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Brain structure characteristics in intellectually superior schizophrenia

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ABSTRACT

The current study aims to fill a gap in the knowledge base by investigating the structural brain characteristics of individuals with schizophrenia and superior intellectual abilities. Subcortical volumes, cortical thickness and cortical surface area were examined in intellectually normal and intellectually superior participants with schizophrenia and their IQ-matched healthy controls, as well as in intellectually low schizophrenia participants. We replicated significant diagnostic group effects on hippocampal and ventricular size after correction for multiple comparisons. There were no statistically significant effects of intellectual level or of the interaction between diagnostic group and intellectual level. Effect sizes indicated that differences between schizophrenia and healthy control participants were of similar magnitude at both intellectual levels for all three types of morphological data. A secondary analysis within the schizophrenia group, including participants with low intellectual abilities, yielded numerical, but no statistically significant differences on any structural brain measure. The present findings indicate that the brain structure abnormalities in schizophrenia are present at all intellectual levels, and individuals with schizophrenia and superior intellectual abilities have brain structure abnormalities of the same magnitude as individuals with schizophrenia and normal intellectual abilities.

1. Introduction

Schizophrenia (SZ) is associated with impaired cognition as well as structural brain abnormalities. Gray matter abnormalities include cortical volume reductions and cortical thinning in frontal and temporal regions (Kuperberg et al., 2003; Nesvåg et al., 2008; Arnone et al., 2009; Ellison-Wright and Bullmore, 2010). Subcortical structural abnormalities such as increased ventricular and basal ganglia volumes, and reduced hippocampal, amygdalar and thalamic volumes, have been consistently reported across studies (Honea et al., 2005; Arnone et al., 2009; Ellison-Wright and Bullmore, 2010). A meta-analysis of volumetric brain alterations in over 18,000 participants (Haijma et al., 2013) found that intracranial and total brain volumes were significantly reduced in SZ compared with healthy control participants (HC). The largest effect sizes were seen for gray matter structures. This meta-analysis noted that there was a trend towards larger volume reductions in studies that did not match SZ and HC groups on IQ, indicating that studies of brain structure characteristics in SZ should take IQ into account.

Although impaired cognition is considered an important feature of SZ, about one quarter of individuals with SZ present with near-normal scores on neuropsychological tests (Kremen et al., 2000; Weickert et al., 2000; Rund et al., 2006). This has led to a longstanding debate on whether it is possible to have schizophrenia and be neuropsychologically normal (Palmer et al., 1997; Wilk et al., 2005). Research evidence indicates that it is not possible, at least not on a group level. Individuals with SZ who score within the normal range on neuropsychological tests have reductions of one kind or another, such as deficits in attention and executive functioning in spite of preserved IQ (Weickert et al., 2000), or lower processing speed and memory scores compared with IQ-matched HC participants (Wilk et al., 2005). Neurocognitive decrements are present in practically all SZ cases (Keefe et al., 2005), even in individuals with SZ and superior intellectual abilities (MacCabe et al., 2012; Gray et al., 2013). In a recent study (Vaskinn et al., 2014), we found that individuals diagnosed with SZ with IQ scores $\geq$120 had the same magnitude of neurocognitive decrements as those with normal or low intelligence when

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compared with IQ-matched HC individuals. Also, symptom profiles and functional deficits were similar across the three IQ strata.

To our knowledge, the brain characteristics of people with SZ and superior intellectual abilities (IQ ≥ 120) have not previously been investigated, although a handful of studies have investigated SZ samples defined as cognitively preserved or neuropsychologically near-normal. There are several ways to investigate brain structure characteristics in (intellectually superior) SZ. One approach focuses on anomalies in brain structure compared with HC individuals (who can be matched on intelligence or not) (Wexler et al., 2009; Cobia et al., 2011; Ortiz-Gil et al., 2011), whereas another looks at differences in brain structure within the SZ population (across cognitive or intellectual level) (Wexler et al., 2009; Cobia et al., 2011; Ortiz-Gil et al., 2011; Ayesa-Arriola et al., 2013). Wexler et al. (2009) found that neuropsychologically near-normal SZ participants had markedly less gray matter volume and larger third ventricles than HC participants in spite of almost intact cognition. A neuropsychologically impaired SZ group had similar gray matter reductions, but in addition had smaller white matter volumes and larger lateral ventricles compared with the HC group. Cobia et al. (2011) found no significant cortical thinning patterns in neuropsychologically near-normal SZ compared with HC participants, but effect sizes indicated mild cortical thinning with moderate effects for several brain areas, in particular bilateral frontal and left temporal regions. Ortiz-Gil et al. (2011) found similar brain volume and gray matter volume reductions and ventricular enlargement in SZ participants who were cognitively preserved and cognitively impaired. Similarly, a recent longitudinal study of first episode psychosis found no morphometric differences between cognitively preserved and cognitively impaired participants at baseline, although greater volume decrease for parietal tissue volume appeared for the cognitively impaired subgroup over a 3-year period (Ayesa-Arriola et al., 2013). In summary, the literature on brain structure in neuropsychologically near-normal/cognitively preserved SZ suggests structural abnormalities, and that some of these abnormalities may be similar to the ones seen in cognitively impaired SZ participants.

The main goal of the present study is to explore whether SZ with superior intellectual abilities is characterized by structural brain abnormalities. This is a follow-up of our recent neuropsychological study (Vaskinn et al., 2014), using an overlapping, but smaller, sample for which structural magnetic resonance imaging (MRI) data were available. Here we examine the brain characteristics of intellectually superior SZ using the two above-mentioned approaches, i.e., by comparing them to HC participants as well as to SZ participants with low or normal intellectual abilities. Earlier studies were limited to either subcortical volumes or cortical thickness. We performed a comprehensive investigation of both cortical thickness and surface area, which together constitute cortical volume, and subcortical volumes, and compare three sets of structural brain measures in SZ and HC participants: (a) subcortical volumetric measures, (b) surface-based measures of cortical area, and (c) surface-based measures of cortical thickness. First, we investigated the presence of MRI abnormalities in SZ versus HC participants matched for level of intelligence in participants with normal and superior intellectual abilities. Previous MRI studies on neuropsychologically near-normal SZ samples (Wexler et al., 2009; Cobia et al., 2011) did not perform such matching. We ask whether intellectually superior SZ participants have abnormalities compared with IQ-matched HC participants, and whether abnormalities, if present, are of the same magnitude as in intellectually normal SZ. Second, we compare MRI characteristics in SZ participants with low, normal and superior intellectual abilities. Based on the findings reviewed above of brain abnormalities in SZ participants with near-normal neuropsychological scores (Wexler et al., 2009) and of similar neurocognitive decrements and symptom and function profiles in SZ participants across the IQ spectrum (Vaskinn et al., 2014), we expected to find relative brain abnormalities of the same degree in SZ participants, regardless of their intellectual level, for all three types of structural brain measures. Because results regarding brain structure in SZ participants with different cognitive abilities have been mixed, we had no specific hypothesis for the intra-diagnostic comparison.

2. Methods

2.1. Participants

The study was conducted within the multi-center Thematically Organized Psychosis (TOP) Study at the NORMENT KG Jebsen Center for Psychosis Research at the University of Oslo, Norway. Only participants with Norwegian as their first language and/or all compulsory schooling in Norway and Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2003) Full Scale IQ scores ≥ 70 were included in the current study. Participant recruitment took place in 2003–2012. From a sample used in a previous study (Vaskinn et al., 2014; SZ, $n=239$; HC, $n=228$), individuals for whom structural MR data had been collected were included. This was the case for 69 individuals with a DSM-IV diagnosis of SZ and for 86 HC participants. Participants with SZ were recruited from hospitals in the Oslo area. HC individuals from the same geographical areas were recruited through national statistical records, invited by letter to participate and screened with an interview to capture symptoms of severe mental illness (Primary Care Evaluation of Mental disorders; PRIME-MD; Spitzer et al., 1994). HC individuals were excluded from the study if mental, neurological or somatic disorder was confirmed or suspected. The TOP study is approved by the Regional Ethics Committee and the Norwegian Data Inspectorate, and is completed in accordance with the Helsinki Declaration. All participants received oral and written information on the study and have signed informed consent.

2.2. Classification of sample

Following the procedure from our above-mentioned neuropsychological study (Vaskinn et al., 2014), the sample was stratified into three IQ levels based on WASI Full Scale IQ, i.e., low, normal or intellectually superior. However, because few HC participants in the low IQ range (IQ=80–95, SZ, $n=16$; HC, $n=5$) had MR data, they were excluded from the current study. Included are participants who are intellectually normal (IQ=100–115) or intellectually superior (IQ ≥ 120), and – for the second research aim – intellectually low SZ participants. A gap of 4 IQ-points between the IQ strata was used to avoid overlap between groups. Participant numbers were 16 in the low SZ group (SZ-low), 41 in the normal SZ group (SZ-normal), 12 in the superior SZ group (SZ-superior), 56 in the intellectually normal HC group (HC-normal) and 30 in the intellectually superior HC group (HC-superior). The demographic characteristics of these five groups are shown in Table 1. For the two IQ strata that included participants from both diagnostic groups, independent samples t-tests comparing WASI IQ between SZ and HC participants within each IQ stratum yielded no statistically significant differences. Further, a multivariate analysis of variance (MANOVA) showed a significant overall effect of demographic variables (age, sex, and education) on intellectual level ($F_{(3,133)}=4.8$, $p=0.004$, $\eta^2=0.10$), but not on diagnostic group ($F_{(3,133)}=1.3$, $p=0.280$, $\eta^2=0.03$). More specifically, education differed across intellectual level ($F_{(1,139)}=12.5$, $p=0.001$, $\eta^2=0.08$), whereas sex and age did not differ across either diagnostic group or intellectual level. A corresponding univariate analysis of variance (ANOVA) within the SZ group yielded, as expected, a significant effect of education ($F_{(1,68)}=4.6$, $p=0.013$), but not of sex or age.

2.3. Clinical assessment

The SZ sample was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Inventory of Depressive Symptomatology (IDS-C; Rush et al., 1996). Global functioning was assessed with the Global Assessment of Functioning Scale-split version (Pedersen et al., 2007). The clinical characteristics of the three SZ groups can be found in Table 1. ANOVAs yielded no significant differences across IQ strata. This was also the case for daily dosage of antipsychotic medication (DDD www.whocc.no), age at illness onset and duration of illness.

2.4. Assessment of brain structure

All participants underwent MRI scanning on a 1.5T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. Two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (echo time=3.93 ms, repetition time=2730 ms, inversion time=1000 ms, flip

Table 1
Demographic characteristics and social functioning in schizophrenia and healthy participant groups and clinical characteristics in participants with schizophrenia.

	SZ-low IQ $n=16$ Mean (standard deviation)	SZ-normal IQ $n=41$ Mean (standard deviation)	HC-normal IQ $n=56$ Mean (standard deviation)	SZ-superior IQ $n=12$ Mean (standard deviation)	HC-superior IQ $n=30$ Mean (standard deviation)	Statistics
WASI IQ	89.7 (4.7)	108.5 (4.7)	107.9 (4.4)	127.0 (4.5)	125.8 (4.1)	d.f.=95, $t=0.69$, $p=0.494$ (normal IQ) d.f.=40, $t=0.87$, $p=0.391$ (superior IQ)
Age	34.5 (9.7)	29.8 (7.9)	34.6 (10.1)	32.4 (5.8)	31.7 (9.0)	Group: d.f.=1,139, $F=1.3$, $p=0.251$ IQ: d.f.=1,139, $F<0.1$, $p=0.940$
Education	11.9 (1.8)	13.0 (2.1)	13.1 (2.3)	14.4 (2.6)	14.7 (1.9)	Group: d.f.=1,139, $F=0.2$, $p=0.670$ IQ: d.f.=1,139, $F=12.5$, $p=0.001$
Sex (males/females) n	12/4	26/15	27/29	9/3	17/13	Group: d.f.=1,139, $F=2.9$, $p=0.092$ IQ: d.f.=1,139, $F=1.0$, $p=0.312$
GAF-function	41.7 (7.2)	44.0 (9.3)	–	44.2 (10.4)	–	d.f.=2,66, $F=0.4$, $p=0.669$
PANSS positive symptoms	13.7 (5.5)	14.7 (5.5)[a]	–	15.4 (6.9)[b]	–	d.f.=2,63, $F=0.3$, $p=0.743$
PANSS negative symptoms	15.3 (7.0)	14.3 (5.6)[c]	–	15.3 (6.2)[b]	–	d.f.=2,64, $F=0.2$, $p=0.814$
IDS-C	13.2 (8.5) [d]	14.1 (12.3)[e]	–	16.0 (8.8) [f]	–	d.f.=2,45, $F=0.1$, $p=0.883$
GAF-symptoms	42.4 (8.5)	41.1 (9.5)	–	45.8 (12.8)	–	d.f.=2,66, $F=1.1$, $p=0.348$
Age of psychosis onset	25.3 (9.0)	22.5 (6.8)	–	24.4 (6.2)	–	d.f.=2,65, $F=0.9$, $p=0.395$
Illness duration	9.7 (6.2)	7.2 (6.6)	–	8.0 (6.5)	–	d.f.=2,65, $F=0.8$, $p=0.446$
Inpatient/outpatient n	6/10	10/31	–	3/9	–	d.f.=2, $x^2=1.04$, $p=0.595$
Defined daily dose antipsychotics	1.71 (1.96)[g] (94%)	1.42 (0.82) [a] (95%)	–	1.58 (1.66)[h] (75%)	–	d.f.=2,59, $F=032$, $p=0.738$.
Total intracranial volume mm^3	1636.2 (169.4)	1641.0 (165.1)	1595.1 (152.5)	1657.7 (131.3)	1644.0 (132.5)	Group: d.f.=1,135, $F=1.0$, $p=0.319$ IQ: d.f.=1,135, $F=1.2$, $p=0.280$
Total brain volume mm^3	1125.4 (935.0)	1149.1 (111.0)	1147.1 (115.9)	1175.3 (114.8)	1175.7 (101.6)	Group: d.f.=1,135, $F=0.1$, $p=0.972$ IQ: d.f.=1,135, $F=1.5$, $p=0.220$

GAF=Global Assessment of Functioning. PANSS=Positive and Negative Syndrome Scale. IDS-C=Inventory of Depressive symptoms-Clinician rated.

[a] $n=39$.
[b] $n=11$.
[c] $n=40$.
[d] $n=9$.
[e] $n=32$.
[f] $n=7$.
[g] $n=15$.
[h] $n=8$.

angle=7°; field of view=24 cm, voxel size=$1.33\times0.94\times1$ mm^3, number of partitions=160) and subsequently averaged together, after rigid body registration, to increase the signal-to-noise ratio. There was no major scanner upgrade during the study period, and SZ and HC participants were scanned consecutively. A neuroradiologist evaluated all scans, and scans with brain pathology were excluded. Also, all scan segmentations were visually inspected and edited after standard procedures by trained and supervised assistants blinded to case-control status. Scans that did not pass the quality control were excluded from the study. We used the MR image analysis program suite FreeSurfer software (version 5.2.0) (available for download online (http://surfer.nmr.mgh.harvard.edu/), which allows for separate investigations of cortical area and cortical thickness. A three-dimensional model of the cortical surface for cortical thickness and cortical surface area measurements was created by using image intensities and continuity information from the entire MR volume to construct representations of the gray/white matter boundary ("white matter surface") and pial surface (Dale et al., 1999; Fischl et al., 1999). The surfaces were aligned to a common coordinate system across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns providing an accurate matching of morphologically homologous cortical locations across participants on the basis of each individual's anatomy while minimizing metric distortion. Each surface consisted of approximately 160,000 vertices arranged in a triangular grid.

The software enables surface division into 34 parcellated and neuroanatomically labeled regions of interest (ROI) in each hemisphere (Desikan et al., 2006). They were subsequently summarized to create eight regional estimates for each measure. Regional cortical thickness was calculated as the average distance between the gray/white boundary and the pial surface within each region. Surface area was calculated as the sum of the areas of each tessellation falling within a given region; this was done in each participant's native space. Subcortical volumes estimates were obtained from the automated procedure for volumetric measures of brain structures implemented in FreeSurfer (Fischl et al., 2002). Intracranial volume (ICV) was estimated using previously described procedures (Buckner et al., 2004).

We investigated the following nine subcortical volumetric variables: hippocampus, amygdala, thalamus, caudate, putamen, pallidum, accumbens, cerebellum, and total ventricular size. Surface-based measures consisted of cortical area (right and left hemisphere, respectively, for the frontal, temporal, parietal and occipital lobes) and cortical thickness (right and left hemisphere, respectively, for the frontal, temporal, parietal and occipital lobes). The total ventricular size variable and lobar regions were used to reduce the number of analyses. Brain volumes and surface-based measures are presented in Tables 2 and 3.

2.5. Statistical analysis

The Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, NY) was used.

Research aims were investigated using a series of univariate analyses of covariance (ANCOVAs). The first research aim focused on SZ–HC comparisons and included SZ and HC participants with normal and superior intellectual abilities. Diagnostic group (SZ or HC) and intellectual level (normal or superior IQ) were entered as independent variables to investigate their effect on brain structure, entered as the dependent variable. Significant interaction effects between diagnostic group and intellectual level indicate that the degree of brain structure abnormalities in a person with SZ depends on his/her intellectual level. In the ANCOVAs for the nine volumetric variables (hippocampus, amygdala, thalamus, caudate, putamen, pallidum, accumbens, cerebellum, and total ventricle size), age and ICV were covariates. The p-level was Bonferroni-adjusted for multiple comparisons (0.05/9 variables=0.006 new alpha level). For the eight cortical area variables and for the eight cortical thickness variables, respectively, age was a covariate in the ANCOVAs. For these $2\times2\times8$ ANCOVAs, the p-level was adjusted for number of analyses (0.05/8 variables=0.006 new alpha level). Effect sizes (Cohen's d) for SZ–HC differences were calculated for all brain variables using mean difference and the pooled standard deviation for the intellectual level in question. Effect sizes for the intellectually superior level reaching at least a medium size according to Cohen's (1998) guidelines (≥0.45) were given special attention and compared with the effect sizes in the intellectually normal level. The Cohen's ds for such brain variables were first converted to r and subsequently, using the Fisher r-to-z transformation,

to *z*. These *z* values were compared for differences in statistical significance using the online tool www.vassarstats.net/rdiff.html.

The second research aim was to compare brain structure characteristics within the SZ group. For these analyses, the intellectually low SZ sample was included. Analyses were identical to the ANCOVAs described above with the exception that only intellectual level (low, normal, superior) was entered as an independent variable.

The effect of antipsychotic medications was investigated by conducting bivariate correlations (Pearson's *r*) between DDD of antipsychotic medication and the 25 brain variables in the 62 SZ participants who were receiving psychopharmacological treatment.

3. Results

We found significant SZ–HC differences for 2 of the total 25 variables: hippocampus ($F_{(1,139)}=12.8$, $p<0.001$, $\eta^2=0.09$) and total ventricular size ($F_{(1,139)}=8.7$, $p=0.004$, $\eta^2=0.06$). There were no significant effects of intellectual level or significant interaction effects. Effect sizes for SZ–HC differences within each intellectual level are reported in Tables 2 and 3. For the intellectually superior level, these were medium-sized for pallidum ($d=0.48$), left frontal cortical area ($d=-0.50$) and left frontal ($d=-0.46$) and right parietal cortical thickness ($d=-0.56$). None of the effect sizes differed significantly from the corresponding effect sizes in the intellectually normal level (pallidum: $z=0.30$, $p=0.382$; left frontal cortical area: $z=0.79$, $p=0.224$; left frontal cortical thickness: $z=0.36$, $p=0.359$; right parietal cortical thickness: $z=0.54$, $p=0.295$).

Analyses of group differences within the SZ sample yielded no significant effects after Bonferroni corrections for multiple testing. Strongest effects were seen for total ventricular size ($F_{(2,69)}=2.8$,

Table 2
Subcortical volumes (mm^3) in schizophrenia and healthy participant groups.

	SZ-low IQ $n=16$ Mean (standard deviation)	SZ-normal IQ $n=41$ Mean (standard deviation)	HC-normal IQ $n=56$ Mean (standard deviation)	Effect size Normal IQ	SZ-superior IQ $n=12$ Mean (standard deviation)	HC-superior IQ $n=30$ Mean (standard deviation)	Effect size Superior IQ
Hippocampus	7.812 (0.657)	8.117 (0.809)	8.494 (0.919)	−0.44	8.257 (1.048)	8.595 (0.824)	−0.36
Amygdala	2.986 (0.395)	3.274 (0.406)	3.223 (0.404)	0.13	3.289 (0.433)	3.323 (0.409)	−0.08
Thalamus	14.232 (0.136)	14.661 (1.143)	14.854 (1.710)	−0.14	15.256 (2.130)	15.594 (1.586)	−0.18
Caudate	7.937 (1.138)	7.759 (0.805)	7.379 (0.925)	0.44	8.010 (0.888)	7.674 (0.893)	0.38
Putamen	11.708 (0.833)	12.117 (1.217)	11.305 (1.153)	0.69	11.895 (0.838)	11.677 (1.341)	0.20
Pallidum	3.263 (0.402)	3.342 (0.372)	3.105 (0.422)	0.60	3.284 (0.413)	3.083 (0.432)	0.48
Accumbens	1.274 (0.242)	1.378 (0.229)	1.392 (0.211)	−0.06	1.337 (0.195)	1.398 (0.167)	−0.34
Cerebellum	104.972 (10.390)	105.625 (11.831)	104.982 (11.749)	0.06	110.198 (12.163)	108.293 (11.406)	0.16
Total ventricular size	28.736 (20.142)	20.192 (8.418)	15.421 (8.057)	0.56	20.071 (8.158)	15.950 (6.346)	0.57

Table 3
Cortical thickness (mm) and cortical surface area (mm^3) in schizophrenia and healthy participant groups.

	SZ-low IQ $n=16$ Mean (standard deviation)	SZ-normal IQ $n=41$ Mean (standard deviation)	HC-normal IQ $n=56$ Mean (standard deviation)	Effect size Normal IQ	SZ-superior IQ $n=12$ Mean (standard deviation)	HC-superior IQ $n=30$ Mean (standard deviation)	Effect size Superior IQ
Cortical thickness (mm)							
Frontal left	2.312 (0.171)	2.434 (0.155)	2.481 (0.136)	−0.32	2.459 (0.104)	2.515 (0.138)	−0.46
Frontal right	2.313 (0.132)	2.381 (0.146)	2.426 (0.126)	−0.33	2.413 (0.110)	2.463 (0.127)	−0.42
Temporal left	2.475 (0.207)	2.627 (0.146)	2.675 (0.129)	−0.35	2.630 (0.107)	2.672 (0.128)	−0.36
Temporal right	2.586 (0.213)	2.698 (0.148)	2.731 (0.120)	−0.25	2.699 (0.133)	2.751 (0.118)	−0.41
Parietal left	2.084 (0.135)	2.135 (0.134)	2.169 (0.110)	−0.28	2.163 (0.096)	2.197 (0.140)	−0.29
Parietal right	2.092 (0.144)	2.123 (0.123)	2.162 (0.110)	−0.35	2.126 (0.111)	2.194 (0.134)	−0.56
Occipital left	3.340 (0.147)	3.350 (0.157)	3.440 (0.158)	−0.57	3.385 (0.127)	3.441 (0.182)	−0.36
Occipital right	3.413 (0.185)	3.434 (0.141)	3.495 (0.158)	−0.41	3.462 (0.146)	3.513 (0.165)	−0.33
Cortical surface area (mm^3)							
Frontal left	23.171 (2.001)	23.349 (2.432)	22.818 (2.338)	0.22	22.298 (2.578)	23.518 (2.276)	−0.50
Frontal right	23.156 (2.133)	23.497 (2.490)	22.895 (2.263)	0.25	23.303 (2.474)	23.771 (2.355)	−0.19
Temporal left	16.704 (1.266)	16.834 (1.797)	16.518 (1.622)	0.19	17.259 (1.672)	17.062 (1.746)	0.12
Temporal right	16.084 (1.299)	16.385 (1.569)	16.132 (1.596)	0.16	17.064 (1.915)	16.569 (1.600)	0.28
Parietal left	20.592 (1.854)	20.806 (2.188)	20.417 (2.116)	0.18	21.262 (2.821)	20.818 (1.843)	0.19
Parietal right	21.504 (1.824)	21.655 (2.235)	21.284 (2.043)	0.17	21.899 (2.738)	21.911 (2.088)	0.00
Occipital left	10.699 (1.181)	10.995 (1.118)	11.352 (1.185)	−0.31	11.442 (1.202)	11.101 (1.155)	0.29
Occipital right	10.888 (1.010)	11.084 (1.064)	11.330 (1.179)	−0.22	11.441 (0.996)	11.0860 (1.044)	0.35

$p=0.071$, $\eta^2=0.08$) and frontal ($F_{(2,69)}=3.2$, $p=0.044$, $\eta^2=0.09$) and temporal ($F_{(2,69)}=4.7$, $p=0.013$, $\eta^2=0.13$) lobe cortical thickness in the left hemisphere (see Figs. 1, 2, and 3). The intellectually low SZ group diverged from the two other groups with larger ventricles and thinner cortex, albeit not significantly so after correction for multiple testing.

DDD of antipsychotic medication showed significant associations of moderate size ($r^2=-0.27$ to -0.33) with several of the brain structure variables (thalamus, amygdala, caudate, cortical area for both frontal and both temporal regions, and the right parietal lobe). As there were no significant associations between DDD and the brain structures that proved to be significantly different compared with the HC group (hippocampus, total ventricular size) or yielded trend-level differences within the SZ group (total ventricular size, frontal and temporal lobe left hemisphere cortical thickness), no further analyses were undertaken.

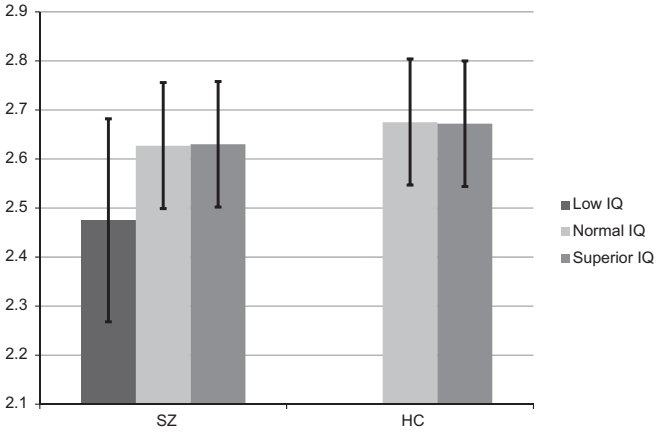

Fig. 3. Cortical thickness (mm) for the left temporal region in schizophrenia and healthy participant groups. SZ=schizophrenia, HC=healthy control participants. Bars indicate the mean values, error bars indicate the standard deviations.

4. Discussion

The main findings of the study were significant SZ–HC differences for two of the brain measures included in the study, subcortical hippocampal volume and ventricular size, with trend effects on other morphological measures, and no significant effect of intellectual level or of the interaction between diagnostic group and intellectual level. These findings were corroborated by analyses of IQ-based differences within the SZ group that yielded no significant results. Having a diagnosis of SZ seems to have more impact on brain structure than intellectual level has, at least in our sample. Although SZ–HC differences were statistically significant for only two brain measures, we do not interpret this as a lack of real group differences. The lack of statistical significance can probably be explained partly by the sample size. Another explanation for non-significant differences could be the exclusion of the intellectually low SZ group in these analyses. This would be in line with Haijma et al. (2013) finding of larger volume reductions in studies that do not match on IQ. Since more people with SZ than HC have low IQ, the inclusion of participants with low IQ can increase SZ–HC differences.

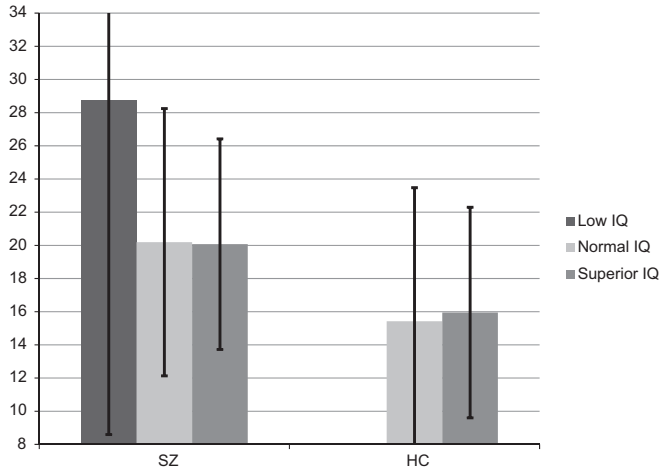

Fig. 1. Total ventricular volume (mm^3) in schizophrenia and healthy participant groups. SZ=schizophrenia, HC=healthy control participants. Bars indicate the mean values, error bars indicate the standard deviations.

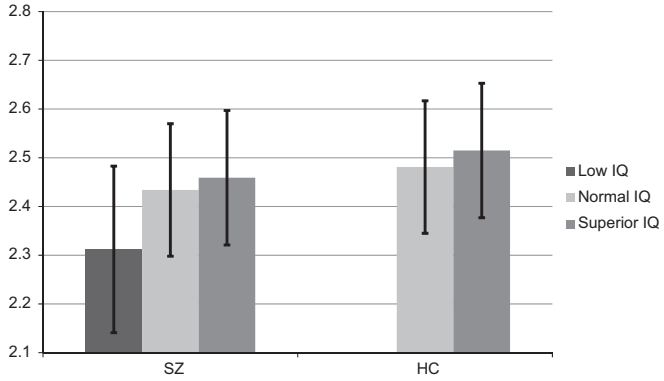

Fig. 2. Cortical thickness (mm) for the left frontal region in schizophrenia and healthy participant groups. SZ=schizophrenia, HC=healthy control participants. Bars indicate the mean values, error bars indicate the standard deviations.

Intellectually superior SZ individuals are not spared structural brain abnormalities. They share the reduced hippocampal and increased ventricle volume (Arnone et al., 2009) and cortical thinning patterns (Kuperberg et al., 2003) with other individuals with SZ. If we consider the medium-sized or larger effect sizes ($\geq$0.45) in our study, we see that compared with their IQ-matched HCs, they have increased ventricular size and pallidum volume; cortical thinning for left frontal and right parietal lobes; and reduced cortical area for the left frontal region. Because these effect sizes do not differ from the corresponding effect sizes within the normal intellectual level, the notion of similar brain abnormalities in SZ participants regardless of intellectual level is further supported. This is line with previous studies of neuropsychologically near-normal or cognitively preserved SZ that did not find this group to differ from cognitively impaired SZ (Ortiz-Gil et al., 2011) as well as with neuropsychological studies of intellectually superior SZ that showed this population to have the same magnitude of neurocognitive decrements (Gray et al., 2013; Vaskinn et al., 2014) and similar clinical (Heinrichs et al., 2008; Vaskinn et al., 2014) and functional characteristics (Vaskinn et al., 2014) as other individuals with SZ.

It is noteworthy that the effect sizes are smaller than in our neuropsychological study of intellectually superior SZ (Vaskinn et al., 2014) where Cohen's *d* for the intellectually superior level ranged from medium-sized such as 0.61 for *attention* (Digit Span) to very large such as 1.11 for *cognitive flexibility* (Category Switching). In the current study the largest MRI effect sizes are in the medium-sized range. This is in line with Heinrichs' (2005) demonstration that effect sizes for SZ–HC differences are twice as large for neuropsychological tests as for structural MRI assessments. Interestingly, the two measures in the present study that constitute the basis of frontal cortical volume (thickness and surface area) align with results from our previous work (Vaskinn et al., 2014). In that study, we found large effect sizes for *semantic*

fluency and *cognitive flexibility* assessed with a verbal fluency task (Semantic Fluency and Category Switching from the Delis–Kaplan Executive Function System Verbal Fluency test). The frontal lobes are an anatomical correlate of fluency tests (Robinson et al., 2012). Based on our previous neuropsychological and current imaging findings, it seems reasonable to hypothesize that intellectually superior SZ has a frontal anomaly.

Although we found no significant differences across IQ level within the SZ group, trend effects were seen for ventricular size, and for cortical thickness in the left hemisphere for frontal and temporal lobes. Inspection of the figures reveals that it is the intellectually low SZ sample that deviates the most from the rest of the group. Wexler et al. (2009) found something similar in that neuropsychologically impaired SZ had larger ventricles than HC, compared with what was the case for neuropsychologically normal SZ. The functions of the ventricles are largely unknown, but volume changes are likely a proxy of changes or pathology in the brain parenchyma. We have previously reported that larger ventricular volumes are correlated with motor speed (Hartberg et al., 2011), while others have reported correlations with visuomotor speed, vocabulary, and executive functions (Lawyer et al., 2006). Therefore, one might speculate that increased ventricular volumes reflect the severity of cognitive dysfunction in schizophrenia. Importantly for our main aim in this study, there is no indication from the figures that intellectually superior SZ has markedly fewer brain abnormalities than intellectually normal SZ.

A strong point of our study is the inclusion of different structural MRI measures, investigating both cortical surface area and cortical thickness. Although the effect sizes were somewhat smaller for cortical surface area than for cortical thickness measures, we cannot make any guesses as to whether either one of these measures of cortical volume is more central to SZ. The two cortical entities are likely to have different developmental origins. Cortical area typically grows until age 8–10 years, so that abnormalities in this measure of cortical volume are likely due to an early impact (Rakic, 1988). There is extensive support for a neurodevelopmental model of SZ (Rapoport et al., 2012), and the reduction of cortical surface area shown at a group level in SZ (Rimol et al., 2012; Haukvik et al., 2014) can be seen as a support for the hypothesis that SZ has a neurodevelopmental origin. Cortical thickness might be more affected by environmental risks (Habets et al., 2010). Both we (Nesvåg et al., 2008; Rimol et al., 2010) and others (Kuperberg et al., 2003) have shown that cortical thinning is a characteristic of SZ, which may be more related to illness-related factors (van Haren et al., 2011). The data from the present study are probably best understood as being consistent with the idea that the brain abnormalities seen in adult participants with SZ can be associated with the disease process after illness onset (cortical thickness) as well as have a neurodevelopmental origin (cortical surface area).

Limitations of the study include the small sample sizes, especially for the intellectually superior SZ group. This has limited the statistical power, and we would like to stress that our results must be considered preliminary and should be replicated in independent studies. Further, due to the statistical restrictions on the number of study variables that it makes sense to include in a study with a limited number of participants, we have refrained from a more fine-grained analysis of more specific regions in regard to cortical thickness and surface area measures. Strengths of the study include the use of a catchment-area based approach, a clinically well-characterized sample, and state-of-the-art structural MRI methods.

In conclusion, this study confirmed SZ–HC differences for morphological measures and found brain structure abnormalities in SZ to be present at all intellectual levels.

Contributors

AV designed the study, collected data, conducted all statistical analyses, and drafted the manuscript. CBH designed the study, collected data, and contributed with statistical advice, interpretation of results and drafting of the manuscript. LTW contributed with methodological and statistical advice and interpretation of results. KS, OAA, IM and IA contributed to the design of the study, data collection and interpretation of results. All authors have critically revised the paper for intellectual content and approved the final version.

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References

Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S.M., Ebmeier, K.P., McIntosh, A.M., 2009. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. British Journal of Psychiatry 195, 194–201.

Ayesa-Arriola, R., Roiz-Santiáñez, R., Pérez-Iglesias, R., Ferro, A., Sainz, J., Crespo-Facorro, B., 2013. Neuroanatomical differences between first-episode psychosis patients with and without neurocognitive deficit: a 3-year longitudinal study. Frontiers in Psychiatry 4, 134. http://dx.doi.org/10.3389/fpsyt.2013.00134.

Buckner, R.L., Head, D., Parker, J., Fotenos, A.F., Marcus, D., Morris, J.,C., Snyder, A.Z., 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage 23, 724–738.

Cobia, D.J., Csernansky, J.G., Wang, L., 2011. Cortical thickness in neuropsychologically near-normal schizophrenia. Schizophrenia Research 133, 68–76.

Cohen, J., 1998. Statistical Power Analysis for the Behavioral Sciences. Erlbaum, Hillsdale, NJ.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179–194.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophrenia Research 117, 1–12.

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.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Gray, B.E., McMahon, R.P., Gold, J.M., 2013. General intellectual ability does not explain the general deficit seen in schizophrenia. Schizophrenia Research 147, 315–319.

Habets, P., Marcelis, M., Gronenschild, E., Drukker, M., van Os, J., 2010. Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. Biological Psychiatry 69, 487–494.

Haijma, S.V., van Haren, N., Cahn, W., Koolschijn, P.C.M.P., Hulshoff Pol, H.E., Kahn, R.S., 2013. Brain volumes in schizophrenia: a meta-analysis in over 18,000 subjects. Schizophrenia Bulletin 38, 1129–1138.

Hartberg, C.B., Sundet, K., Rimol, L.M., Haukvik, U.K., Lange, E.H., Nesvåg, R., Melle, I., Andreassen, O.A., Agartz, I., 2011. Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35, 1122–1130.

Haukvik, U.K., Rimol, L.M., Roddey, J.C., Hartberg, C.B., Lange, E.H., Vaskinn, A., Melle, I., Andreassen, O.A., Dale, A., Agartz, I., 2014. Normal birth weight variation is related to cortical morphology across the psychosis spectrum. Schizophrenia Bulletin 40, 410–419.

Heinrichs, R.W., 2005. The primacy of cognition in schizophrenia. American Psychologist 60, 229–242.

Heinrichs, R.W., Miles, A.A., Smith, D., Zargarian, T., Vaz, S.M., Goldberg, J.O., Ammari, N., 2008. Cognitive, clinical, and functional characteristics of verbally superior schizophrenia patients. Neuropsychology 22, 321–328.

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. American Journal of Psychiatry 162, 2233–2245.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13, 261–276.
Keefe, R.S.E., Eesley, S.E., Poe, M.P., 2005. Defining a cognitive function decrement in schizophrenia. Biological Psychiatry 57, 688–691.
Kremen, W.S., Seidman, L.J., Faraone, S.V., Toomey, R., Tsuang, M.T., 2000. The paradox of normal neuropsychological function in schizophrenia. Journal of Abnormal Psychology 109, 743–752.
Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., van der Kouwe, A.J., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Archives of General Psychiatry 60, 878–888.
Lawyer, G., Nyman, H., Agartz, I., Arnborg, S., Jönsson, E.G., Sedvall, C.G., Hall, H., 2006. Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression. BMC Psychiatry 6, 31.
MacCabe, J.H., Brébion, G., Reichenberg, A., Ganguly, T., McKenna, P.J., Murray, R.M., David, A.S., 2012. Superior intellectual ability in schizophrenia: neuropsychological characteristics. Neuropsychology 26, 181–190.
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. Schizophrenia Research 98, 16–28.
Ortiz-Gil, J., Pomarol-Clotet, E., Salvador, R., Canales-Rodríguez, E.J., Sarró, S., Gomar, J.J., Guerrero, A., Sans-Sansa, B., Capdevila, A., Junqué, C., McKenna, P.J., 2011. Neural correlates of cognitive impairment in schizophrenia. British Journal of Psychiatry 199, 202–210.
Palmer, B.W., Heaton, R.K., Paulsen, J.S., Kuck, J., Braff, D., Harris, M.J., Zisook, S., Jeste, D.V., 1997. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 11, 437–446.
Pedersen, G., Hagtvedt, K.A., Karterud, S., 2007. Generalizability studies of the global assessment of functioning-split version. Comprehensive Psychiatry 48, 88–94.
Rakic, P., 1988. Specification of cerebral cortical areas. Science 241, 170–176.
Rapoport, J.L., Giedd, J.N., Gogtay, N., 2012. Neurodevelopmental model of schizophrenia. Update 2012. Molecular Psychiatry 17, 1228–1238.
Rimol, L.M., Hartberg, C.B., Nesvåg, R., Fennema-Notestine, C., Hagler jr, D.J., Pung, C.J., Jennings, R.G., Haukvik, U.K., Lange, E., Nakstad, P.E., Melle, I., Andreassen, O.A., Dale, I., Agartz, I., 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biological Psychiatry, 68; , pp. 41–50.
Rimol, L.M., Nesvåg, R., Hagler jr, 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. Biological Psychiatry, 71; , pp. 552–560.
Robinson, G., Shallice, T., Bozzali, M., Cipolotti, L., 2012. The differing roles of the frontal cortex in fluency tests. Brain 135, 2202–2214.
Rund, B.R., Sundet, K., Asbjørnsen, A., Egeland, J., Landrø, N.I., Lund, A., Roness, A., Stordal, K.I., Hughdahl, K., 2006. Neuropsychological test profiles in schizophrenia and non-psychotic depression. Acta Psychiatrica Scandinavica 113, 350–359.
Rush, A.J., Gullion, C.M., Basco, M.R., Jarett, R.B., Trivedi, M.H., 1996. The inventory of depressive symptomatology (IDS): psychometric properties. Psychological Medicine 26, 477–486.
Spitzer, R.L., Williams, J.B., Kroenke, K., Linzer, M., deGruy 3rd, F.V., Hahn, S.R., Brody, D., Johnson, J.G., 1994. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 272, 1749–1756.
van Haren, N.E., Schnack, H.G., Cahn, W., van den Heuvel, M.P., Lepage, C., Collins, L., Evans, A.C., Hulshoff Pol, H.E., Kahn, R.S., 2011. Changes in cortical thickness during the course of illness in schizophrenia. Archives of General Psychiatry 38, 871–880.
Vaskinn, A., Ueland, T., Melle, I., Agartz, I., Andreassen, O.A., Sundet, K., 2014. Neurocognitive decrements are present in intellectually superior schizophrenia. Frontiers in Psychiatry 5, 45. http://dx.doi.org/10.3389/fpsyt.2014.00045.
Wechsler, D., 2003. Wechsler Adult Intelligence Scale – third edition (WAIS-III) Norwegian Manual. Pearson Assessment, Stockholm.
Weickert, T.W., Goldberg, T.E., Gold, J.M., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2000. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Archives of General Psychiatry 57, 907–913.
Wexler, B.E., Zhu, H., Bell, M.D., Nicholls, S.S., Fulbright, R.K., Gore, J.C., Colibazzi, T., Arnat, J., Bansal, R., Peterson, B.S., 2009. Neuropsychological near normality and brain structure abnormality in schizophrenia. American Journal of Psychiatry 166, 189–195.
Wilk, C.M., Gold, J.M., McMahon, R.P., Humber, K., Iannone, V.N., Buchanan, R.W., 2005. No, it is not possible to be schizophrenic yet neuropsychologically normal. Neuropsychology 19, 778–786.