Brain structure characteristics in intellectually superior schizophrenia

Anja Vaskinn [a,b,*], Cecilie B. Hartberg [b,c], Kjetil Sundet [a,b], Lars T. Westlye [a,b], Ole A. Andreassen [b,d], Ingrid Melle [b,d], Ingrid Agartz [b,c,d]

[a] Department of Psychology, University of Oslo, Norway
[b] NORMENT K.G. Jebsen Centre for Psychosis Research, Oslo University Hospital, Norway
[c] Department of Psychiatric Research, Diakonhjemmet Hospital Oslo, Norway
[d] Department of Mental Health and Addiction, Institute of Clinical Medicine, University of Oslo, Norway

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.

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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

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