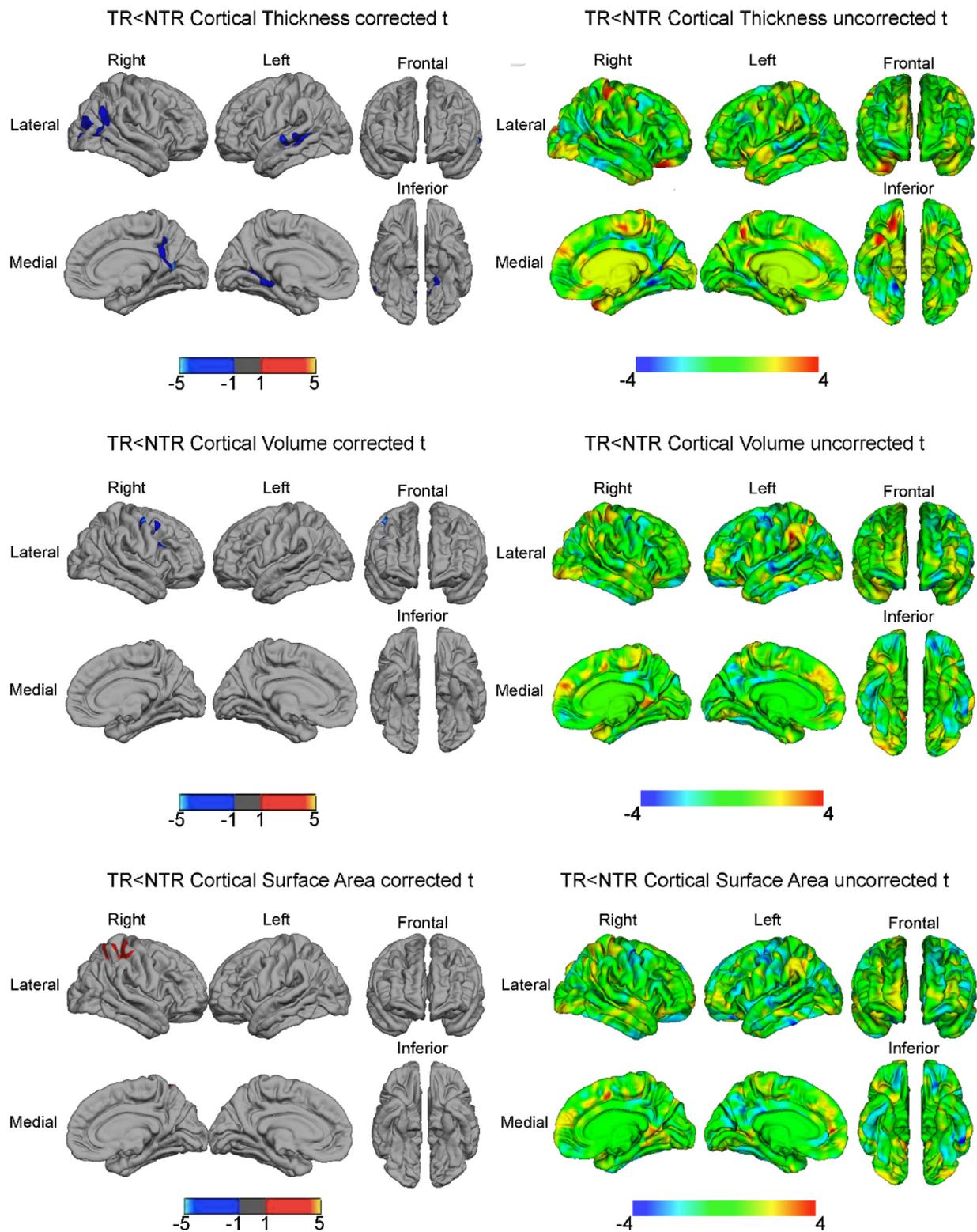


Fig. 2. Reduced cortical measure clusters for Treatment Resistant compared to Non-Treatment Resistant. Regions of significantly reduced (RFT, $p < 0.05$) cortical thickness, cortical volume, and cortical surface area in individuals with Treatment Resistant schizophrenia compared to Non-Treatment Resistant schizophrenia. See [Table 2](#) for further statistical cluster details.

[Rimol et al., 2012](#)). Previous evidence suggests that cortical volume is a function of CT and cortical SA which are independent and heritable measures ([Winkler et al., 2010](#); [Panizzon et al. 2009](#)). CT has been shown to be influenced by neuronal size, intra-neuronal neuropil, number of glial cells and blood vessels. Taken together, it could be proposed that reductions in the specific factors that make up CT may

play a significant role in CV reductions in schizophrenia. While further research with a larger sample size is required, these preliminary results could indicate the existence of a neurobiological mechanism specific to CT that is influencing treatment response.

The neurobiological mechanisms underlying treatment resistance are unclear. Elevated dopamine levels in the striatum and midbrain

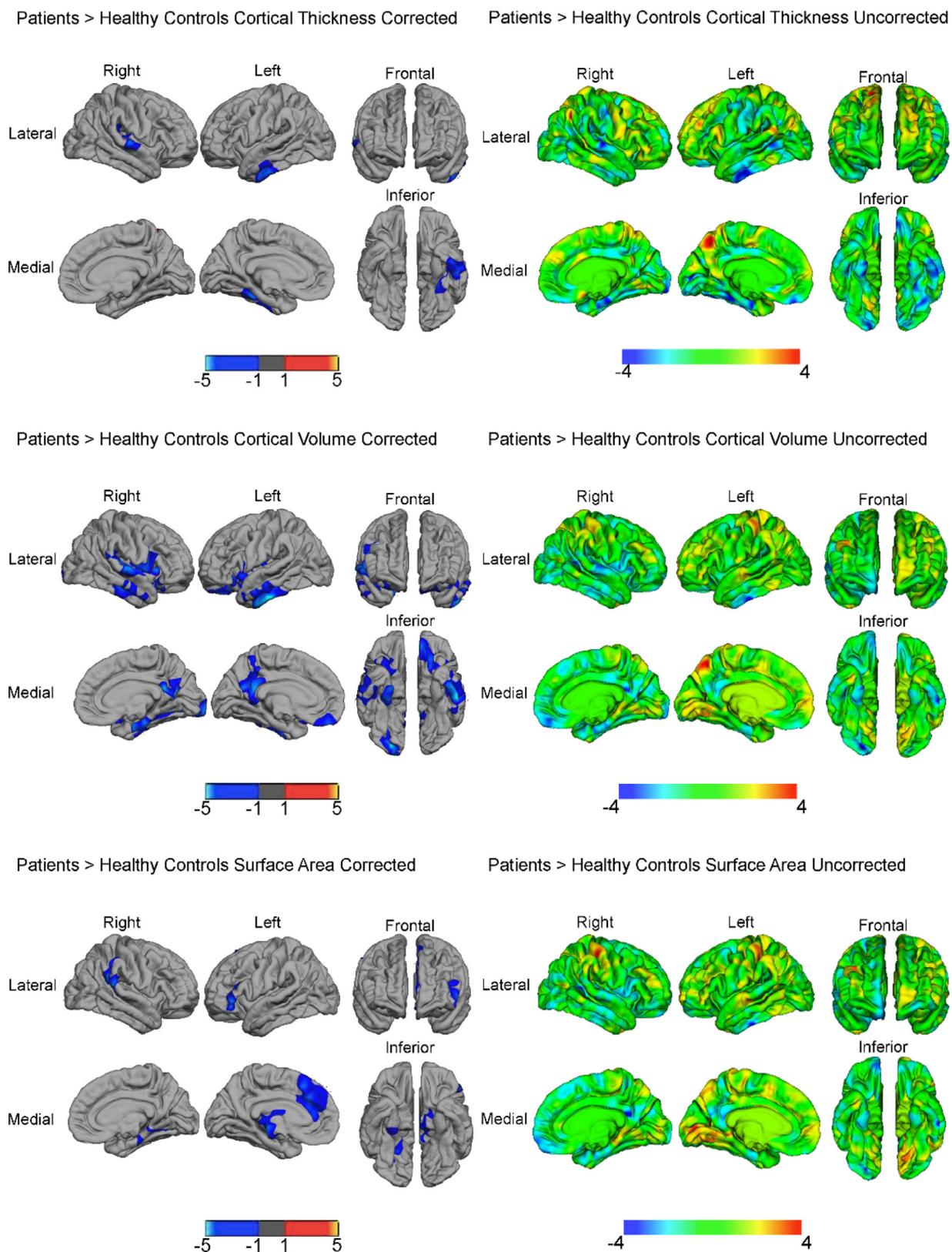


Fig. 3. Reduced cortical measure clusters for patients compared to healthy controls. Regions of significantly reduced (RFT, $p < 0.05$) cortical thickness, cortical volume, and cortical surface area in individuals with schizophrenia compared to HC. Corrected t -maps see on the left and uncorrected t -maps seen on the right. See [Table 3](#) for further statistical cluster details.

Table 3

Clusters of significant reduction (RFT, $p < 0.05$) between patients and HC on cortical surface measures. Brodmann Area (BA), left(L), right(R), 'Vertices' indicates the number of vertices within the cluster, tmax represents the maximum t statistic within the cluster at the x y z Talairach coordinates reported, pcluster is the cluster corrected P value for significance reporting.

Measure	Cluster	Region Labels	H	BA (tmax)	Vertices	Talairach			tmax	Pcluster
						X	Y	Z		
Cortical Thickness Patients>HC	1	Insula, precentral gyrus, superior temporal gyrus, supramarginal gyrus, transverse temporal cortex	R	13	4764	33	7	12	-3.48	1.21×10^{-3}
	2	fusiform gyrus, inferior temporal gyrus, middle temporal gyrus	L	20	2586	-31	-38	-16	-3.61	1.05×10^{-2}
Cortical Volume Patients>HC	1	Insula, lateral orbital frontal cortex, pars opercularis, postcentral gyrus, precentral gyrus, superior temporal gyrus, supramarginal gyrus, transverse temporal cortex	R	44	14,537	48	5	13	-4.07	7.95×10^{-6}
	2	Insula, lateral orbital frontal cortex, medial orbital frontal cortex, pars opercularis, precentral gyrus, superior temporal gyrus	L	11	6797	-6	44	-20	-3.31	1.93×10^{-5}
	3	inferior temporal gyrus, middle temporal gyrus	L	20	3423	-53	-22	-25	-5.51	5.74×10^{-4}
	4	entorhinal cortex, fusiform gyrus, lateral occipital cortex, parahippocampal gyrus	R	17	3789	21	-89	-2	-4.54	5.73×10^{-4}
	5	isthmus-cingulate cortex, precuneus cortex	L	30	4093	-5	-46	22	-4.00	1.67×10^{-3}
	6	inferior temporal gyrus, middle temporal gyrus	R	20	2270	53	-27	-16	-3.16	2.06×10^{-2}
	7	isthmus-cingulate cortex, precuneus cortex	R	23	2500	5	-46	22	-4.04	4.21×10^{-2}
Cortical Surface Area Patients>HC	1	isthmus-cingulate cortex, precuneus cortex	L	30	4207	-6	-47	20	-4.00	3.83×10^{-4}
	2	pars opercularis, postcentral gyrus, precentral gyrus	R	9	3646	49	4	21	-3.33	2.24×10^{-3}
	3	inferior temporal gyrus, middle temporal gyrus	L	20	1806	-53	-23	-25	-5.08	6.50×10^{-3}
	4	Superior temporal gyrus, transverse temporal cortex	R	22	2255	55	-7	-2	-3.84	9.92×10^{-3}
	5	medial orbital frontal cortex, superior frontal cortex	R	11	1541	10	50	-20	-3.59	2.84×10^{-2}

have formed the key hypothesis central to the pathophysiology of schizophrenia (Howes et al., 2012) and typical antipsychotic drugs act to block dopamine D2/3 receptors in the brain. NTR patients have been shown to have significantly elevated striatal dopamine function compared to healthy controls but TR patients appear to have similar dopamine functioning to healthy controls (Demjaha et al., 2012; Jauhar et al., 2018). This suggests that an alternative mechanism is driving psychosis in TR schizophrenia that is not targeted by typical antipsychotic medication. Previous evidence shows reductions in CT and CV in several regions in schizophrenia, particularly frontal and temporal cortices (e.g. Kuperberg et al., 2003; Yoon et al., 2007; Schultz et al., 2010). In treatment resistance, several studies have reported grey matter reductions; with the left middle frontal, right precentral and right middle temporal gyri being most commonly reported (as reviewed by Mouchlianitis et al., 2016). Similarly, the current data show greater reductions in CT and CV in parietal and temporal regions in TR patients and these regions are broadly in line with structures that process both reward and sensory/action information important for goal-directed behaviour (i.e. parietal association cortex, the inferotemporal cortex and the dorsolateral prefrontal cortex) (Schultz (2015)). As reviewed by Schultz (2015), these cortical regions connect to, and interact with, dopaminergic subcortical regions of the reward processing network including the striatum. Indeed, fMRI studies have shown altered reward processing in cortical regions and dysfunctional connectivity of the reward processing network associated with treatment resistance in schizophrenia (White et al., 2015; Vanes et al., 2018). Therefore, the current findings could represent structural deficits that underlie faulty reward processing in TR patients which contribute to the development of psychosis through a non-dopaminergic pathway meaning antipsychotic medications are not effective.

We also observed significant CV and CT reductions in TR compared to NTR patients in regions previously reported as atypical in schizophrenia, including the inferior parietal, lateral occipital cortex, superior temporal sulcus, and lingual and superior temporal gyrus (Nesvåg et al., 2008; Rimol et al., 2010; Szeszko et al., 2012). CV reductions in patients with schizophrenia are one of the most common findings in the condition, beginning with global grey matter reductions characterized by an increase in ventricular volume (Harvey et al., 1993; Honea et al., 2005; Kong et al., 2015; Shergill et al., 2001). The few studies that have compared TR and NTR patients with schizophrenia have found specific CV decreases in the dorso-lateral prefrontal cortex, temporal regions

(Zugman et al., 2013), putamen and caudate nucleus (Molina et al., 2010). In contrast to Zugman et al. (2013), the current data did not show specific CT reductions in the dorso-lateral prefrontal cortex in TR compared to NTR patients. However, TR patients were shown to be taking a significantly higher dose of antipsychotic medication compared to NTR patients and 72% of patients were taking clozapine. Differences in findings between studies may therefore be related to type and dose of medication rather than treatment response making the two studies difficult to compare. Zugman et al. (2013) also had a larger sample size ($n = 128$ patients) and so the current data may have lacked power to detect these specific changes.

In addition to CV, the current study examined CT and SA measures in TR schizophrenia as earlier work has highlighted each of these component measures to represent unique aspects of cortical architecture (Rakic, 1995). CT is a marker of neuronal integrity in a cortical column whereas SA is thought to be a marker of the number and spacing of cortical columns and both measures have different aetiologies, genetic determinants (Nesvåg et al., 2008; Panizzon et al., 2009) and neurodevelopmental trajectories (Ecker et al., 2014; Hyde et al., 2010). The current findings therefore suggest that neuronal integrity and the number of cortical columns (functions of CV) are important structural markers associated with treatment resistance. Brain regions found to have decreased CT among schizophrenia patients in this study have been previously indicated across several stages of the disease/condition including; ultra-high risk, first episode psychosis, and chronic schizophrenia (Narr et al., 2005; Plitman et al., 2016; Xiao et al., 2015). Therefore, it has been suggested that reduced CT could be a potential risk factor for schizophrenia and thus may have potential to act as marker of TR (Hedman et al., 2016; Narr et al., 2005; Plitman et al., 2016; Xiao et al., 2015).

There also appeared to be a distinction in regions of CT reductions in TR patients. In agreement with previous literature, this study found significant CT reductions in TR patients in the temporal cortex of the left hemisphere (Cui et al., 2018; Rimol et al., 2010). This lateralisation of reductions in temporal CT may be an important part of treatment response and symptomatology as it is estimated up to 95% of language process occurs laterally in the left hemisphere (Barrick et al., 2005; Geschwind and Levitsky, 1968). Previous research has suggested that the left hemisphere has a dominant role in language processing in HC and it has been suggested that this lateralisation may be dysfunctional or disrupted in schizophrenia (Barrick et al., 2005; Geschwind and

Levitsky, 1968). This disruption has been suggested to contribute to auditory hallucinations and language conceptual disorganisation symptoms in patients with schizophrenia (Shenton et al., 1992). The superior temporal sulcus and middle temporal gyrus in particular have been consistently found to be associated with auditory hallucinations in both structural and functional imaging studies (Cui et al., 2018; Shergill et al., 2004, 2003, 2001).

In contrast to previous literature, which has reported no differences or reductions in SA (Szeszko et al., 2012), our data showed an increase in SA in the right postcentral and superior parietal gyrus in TR patients. The parietal lobe has been suggested to be crucial to social cognition, agency and biological motion (Frith et al., 2000; Iacoboni and Dapretto, 2006; Kato et al., 2011). Over-activation of the parietal cortex has been associated with delusions of control, where patients are unable to recognise internal and external biological motion (Kato et al., 2011). Guo et al. (2014) found that a consistent disruption of the medial and mirror neuron system was associated with sensory and cognitive functions, particularly self-processing and agency, over varied illness duration. One could speculate the increase in SA in the superior parietal gyrus in the TR patient group could reflect an over-activation in this region, although this should be interpreted with caution due to the correlational nature and the relatively small sample size in this study.

Previous studies of cortical measures in patients with schizophrenia have included patients treated with clozapine and reported prefrontal cortical atrophy in individuals with a poor response to this treatment (Chiappelli et al., 2017). This study investigated the TR schizophrenia population while controlling for potential confounding effects by excluding patients with schizophrenia who were on or had been on clozapine. This exclusion criterion allowed for the homogeneity of the patient sample to be maintained while still meeting the criteria for TR. However, while CV and CT reduction was observed at this late stage of illness, due to the chronicity of the illness these results could be confounded by several factors. While this study found no significant differences across patient groups in age, illness duration, age of illness onset and intra-cranial volume (ICV), medication dose and cumulative medication over the lifespan may be a significant factor affecting CV and CT which assumedly would be higher in TR compared to NTR patients (Harrison et al., 2003). Indeed, a number of systematic reviews and meta analyses have reported that treatment with antipsychotic medication is associated with regional grey matter volume reductions in schizophrenia; particularly in frontal and temporal lobes (Smieskova et al., 2009), and that these volume decreases are continuously progressive with antipsychotic exposure (Olabi et al., 2011; Hulshoff and Kahn, 2008). While medication type and dose were accounted for in this study, cumulative medication exposure is much harder to quantify and so its effect on the current findings is unknown and presents a limitation of the study. Medication adherence and its influence on the treatment response of both groups also remains unqualified. In addition, this study mainly included males with schizophrenia and cortical surface measures may differ in the female population. The genesis of these cortical decreases can only be speculated from this patient population as data was collected at a singular time point and thus future longitudinal studies should be required to follow up participants at a number of time points and begin participation in the study when patients are medication-free. In addition this chronic population could have been exposed to earlier comorbidities such as depression or mood disorders and secondary illnesses such as substance abuse and prolonged stress, which may have impacted the underlying brain pathology (Heinrichs et al., 2017; Konopaske et al., 2007). Recent studies have suggested that stress could contribute to an increased rate of cortical thinning, which should be considered when discussing patients with chronic schizophrenia (Harrison, 1999; Konopaske et al., 2007). While these various factors make it difficult to fully characterize cortical differences between TR and NTR patients, there is no reason to conclude that these factors would differentially impact TR versus NTR patients.

In summary, this study demonstrated that TR patients with schizophrenia show specific and significant reductions in CT and CV and increases in SA compared to NTR patients. These cortical differences were located in regions of particular interest to schizophrenia in the temporal, parietal and medial regions (Rimol et al., 2012; Shergill et al., 2001). Since CT reductions have been reported at all stages of schizophrenia, further research should be conducted to determine the nature of the relationship between CT, schizophrenia age of illness onset and trajectory. While the causal impact of these cortical changes remains elusive, it can be speculated that a deficit in CT may make an organism more intolerant to insult and therefore predispose the organism to neurological insult or illness outbreak. These cortical measures may reflect mechanisms underlying aspects of neurological disorganisation and pathology in many respects. Future studies require longitudinal scans at several time points to determine reliable pathological trajectories, and larger sample sizes are needed to confidently show generalizable effects.

Acknowledgments

We thank the radiographic team at the Centre for Neuroimaging Sciences for their support, and Felix Dransfield, Christiana Ilesanmi, Jessica Proctor, Valentina Forassi and Juliet Gillam for assistance with fMRI scanning and behavioural testing.

Funding

This paper represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Conflict of interest

None.

References

- Anderson, V.M., Goldstein, M.E., Kydd, R.R., Russell, B.R., 2015. Extensive gray matter volume reduction in treatment-resistant schizophrenia. *Int. J. Neuropsychopharmacol.* 18 <https://doi.org/10.1093/ijnp/pyv016>. pyv016.
- Andreasen, N.C., Carpenter, W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am. J. Psychiatry* 162, 441–449. <https://doi.org/10.1176/appi.ajp.162.3.441>.
- Barrick, T.R., Mackay, C.E., Prima, S., Maes, F., Vandermeulen, D., Crow, T.J., Roberts, N., 2005. Automatic analysis of cerebral asymmetry: an exploratory study of the relationship between brain torque and planum temporale asymmetry. *Neuroimage* 24, 678–691. <https://doi.org/10.1016/j.neuroimage.2004.09.003>.
- Bazire, S., 2016. *Psychotropic Drug Directory 2016: The Professionals' Pocket Handbook and Aide Memoire*. Lloyd-Reinhold Communications.
- Bodén, R., Persson, J., Wall, A., Lubberink, M., Ekselius, L., Larsson, E.-M., Antoni, G., 2017. Striatal phosphodiesterase 10A and medial prefrontal cortical thickness in patients with schizophrenia: a PET and MRI study. *Transl. Psychiatry* 7, e1050. <https://doi.org/10.1038/tp.2017.11>.
- Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., Sheitman, B., 2001. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am. J. Psychiatry* 158, 518–526. <https://doi.org/10.1176/appi.ajp.158.4.518>.
- Chiappelli, J., Kochunov, P., Savransky, A., Fisseha, F., Wisner, K., Du, X., Rowland, L.M., Hong, L.E., 2017. Allostatic load and reduced cortical thickness in schizophrenia. *Psychoneuroendocrinology* 77, 105–111. <https://doi.org/10.1016/j.psyneuen.2016.11.021>.
- Conley, R.R., Kelly, D.L., 2001. Management of treatment resistance in schizophrenia. *Biol. Psychiatry* 50, 898–911. [https://doi.org/10.1016/S0006-3223\(01\)01271-9](https://doi.org/10.1016/S0006-3223(01)01271-9).
- Crespo-Facorro, B., Kim, J., Andreasen, N.C., O'Leary, D.S., Magnotta, V., 2000. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. *Biol. Psychiatry* 48, 110–119.
- Cui, Y., Liu, B., Song, M., Lipnicki, D.M., Li, J., Xie, S., Chen, Y., Li, P., Lu, L., Lv, L., Wang, H., Yan, H., Yan, J., Zhang, H., Zhang, D., Jiang, T., 2018. Auditory verbal hallucinations are related to cortical thinning in the left middle temporal gyrus of patients

- with schizophrenia. *Psychol. Med.* 48, 115–122. <https://doi.org/10.1017/S0033291717001520>.
- Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage* 9, 179–194. <https://doi.org/10.1006/nimg.1998.0395>.
- Demjaha, A., Murray, R.M., McGuire, P.K., Kapur, S., Howes, O.D., 2012. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am. J. Psychiatry* 169, 1203–1210. <https://doi.org/10.1176/appi.ajp.2012.12010144>.
- Ecker, C., Shahidani, A., Feng, Y., Daly, E., Murphy, C., D'Almeida, V., Deoni, S., Williams, S.C., Gillan, N., Gudbrandsen, M., Wichers, R., Andrews, D., Van Hemert, L., Murphy, D.G.M., 2014. The effect of age, diagnosis, and their interaction on vertex-based measures of cortical thickness and surface area in autism spectrum disorder. *J. Neural Transm.* 121, 1157–1170. <https://doi.org/10.1007/s00702-014-1207-1>.
- Elkis, H., Buckley, P.F., 2016. Treatment-resistant schizophrenia. *Psychiatr. Clin. North Am.* 39, 239–265. <https://doi.org/10.1016/j.psc.2016.01.006>.
- Emami, S., Guimond, S., Mallar Chakravarty, M., Lepage, M., 2016. Cortical thickness and low insight into symptoms in enduring schizophrenia. *Schizophr. Res.* 170, 66–72. <https://doi.org/10.1016/j.schres.2015.10.016>.
- Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11050–11055. <https://doi.org/10.1073/pnas.200033797>.
- Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9, 195–207. <https://doi.org/10.1006/nimg.1998.0396>.
- Frith, C.D., Blakemore, S., Wolpert, D.M., 2000. Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. *Brain Res. Brain Res. Rev.* 31, 357–363.
- Geschwind, N., Levitsky, W., 1968. Human brain: left-right asymmetries in temporal speech region. *Science* 161, 186–187.
- Goghari, V.M., Sponheim, S.R., MacDonald, A.W., 2010. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. *Neurosci. Biobehav. Rev.* 34, 468–486. <https://doi.org/10.1016/j.neubiorev.2009.09.004>.
- Guo, S., Kendrick, K.M., Yu, R., Wang, H.-L.S., Feng, J., 2014. Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. *Hum. Brain Mapp.* 35, 123–139. <https://doi.org/10.1002/hbm.22162>.
- Harrison, P.J., 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 122 (Pt 4), 593–624.
- Harrison, P.J., Freemantle, N., Geddes, J.R., 2003. Meta-analysis of brain weight in schizophrenia. *Schizophr. Res.* 64, 25–34.
- Harvey, I., Ron, M.A., Du Boulay, G., Wicks, D., Lewis, S.W., Murray, R.M., 1993. Reduction of cortical volume in schizophrenia on magnetic resonance imaging. *Psychol. Med.* 23, 591–604.
- Harvey, P.D., Rosenthal, J.B., 2016. Treatment resistant schizophrenia: course of brain structure and function. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 70, 111–116. <https://doi.org/10.1016/j.pnpb.2016.02.008>.
- Hayasaka, S., Phan, K.L., Liberzon, I., Worsley, K.J., Nichols, T.E., 2004. Nonstationary cluster-size inference with random field and permutation methods. *Neuroimage* 22, 676–687. <https://doi.org/10.1016/j.neuroimage.2004.01.041>.
- Hedman, A.M., van Haren, N.E.M., van Baal, G.C.M., Brouwer, R.M., Brans, R.G.H., Schnack, H.G., Kahn, R.S., Hulshoff Pol, H.E., 2016. Heritability of cortical thickness changes over time in twin pairs discordant for schizophrenia. *Schizophr. Res.* 173, 192–199. <https://doi.org/10.1016/j.schres.2015.06.021>.
- Heinrichs, R.W., Pincock, F., Parlar, M., Hawco, C., Hanford, L., Hall, G.B., 2017. Cortical thinning in network-associated regions in cognitively normal and below-normal range schizophrenia. *Schizophr. Res. Treat.*, 9760905. <https://doi.org/10.1155/2017/9760905>.
- Honea, R., Crow, T.J., Passingham, D., Mackay, C.E., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am. J. Psychiatry* 162, 2233–2245. <https://doi.org/10.1176/appi.ajp.162.12.2233>.
- Howes, O.D., Kapur, S., 2014. A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *Br. J. Psychiatry* 205, 1–3. <https://doi.org/10.1192/bjp.bp.113.138578>.
- Howes, O.D., Kambaitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., 2012. The Nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysis of imaging studies. *Arch. Gen. Psychiatry* 69 (8), 776–786. <https://doi.org/10.1001/archgenpsychiatry.2012.169>.
- Hulshoff Pol, H.E., Kahn, R.S., 2008. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr. Bull.* 34, 354–366.
- Hyde, K.L., Samson, F., Evans, A.C., Mottron, L., 2010. Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. *Hum. Brain Mapp.* 31, 556–566. <https://doi.org/10.1002/hbm.20887>.
- Iacoboni, M., Dapretto, M., 2006. The mirror neuron system and the consequences of its dysfunction. *Nat. Rev. Neurosci.* 7, 942–951. <https://doi.org/10.1038/nrn2024>.
- Jauhar, S., Veronese, M., Nour, M.M., Rogdaki, M., Hathway, P., Turkheimer, F.E., 2018. Determinants of treatment response in first-episode psychosis: an ¹⁸F-DOPA PET study. [published online ahead of print Apr 20]. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-018-0042-4>.
- Jørgensen, K.N., Nesvåg, R., Gunleiksrud, S., Raballo, A., Jönsson, E.G., Agartz, I., 2016. First- and second-generation antipsychotic drug treatment and subcortical brain morphology in schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* 266, 451–460. <https://doi.org/10.1007/s00406-015-0650-9>.
- Jovicich, J., Czanner, S., Greve, D., Haley, E., van der Kouwe, A., Gollub, R., Kennedy, D., Schmitt, F., Brown, G., Macfall, J., Fischl, B., Dale, A., 2006. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *Neuroimage* 30, 436–443. <https://doi.org/10.1016/j.neuroimage.2005.09.046>.
- Kato, Y., Muramatsu, T., Kato, M., Shibukawa, Y., Shintani, M., Mimura, M., 2011. Magnetoencephalography study of right parietal lobe dysfunction of the evoked mirror neuron system in antipsychotic-free schizophrenia. *PLoS One* 6, e28087. <https://doi.org/10.1371/journal.pone.0028087>.
- Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1989. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br. J. Psychiatry* 155, 59–65. <https://doi.org/10.1093/schbul/13.2.261>.
- Kong, L., Herold, C.J., Zöllner, F., Salat, D.H., Lässer, M.M., Schmid, L.A., Fellhauer, I., Thomann, P.A., Essig, M., Schad, L.R., Erickson, K.I., Schröder, J., 2015. Comparison of grey matter volume and thickness for analysing cortical changes in chronic schizophrenia: a matter of surface area, grey/white matter intensity contrast, and curvature. *Psychiatry Res.* 231, 176–183. <https://doi.org/10.1016/j.pscychresns.2014.12.004>.
- Konopaske, G.T., Dorph-Petersen, K.-A., Pierri, J.N., Wu, Q., Sampson, A.R., Lewis, D.A., 2007. Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. *Neuropsychopharmacology* 32, 1216–1223. <https://doi.org/10.1038/sj.npp.1301233>.
- Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C.R., van der Kouwe, A.J.W., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch. Gen. Psychiatry* 60, 878–888. <https://doi.org/10.1001/archpsyc.60.9.878>.
- Maller, J.J., Daskalakis, Z.J., Thomson, R.H.S., Daigle, M., Barr, M.S., Fitzgerald, P.B., 2012. Hippocampal volumetrics in treatment-resistant depression and schizophrenia: the devil's in de-tail. *Hippocampus* 22, 9–16. <https://doi.org/10.1002/hipo.20873>.
- Molina, V., Hernández, J.A., Sanz, J., Paniagua, J.C., Hernández, A.I., Martín, C., Matías, J., Calama, J., Bote, B., 2010. Subcortical and cortical gray matter differences between Kraepelinian and non-Kraepelinian schizophrenia patients identified using voxel-based morphometry. *Psychiatry Res.* 184, 16–22. <https://doi.org/10.1016/j.pscychresns.2010.06.006>.
- Molina, V., Reig, S., Sanz, J., Palomo, T., Benito, C., Sánchez, J., Sarramea, F., Pascau, J., Desco, M., 2005. Increase in gray matter and decrease in white matter volumes in the cortex during treatment with atypical neuroleptics in schizophrenia. *Schizophr. Res.* 80, 61–71. <https://doi.org/10.1016/j.schres.2005.07.031>.
- Molina, V., Reig, S., Sanz, J., Palomo, T., Benito, C., Sarramea, F., Pascau, J., Sánchez, J., Martín-Loeches, M., Muñoz, F., Desco, M., 2008. Differential clinical, structural and P300 parameters in schizophrenia patients resistant to conventional neuroleptics. *Prog. Neuropharmacol. Biol. Psychiatry* 32, 257–266. <https://doi.org/10.1016/j.pnpb.2007.08.017>.
- Mouchlianitis, E., McCutcheon, R., Howes, O.D., 2016. Brain-imaging studies of treatment-resistant schizophrenia: a systematic review. *Lancet Psychiatry* 3, 451–463. [https://doi.org/10.1016/S2215-0366\(15\)00540-4](https://doi.org/10.1016/S2215-0366(15)00540-4).
- Nakajima, S., Takeuchi, H., Plitman, E., Fervaha, G., Gerretsen, P., Caravaggio, F., Chung, J.K., Iwata, Y., Remington, G., Graff-Guerrero, A., 2015. Neuroimaging findings in treatment-resistant schizophrenia: a systematic review: lack of neuroimaging correlates of treatment-resistant schizophrenia. *Schizophr. Res.* 164, 164–175. <https://doi.org/10.1016/j.schres.2015.01.043>.
- Narr, K.L., Bilder, R.M., Toga, A.W., Woods, R.P., Rex, D.E., Szeszko, P.R., Robinson, D., Sevy, S., Gunduz-Bruce, H., Wang, Y.-P., DeLuca, H., Thompson, P.M., 2005. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cereb. Cortex* 15, 708–719. <https://doi.org/10.1093/cercor/bhh172>.
- Nesvåg, R., Lawyer, G., Varnäs, K., Fjell, A.M., Walhovd, K.B., Frigessi, A., Jönsson, E.G., Agartz, I., 2008. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. *Schizophr. Res.* 98, 16–28. <https://doi.org/10.1016/j.schres.2007.09.015>.
- Olabi, B., Ellison-Wright, I., McIntosh, A.M., Wood, S.J., Bullmore, E., Lawrie, S.M., 2011. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biol. Psychiatry* 70 (1), 88–96.
- Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Jernigan, T.L., Prom-Wormley, E., Neale, M., Jacobson, K., Lyons, M.J., Grant, M.D., Franz, C.E., Xian, H., Tsuang, M., Fischl, B., Seidman, L., Dale, A., Kremen, W.S., 2009. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb. Cortex* 19, 2728–2735. <https://doi.org/10.1093/cercor/bhp026>.
- Plitman, E., Patel, R., Chung, J.K., Pipitone, J., Chavez, S., Reyes-Madriral, F., Gómez-Cruz, G., León-Ortiz, P., Chakravarty, M.M., de la Fuente-Sandoval, C., Graff-Guerrero, A., 2016. Glutamatergic metabolites, volume and cortical thickness in antipsychotic-naïve patients with first-episode psychosis: implications for excitotoxicity. *Neuropsychopharmacology* 41, 2606–2613. <https://doi.org/10.1038/npp.2016.84>.
- Quarantelli, M., Palladino, O., Prinster, A., Schiavone, V., Carotenuto, B., Brunetti, A., Marsili, A., Casiello, M., Muscettola, G., Salvatore, M., de Bartolomeis, A., 2014. Patients with poor response to antipsychotics have a more severe pattern of frontal atrophy: a voxel-based morphometry study of treatment resistance in schizophrenia. *Biomed. Res. Int.* 2014, 325052. <https://doi.org/10.1155/2014/325052>.
- Rakic, P., 1995. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. *Trends Neurosci.* 18, 383–388.
- Rimol, L.M., Hartberg, C.B., Nesvåg, R., Fennema-Notestine, C., Hagler, D.J., Pung, C.J., Jennings, R.G., Haukvik, U.K., Lange, E., Nakstad, H., Melle, I., Andreassen, O.A., Dale, A.M., Agartz, I., 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *BPS* 68, 41–50. <https://doi.org/10.1016/j.biopsych.2010.03.036>.
- Rimol, L.M., Nesvåg, R., Hagler, D.J., Bergmann, Ø., Fennema-Notestine, C., Hartberg, C.B., Haukvik, U.K., Lange, E., Pung, C.J., Server, A., Melle, I., Andreassen, O.A.,

- Agartz, I., Dale, A.M., 2012. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biol. Psychiatry* 71, 552–560. <https://doi.org/10.1016/j.biopsych.2011.11.026>.
- Schultz, W., 2015. Neuronal reward and decision signals: from theories to data. *Physiol. Rev.* 95, 853–951.
- Schultz, C.C., Koch, K., Wagner, G., Roebel, M., Nenadic, I., Schachtzabel, C., Reichenbach, J.R., Sauer, H., Schlösser, R.G., 2010. Complex pattern of cortical thinning in schizophrenia: results from an automated surface-based analysis of cortical thickness. *Psychiatry Res.* 182, 134–140.
- Ségonne, F., Dale, A.M., Busa, E., Glessner, M., Salat, D., Hahn, H.K., Fischl, B., 2004. A hybrid approach to the skull stripping problem in MRI. *Neuroimage* 22, 1060–1075. <https://doi.org/10.1016/j.neuroimage.2004.03.032>.
- Selemon, L.D., Goldman-Rakic, P.S., 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol. Psychiatry* 45, 17–25.
- Shenton, M.E., Kikinis, R., Jolesz, F.A., Pollak, S.D., LeMay, M., Wible, C.G., Hokama, H., Martin, J., Metcalf, D., Coleman, M., McCarley, R.W., 1992. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. *N. Engl. J. Med.* 327, 604–612. <https://doi.org/10.1056/NEJM199208273270905>.
- Shergill, S.S., Brammer, M.J., Amaro, E., Williams, S.C.R., Murray, R.M., McGuire, P.K., 2004. Temporal course of auditory hallucinations. *Br. J. Psychiatry* 185, 516–517. <https://doi.org/10.1192/bjp.185.6.516>.
- Shergill, S.S., Brammer, M.J., Fukuda, R., Williams, S.C.R., Murray, R.M., McGuire, P.K., 2003. Engagement of brain areas implicated in processing inner speech in people with auditory hallucinations. *Br. J. Psychiatry* 182, 525–531.
- Shergill, S.S., Bullmore, E.T., Brammer, M.J., Williams, S.C., Murray, R.M., McGuire, P.K., 2001. A functional study of auditory verbal imagery. *Psychol. Med.* 31, 241–253.
- Smiley, J.F., Konnova, K., Bleiwas, C., 2012. Cortical thickness, neuron density and size in the inferior parietal lobe in schizophrenia. *Schizophr. Res.* 136, 43–50. <https://doi.org/10.1016/j.schres.2012.01.006>.
- Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., Radue, E.W., McGuire, P.K., Riecher-Rössler, A., Borgwardt, S.J., 2009. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia? – a systematic review. *Curr Pharm Des* 15 (22), 2535–2549.
- Sugihara, G., Oishi, N., Son, S., Kubota, M., Takahashi, H., Murai, T., 2017. Distinct patterns of cerebral cortical thinning in schizophrenia: a neuroimaging data-driven approach. *Schizophr. Bull.* 43, 900–906. <https://doi.org/10.1093/schbul/sbw176>.
- Szeszko, P.R., Narr, K.L., Phillips, O.R., McCormack, J., Sevy, S., Gunduz-Bruce, H., Kane, J.M., Bilder, R.M., Robinson, D.G., 2012. Magnetic resonance imaging predictors of treatment response in first-episode schizophrenia. *Schizophr. Bull.* 38, 569–578. <https://doi.org/10.1093/schbul/sbq126>.
- Vanes, L., Mouchlianitis, E., Collier, T., Averbeck, B., Shergill, S., 2018. Differential neural reward mechanisms in treatment-responsive and treatment-resistant schizophrenia. *Psychol. Med.* 48 (14), 2418–2427. <https://doi.org/10.1017/S0033291718000041>.
- van Haren, N.E.M., Pol, H.E.H., Schnack, H.G., Cahn, W., Brans, R., Carati, I., Rais, M., Kahn, R.S., 2008. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biol. Psychiatry* 63, 106–113. <https://doi.org/10.1016/j.biopsych.2007.01.004>.
- van Haren, N.E.M., Rijdsdijk, F., Schnack, H.G., Picchioni, M.M., Touloupoulou, T., Weisbrod, M., Sauer, H., van Erp, T.G., Cannon, T.D., Huttunen, M.O., Boomsma, D.I., Hulshoff Pol, H.E., Murray, R.M., Kahn, R.S., 2012. The genetic and environmental determinants of the association between brain abnormalities and schizophrenia: the schizophrenia twins and relatives consortium. *Biol. Psychiatry* 71, 915–921. <https://doi.org/10.1016/j.biopsych.2012.01.010>.
- Velligan, D.I., Alphas, L., Lancaster, S., Morlock, R., Mintz, J., 2009. Association between changes on the Negative Symptom Assessment scale (NSA-16) and measures of functional outcome in schizophrenia. *Psychiatry Res.* 169, 97–100. <https://doi.org/10.1016/j.psychres.2008.10.009>.
- Weschler, D., 2008. Wechsler Adult Intelligence Scale - Fourth Edition. *Stat Solutions*, pp. 1–3.
- White, T.P., Wigton, R., Joyce, D.W., Collier, T., Fornito, A., Shergill, S.S., 2015. Dysfunctional striatal systems in treatment-resistant schizophrenia. *Neuropsychopharmacol. Off. Publ. Am. College Neuropsychopharmacol.* 41 (5), 1274–1285.
- Winkler, A.M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P.T., Duggirala, R., Glahn, D.C., 2010. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage* 53, 1135–1146. <https://doi.org/10.1016/j.neuroimage.2009.12.028>.
- Winkler, A.M., Sabuncu, M.R., Yeo, B.T.T., Fischl, B., Greve, D.N., Kochunov, P., Nichols, T.E., Blangero, J., Glahn, D.C., 2012. Measuring and comparing brain cortical surface area and other areal quantities. *Neuroimage* 61, 1428–1443. <https://doi.org/10.1016/j.neuroimage.2012.03.026>.
- Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J. Clin. Psychiatry* 64, 663–667. <https://doi.org/10.4088/JCP.v64n0607>.
- Worsley, K.J., Taylor, J.E., Tomaiuolo, F., Lerch, J., 2004. Unified univariate and multivariate random field theory. *Neuroimage* 23 (Suppl 1), S189–S195. <https://doi.org/10.1016/j.neuroimage.2004.07.026>.
- 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. *Schizophr. Bull.* 41, 201–210. <https://doi.org/10.1093/schbul/sbt177>.
- Yoon, U., Lee, J.-M., Im, K., Shin, Y.-W., Cho, B.H., Kim, I.Y., Kwon, J.S., Kim, S.I., 2007. Pattern classification using principal components of cortical thickness and its discriminative pattern in schizophrenia. *Neuroimage* 34 (4), 1405–1415.
- Zugman, A., Gadelha, A., Assunção, I., Sato, J., Ota, V.K., Rocha, D.L., Mari, J.J., Belangero, S.I., Bressan, R.A., Brietzke, E., Jackowski, A.P., 2013. Reduced dorso-lateral prefrontal cortex in treatment resistant schizophrenia. *Schizophr. Res.* 148, 81–86. <https://doi.org/10.1016/j.schres.2013.05.002>.