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Association between cortical volume and gray-white matter contrast with second generation antipsychotic medication exposure in first episode male schizophrenia patients

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Abstract

This cross-sectional study examines the differences in cortical volume and gray-to-white matter contrast (GWC) in first episode schizophrenia patients (SCZ) compared to heathy control participants (HC) and in SCZ patients as a function of exposure to second generation antipsychotic medication. We hypothesize 1) SCZ exhibit regionally lower cortical volumes relative to HCs, 2) cortical volume will be greater with longer exposure to second generation antipsychotics prior to the MRI scan, and 3) lower GWC with longer exposure to second generation antipsychotics prior to the MRI scan, suggesting more blurring from greater intracortical myelin. To accomplish this, MRI scans from 71 male SCZ patients treated with second generation oral risperidone and 42 male HCs were examined. 3D T1-weighted MPRAGE images collected at 1.5T were used to estimate cortical volume and GWC by sampling signal intensity at 30% within the cortical ribbon. Average cortical volume and GWC were calculated and compared between SCZ and HC. Cortical volume and GWC in SCZ patients were correlated with duration of medication exposure for the time

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Author Contributions:

Nuechterlein, Ellingson, and Tishler designed the study and wrote the protocol. Chwa performed image analyses, drafted, and edited the manuscript. Chwa, Tishler, Anwar, Raymond, Tran, Villablanca, Ventura, Subotnik, and Ellingson performed technical and statistical analyses. All authors contributed to and have approved the final manuscript.

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period prior to the scan. First-episode SCZ patients had significantly lower cortical volume compared to HCs in bilateral temporal, superior and rostral frontal, postcentral gyral, and parahippocampal regions. In SCZ patients, greater cortical volume was associated with (log-transformed) duration of second-generation antipsychotic medication exposure in bilateral precuneus, right lingual, and right superior parietal regions. Lower GWC was correlated with longer duration of medication exposure bilaterally in the superior frontal lobes. In summary, second generation antipsychotics may increase cortical volume and decrease GWC in first episode SCZ patients.

Keywords

Schizophrenia; intracortical myelin; cortical volume; second generation antipsychotics

INTRODUCTION

Schizophrenia (SCZ) is a debilitating neuropsychiatric disorder associated with a conglomeration both of positive clinical symptoms, including auditory or visual hallucinations and delusional perceptions of reality, and of negative clinical symptoms such as impoverished volition, diminished motivation, and disjointed, disorganized communication(Kuperberg, 2010; Saha et al., 2005). SCZ affects approximately 0.5% to 1% of the population worldwide(Moreno-Kustner et al., 2018). Its underlying etiology remains largely obscure (Picchioni and Murray, 2007; Shenton et al., 2001) and includes various neuropathological and neurodevelopmental abnormalities including structural (DeLisi et al., 1991; DeLisi et al., 1995; Lieberman et al., 2001b), genetic (Hulshoff Pol et al., 2004; van Haren et al., 2004), and neurochemical abnormalities (Wijtenburg et al., 2015).

Antipsychotic medications are one of the primary treatments for schizophrenia (Lehman et al., 2004; Patel et al., 2014). Investigations on the effects of antipsychotics have shown favorable response and remission of symptoms ranging from 70-80% in first-episode schizophrenics (Desamericq et al., 2014; Emsley et al., 2006, 2007; Kahn et al., 2008; Lieberman et al., 1993; Nuechterlein et al., 2006; Robinson et al., 1999; Robinson et al., 2004; Subotnik et al., 2014), but complete remission of symptoms is uncommon and approximately 80-95% of patients eventually relapse, (Emsley et al., 2013; Gitlin et al., 2001) often due to poor adherence, (Morken et al., 2008; Subotnik et al., 2011; Ucok et al., 2006) followed by deteriorating clinical trajectory (Lieberman, 2006). Reduced efficacy of second generation antipsychotic medication often develops with repeated episodes, with some patients becoming treatment-refractory (Bondolfi et al., 1998; Caspi et al., 2004; Kane et al., 1988).

Poor adherence and eventual relapse of symptoms is often attributed to serious side effects known to occur after long-term use of first-generation antipsychotics, including tardive dyskinesia (Chouinard et al., 1986; Glazer et al., 1993; Kane et al., 1984). Second generation, or atypical, antipsychotics have fewer motor side effects and, thus, potentially lower risks for long-term treatment (Meltzer, 1995); however, investigations have shown this risk remains nonnegligible (Correll and Schenk, 2008). Second generation antipsychotics

also have different side-effects, including metabolic alterations (Newcomer, 2007) and hyperprolactinaemia (Bostwick et al., 2009).

In addition to adverse side effects, long-term use of antipsychotics has been shown to be associated with measurable changes in brain morphology. Specifically, a number of animal (Dorph-Petersen et al., 2005; Konopaske et al., 2007; Konopaske et al., 2008) studies have reported progressive brain tissue loss proportional to the intensity and duration of antipsychotic therapy; however, human studies have been less conclusive, with some studies showing brain tissue loss proportional to medication exposure (Cahn et al., 2002), particularly with first generation antipsychotics (Lieberman et al., 2005; van Haren et al., 2007; Vita et al., 2015), while other studies have shown no association (Kasai et al., 2003b; Lieberman et al., 2005; Mathalon et al., 2001) or slowing of brain tissue loss (DeLisi et al., 1997; Lieberman et al., 2001a; van Haren et al., 2007) in schizophrenia patients in proportion to duration of antipsychotic exposure. Whether this progressive brain tissue loss is attributable to illness progression in schizophrenia or long-term antipsychotic medication remains controversial (Andreasen et al., 2011).

Neuroanatomical (Hof et al., 2002; Uranova et al., 2011; Uranova et al., 2004; Vostrikov and Uranova, 2011; Vostrikov et al., 2007), genetic (Flynn et al., 2003; Hakak et al., 2001; Sugai et al., 2004; Tkachev et al., 2003), and radiographic (Andreone et al., 2007; Bartzokis, 2002; Bartzokis and Altshuler, 2005; Bartzokis et al., 2003; Flynn et al., 2003; Iwatani et al., 2015; Tishler et al., 2018) studies have suggested that cortical oligodendrocyte density, myelin microstructure, myelin-related gene expression, and intracortical myelin (ICM), or the degree of myelination observed within the cortical ribbon, are reduced in the frontal lobe in patients with schizophrenia compared with healthy individuals. While initial treatment with oral second generation antipsychotics may prevent this decrease, after the first year of treatment the decline is proportional to duration of exposure to oral second generation antipsychotics (Bartzokis et al., 2009; Tishler et al., 2018). Nonadherence to oral antipsychotic medication is extremely common after initial adherence (Weiden and Olfson, 1995), so the ICM decline may be associated with nonadherence. This suggests a promyelinating effect of second generation antipsychotic medication that might increase ICM in response to prolonged consistent treatment (Bartzokis et al., 2012; Bartzokis et al., 2009; Selemon et al., 1999; Zhang et al., 2012) (reviewed in Bartzokis, 2012; Haroutunian et al., 2014). Interestingly, the observed frontal lobe ICM modulation appears spatially concordant with reported cortical atrophy.

Measurement of brain morphometry often involves use of volumetric T1-weighted MR imaging to segment gray and white matter based on differences in relative signal intensity between the two tissue types. It is conceivable that blurring at the interface of gray and white matter, consistent with elevated ICM, may augment measurements of cortical morphology (Fig. 1). Consistent with this hypothesis, Salat *et al.* (Salat et al., 2009) and Panizzon *et al.* (Panizzon et al., 2012) both reported age-related changes in the gray-to-white matter contrast ratio (GWR) in various brain regions in healthy subjects, with especially strong changes in frontal regions, which were interpreted as potentially reflective of regional patterns of cortical myelination. In a study of aging, Westlye *et al.* (2009) utilized measures of regional GWR to increase the sensitivity of their cortical morphological results. Additionally, a recent

study by Jorgensen *et al.* (Jorgensen et al., 2016) observed altered gray-to-white matter contrast (GWC), a slightly different measure of the difference in signal intensity between gray and white matter, in sensory and motor regions in patients with schizophrenia, concluding unique patterns in GWC may reflect abnormal patterns in myelination.

Based on these contemporary studies using both brain morphometry (Cahn et al., 2002; Cahn et al., 2009; DeLisi et al., 1997; Gur et al., 1998; Ho et al., 2003; Kasai et al., 2003a; Kasai et al., 2003b; Lieberman et al., 2001a; Lieberman et al., 2005; Mathalon et al., 2001; van Haren et al., 2007) and the contrast between gray and white matter at the cortical boundary (Jorgensen et al., 2016; Kong et al., 2012; Kong et al., 2015; Panizzon et al., 2012; Salat et al., 2009; Glasser and Van Essen, 2011; Grydeland et al., 2013; Rowley et al., 2015) to estimate cortical thickness and myelination, respectively, combined with previous ICM studies using specialized MRI sequences to quantify myelination alterations during long-term exposure to antipsychotics (Bartzokis et al., 2009; Tishler et al., 2018), we hypothesized that alterations in both cortical volume and GWC (Fig. 1) would be associated with duration of exposure to second generation antipsychotics in first episode schizophrenia patients. Specifically, we theorized that cortical volume would be significantly lower in schizophrenia patients compared with healthy volunteers, that cortical volume would change with longer exposure to second generation antipsychotics for the time period prior to the scan, and that GWC would be lower with longer exposure to second generation antipsychotics prior to the scan, suggesting more blurring from higher intracortical myelin with increasing drug exposure.

MATERIALS AND METHODS

Subjects

A total of 113 male subjects participated in the study, of which 71 were SCZ subjects between the ages of 18 and 36. The SCZ subjects were participating in longitudinal studies of first episode schizophrenia conducted at the UCLA Aftercare Research Program (Nuechterlein et al., 2011; Nuechterlein et al., 2019; Subotnik et al., 2015). All patients had been prescribed oral second-generation antipsychotics, with initial exposure to medication occurring 1 – 26 months prior to MRI scan (mean=8.1, sd=6.1, median=6.4). Because the distribution was positively skewed (skew=1.4, Kolmogorov-Smirnov p=0.031), with most patients having shorter duration of exposure, the values were log-transformed prior to subsequent analyses. At time of the MRI used in these analyses, all SCZ subjects were on oral risperidone.

Sixty-eight out of the 71 SCZ patients had sufficient information for estimation of cumulative lifetime antipsychotic medication exposure. In these patients, total chlorpromazine equivalent exposure (CPZ) up until the time of the MRI scan was calculated, per methods described by Andreasen et al., 2010 (Biol. Psychiatry 67: 255-262).

The patients had a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective (depressed type) disorder, which was established using the Structured Diagnostic Interview for DSM-IV (SCID) by diagnosticians with demonstrated inter-rater reliability (Nuechterlein et al., 1992; Ventura et al., 1998). Patients with significant

substance abuse within 6 months of psychosis onset or history of neurological disorders or significant head trauma were excluded (Nuechterlein et al., 2011; Nuechterlein et al., 2008). In addition to antipsychotic medication, at the time of the MRI 26/71 SCZ subjects were taking one or more medications that had been prescribed for depression (n=16), anxiety (n=3), or parkinsonian side effects (n=16). It is not known how exposure to these may have affected morphology.

A group of 42 male healthy control (HC) subjects between 15 and 35 years of age were recruited from the community to form an age-comparable HC comparison group for the cohort with SCZ. Age did not differ significantly between SCZ (*mean ± sd: 23.3 ± 3.7 y*) and HC (*mean ± sd: 23.6 ± 4.0 y*) groups in the current study (*t-test, P=0.5*). Most subjects were administered a formal SCID. The others were administered a similar diagnostic interview by a psychiatrist. Selection criteria were as follows: no evidence of significant current or past major psychiatric diagnosis or substance dependence based on DSM-IV criteria; no evidence of substance use disorder in the 6 months before study entry; no history or gross evidence of central nervous system impairment or any history of neurological disorder including head trauma with loss of consciousness for greater than 15 minutes, no history of chronic medical conditions that are likely to result in structural brain abnormalities (i.e., stroke, transient ischemic attack, seizures, hypertension, diabetes, etc.); and self-report that no first-degree relatives had been treated for a psychotic disorder. All subjects received written and oral information about the study and signed written informed consents approved by the local Institutional Review Board prior to study participation. Additional patient demographics are shown in Table 1.

MR Imaging Acquisition

MRI data were acquired with a 1.5 Tesla MR scanner (Avanto; Siemens Healthcare, Erlangen, Germany), using a T1-weighted 3D magnetization prepared rapid gradient echo sequence (MP-RAGE) with the following imaging parameters: repetition time (TR) = 2000 ms; echo time (TE) = 2.49 ms; inversion time (TI) = 900 ms; flip angle = 8°; 1 average; field of view = 25.6 cm; slices = 224; slice thickness = 1 mm (no interslice gap); image matrix = 256 × 192; voxel size =1 × 1 × 1 mm^3.

MRI Post-Processing and Cortical Morphometry

Image processing and analyses of MR data for segmentation, cortical reconstruction, cortical volume, and gray-white matter intensity contrast were conducted at the UCLA Brain Tumor Imaging Laboratory and the Center for Computer Vision and Imaging Biomarkers. In addition to checking for quality control issues such as the presence of image artifacts, scans were assessed by a neuroradiologist for possible incidental findings. The MR data were processed using FreeSurfer (version 5.3; http://surfer.nmr.mgh.harvard.edu) cortical reconstruction pipeline wherein each subject's cortical surface and thickness at each vertex were computed using a semi-automated approach described elsewhere (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2002; Fischl et al., 1999a; Fischl et al., 1999b). In summary, automated serial manipulations of MR data for cortical rendering included 1) transforming the MRI data into Talairach coordinates, 2) normalizing image signal intensity to correct for unwanted variations in intensity due to RF-field

inhomogeneity, 3) the stripping of the skull and other extra-cerebral tissue using a watershed algorithm, 4) parcellating and labeling the white matter volume based upon normalized intensity, 5) correcting topological errors and smoothing the generated surfaces, and 6) the construction of cortical surface from the white/gray matter interface to the pial surface at the gray matter/CSF interface. The resulting segmentations were visually inspected on a slice-by-slice basis to ensure correct delineation of pial from dura surfaces and parcellation of subcortical white matter structures. From this inspection, two patients were excluded from the study due to substantial problems cortical segmentation in the frontal lobe due to image quality. The volume of gray matter and subcortical white matter structures were measured automatically using FreeSurfer, the technique of which has been described in detail elsewhere (Dale et al., 1999; Dale and Sereno, 1993). In short, the technique utilizes a probabilistic atlas derived from manually training set and a Bayesian classification to assign neuroanatomical designations on a voxel-by-voxel basis with the MRI volume. Cortical volume measures were smoothed with a 10-mm full width at half maximum Gaussian kernel for statistical analysis.

Gray-to-White Matter Contrast (GWC)

Gray-to-white matter contrast (GWC) at the cortical boundary was used as a potential surrogate for intracortical myelin. Briefly, if a high GWC is observed at the boundary of the cortex, this may be indicative of a low degree of myelin within the cortical layers as there would be a relatively crisp transition from white to gray matter (Fig. 1A). Alternatively, if GWC is low, this may represent a higher degree of myelination within the cortical layers, as partial volume contamination from a mixture of gray and white matter would result in intermediate signal intensity on MR (Fig. 1B). FreeSurfer was used to automatically quantify GWC based on the gray-white matter and gray matter/cerebrospinal fluid boundaries generated during standard cortical segmentation. The gray matter was sampled 30% of the thickness into the cortex, in a direction normal to the gray matter/cerebrospinal fluid boundary, while white matter was sampled 1mm below and normal to the white matter surface, as described previously (Jorgensen et al., 2016; Kong et al., 2012; Kong et al., 2015; Salat et al., 2009). Final measures of GWC were calculated by:

$$GWC = 100 \times \left(\frac{S_{WM}\, S_{GM}}{\hat{S}_{GM+WM}} \right)$$

where S_{WM} is the MR signal intensity of white matter, S_{GM} is the MR signal intensity for gray matter 30% into the cortex, and $\hat{S}_{GM+WM}$ is the average signal intensity of gray and white matter (i.e. $[S_{GM} + S_{WM}] / 2$). This measure was then smoothed using a 10-mm full width at half maximum (FWHM) Gaussian kernel for subsequent statistical analysis, similar to previous studies (Jorgensen et al., 2016; Kong et al., 2012; Kong et al., 2015; Salat et al., 2009).

Statistical Analysis

To compare cortical volume and gray-white matter intensity contrast ratio measurements from the two sample groups, pairwise group comparisons were performed vertex-wise on the whole brain using the Query, Design, Estimate, Contrast (QDEC) tool, FreeSurfer's

graphical user interface for analyzing group data (https://surfer.nmr.mgh.harvard.edu/fswiki/Qdec). Utilizing the general linear model functionality within QDEC, regions that had significantly different cortical volume or gray-white matter intensity contrast were able to be visualized in vertex-wise statistical difference maps. QDEC also provides two different options for creating a design matrix: DOSS (different offset, same slope) and DODS (different offset, different slope). In this particular test, DOSS assumes that there is no significant interaction between covariates and the clinical group, whereas DODS assumes that there is a significant interaction between covariates and the clinical group (Worker et al., 2014). It is plausible that there exists a significant difference in the effects of the covariate (age) on the outcome measures of the two clinical groups, and thus DODS was utilized. P values of less than 0.05 were considered significant. Correlation analyses with cortical volume and intensity contrasts were done with medication exposure duration, as well as CPZ equivalents, as covariates, while still accounting for age. Furthermore, regional differences in GWC were also estimated after controlling for cortical volume in order to verify changes were not dependent on differences in cortical volume (https://surfer.nmr.mgh.harvard.edu/fswiki/mri_glmfit). For all of these tests, correction for multiple comparisons was applied by cluster-wise correction, based on the Monte Carlo Z simulation, a functionality also included in QDEC. Corrections were applied with an absolute threshold of 0.05 (Hagler et al., 2006).

Raw data for the cortical measures and the intensity contrast were extracted from the significant clusters generated by QDEC, by using FreeSurfer to compute statistics on the segmented volumes (https://surfer.nmr.mgh.harvard.edu/fswiki/mri_segstats). The reported measures were calculated by averaging the respective values from all the vertices included within the significant clusters for each subject (Voets et al., 2008).

RESULTS

Cortical Volume and GWC Between SCZ and HC

Cortical volume was significantly lower in SCZ patients compared with HC in seven specific regions (Figs. 2–3; Table 2). A left transverse temporal region (Figs. 2A,3A), left superior frontal region (Figs. 2B,3B), right superior temporal region (Figs. 2C,3C), two right rostral middle frontal regions, one medial and one more lateral (Figs. 2D–E,3D–E), a right postcentral region (Figs. 2F,3F), and a right parahippocampal region (Figs. 2G,3G) all showed significant reductions of between 9 to 12% in cortical volume in SCZ patients compared with healthy controls. After controlling for cortical volume, a significantly higher GWC was observed in SCZ patients within the right superior frontal lobe encompassing the sensorimotor regions (Figs. 2H,3H; $P<0.0001$).

Cortical Volume in SCZ vs. Medication Exposure

Within SCZ patients, results illustrated a significant positive association between cortical volume and log-transformed medication exposure duration in four distinct brain regions (Fig. 4–5; Table 3), including bilateral regions within the left and right parieto-occipital sulcus (Fig. 4A,5A and Fig. 4B,5B, respectively), as well as a region in the right precuneus (Fig. 4C,5C), and a superior parietal region (Fig. 4D,5D). On average, cortical volume

increased approximately 0.245 uL per $log\text{-}_{10}$(months). A significant positive association was also found in SCZ patients between cortical volume and cumulative lifetime chlorpromazine equivalent exposure in three distinct brain regions (Fig. 4E–G; Table 3), including left and right lateral-occipital (Fig. 4F and Fig. 4G, respectively), and a left superior parietal region (Fig. 4E).

GWC in SCZ vs. Medication Exposure

GWC appeared to decrease within SCZ patients as a function of second-generation antipsychotic medication exposure (Fig. 6–7; Table 4). Specifically, GWC decreased with the duration of medication exposure bilaterally within the left and right superior frontal lobe (Fig. 6A,7A and Fig. 6C,9C, respectively) as well as the bank of the superior temporal sulcus within the left hemisphere (Fig. 6B,7B) at an average rate of −1.98% per log_{10}(months) of exposure. These same trends were apparent after controlling for cortical volume differences (Fig. 6E–F; Table 4), demonstrating a decrease in GWC with increasing medication exposure bilaterally in the frontal lobe (Fig. 6D–E) and within the right orbital frontal cortex (Fig. 6F).

GWC also decreased with increasing cumulative chlorpromazine equivalent antipsychotic exposure in similar regions (Fig 8; Table 4). Significant decreases in GWC with increasing exposure were observed bilaterally within the medial frontal lobe (Fig. 8B,D), the left rostral middle frontal lobe (Fig. 8A), fusiform gyrus within the left hemisphere (Fig. 8C), and near the right inferior temporal lobe (Fig. 8E). After controlling for cortical volume only the bilateral medial frontal lobe regions (Fig. 8F,H) and left rostal middle frontal lobe (Fig. 8G) showed significantly lower GW C with increasing cumulative dosage exposure in SCZ patients.

DISCUSSION

Results from the current study indicate that patients with a recent first episode of SCZ have lower cortical volume in particular brain regions when compared with HC subjects, including the temporal and frontal lobe regions as well as the postcentral gyrus and parahippocampal regions. This appears consistent with work by Sprooten *et al.*(Sprooten et al., 2013), who noted significant cortical thinning in similar regions in first-episode SCZ patients as well as in individuals with high familial risk of SCZ compared with HC. This is also consistent with a study by Narr *et al.* (Narr et al., 2005) that found cortical thinning and a reduction in gray matter concentration in the frontal, temporal, and parietal lobes in first episode SCZ patients compared with age-matched HCs. A number of additional, contemporary studies examining cortical morphometry in a variety of SCZ subtypes have also demonstrated reductions in cortical thickness in similar brain regions (Goldman et al., 2009; Nesvag et al., 2008; Rimol et al., 2010), which was confirmed in a large cohort (4,474 SCZ and 5,098 HC) as part of the “Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium (van Erp et al., 2018). Indeed, cortical thinning and structural abnormalities in the temporal and prefrontal lobes as well as medial temporal lobe structures including the amygdala, hippocampus, and parahippocampal regions in SCZ are well documented in the literature (reviewed in Shenton *et al.*(Shenton et al., 2001), Lawrie

and Abukmeil (Lawrie and Abukmeil, 1998), and Glahn *et al.*(Glahn et al., 2008)). These regions correlate with abnormalities in cognition that manifest in patients (Buchsbaum, 1990). With regards to ICM and the measure of GWC, it has already been demonstrated that ICM is reduced in the frontal lobe in schizophrenia patients, indicative of oligodendrocyte abnormality (Hof et al., 2002, Bartzokis et al., 2012), which is correlative with neurocognitive dysfunction. Our findings are consistent with these results, as ICM was decreased among patients, and second-generation antipsychotics seem to target this phenomenon by restoring oligodendrocytes at the gray-white matter interface. It is notable that these patterns of restoration largely coincide with the regions of cortical thinning in schizophrenia patients, specifically within the frontal and temporal regions. This suggests that second generation antipsychotics promote ICM development particularly within the regions that are significantly reduced by schizophrenia. Differential effects in different regions are suggested to be dependent on a number of variables, including psychopathological symptoms and different methodologies of measurement (Kuperberg et al., 2003, Narr et al., 2005). Therefore, these factors could also potentially account for these regional differences.

Although only correlative, the current study suggests cortical volume may be higher in SCZ patients who have longer exposure to second generation antipsychotic medications in the parietal lobe, lingual area, and precuneus brain regions. Interestingly, these observations appear to contradict previous preclinical (Dorph-Petersen et al., 2005; Konopaske et al., 2007; Konopaske et al., 2008) and human studies (Cahn et al., 2002; Cahn et al., 2009; DeLisi et al., 1997; Gur et al., 1998; Ho et al., 2003; Kasai et al., 2003a; Kasai et al., 2003b; Lieberman et al., 2001a; Lieberman et al., 2005; Mathalon et al., 2001; van Haren et al., 2007) involving first generation antipsychotic medications, which illustrated overall brain tissue loss proportional to the intensity and duration of therapy. Ansell *et al.*(Ansell et al., 2015) first noted this divergent effect of first and second generation antipsychotics on cortical thickness in first episode SCZ patients, documenting a higher cortical thickness in patients treated with second generation compared with first generation antipsychotics. Results from the current study expand these observations, suggesting the increase in cortical tissue may be additionally linked with the total duration of second-generation medication exposure.

Several approaches have been developed to quantify ICM using MRI. For example, a surrogate of ICM derived by subtracting cortical volume measurements from optimized inversion recovery (IR) and proton density (PD) images has been proposed (Bartzokis et al, 2009; Tishler et al., 2018). Additionally, Glasser and Van Essen (2011) developed a novel whole-brain method for estimating ICM using the ratio of T1w and T2w signal intensities on 3D images. Rowley et al. (2015) similarly applied a technique that leveraged information from multiple image contrasts to create a final set of images reflecting high degree of intracortical contrast theorized to mirror ICM. Similar to our hypothesis, prior studies have also suggested GWC at the interface of the cortical ribbon may be a surrogate measure of ICM (Jorgensen et al., 2016). In the current study, no significant differences in regional GWC were observed between first-episode SCZ and HC subjects. Although previous studies have identified a significantly reduced ICM in SCZ patients compared with HC (Bartzokis, 2002; Bartzokis et al., 2003; Hof et al., 2002; Uranova et al., 2004; Vostrikov and Uranova,

2011; Vostrikov et al., 2007), these changes appear to be pronounced in more chronic phases of the disease (Bartzokis, 2012) and may not be observed in the relatively young patient cohort investigated in the current study (Tishler et al., 2018). Iwatani et al. (2015), using a technique similar to that of Glasser and Van Essen (2011), found lower signal contrast in SCZ compared to HC, which they interpreted as reduced intracortical myelin. They did not find a correlation with antipsychotic medication duration; however, they included older, chronic SCZ (rather than younger, first episode subjects as in the current study), and their results may have been limited by the sample size.

Recent work by Tishler *et al.*(Tishler et al., 2018) demonstrated an increase in *in vivo* ICM measurements using MRI within the frontal lobe in SCZ patients during the first year of second generation antipsychotic medication exposure. The 2018 finding of ICM increase during the initial year of antipsychotic treatment is consistent with prior work from Bartzokis *et al.* (Bartzokis et al., 2009) and may suggest that second generation antipsychotics have a promyelinating effect with consistent use. Results from the current study are strikingly consistent with these previous observations, demonstrating a focal decrease in GWC, indicative of increased blurring at the cortical interface due to a higher degree of cortical myelination, occurring bilaterally within the superior frontal lobe with increasing duration of exposure to second generation antipsychotics in patients with SCZ. These results appear to support the hypotheses that GWC may be related to prior measures of ICM and, unlike first generation antipsychotics, long-term consistent exposure to second generation antipsychotics might result in an increase in cortical myelination in patients with first episodic SCZ. Our group's initial 6-month longitudinal comparison of long-acting injectable versus oral risperidone after a first psychotic episode is consistent with the view that consistent adherence to a second-generation antipsychotic is a key factor in this promyelinating effect. It should be noted that 15/71 SCZ and 22/42 HC subjects in the current study were also included in the Tishler et al. 2018 study. Although both studies have a similar cross-sectional design, there were important differences including the fact the current study was restricted to male subjects, no patients with chronic SCZ were included in the current manuscript, and the particular sequences used in each study were distinctly different (2D coronal proton density and optimized inversion recovery sequence vs. 3D MPRAGE in the current study).

A few important limitations to the current study should be considered. The current study was only cross-sectional in nature and therefore causal relationships between antipsychotic medication exposure and brain morphometric changes are speculative. Establishment of these causal relationships will require prospective examination of cortical changes in the same set of patients during continued medication exposure. Additionally, although patients were assessed and diagnosed by the same research group using similar criteria, the antipsychotic treatment of the subjects with SCZ was not completely uniform, and therefore may have contributed to increased measurement variability. The effects of exposure to non-antipsychotic medications (described in the Methods section) may have further influenced the results. It is important to note that measures of GWC are only a surrogate measure of degree of myelination within the cortex and the measurement itself is potentially influenced by additional biological and technical factors. Additionally, the current study utilized patient images acquired on a 1.5T MRI scanner, which has only half the signal-to-noise as more

widely used 3T MR research scanners. Therefore, additional variability in cortical volume measurements may have occurred due to lower image quality. Also, the gray and white matter signal intensities and contrast are known to be dependent on the static magnetic field strength. Thus, findings regarding GWC differences in the current study may not be widely generalizable across all MR scanners and field strengths. Future studies aimed at replicating the current observations on MR systems with higher field strengths are warranted. Lastly, the current study included only male subjects, so it is unclear whether our results generalize to female SCZ patients.

CONCLUSIONS

The current study identified significantly lower cortical volume in first episode SCZ patients compared to HCs in areas consistent with previous studies, including the temporal, frontal, parietal, and medial temporal lobes. Within the SCZ patients, higher cortical volume was significantly associated with longer duration of second-generation antipsychotic medication exposure in the precuneus, lingual, and right superior parietal regions. Lower GWC, suggesting more myelination in the lower layers of the cortex, was significantly correlated with (log-transformed) duration of medication exposure bilaterally in the superior frontal lobes. This GWC finding is consistent with our prior finding of higher ICM with longer exposure after a first psychotic episode when ICM is measured by a different procedure involving subtraction of volumes from inverse recovery and proton density MRI sequences.

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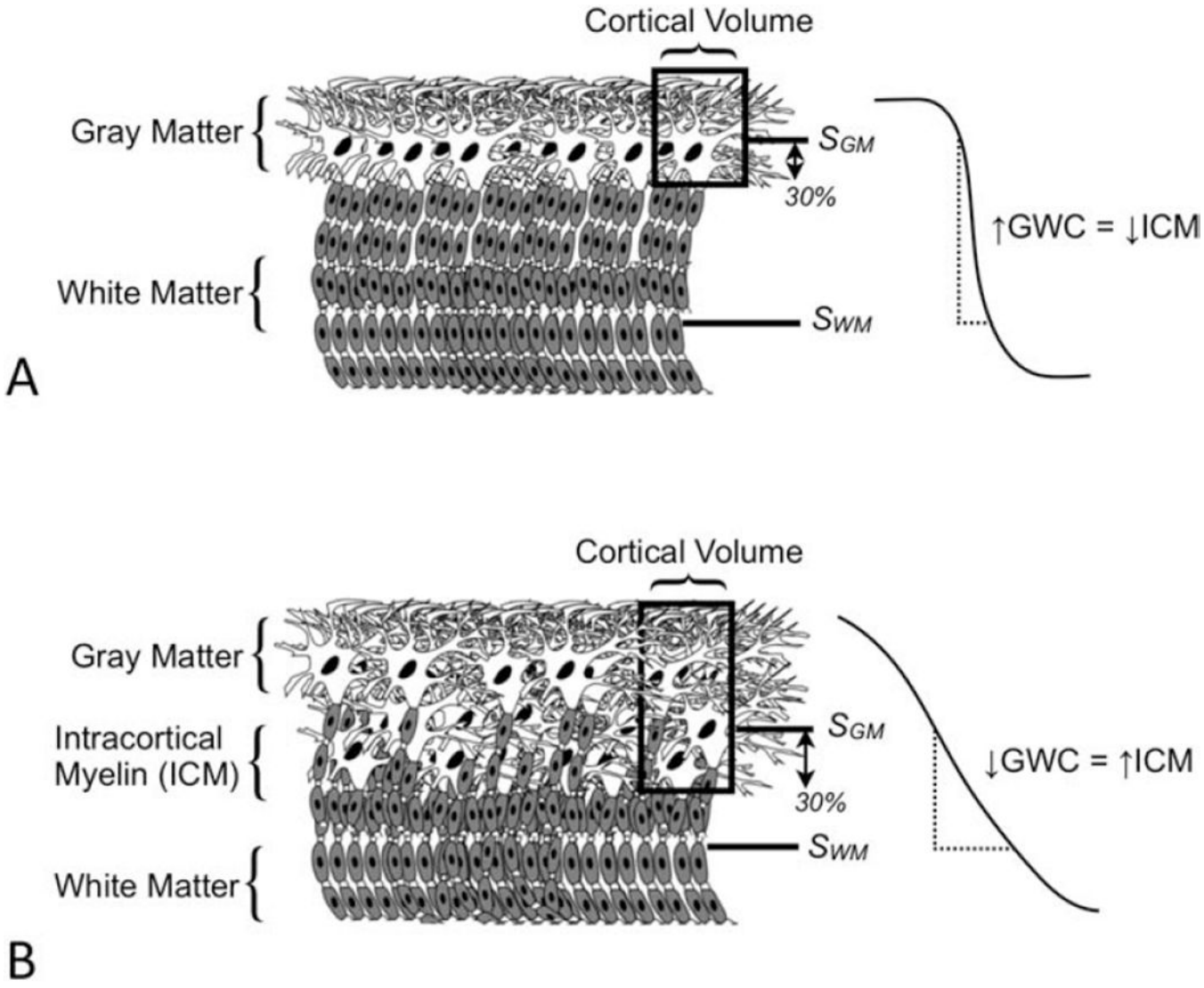

Fig. 1. Illustration of hypothesized low and high cortical volume and gray-to-white matter contrast (GWC).

A) Hypothetical depiction of thin cortical volume and high gray-to-white matter contrast (GWC), or crisp demarcation of the gray and white matter boundary at the site of the cortical ribbon suggestive of truncated intracortical myelin (ICM). B) Circumstance of high measured cortical volume and low GWC, suggestive of increased ICM.

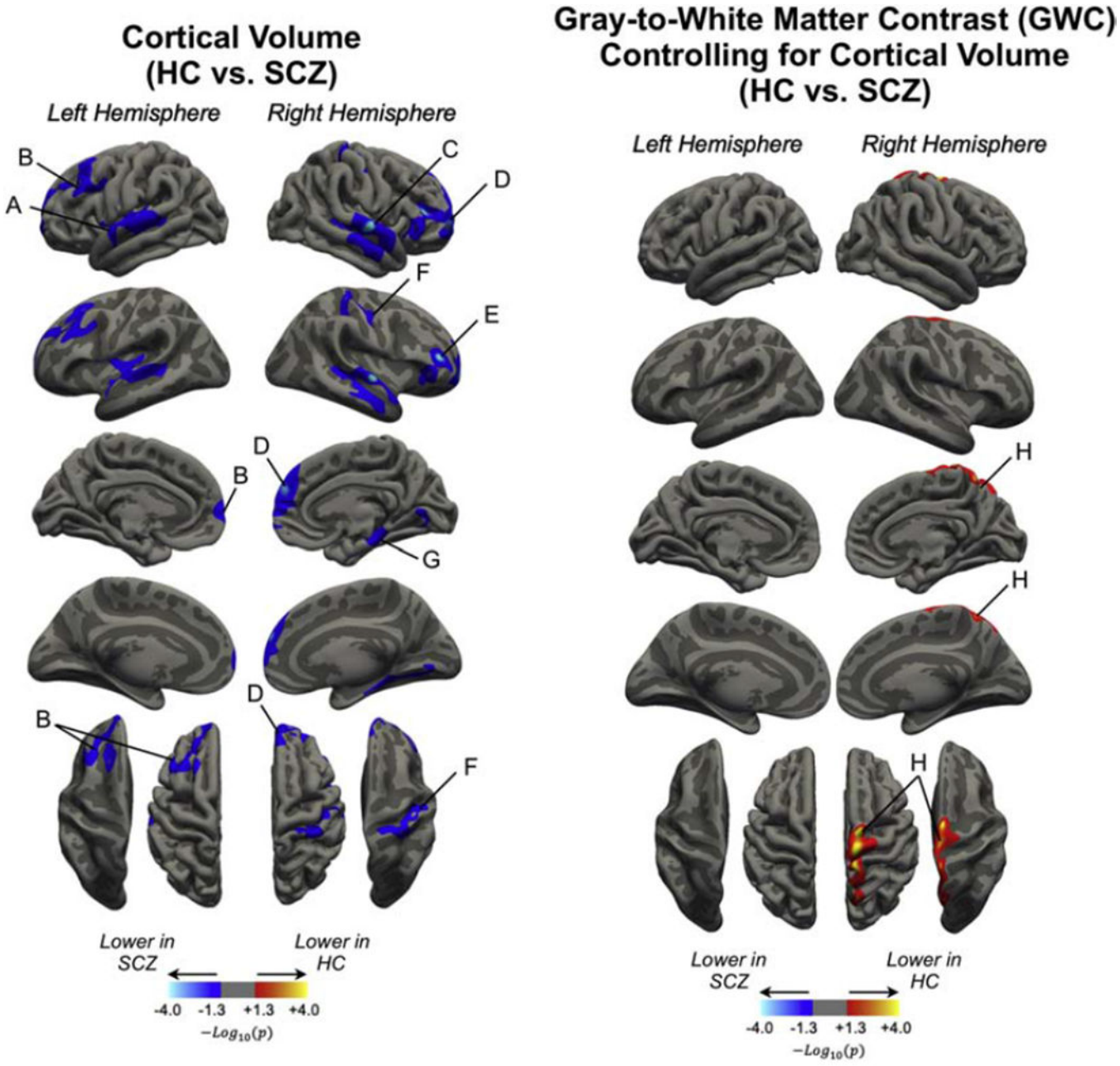

Fig. 2. Regional differences in cortical volume and gray-to-white matter contrast (GWC), controlling for cortical volume, between SCZ and HC.

Regions represented include: A) left transverse temporal, B) left superior frontal, C) right superior temporal, D-E) two spatially distinct right rostal middle frontal lobe regions, F) a region in the right frontal postcentral gyrus, and G) a right medial temporal lobe region consistent within the parahippocampal gyrus. After controlling for cortical volume, a significantly higher GWC was observed in SCZ patients compared to HCs within H) the right superior frontal lobe encompassing sensorimotor regions.

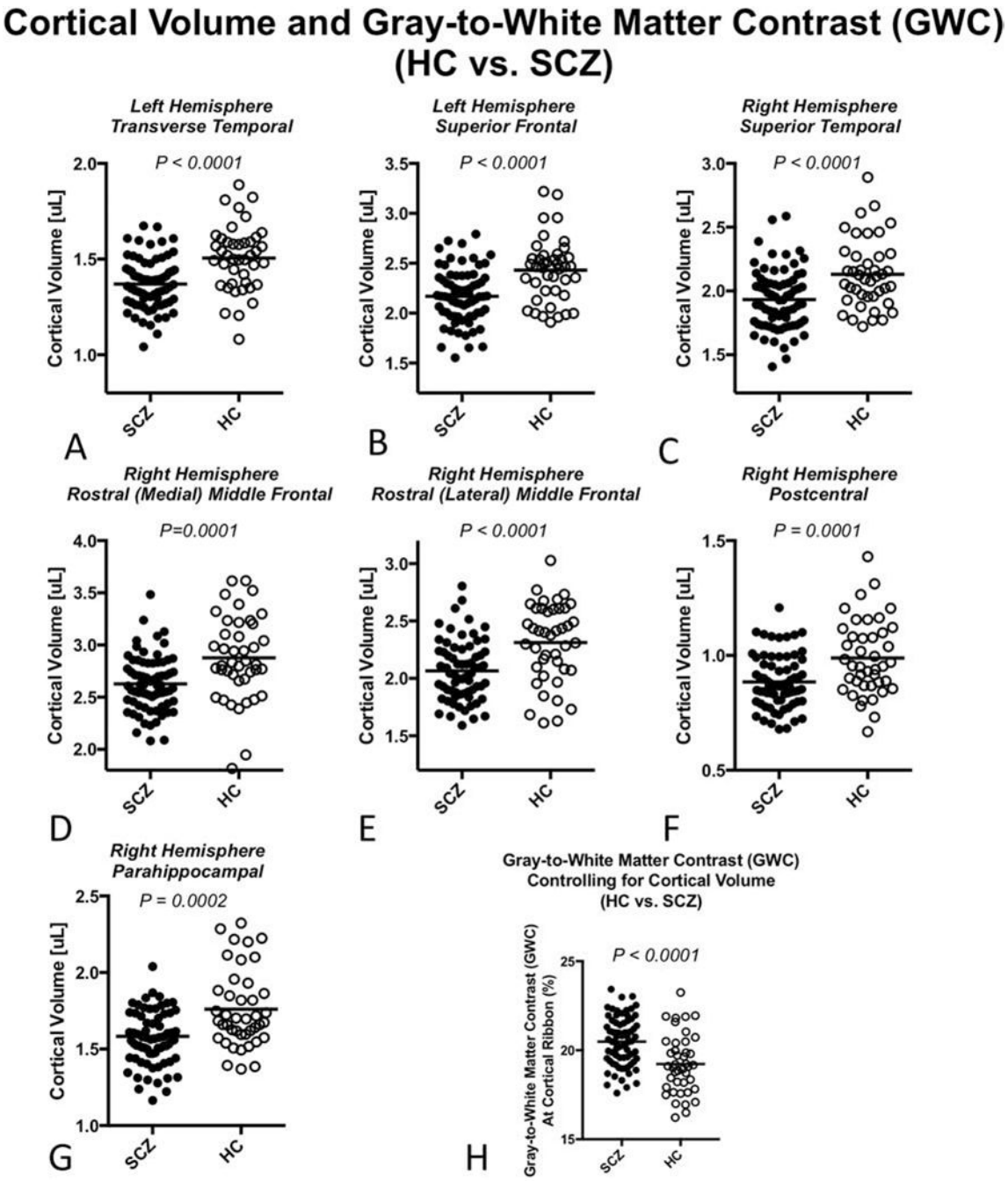

Fig. 3.

Average quantitative comparisons of cortical volume and GWC differences between SCZ and HC within specific brain regions.

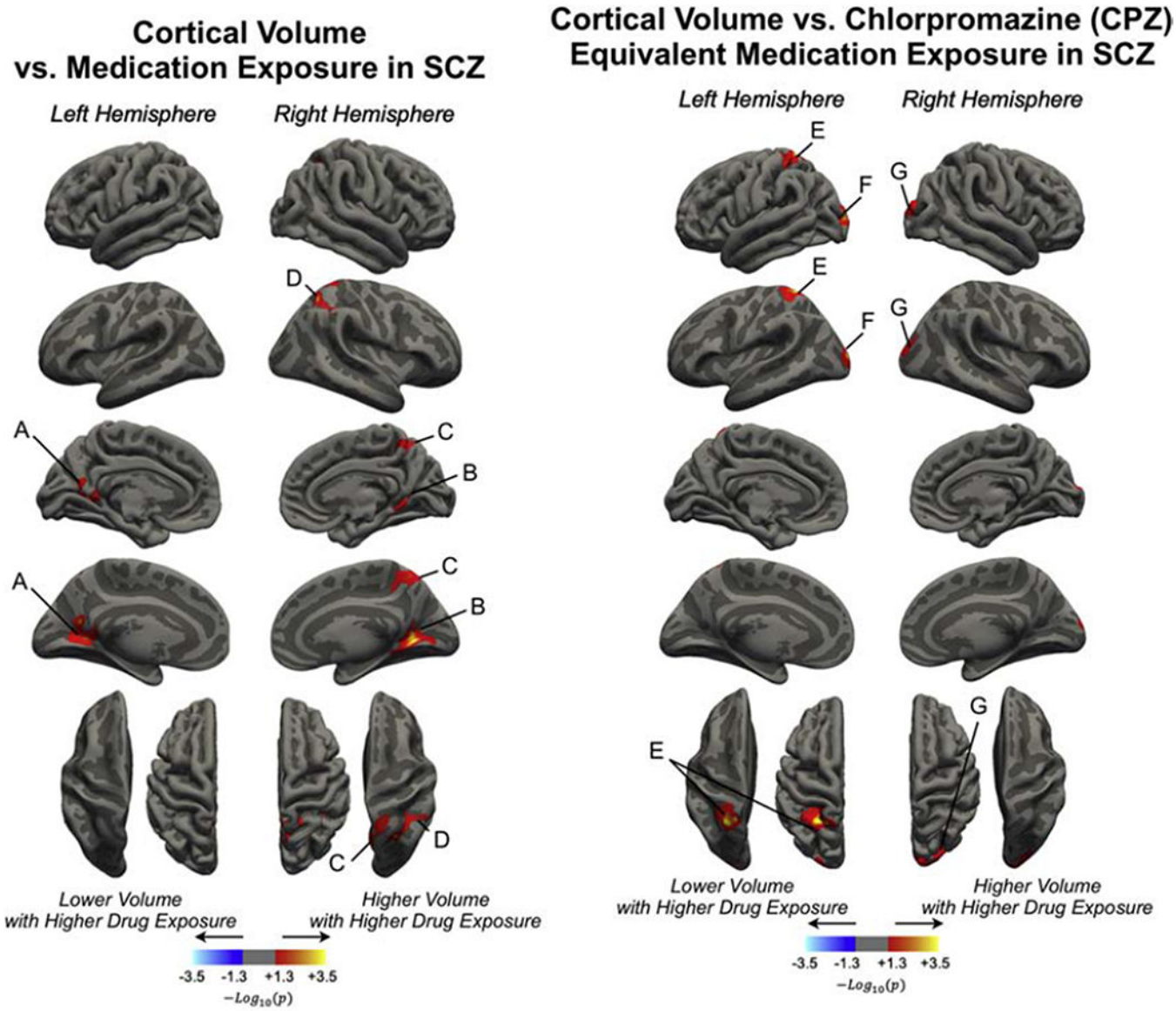

Fig. 4. Regional differences in cortical volume as a function of log_{10}-transformed duration of antipsychotic medication exposure and log_{10}-transformed measures of chlorpromazine (CPZ) equivalent cumulative exposure to second generation antipsychotic medications.

Regions include the: A) left parieto-occipital sulcus, B) right parieto-occipital sulcus, C) right precuneus, and D) right superior parietal areas when examining the relationship with log_{10}-transformed duration of exposure and the E) superior parietal, and F-G) bilateral occipital lobe regions when examining the relationship to cumulative CPZ exposure.

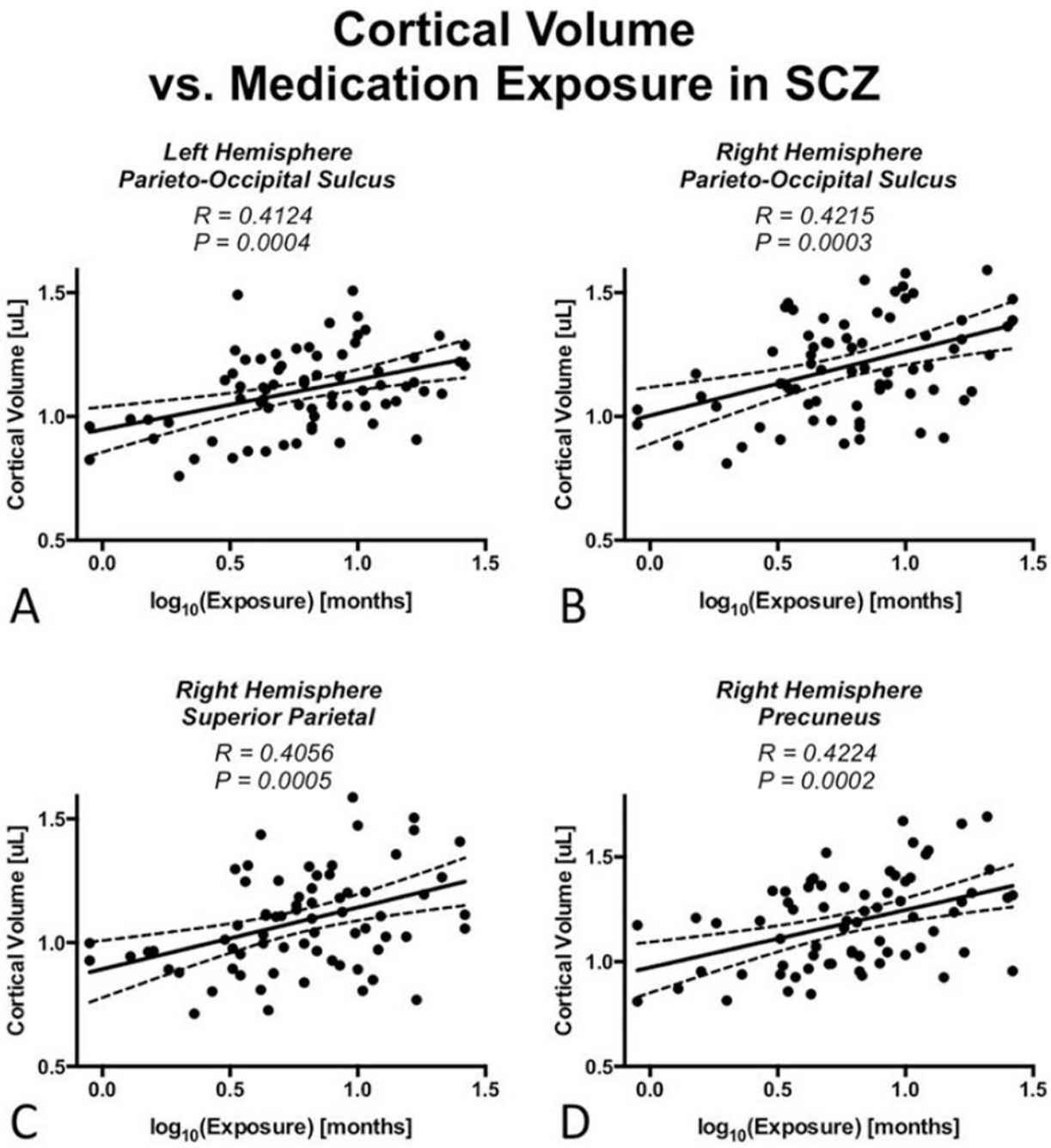

Fig. 5.

Average quantitative measurements of cortical volume as a function of log_{10}-transformed measures of duration of exposure to second generation antipsychotic medications in SCZ patients.

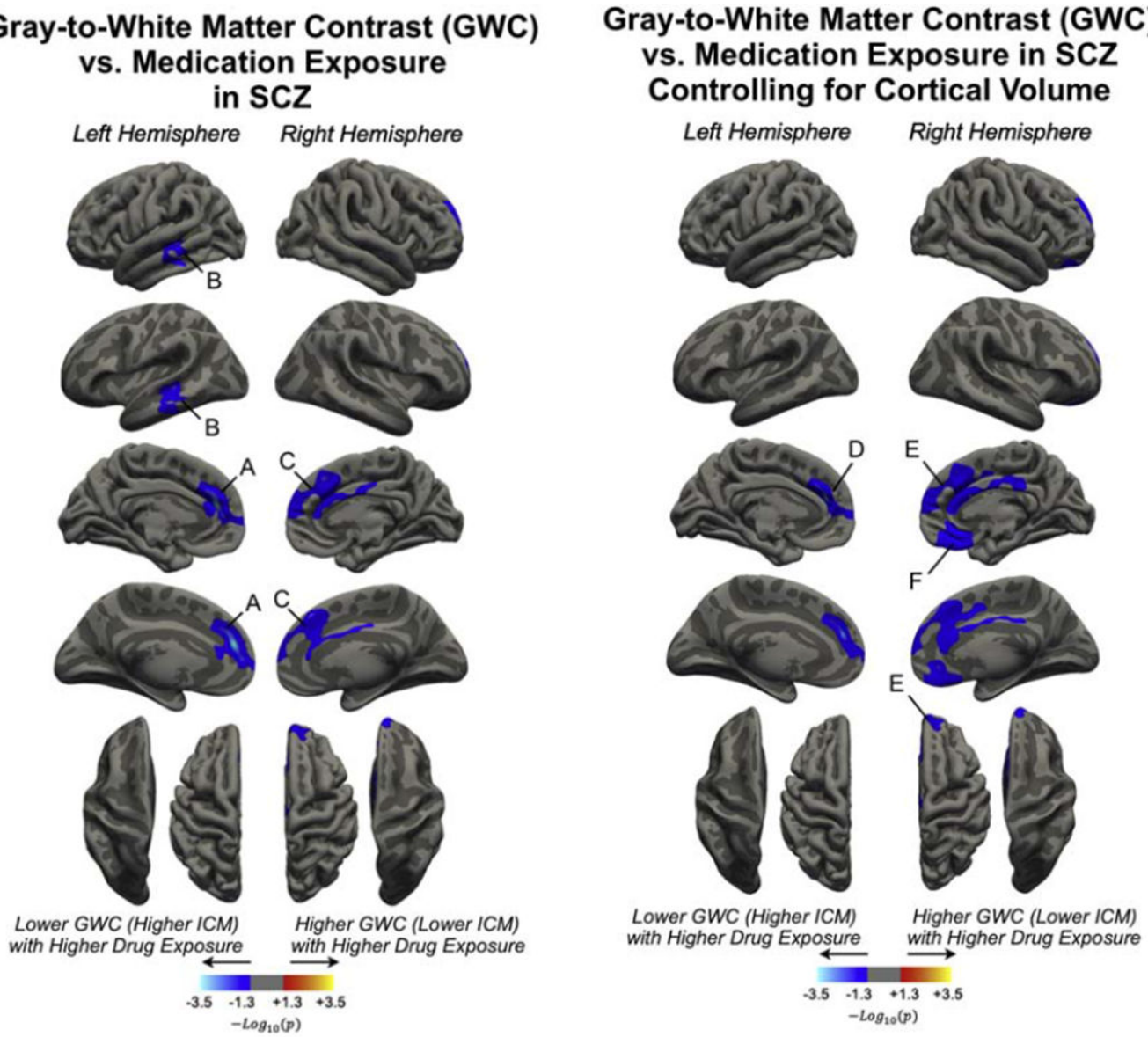

Fig. 6. Regional differences in gray-to-white matter contrast (GWC) as a function of log_{10}-transformed measures of duration of exposure to second generation antipsychotic medications.

Regions include the: A) left superior frontal, B) left bank of the superior temporal sulcus, and C) right superior frontal lobe. After controlling for cortical volume differences, D-E) bilateral frontal lobe regions and F) the right orbital frontal cortex demonstrated a decrease on GWC with increasing exposure in SCZ patients.

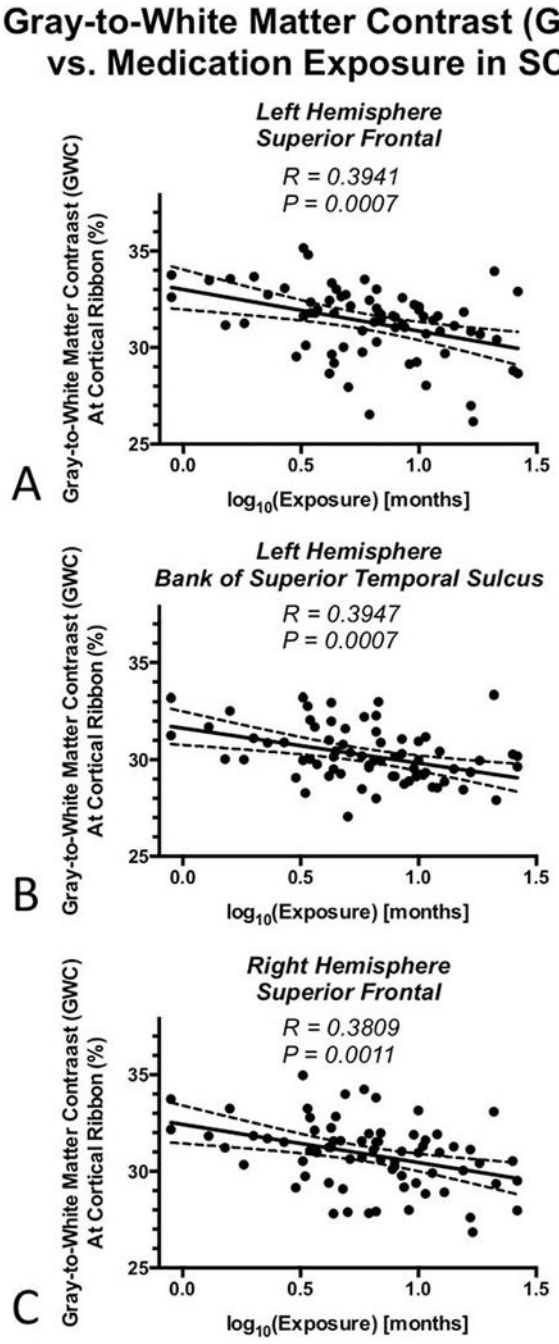

Fig. 7.

Average quantitative measurements of GWC as a function of log_{10}-transformed duration of exposure to second generation antipsychotic medications in SCZ patients.

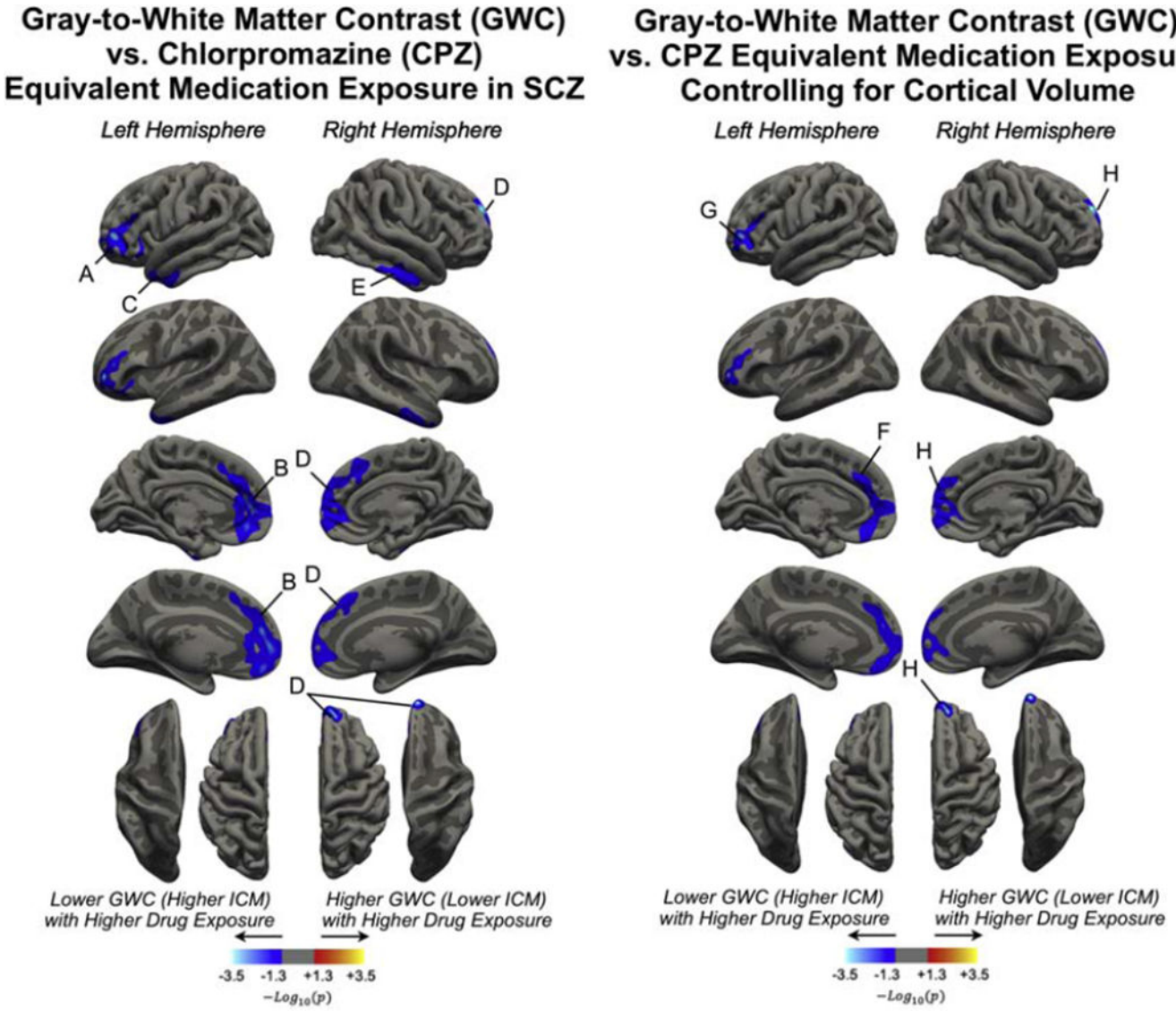

Fig. 8. Regional differences in gray-to-white matter contrast (GWC) as a function of log_{10}-transformed cumulative CPZ exposure to second generation antipsychotic medications.

Regions include the: A) rostral middle frontal, B) left superior frontal, C) left fusiform gyrus, D) right superior frontal, and E) right inferior temporal. After controlling for cortical volume variations, F-H) bilateral frontal lobe and G) left rostral middle frontal lobe regions showed significantly lower GWC with increasing exposure.

Table 1.

Patient Demographics and Clinical Characteristics

	Patients with Schizophrenia N=71	Healthy Controls N=42
Sex (Males/Females)	71/0	42/0
Race (Asian/Black/Hispanic/White)	7 / 22 / 22 / 20	5 / 7 / 12 / 18
Avg. Age [Years] (Range)	23.3 (18.3-36.0)	23.8 (14.7 – 35.0)
Average time since 1st Psychotic Episode at MRI Scan [Months] (Range)	11.9 (1.4 – 27.6)	
Duration of Antipsychotic Exposure at MRI Scan [Months] (Range)	8.1 (0.9 – 26.3)	
Average Total 24-Item BPRS Level (Range)	41 (24 – 74)	
Distribution of Diagnosis		
Schizophrenia	40 (56.3%)	
Schizoaffective Disorder	8 (11.3%)	
Schizophreniform Disorder	23 (32.4%)	

Table 2.

Differences in cortical volume and gray-to-white matter contrast (GWC), controlling for cortical volume, between schizophrenia (SCZ) patients and healthy control (HC) participants.

				Talairach Coordinates [mm]			Average Cortical Volume [uL]		Difference (%)	P-Value
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**SCZ**	**HC**		**(t-test)**
Fig. 2A,3A	Left	Transverse Temporal	2,835.4	−41.6	−21.7	6.8	1.370	1.506	9.5%	< 0.0001
Fig. 2B,3B	Left	Superior Frontal	3,329.6	−20.8	21.0	44.1	2.169	2.431	11.4%	< 0.0001
Fig. 2C,3C	Right	Superior Temporal	2,272.5	60.8	−9.4	−1.7	1.932	2.131	9.8%	< 0.0001
Fig. 2D,3D	Right	Rostral Middle Frontal	2,659.0	19.8	52.0	−5.7	2.628	2.878	9.1%	0.0001
Fig. 2E,3E	Right	Rostral Middle Frontal	1,526.0	35.6	35.2	7.0	2.066	2.312	11.2%	< 0.0001
Fig. 2F,3F	Right	Postcentral	1,712.7	34.9	−30.2	56.6	0.884	0.989	11.2%	0.0001
Fig. 2G,3G	Right	Parahippocampal	1,096.9	19.6	−34.8	−8.7	1.583	1.760	10.6%	0.0002
				Talairach Coordinates [mm]			**Average GWC [%]**		**Difference (%)**	**P-Value**
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**SCZ**	**HC**		**(t-test)**
Fig. 2H, 3H	Right	Superior Frontal/ Sensorimotor Cortex	1,446.8	11.3	−5.7	62.4	20.5%	19.2%	1.3%	< 0.0001

Table 3.

Correlation between cortical volume and second-generation antipsychotic medication exposure in SCZ patients.

				Talairach Coordinates [mm]			Change in Volume per change in log(exposure)	R-Value	P-Value
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**[uL/ log$_{10}$(months)]**	**(Regression)**	**(Regression)**
Fig.4A,5A	Left	Parieto-occipital Sulcus	1,432.4	−9.6	−57.4	20.1	0.201	0.4124	0.0004
Fig.4B,5B	Right	Parieto-occipital Sulcus	1,615.0	15.9	−58.6	5.0	0.258	0.4215	0.0003
Fig.4C,5C	Right	Precuneus	1,006.7	24.5	−50.8	47.8	0.249	0.4056	0.0005
Fig.4D,5D	Right	Superior Parietal	1,032.2	8.6	−50.2	53.7	0.274	0.4224	0.0002
				Talairach Coordinates [mm]			Change in Volume per change in log(CPZ)	R-Value	P-Value
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**[uL/log$_{10}$(Dose-Years)]**	**(Regression)**	**(Regression)**
Fig.4E	Left	Superior Parietal	1,194.5	−23.9	−45.4	58.4	0.308	0.4790	0.00004
Fig.4F	Left	Lateral-Occipital	1,010.5	−19.8	−92.3	13.1	0.329	0.3900	0.001
Fig.4G	Right	Lateral-Occipital	1,113.9	26.7	−88.2	16.7	0.342	0.3540	0.0031

Table 4.

Correlation between gray-to-white matter contrast (GWC) and second-generation antipsychotic medication exposure and cumulative exposure in SCZ patients.

				Talairach Coordinates [mm]			Change in GWC per change in log(exposure)	R-Value	P-Value
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**[%/ log$_{10}$(months)]**	**(Regression)**	**(Regression)**
Fig.6A,7A	Left	Superior Frontal	1,470.9	−10.2	42.3	15.8	−2.15	0.394	0.0007
Fig.6B,7B	Left	Bank of Superior Temporal Sulcus	1,343.5	−45.3	−33.2	1.0	−1.81	0.395	0.0007
Fig.6C,7C	Right	Superior Frontal	2,320.5	7.3	33.0	39.6	−1.97	0.381	0.0011
				Talairach Coordinates [mm]			Change in GWC per change in log(exposure)	R-Value	P-Value
							Controlling for Cortical Volume		
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**[%/ log$_{10}$(months)]**	**(Regression)**	**(Regression)**
Fig.6E	Left	Superior Frontal	1,061.6	−10	42	16.4	−2.16	−0.398	0.0006
Fig.6F	Rihgt	Superior Frontal	3,236.0	12.2	10.5	32.6	−1.84	−0.366	0.0017
Fig.6G	Right	Lateral Orbital Frontal	1,202.7	11.5	41.1	−21.9	−1.79	−0.256	0.031
				Talairach Coordinates [mm]			Change in Volume per change in log(CPZ)	R-Value	P-Value
Figure Reference	**Hemisphere**	**Anatomic Region**	**Cortical Region Size [mm^2]**	**X**	**Y**	**Z**	**[uL/log$_{10}$(Dose-Years)]**	**(Regression)**	**(Regression)**
Fig. 8A	Left	Rostral Middle Frontal	1,727.7	−36.5	46.7	−0.6	−1.59	−0.388	0.0011
Fig. 8B	Left	Superior Frontal	2,616.7	−10.7	42.8	14.4	−1.98	−0.414	0.0004
Fig. 8C	Left	Fusiform	975.5	−33.7	−4.1	−35.3	−1.65	−0.358	0.0027
Fig. 8D	Right	Superior Frontal	2,356.0	13	55.3	20.5	−1.85	−0.380	0.0014
Fig. 8E	Right	Inferior Temporal	1,172.5	43.1	−12.6	−25.6	−1.74	−0.386	0.0011

				Talairach Coordinates [mm]			Change in GWC per change in log(exposure)	R-Value	P-Value
Figure Reference	Hemisphere	Anatomic Region	Cortical Region Size [mm^2]	X	Y	Z	[%/ log_{10}(months)]	(Regression)	(Regression)
				Talairach Coordinates [mm]			Change in Volume per change in log(CPZ)	R-Value	P-Value
							Controlling for Cortical Volume		
Figure Reference	Hemisphere	Anatomic Region	Cortical Region Size [mm^2]	X	Y	Z	[uL/log_{10}(Dose-Years)]	(Regression)	(Regression)
Fig. 8F	Left	Superior Frontal	1,634.3	−10.7	42.8	14.4	−2.03	−0.433	0.0002
Fig. 8G	Left	Rostral Middle Frontal	1,114.8	−36.4	47	−1.1	−1.64	−0.394	0.0009
Fig. 8H	Right	Superior Frontal	1,750.6	12.9	55.1	21.2	−1.93	−0.382	0.0013