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Volumes of brain, grey and white matter and cerebrospinal fluid in schizophrenia in the Northern Finland 1966 Birth Cohort: An epidemiological approach to analysis

Päivikki Tanskanen [a,*], Marianne Haapea [a,b], Juha Veijola [b,c], Jouko Miettunen [b], Marjo-Riitta Järvelin [d,e], Juhani Pyhtinen [a], Peter B. Jones [f], Matti Isohanni [b]

[a] University of Oulu, Department of Diagnostic Radiology, P.O. Box 50, FIN-90029 Oulu, Finland
[b] University of Oulu, Department of Psychiatry, P.O. Box 5000, FIN-90014 Oulu, Finland
[c] Academy of Finland, PL 99, FIN-00501 Helsinki, Finland
[d] University of Oulu, Department of Public Health Science and General Practice, P.O. Box 5000, FIN-90014 Oulu, Finland
[e] Department of Epidemiology and Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK
[f] University of Cambridge, Department of Psychiatry, Box 189, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

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ABSTRACT

Magnetic resonance imaging (MRI) studies in schizophrenia have seldom involved a general population birth cohort or other epidemiological samples. We studied the Northern Finland 1966 Birth Cohort and identified all people with psychotic disorders. Along with an unaffected age-matched control sample ($n = 100$) from the cohort, 54 subjects with schizophrenia underwent MRI brain scan at age 33–35 years from which we defined volumes of whole brain, grey and white matter and intracranial cerebrospinal fluid (CSF). Whole brain, grey and white matter volumes were 2–3% smaller in the schizophrenia subjects, who showed a 7% increase in CSF volume. These volume changes were independent of the effects of gender, family history of psychosis, perinatal risks or age at onset of illness. Moreover, there was no evidence that the effects were due to particular subgroups of cases having very low or high values. Rather, there were linear trends in the associations between whole brain and grey matter volume measures and schizophrenia. Our study replicates the previous findings of brain volume differences in schizophrenia on a general population level.

1. Introduction

Structural brain differences have been associated with schizophrenia, but there are very few epidemiological studies and, as far as we know, only one study using a general population birth cohort (Cannon et al., 2002b). Enlargements of the lateral ventricles and the cortical sulci have been consistent findings in computed tomography (CT) or magnetic resonance imaging (MRI) studies in schizophrenia (Johnstone et al., 1976; Pfefferbaum et al., 1988; Jones et al., 1994a; Pearlson and Marsh, 1999; Wright et al., 2000; Shenton et al., 2001). Meta-analyses on MRI studies by Ward et al. (1996) and Woods et al. (2005) suggest a small but statistically significant reduction of brain and intracranial size. The brain volume reduction has been about 3%, mainly consisting of grey matter loss (4%) (Lawrie and Abukmeil, 1998). A meta-analysis of neuropathological studies (Harrison et al., 2003) is consistent with MRI volumetric findings in direction and magnitude (2%).

The general lack of an epidemiological approach is a concern for several reasons. First, studies consisting of chronic or severe cases may accentuate true effects or be showing effects of chronicity rather than those associated with disease onset (Lawrie and Abukmeil, 1998). Second, we know from the CT scanning literature that many effects may, in fact, be driven more by choice of control subjects rather than cases (Smith and Iacono, 1986), something that an epidemiological design can address. Third, the vast majority of studies and meta-analyses (Wright et al., 2000) concentrate on mean differences in volumes. This means that they cannot ascertain whether differences are driven by a minority of subjects with very aberrant values, whether there are thresholds in risk, such that the association with schizophrenia is seen only over or under a certain value, or whether there are linear trends in risk such as is found in many areas of medicine: higher blood pressure and cerebrovascular disease risk, for example. There has been only one study that has systematically investigated this last issue (Jones et al., 1994a) with an epidemiological approach to analysis, finding evidence for the linear trends, rather than the alternative hypotheses. However, the study did not have a truly epidemiological sample and relied on measures from

* Corresponding author. Tel.: +358 8 315 5363; fax: +358 8 315 5455.
E-mail addresses: paivikki.tanskanen@ppshp.fi (P. Tanskanen), marianne.haapea@oulu.fi (M. Haapea), juha.veijola@oulu.fi (J. Veijola), jouko.miettunen@oulu.fi (J. Miettunen), m.jarvelin@ic.ac.uk (M.-R. Järvelin), juhani.pyhtinen@professori.fi (J. Pyhtinen), pbj21@cam.ac.uk (P.B. Jones), matti.isohanni@oulu.fi (M. Isohanni).

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computerized tomography, rather than the more precise volumes that are derived from MRI.

We aimed to take this approach further by using whole brain, grey and white matter and CSF volumes from MRI in a truly epidemiological sample. We hypothesized that there would be linear associations between smaller brain, grey and white matter, as well as larger cerebrospinal fluid (CSF) volumes, and diagnosis of schizophrenia. Furthermore, we tested the effect of genetic or perinatal factors or age at onset of illness on brain volumes.

2. Materials and methods

2.1. The Northern Finland 1966 Birth Cohort

The Northern Finland 1966 Birth Cohort of 12 068 women and their 12 058 live-born children (96% of those eligible) is an unselected, general population cohort ascertained during mid-pregnancy in the provinces of Lapland and Oulu with an expected date of birth during 1966 (Rantakallio, 1969). The present study is based on 10 934 individuals living in Finland at the age of 16 years who did not refuse the use of their data. Permission to gather data was obtained from the Ministry of Social and Health Affairs, and the study design has been approved by and is under review of the Ethical Committee of the Northern Ostrobothnia Hospital District. The material and methods are described in detail by Tanskanen et al. (2005), Ridler et al. (2006) and Haapea et al. (2007).

2.2. Ascertainment and sampling of people with psychosis

The Finnish Hospital Discharge Register (FHDR) was used to identify cohort members with psychosis. All cohort members over 16 years appearing on the FHDR until the end of 1997 for any mental disorder (ICD-8 290–309, ICD-9 290–316, and ICD-10 F00–F69, F99) were identified. All case records were scrutinized and diagnoses were validated using DSM-III-R criteria (Isohanni et al., 1997; Moilanen et al., 2003).

Those 146 living subjects (84 men) who were found according to the FHDR to have had a history of one or more known psychotic episodes were invited to participate in the present study; 92 (63%, 52 men) attended and gave written informed consent. Fourteen subjects with a psychotic episode had died by 2001.

The Structured Clinical Interview for DSM-III-R (SCID, Spitzer et al., 1989) and anamnestic information including review of individual hospital case notes were the main diagnostic instruments. Three subjects did not fulfill the criteria of psychosis. Two subjects were excluded after MRI scan due to gross structural lesions (hydrocephalus). Altogether 87 participants (49 men) with a history of psychosis were sampled, including 61 people (36 men) with a diagnosis of DSM-III-R schizophrenia.

The age at onset of illness did not differ between the participants ($n=61$; mean 23.3 years, S.D. 4.4 years) and non-participants ($n=40$;mean 21.8 years, S.D.4.1 years). The hospital treatment periods of non-participants had been longer (median 378 days) compared with participants (167 days) (Tanskanen et al., 2005; Haapea et al., 2007).

The aim was to have two sex-matched control subjects for every subject with schizophrenia. The control subjects without a psychotic episode according to FHDR were randomly selected from cohort members living in the Oulu area. Altogether 187 control subjects were invited; 104 (62 men) consented in writing to participate.

2.3. Assessment of putative etiological factors

The summary statistics on demographic and clinical characteristics and putative etiological factors in subjects with adequate MRI data are presented in Table 1. We used the Family Interview for Genetic Studies (FIGS; Maxwell, 1992) to investigate family history of psychosis.

Perinatal risk was defined as one or more of the following events: low birth weight (<2500 g), short gestation (<37 weeks) or perinatal brain damage (an Apgar score of 0 at 1 min or less than 5 at 15 min , convulsions during the neonatal period, or a diagnosis of asphyxia, brain injury or intraventricular hemorrhage at discharge (Rantakallio et al., 1987; Jones et al., 1998).

Mean age at onset of illness was 23.1 years (S.D. 4.3 years) in schizophrenia subjects with adequate MRI data ($n=54$). Age at onset of illness was categorized as 1) 20 years or less and 2) 21 years or more.

2.4. Image acquisition, image analysis and data processing

All subjects were scanned with a GE Signa MRI scanner (General Electric, Milwaukee, WI) operating at 1.5 T in Oulu University Hospital. Dual echo fast spin echo (T2- and proton density-weighted) images of the whole brain were used for volumetric analyses (with 3 mm slice thickness in coronal plane; repetition time = 4000 ms; echo time = 24 ms for proton density images and 96 ms for T2 images).

Subjects who did not consent to imaging or who had images of inadequate quality were excluded from the analysis ($n=7$ within the schizophrenia group; $n=4$ within the control group). Adequate MRI scans were obtained from 54 schizophrenia subjects and 100 control subjects.

The MRI data were segmented and probabilistic maps of grey matter, white matter, and CSF were created for each subject by using BAMM software (Brammer et al., 1997; Suckling et al., 1999b). Voxels representing extra-cerebral tissue were automatically identified and set to zero using a linear scale-space set of features obtained from derivatives of the Gaussian kernel (Suckling et al., 1999a). Manual editing of the segmented images was necessary only to remove the brain stem below a line parallel to the base of the cerebellum. The probability of each intra-cerebral voxel belonging to each of four possible tissue classes (grey matter, white matter, CSF or dura/vasculature) was then estimated by a modified fuzzy clustering algorithm in the two-dimensional feature space formed by the proton density and T2 intensities (Suckling et al., 1999b).

2.5. Statistical analysis

First, mean volumes of whole brain (grey and white matter summed), grey matter, white matter, CSF and intracranial volume (ICV, *i.e.*, grey and white matter and CSF summed) were compared between schizophrenia and control subjects using Student's *t*-tests. Differences in volumes were contrasted with the control group, and the significance reported both for unadjusted volumes and volumes adjusted for intracranial volume.

Second, we went on to adapt the epidemiological approach used by Jones et al. (1994a). The distribution of volumes in the control group was divided into thirds by assigning the same number of controls into each tertile. If there were no differences between the subjects with schizophrenia and control subjects, a third of the subjects with schizophrenia would be found within each of these groups defined by these tertiles, and the odds ratios comparing the associations between volume group and schizophrenia would be unity. We tested the hypothesis that there would be a linear trend for subjects with schizophrenia to be found more frequently in the lower tertiles in whole brain, grey and white matter volumes, and in the higher tertiles in CSF. These analyses were adjusted for intracranial volume, gender, family history of psychosis and perinatal risk.

Within the schizophrenia group the mean volumes were compared between subjects with early and later age at onset of illness using Student's *t*-test. SPSS for Windows version 14.0 was used for the analyses; Intercooled Stata for Windows version 8.0 was used for the linear analysis.

3. Results

Mean volumes of whole brain, grey matter, white matter, CSF and ICV in schizophrenia and control subjects, stratified for men and women and both unadjusted and adjusted for, are shown in Table 2. There was a pattern for lower volumes of whole brain, grey and white matter and larger CSF spaces in both men and women, though the effects were larger (and so more often statistically significant) for women than for men.

The statistical analysis with tertiles of volumes (Table 3) showed trends in the association between volumes and diagnosis of schizophrenia; the subjects with schizophrenia were systematically more likely to be in the middle or lowest tertiles of whole brain, grey and white matter volumes, and more often in the highest tertile of CSF volume; this was in line with our hypotheses. However, the odds ratios for linear trend were statistically significant only for whole brain volume and grey matter, not white matter or increased CSF, when ICV was taken into account.

Table 1
Summary statistics on demographic and clinical characteristics.

	Schizophrenia ($N=54$)			Control group ($N=100$)		
	N	%	M/W	*N*	%	M/W
Gender						
Men	31	57		60	60	
Women	23	43		40	40	
Family history of psychosis						
No	44	82	26/18	91	91	57/34
Yes	10	18	5/5	9	9	3/6
Perinatal risk						
No	46	85	26/20	90	90	53/37
Yes	8	15	5/3	10	10	7/3
Age at onset of illness						
20 years or less	21	39	12/9			
21 years or more	33	61	19/14			

Table 2
Intracranial (ICV), whole brain, grey matter, white matter and cerebrospinal fluid (CSF) volumes in subjects with schizophrenia (SZ) and in control subjects in relation to gender.

		ICV				Whole brain					Grey matter					White matter					CSF				
		Student's *t*-test				Student's *t*-test			ANOVA		Student's *t*-test			ANOVA		Student's *t*-test			ANOVA		Student's *t*-test			ANOVA	
	N	Volume (ml)	Δ (%)	*t*	Sig.[1]	Volume (ml)	Δ (%)	*t*	Sig.[1]	*F*	Sig.[2]	Volume (ml)	Δ (%)	*t*	Sig.[1]	*F*	Sig.[2]	Volume (ml)	Δ (%)	*t*	Sig.[1]	*F*	Sig.[2]	Volume (ml)	Δ (%)	*t*	Sig.[1]	*F*	Sig.[2]
All																											
SZ	54	1462 ± 136	−1.3	0.8	0.40	1266 ± 120	−2.4	1.6	0.12	8.2	<0.01	682 ± 57.7	−2.2	1.5	0.14	3.4	0.07	584 ± 67.4	−2.7	1.5	0.15	3.1	0.08	196 ± 41.2	6.5	−1.9	0.07	8.2	<0.01
Controls	100	1481 ± 135				1297 ± 117						697 ± 57.3						600 ± 65.6						184 ± 35.2					
Men																													
SZ	31	1534 ± 125	−1.0	0.6	0.53	1328 ± 110	−1.7	1.0	0.32	1.9	0.17	710 ± 53.3	−1.7	1.1	0.27	1.7	0.20	618 ± 61.1	−1.8	0.8	0.43	0.2	0.62	206 ± 41.9	3.5	−0.9	0.39	1.9	0.17
Controls	60	1550 ± 114				1351 ± 101						722 ± 49.7						629 ± 59.7						199 ± 31.6					
Women																													
SZ	23	1365 ± 79	−0.9	0.5	0.59	1182 ± 73	−2.7	1.5	0.13	7.6	<0.01	645 ± 40.3	−2.0	1.2	0.25	1.6	0.21	537 ± 43.3	−3.6	1.6	0.11	5.5	0.02	183 ± 37.3	13.0	−2.5	0.02	7.6	<0.01
Controls	40	1378 ± 91				1215 ± 88						658 ± 45.3						557 ± 48.3						162 ± 28.7					

Differences in volume (Δ(%)) are calculated in group of schizophrenia contrasted with the control group.
Sig.[1] = unadjusted significance from Student's *t*-test (*df* = 152 for all; *df* = 89 for men; *df* = 61 for women).
Sig.[2] = significance adjusted for ICV from univariate ANOVA (*df* = 153 for all; *df* = 90 for men; *df* = 62 for women).

Table 3
Odds ratios for tertiles of volumes in schizophrenia and odds ratios with 95% confidence intervals for linear trends.

Schizophrenia									
	Controls	Whole brain		Grey matter		White matter		CSF	
	N	*N*	OR	*N*	OR	*N*	OR	*N*	OR
Lowest tertile	33	24	2.18	27	2.25	21	1.57	18	1.00[a]
Middle tertile	34	19	1.68	15	1.21	20	1.54	12	0.65
Highest tertile	33	11	1.00[a]	12	1.00[a]	13	1.00[a]	24	1.33
OR (95% C.I.) for linear trend									
Unadjusted		1.5 (1.0–2.2) *P* = 0.08		1.5 (1.0–2.3) *P* < 0.05		1.2 (0.8–1.9) *P* = 0.31		1.2 (0.8–1.8) *P* = 0.43	
Adjusted for									
ICV		3.2 (1.2–8.6) *P* = 0.02		2.9 (1.3–6.8) *P* = 0.01		1.3 (0.6–2.9) *P* = 0.57		1.4 (0.9–2.3) *P* = 0.15	
Gender, familial risk and perinatal risk		1.7 (1.0–2.9) *P* = 0.04		1.8 (1.1–3.0) *P* = 0.02		1.4 (0.8–2.3) *P* = 0.22		1.3 (0.8–2.1) *P* = 0.23	
ICV, gender, familial risk and perinatal risk		3.5 (1.3–9.7) *P* = 0.01		3.0 (1.3–7.1) *P* = 0.01		1.4 (0.6–3.3) *P* = 0.42		1.5 (0.9–2.5) *P* = 0.11	

ICV = intracranial volume.
[a] Baseline odds.

The results did not change after adjusting the tertiles of volumes for the covariates (gender, family history of psychosis, perinatal risk), *i.e.,* the changes were independent of the effects of the covariates.

Finally, within the schizophrenia group the volumes of whole brain, grey or white matter or CSF did not differ between subjects with early age at onset of illness (20 years or less) and later age at onset (21 years or more) (results not shown).

4. Discussion

We have replicated previous results regarding brain volume reduction in schizophrenia, but extended the finding through the use of a general population sample showing the potential importance of a population shift (Jones et al., 1994a,b), rather than a sub-group effect where a minority of cases generated the effect, and may have represented an etiologically distinct class (Murray et al., 1985); we find no support for this view. Furthermore, the effects were independent of the effect of gender, family history of psychosis, perinatal risk, or the age at onset of illness.

Many neuroimaging studies in schizophrenia have relied upon non-random, convenience samples, rather than epidemiologically valid designs; the generalizability of the findings based on such studies may be limited. The use of chronic, hospitalized patients, usually mainly men, or hospital staff as control subjects limits interpretation, and the ethnic constitution is reported by few investigators (Jones et al., 1994a; Lawrie and Abukmeil, 1998). All these problems can lead to major bias in imaging studies, with Smith and Iacono (1986) demonstrating the vital importance of appropriate controls. We consider that our study circumvents many of these problems (Tanskanen et al., 2005).

Normal variation in head and brain size is considerable, affected both by gender and ethnic differences (Khang-Cheng et al., 1980; Jones et al., 1994a). Brain volume decreases and CSF volume increases in normal aging, and there are also reports of the duration of illness having an effect on brain structure (Lieberman et al., 2001; Velakoulis et al., 2002). We were able to exclude the effect of ageing, gender and ethnic differences in brain structure because our subjects with schizophrenia and their controls were of the same age (33–35 years) and ethnic background. Additionally, we had approximately two control subjects in both genders for each schizophrenia subject to strengthen the statistical power. We also had a representative sample of women with schizophrenia (39%), a group often neglected (Lawrie and

Abukmeil, 1998). The sample of subjects in this study does not over-represent people with chronic or severe schizophrenia.

Our study sample is relatively large within the context of the imaging literature, though the possibility of Type 2 error remains for some negative results, such as putative risk factors on brain volumes. Another limitation was the moderate non-participation in the schizophrenia group (Tanskanen et al., 2005; Haapea et al., 2007). Our sample may, therefore, be slightly biased towards the less severe cases of schizophrenia, with a consequent reduction in detecting brain changes related to the severity of schizophrenia.

The brain volume reduction in our study was of a similar magnitude to that found in the meta-analysis of neuropathological studies by Harrison et al. (2003), (2%), and the meta-analysis of MRI studies by Wright et al. (2000). In that analysis, brain volume was reported to be 2%, grey matter 4% and white matter 2% smaller in subjects with schizophrenia than in controls. We used two statistical methods: analysis of means in Table 2, which is rather robust and non-sensitive, and the more sensitive and illustrative odds ratio analysis (Table 3), which is a standard method in epidemiological studies though less standard in imaging studies. This gave significant effects on whole brain and grey matter volume reductions. White matter reduction was not statistically significant in this analysis. This finding is in concordance with some other quantitative MRI studies suggesting only grey matter reduction (Zipursky et al., 1992; Sullivan et al., 1998).

The CSF increase (7%) in our study was smaller than indicated from the 20–30% increase in the most relevant meta-analysis (Wright et al., 2000). This may be due to the fact that we measured both ventricular and external CSF, which may be less pronounced than mere ventricular enlargement in this age group. An alternative explanation may be the large epidemiological sample: the larger and more representative sample leads to a more realistic estimate of effect.

The associations between brain and grey matter volume changes and schizophrenia became stronger after adjustment for ICV, gender, family history of psychosis and perinatal risk, indicating that the effects were attributable to schizophrenia itself, rather than these factors. Nevertheless, in previous studies genetic factors or obstetric complications have been associated with schizophrenia as well as with brain structure in schizophrenia (Jones et al., 1998; Baare et al., 2001; Cannon et al., 2002a,b). In our previous study focusing on the hippocampus, the volume reduction was also not explained by genetic or perinatal risks (Tanskanen et al., 2005). However, we have noted the problem of power, as mentioned above.

Age at onset of illness did not have an effect on brain volumes in schizophrenia in our study. Early age at onset is related to long duration of illness in birth cohort setting. The negative finding is in concordance with the CT study by Jones et al. (1994a) and the meta-analysis of neuropathological studies by Harrison et al. (2003). Additionally, brain volume reduction was found at a rather young age in our study (33–35 years). In a meta-analysis by Harrison et al. (2003) subjects were much older (mean 61 years). However, contradictory findings have been reported: increased illness duration was associated with reduced grey matter in specific areas in patients with schizophrenia in a study by Velakoulis et al. (2002). Total brain, grey or white matter volume measurements are a rather rough and insensitive approach and may not give information on regional brain volume differences; this is also true regarding our dichotomous categorization of age at onset.

In conclusion, we have replicated previous findings of brain volume differences in schizophrenia on a general population level. The main importance of our study is the epidemiological basis for the sample, which is uncommon in the scanning literature. It is well known that large effect sizes from initial studies in a field are often reduced in subsequent work with larger, more representative samples. The present study has these features and yet yields significant results. In future investigations, juxtaposition of chronic schizophrenia patients and healthy control subjects should be avoided, because it can emphasize structural changes related to the severity of schizophrenia. Population-based strategies are needed to assess structural changes in schizophrenia reliably.

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