Päivikki Tanskanen

BRAIN MRI IN SUBJECTS WITH SCHIZOPHRENIA AND IN ADULTS BORN PREMATURELY

THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY
PÄIVIKKI TANSKANEN

BRAIN MRI IN SUBJECTS WITH SCHIZOPHRENIA AND IN ADULTS BORN PREMATURELY
The Northern Finland 1966 Birth Cohort Study

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Faculty of Medicine, Institute of Clinical Medicine, Department of Psychiatry, Institute of Diagnostics, Department of Diagnostic Radiology, Institute of Health Sciences, University of Oulu, P.O.Box 5000, FI-90014 University of Oulu, Finland
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Abstract
The Northern Finland 1966 Birth Cohort (NFBC 1966) is a general population study started in the 1960’s including 12,058 people born in the provinces of Oulu and Lapland. We studied magnetic resonance imaging (MRI) changes of the brain in subjects with schizophrenia at age 33–35 years. Another sub-group consisted of non-psychotic members of the NFBC 1966 who were born premature.

In subjects with schizophrenia (n = 54) the volumes of whole brain, grey and white matter were reduced 2–3% and the volume of CSF was increased 7% compared to the general population control subjects (n = 100) without a psychotic episode. Regional grey matter density was reduced in several regions including frontal, temporal, parietal and occipital cortices, deep grey matter and cerebellum. Grey matter density was increased in the basal ganglia, anterior cingulate and medial orbitofrontal cortex. There were white matter deficits in inter- and intrahemispheric tracts bilaterally in the frontal, temporal, parietal and occipital lobes, subcortical structures, cerebellum and brainstem. CSF excesses were found in the lateral and third ventricles. Grey and white matter deficits were associated with duration of illness, so that the longer the duration, the smaller the density in the deficit regions. The hippocampal volume was reduced 2-3%, but the change was explained by the total brain volume reduction.

We also investigated the effect of preterm birth or low birth weight on education, occupation (n = 715; controls 10,132), cognitive capacity and brain structure (n = 9; controls 95) in adulthood in the non-psychotic group of the NFBC 1966. The premature subjects had slightly lower educational and occupational performance in adulthood and they performed more poorly in verbal learning. There were no differences in the tissue segmentation analysis of the brain; however, we could not determine whether the negative finding was due to small sample size.

In conclusion, we have confirmed previous findings of brain abnormalities in schizophrenia in an epidemiological population-based sample. The grey and white matter deficits were widespread and the abnormalities were associated with duration of illness, suggesting progressive changes. In the premature group of the NFBC, minor adult cognitive deviances were found in the absence of major imaging findings.

Keywords: birth cohort, brain, MRI, preterm, schizophrenia
Tanskanen, Päivikki, Aivojen magneettikuvaus skitsofreniapotilailla ja keskosena syntyneillä aikuisilla. Pohjois-Suomen 1966 syntymäkohorttiittutkimus

Lääketieteellinen tiedekunta, Kliinisen lääketieteet laitos, Psykiatria, Diagnostiikan laitos, Radiologia, Terveystieteiden laitos, Oulun yliopisto, PL 5000, 90014 Oulun yliopisto

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Oulu

Tiivistelmä


Aivotilavuus, harmaan ja valkean aineen tilavuus olivat 2–3 % pienempiä ja aivoselkädyinnesteen tilavuus 7 % suurempi skitsofreniapotilaita (n = 54) verrattuna syntymäkohortin kontrolihenkilöihin (n = 100), joilla ei ollut sairaushistoriaan psykoosiepisoedia. Skitsofreniapoti-lailla harmaan aineen tiheys oli alentunut otsa-, ohimo-, päälaen- ja takaraivon lohkon kuorikeroksessa, syvällä harmaan aineen alueella sekä pikkuaivoissa. Harmaa aineen tiheys oli lisääntynyt tyvitumakealueilla sekä paikallisesti otsalohkon kuorikeroksessa. Harmaan aineen tiheys oli vähentynyt laaja-alaisesti aivojen eri lohkoissa. Aivoselkädyinnesteen määrä oli lisääntynyt aivokammioissa. Harmaa ja valkeaa aineen tiheyden muutos edellä mainituilla alueilla oli suhteessa sairauden keston siten, että pitkäaikaan sairastaneilla tiheys oli vähentynyt enemmän. Hippokampustilavuus oli pienentynyt 2–3 %, mutta tämä selittyi aivojen kokonaistilavuuden pienemislle.

Selvitimme kohortin ei-psykkoottisten ryhmässä ennenkaikaisen syntyin ja pienen syntymä-painon vaikutusta aikuisiin koulutustasoon, työllistymiseen (n = 715; kontrolleja 10,132), sekä kognitiivisissa testeissä suorituskykyyn ja aivorakenteisiin (n = 9; kontrolleja 95). Keskosena syntyneillä oli hieman keskimääräistä alhaisempi koulutustaso ja työllistyminen aikuisissa. Lisäksi he suorittivat hyväntä, että heillä ei kuitenkaan löytynyt, mutta tämä negatiivinen löytyminen jää epävarmaksi pienuukaloon vuoksi.


Asiasanat: aivot, keskone, magneettikuvaus, MRI, skitsofrenia, syntymäkohortti
To Jouni, Sonja, Johanna and Ninni
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Oulu, September 2010

Päivikki Tanskanen
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAL</td>
<td>Automated Anatomical Labelling</td>
</tr>
<tr>
<td>AIM</td>
<td>Abstraction, Inhibition and Working Memory task</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Repeated-measures analysis of covariance</td>
</tr>
<tr>
<td>BAMM</td>
<td>Brain Activation and Morphological Mapping</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVLT</td>
<td>California Verbal Learning Test</td>
</tr>
<tr>
<td>DSM-III-R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders. 3rd ed., revised</td>
</tr>
<tr>
<td>3D SPGR</td>
<td>Three-dimensional spoiled gradient echo</td>
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<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
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<tr>
<td>FHDR</td>
<td>Finnish Hospital Discharge Register</td>
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<tr>
<td>FIGS</td>
<td>Family Interview for Genetic Studies</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FSL</td>
<td>FMRIB Software Library</td>
</tr>
<tr>
<td>GE</td>
<td>General Electric</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ICD-8</td>
<td>International Classification of Diseases, 8th ed.</td>
</tr>
<tr>
<td>ICV</td>
<td>Intracranial volume</td>
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<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
</tr>
<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NFBC 1966</td>
<td>Northern Finland 1966 Birth Cohort</td>
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<tr>
<td>NFBC 1986</td>
<td>Northern Finland 1986 Birth Cohort</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PD</td>
<td>Proton density</td>
</tr>
<tr>
<td>PEG</td>
<td>Pneumoencephalography</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Diagnostic Interview for DSM</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>T1</td>
<td>Longitudinal relaxation time</td>
</tr>
<tr>
<td>T2</td>
<td>Transversal relaxation time</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel-based morphometry</td>
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<tr>
<td>VOLT</td>
<td>Visual Object Learning Test</td>
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List of original publications


The original papers have been reprinted with the permission from Elsevier (I, III, IV) and Oxford University Press (II). In addition, some unpublished data have been added to this dissertation.
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1 Introduction

Schizophrenia is a severe mental illness beginning early in adult life and the prognosis is poor. It causes impairments in social, occupational, cognitive and global functioning, often permanent disability, unemployment, excess somatic and psychiatric morbidity and increased mortality. Schizophrenia is a major public health problem and it is among the leading unsolved diseases, affecting about 1% of people. Schizophrenia is a polymorphous clinically complex disease; neither cure nor prevention is yet in sight, and its causes and development remain poorly understood.

Neuroimaging studies have shown structural brain differences in patients with schizophrenia: enlargement of lateral ventricles and cortical sulci (Johnstone et al. 1976, Wright et al. 2000), and brain volume reductions especially in the frontal and temporal lobes (Lawrie & Abukmeil 1998, Nelson et al. 1998). However, these findings are not specific for schizophrenia, as they are found in other medical conditions. Morphometric neuroimaging studies have not found a specific aetiological cause for schizophrenia.

There has been variability in results of schizophrenia MRI studies. Many factors may contribute to this variability, including differences in analysis methods, variability in the disorder itself, as well as variations in sampling selection concerning both patient and control samples (Smith & Iacono 1986, Honea et al. 2005). Most imaging studies have been drawn from non-random samples, which can constrain generalizability of their findings (Jones et al. 1994a, Haapea et al. 2007). Population-based studies are more robust against recruitment biases than other research methodologies (Lawrie & Abukmeil 1998). As far as we are aware, only one previous population-based sample, a Helsinki birth cohort, has reported case-control structural brain results in schizophrenia (Cannon et al. 1998). In the light of this paucity of epidemiologically principled imaging studies in schizophrenia, the first three papers contributing to this thesis examine differences in brain structure between schizophrenia patients and controls sampled in a population-based manner.

Additionally, whether the structural brain abnormalities in schizophrenia are progressive or not remains unclear. Some studies suggest that there are morphometric brain abnormalities even before illness onset and at transition to illness (Pantelis et al. 2003), as well as in first-episode patients (Job et al. 2002, Salokangas et al. 2002). Nevertheless, some longitudinal studies suggest progressive changes in the disorder (Cahn et al. 2002, DeLisi et al. 2004, Pantelis et al. 2007, Wood et al. 2017).
2008). Thus, the second paper in the thesis also examines the relationship between brain structure in schizophrenia and duration of illness.

Although the exact cause for schizophrenia is not known, there are some risk factors for the disease. Family history of psychosis increases the risk of schizophrenia (Hallmayer 2000), and complications of pregnancy or delivery have also been found to be associated with the disorder (Jones et al. 1998, Cannon et al. 2002a). However, the data on the effects of risk factors on brain structure are still quite scarce, and it is important to understand the effects of obstetric and other risk factors on brain development, not just in patients but also in non-schizophrenic individuals.

The fourth paper, therefore, does not examine schizophrenia patients, but rather addresses the relationship between obstetric complications and various outcome measures including brain structure. Prematurity causes a marked public health problem as 4.5% of all singleton pregnancies in Finland end up in preterm delivery, and 3.0% have low-birth weight (Xu & Rantakallio 1998). Preterm and low-birth weight babies are at risk of brain injury during the neonatal period, and these persons are liable to structural brain abnormalities (Olsén et al. 1997, Cooke & Abernethy 1999). Brain abnormalities are linked to poor neurocognitive function and can manifest as difficulties in educational contexts (Rantakallio 1985, Strauss 2000, Hille et al. 2007). Though there are many studies on neurocognitive function and brain structure in childhood and adolescence among premature subjects (Stewart et al. 1999, Allin et al. 2001), little is known about their long-term outcome in adulthood (Olsén et al. 1994, Allin et al. 2004, Spencer et al. 2008). Additionally, the majority of research studies concerning outcome of preterm children have focused on subjects with very low gestation weeks and very low birth weight, although ‘moderate’ to ‘mild’ preterm births account for the majority of preterm births. These subjects have increased neonatal morbidity, more medical problems than term infants and inferior academic performance at school age (Kirkegaard et al. 2006, Engle et al. 2007). Therefore, in the fourth paper we focus on the long-term outcome of subjects born as moderate-to-late premature infants.

The Northern Finland Birth Cohort Studies are extensive epidemiological and longitudinal research programs, aimed to promote the health and well-being of the population. The MRI study and this dissertation continue the longitudinal survey of the Northern Finland 1966 Birth Cohort (NFBC 1966) by investigating structural brain abnormalities at age 33–35 years in two special groups: subjects with schizophrenia (I–III) and subjects who were born prematurely (IV).
2 Literature review

2.1 Brain development

Development of the central nervous system starts at 19 days of pregnancy when the neural plate begins to form. At 11 foetal weeks the major components of the brain are identifiable (Langman 1981). The size of the brain of a newborn is about 25% of the size of an adult brain. Brain structure and whole brain, grey and white matter volumes change throughout life.

The bodies of the neural cells are located in the grey matter. Grey matter volume increases before puberty, while starting to decrease during puberty. This volume reduction is associated with maturation, and continues into young adulthood especially in the temporal and frontal lobes. The grey matter decrease continues through adult life.

The white matter consists of neural axons that connect different brain regions. The white matter increases throughout childhood and adolescence. The axons begin to develop a myelin sheath around them by the fifth month of pregnancy, this process continues through childhood, adolescence and adulthood until the fifth decade of life. The myelinization continues longest in the frontal and temporal lobes, and the white matter volume is at its largest in middle age. A decrease in white matter volume starts in adult midlife (Giedd et al. 1999, Ge et al. 2002, Kettunen et al. 2009).

The structural brain maturation, and the speed and timing of the changes are different in boys and girls in adolescence. The sex hormones form the structure of the brain differently between genders. Thus, brain volume is about 10% larger in boys than in girls, with the female brain reaching its maximum size at 11–12 years of age and the male brain at 14–15 years. The relative volumes of grey and white matter differ between genders in various lobes; the volumes of deep grey matter structures, which are associated with regulation of mood and emotions, also vary between genders in adolescence (Kettunen et al. 2009).

2.2 Brain imaging methods

Pneumoencephalography (PEG) is an early neuroradiological imaging method that has been used to study the size of ventricles and cortical sulci. In a PEG study, first some cerebrospinal fluid is drained away by lumbar puncture, and is replaced by air, oxygen or helium, which allows the structure of ventricles and cortical sulci
to show up in an X-ray image. It is an invasive and painful medical procedure involving side effects and risks. The procedure was introduced in 1919; it was replaced in the 1980’s by slice imaging techniques.

**Computed tomography (CT)** is a radiological imaging method using X-rays in slices of the head or body. By computer processing it creates a two-dimensional image of each slice, based on the density differences of the object. CT was invented by Hounsfield in 1967, and it is widely used in medical imaging today. In a CT image of the brain, ventricles and cortical sulci can be very well differentiated from brain parenchyma; also grey and white matter can be differentiated from each other.

**Magnetic resonance imaging (MRI)** is a noninvasive medical imaging technique that is used to visualize detailed internal structures of the body or head. MRI uses a powerful magnetic field to align the nuclear magnetization of hydrogen atoms in the body. Radio frequency fields are used to alter the alignment of this magnetization. This causes the hydrogen nuclei to produce a rotating magnetic field detectable by a scanner. The first MRI studies performed in humans were published in 1977. MRI is a superior imaging modality in most fields of medical imaging, especially neuroimaging. It has excellent contrast resolution (the ability to distinguish between different tissues e.g. grey and white matter and cerebrospinal fluid). MRI does not use ionizing radiation, and it is believed to be harmless to patients.

**Diffusion tensor imaging (DTI)** is a magnetic resonance imaging technique that enables the measurement of the restricted diffusion of water in tissue e.g. in neural axons of white matter in order to produce neural tract images. Water will diffuse more rapidly in the direction aligned with the internal structure, and more slowly as it moves perpendicular to the preferred direction. The directional information can be exploited at a higher level of structure to select and follow neural tracts through the brain - a process called *tractography*. With DTI it is possible to study white matter tracts in vivo, to detect damages in neural axons or detect new organization of neural tracts (Cascio et al. 2007).
2.3 Structural brain abnormalities in schizophrenia and other psychoses

2.3.1 Total brain, grey matter, white matter and cerebrospinal fluid volumes

Although the underlying pathology of schizophrenia remains unknown, both Kraepelin (1919/1971) and Bleuler (1911/1950) who first described “dementia praecox” and “schizophrenia”, believed that brain abnormalities would be linked to the aetiology of schizophrenia. Since then imaging studies have shown structural brain differences in patients with schizophrenia. Early PEG studies showed enlargement of the lateral ventricles and cortical sulci in patients with schizophrenia or other mental disorders (Jacobi & Winkler 1927, Moore & Nathan 1933, Haug 1962); however, not consistently in the third ventricle (Peltonen 1962). After the 1970’s with the development of non-invasive slice imaging techniques the knowledge of brain morphology in schizophrenia has increased enormously. However, the newer imaging methods have not been able to make a breakthrough in the aetiology of schizophrenia; the same is also true considering the pathophysiology of the disease.

Neuropathological studies have reported decrease in brain volume and brain length and volume of the cerebral hemispheres, enlargement of lateral ventricles, reduced size of temporal lobe structures, decrease in thalamic volume and enlargement of basal ganglia in autopsy reports in patients with schizophrenia (Harrison 1999). Neuropathological examinations of postmortem tissue have in some cases shown cell loss, misalignment of cells, altered structure in specific brain regions or gliosis (Sadock et al. 2009).

In imaging studies, enlargement of lateral ventricles and cortical sulci have been consistent findings in CT and MRI studies of schizophrenia (Pearlson & Marsh 1999). Johnstone et al. (1976) reported increased cerebral ventricular size in their early CT study of 17 institutionalized patients with schizophrenia. Pfefferbaum et al. (1988) reported slightly larger ventricles and considerably larger sulci in patients with schizophrenia compared to controls. The cerebral atrophy was diffuse in nature. Jones et al. (1994a) demonstrated significant linear trends in association between larger lateral and third ventricle volumes in both schizophrenia and schizoaffective disorder. The mean total ventricular volume of the subjects with schizophrenia was increased by 26% compared to controls in the meta-analysis by Wright et al. (2000). The review by Shenton et al. (2001) included 55 MRI studies investigating lateral ventricle enlargement, and 80% of them reported positive findings; 73% of 33 studies investigating the third ventricle reported positive findings.
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 & Abukmeil 1998), as also suggested by some other quantitative MRI studies (Zipursky et al. 1992, Sullivan et al. 1998). In the meta-analysis by Wright et al. (2000) brain volume was reported to be 2%, grey matter 4% and white matter 2% smaller in subjects with schizophrenia compared to controls. Relative volume reductions of whole brain grey matter and white matter were approximately in line with the global difference: 2% reduction for grey matter and 1% for white matter (Wright et al. 2000). A meta-analysis of neuropathological studies (Harrison et al. 2003) is consistent with MRI volumetric findings of brain volume reduction in terms of direction and magnitude: the brains of 540 schizophrenia subjects were 2% lighter than those of 794 controls.

2.3.2 Regional grey and white matter findings

Volume reductions in temporal and frontal lobes have been common findings in previous manually drawn, region-of-interest (ROI) studies (Lawrie & Abukmeil 1998, Nelson et al. 1998, Wright et al. 2000, Shenton et al. 2001). Consistent with these findings, newer computerized voxel-based morphometry (VBM) schizophrenia studies have frequently reported regional differences in specific areas of these lobes. The grey and white matter findings based on ROI or VBM studies referred to in this thesis are summarized in Table 1, which includes both original and review studies.

In their VBM study Hulshoff Pol et al. (2001) reported decreases in grey matter density in the left amygdala, left hippocampus, right supramarginal gyrus, thalamus, orbitofrontal, superior temporal, occipitotemporal, precuneus, posterior cingulate, and insular cortices bilaterally in patients with schizophrenia or schizophreniform psychosis compared to controls. Increases in grey matter density were found in the right caudate and globus pallidus.

Sigmundsson et al. (2001) reported significant deficits of grey matter volume in the patient group in the left superior temporal gyrus and insula, the left medial temporal lobe (including the parahippocampal gyrus and hippocampus), the anterior cingulate and medial frontal gyri. The volume of these regions combined was 14% lower in the patients compared to the comparison subjects. White matter deficits were found in similar locations in the left temporal lobe and they extended into the left frontal lobe. The patient group showed a relative excess of grey matter volume in the basal ganglia.
Wilke et al. (2001) found grey matter reductions in the left frontal, temporal and insular cortices, and grey matter increases in the right basal ganglia and bilateral superior cerebellum. Kubicki et al. (2002) showed grey matter density reductions in the left superior temporal gyrus, bilateral anterior cingulate gyri and insula, unilateral parietal lobe and left hippocampus.

Suzuki et al. (2002) found relative grey matter reduction in the left superior temporal, left middle and inferior frontal, right inferior frontal, and bilateral anterior cingulate and medial temporal areas. Grey matter increases were found in the parietal areas and cerebellum. White matter reduction was found in the bilateral anterior limbs of the internal capsule and the superior occipitofrontal fasciculus, whereas the bilateral parietal white matter showed significant increases. Moorhead et al. (2004) localized the significant grey matter reductions to the prefrontal and temporal lobes. An increase in the basal ganglia of patients with schizophrenia was identified.

In all, 50% of the studies in the meta-analysis by Honea et al. (2005) reported grey matter deficits in schizophrenia in the left medial temporal lobe, superior temporal, parahippocampal, inferior and medial frontal gyri; and in the right superior temporal gyrus. Reductions in other lobes have also been reported, although less often (Honea et al. 2005).

Recently Meda et al. (2008) reported in their large scale investigation (n=400) less grey matter concentration in multiple cortical and subcortical regions, some previously unreported in schizophrenia patients compared to healthy controls. They documented frontal, parietal, temporal, and subcortical grey matter reductions in schizophrenia, plus areas including the superior parietal lobule, caudate, rectal gyrus, and transverse temporal gyrus. The only region previously documented as containing less grey matter in schizophrenia but undetected in their analyses was the hippocampus. Also the recent meta-analyses of VBM studies in schizophrenia by Ellison-Wright et al. (2008) and Fornito et al. (2009a&b) detected grey matter decreases in the frontal, temporal, thalamic, striatal and thalamic regions, left uncus/amygdala, in the insula bilaterally and in the anterior cingulate.

Two meta-analyses on anterior cingulate studies have shown significant volume reduction in patients with schizophrenia compared to healthy controls (Baiano et al. 2007, Fornito et al. 2009b). However, the anterior cingulate findings are not consistent: at least two studies have reported a larger volume for the anterior cingulate, which have been interpreted as possibly stemming from medication effects (Kopelman et al. 2005, McCormick et al. 2005).

Although parietal and occipital lobes have perhaps been somewhat neglected in schizophrenia research in comparison with studies focusing on frontal and
temporal pathology, in fact 60% of the MRI studies of the parietal and 44% of those of the occipital lobe have reported volume reductions (Shenton et al. 2001). Also VBM studies and meta-analyses report volume reductions in parietal or occipital cortices (Gaser et al. 1999, Hulshoff Pol et. al 2001, Honea et al. 2005, Ellison-Wright et al. 2008, Meda et al. 2008).

Similarly, the cerebellum has rarely been the focus of schizophrenia studies. Cerebellar volume reductions in schizophrenia have been reported by several studies (Gaser et al. 1999, Marcelis et al. 2003, Pantelis et al. 2003, Honea et al. 2005, Ellison-Wright et al. 2008), although cerebellar volume increase has also been reported (Wilke et al. 2001, Suzuki et al. 2002).

Previous studies have also reported subcortical findings in schizophrenia. Bilateral thalamic volume reduction have been found in meta-analyses by Wright et al. (2000), Konick & Friedman (2001), Honea et al. (2005) and Ellison-Wright et al. (2008). Grey matter excess has been reported in the basal ganglia in the meta-analysis by Wright et al. (2000) and in the review by Shenton et al. (2001). It has been suggested that these basal ganglia excesses could be secondary to neuroleptic medication (Chakos et al. 1994, Chakos et al. 1998, Corson et al. 1999).

Some studies concentrate on grey matter findings; e.g. seven studies included in the meta-analysis by Honea et al. (2005) had studied only grey matter whereas seven studies had explored both tissues, and only one was restricted to white matter. Hence, the literature supporting white matter loss is not yet as strong as that documenting grey matter deficits (Lawrie & Abukmeil 1998, Wright et al. 2000).

DTI studies investigating white matter tracts in schizophrenia suggest a disturbance in connectivity between different brain regions rather than abnormalities within separate regions themselves. Thus, the abnormalities in connectivity could be responsible for the clinical symptoms and cognitive dysfunctions observed in this disorder (Kubicki et al. 2007).

Decreased fractional anisotropy, along with increased diffusivity within prefrontal and temporal lobes, as well as abnormalities within the fibre bundles connecting these regions (including uncinate fasciculus, cingulum bundle and arcuate fasciculus) are the most frequent positive findings in schizophrenia studies (Kubicki et al. 2007). In addition, changes in the genu of the corpus callosum, internal capsule, cerebellar peduncles, as well as parietal, temporal, prefrontal and occipital white matter have been reported in schizophrenia (Kubicki et al. 2007).
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Number of subjects (males)</th>
<th>Mean age (years)</th>
<th>Deficits compared to controls</th>
<th>Increases compared to controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawrie &amp; Abukmeil (1998)¹</td>
<td>1314 (931)</td>
<td></td>
<td>Whole brain, whole grey matter, temporal lobe, amygdala/hippocampal complex, parahippocampal</td>
<td>Whole white matter</td>
</tr>
<tr>
<td>Nelson et al. (1998)¹,²</td>
<td>522 (391)</td>
<td>31</td>
<td>Bilateral hippocampus</td>
<td></td>
</tr>
<tr>
<td>Wright et al. (2000)¹</td>
<td>1909 (1373)</td>
<td>30</td>
<td>Whole brain, whole grey and white matter, bilateral amygdala, hippocampus, parahippocampus and thalamus, left anterior superior temporal gyrus</td>
<td>Bilateral caudate, putamen and globus pallidus</td>
</tr>
<tr>
<td>Shenton et al. (2001)¹</td>
<td>6052</td>
<td></td>
<td>Medial temporal lobe (amygdala, hippocampus, parahippocampus, superior temporal gyrus), frontal lobe (prefrontal grey matter, orbitofrontal regions), parietal lobe (inferior parietal lobule), occipital lobe, cerebellum, thalamus</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>Hulshoff Pol et al. (2001)</td>
<td>159 (112)</td>
<td>36</td>
<td>Left amygdala, left hippocampus, right supramarginal gyrus, thalamus, orbitofrontal, superior temporal, occipitotemporal, precuneus, posterior cingulate, and insular cortices bilaterally</td>
<td>Right caudate and globus pallidus</td>
</tr>
<tr>
<td>Sigmundsson et al. (2001)</td>
<td>27 (26)</td>
<td>35</td>
<td>Left superior temporal gyrus and insula, the left medial temporal lobe (including the parahippocampal gyrus and hippocampus), the anterior cingulate and medial frontal gyri</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>Wilke et al. (2001)</td>
<td>48 (27)</td>
<td>33</td>
<td>Left frontal, temporal, and insular grey matter</td>
<td>Right basal ganglia and bilateral superior cerebellum</td>
</tr>
<tr>
<td>Kubicki et al. (2002)</td>
<td>16 (14)</td>
<td>26</td>
<td>Left superior temporal gyrus, bilateral anterior cingulate gyri and insula, and unilateral parietal lobe, and left hippocampus</td>
<td></td>
</tr>
<tr>
<td>Authors (year)</td>
<td>Number of subjects</td>
<td>Mean age</td>
<td>Deficits compared to controls</td>
<td>Increases compared to controls</td>
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<td>---------------</td>
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</tr>
<tr>
<td></td>
<td>(males)</td>
<td>(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suzuki et al. (2002)</td>
<td>45 (23)</td>
<td>26</td>
<td>Left superior temporal, left middle and inferior frontal, right inferior frontal, and bilateral anterior cingulate and medial temporal areas</td>
<td>Parietal grey matter, cerebellum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bilateral anterior limbs of the internal capsule and the superior occipitofrontal fasciculus white matter</td>
<td>Bilateral white matter</td>
</tr>
<tr>
<td>Moorhead et al. (2004)</td>
<td>25 (14)</td>
<td>51</td>
<td>Prefrontal and temporal lobes</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td>Honea et al. (2005)</td>
<td>390</td>
<td></td>
<td>Medial temporal lobe, superior temporal gyrus, parahippocampal gyrus, inferior frontal gyrus, medial frontal gyrus, right anterior cingulate gyrus, insula, thalamus</td>
<td></td>
</tr>
<tr>
<td>Baiano et al. (2007)</td>
<td>354 (241)</td>
<td>32</td>
<td>Anterior cingulate</td>
<td></td>
</tr>
<tr>
<td>Meda et al. (2008)</td>
<td>200 (122)</td>
<td>40</td>
<td>Inferior frontal gyrus, medial frontal gyrus, insula, superior temporal gyrus, anterior cingulate, precentral gyrus, postcentral gyrus, cingulate gyrus, transverse temporal gyrus, thalamus, caudate, orbital gyrus, posterior cingulate, rectal gyrus, subcallosal gyrus, middle temporal gyrus, inferior parietal lobule, inferior temporal gyrus, uncus, middle occipital gyrus, superior parietal lobule</td>
<td></td>
</tr>
<tr>
<td>Ellison-Wright et al. (2008)</td>
<td>979</td>
<td></td>
<td>Thalamus, left uncus/amygdala region, insula bilaterally, and anterior cingulate</td>
<td></td>
</tr>
<tr>
<td>Fornito et al. (2009a&amp;b)</td>
<td>1646</td>
<td></td>
<td>Frontal, temporal, thalamic and striatal regions, insula, medial prefrontal, medial temporal, dorso-medial frontal cortex, lateral and orbital frontal areas</td>
<td></td>
</tr>
</tbody>
</table>

1 Meta-analysis or review study. 2 Study restricted to one structure.
2.3.3 Hippocampus and amygdala

The pathophysiology of schizophrenia is thought to involve abnormalities of hippocampal or amygdala anatomy and function. The hippocampus plays an essential role in normal physiological functions, such as information processing, learning and memory, and impairments in memory are commonly found in schizophrenia. The amygdala is known to play an important role in emotion and normal fear conditioning, and anxiety and fears are common symptoms in psychosis (Sadock et al. 2009).

Reviews of ROI-based MRI studies of structural brain differences in schizophrenia have reported volume reductions of hippocampus and amygdala or the amygdala–hippocampal complex. A meta-analysis by Nelson et al. (1998), consisting of 18 studies with 522 patients with schizophrenia and 426 control subjects, found bilateral hippocampal volume reduction of 4%. A review by Shenton et al. (2001) consisted of 49 studies that had evaluated medial temporal lobe structures, which include the amygdala-hippocampal complex and the parahippocampal gyrus; the meta-analysis showed that 74% of the studies reported positive and 26% reported negative findings. Another meta-analysis by Wright et al. (2000), consisting of 24 studies with 677 patients with schizophrenia, reported that the left hippocampus was reduced by 7% and the right by 6% compared to controls.

However, not all studies have found hippocampus volume differences, e.g. a study by Csernansky et al. (2002) suggests that there may not be significant volume reductions in schizophrenia after controlling for the effects on hippocampal volume of variation in total cerebral volume. Additionally, the recent VBM study by Meda et al. (2008) did not support hippocampal volume reduction in schizophrenia, either. Further, while the findings in chronic schizophrenia are supported in the large cross-sectional study by Velakoulis et al. (2006), this study found that such reduction was not apparent at the earliest stages of illness, suggestive of progression with increased illness duration.

Post-mortem studies have also reported inconsistent findings. Bogerts et al. (1985) reported reduction of hippocampal volume in an early postmortem investigation, but more recent neuropathological studies have not suggested significant volume reduction or change in hippocampal cell size or number in schizophrenia (Heckers et al. 1990, Heckers et al. 1991, Walker et al. 2002, Highley et al. 2003).

Hippocampal shape has been proposed to be more sensitive to pathological change in schizophrenia than volume differences (Csernansky et al. 1998,
Csernansky et al. 2002). Recent studies have not shown consistent hippocampal shape differences; many studies suggest anterior hippocampal volume reductions or shape abnormalities (Csernansky et al. 1998, Lieberman et al. 2001, Pegues et al. 2003), though some suggest posterior (Narr et al. 2001), and some diffuse hippocampal volume reductions in schizophrenia patients (Weiss et al. 2005). It has also been suggested that there may be disturbances in the normal right–left asymmetry in schizophrenia (Fukuzako et al. 1997).

The question of amygdala volume reduction in schizophrenia has been even more inconsistent. Meta-analyses of MRI findings in schizophrenia (Wright et al. 2000, Shenton et al. 2001) suggest that there might be amygdala volume reductions. In the meta-analysis by Wright et al. (2000) seven studies with 146 patients with schizophrenia had investigated the amygdala. The amygdala volume was bilaterally reduced by 9%. Amygdala volume reductions have been reported even in first-episode never-medicated schizophrenia patients (Joyal et al. 2003). However, a post-mortem study by Chance et al. (2002) reported no significant reduction of the amygdala, which was also consistent with the imaging findings of Velakoulis et al. (2006).

2.3.4 Brain structure, duration of illness and onset of illness in schizophrenia

Whether structural brain abnormalities in schizophrenia are progressive in nature or not remains unclear. It is unknown whether the brain reductions develop over time or are progressive in terms of excessive decrease of brain matter particularly after the first years of onset. Jones et al. (1994a) did not find an association between ventricle dimensions and age at onset or duration of illness in schizophrenia. The meta-analysis of neuropathological studies (Harrison et al. 2003) did not find a correlation between brain volume loss and duration of illness.

However, some longitudinal studies suggest progressive changes in schizophrenia. The first evidence of possible progression was shown by Moore et al. (1935) in their PEG study of 6 subjects with schizophrenia with follow-up of 2–3.5 years. DeLisi et al. (1997) reported difference in the rate of change in the volumes of both hemispheres, right cerebellum and the isthmus of the corpus callosum in 50 patients with schizophrenia compared to 20 controls over a four-year period; additionally, the left cerebral ventricle had significantly greater enlargement. In the longitudinal study by Wood et al. (2000), a reduction in whole brain volume was found in first episode patients over a 2–4 year period. In a
study by Cahn et al. (2002) total brain volume (-1.2%) and grey matter volume of the cerebrum (-2.9%) decreased and lateral ventricle volume increased (7.7%) in patients with first episode schizophrenia during a one-year follow-up. Ho et al. (2003) found accelerated enlargement in cortical sulcal cerebrospinal fluid spaces, progressive reduction in frontal lobe white matter volume, and increase in frontal lobe cerebrospinal fluid volume in 73 recent-onset schizophrenia patients compared to 23 controls during a three-year period. In a longitudinal study over a five year interval, van Haren et al. (2007) found excessive decreases in grey matter density in patients in the left superior frontal area, left superior temporal gyrus, right caudate nucleus and right thalamus as compared to healthy individuals. Salisbury et al. (2007) reported progressive grey matter volume reduction in left hemisphere Heschl gyrus in a longitudinal study during 1.5 year period in patients with schizophrenia.

Increased duration of illness has been associated with reduced grey matter in fronto-temporal regions. Longer duration was associated with smaller right medial temporal volume, medial cerebellar and bilateral anterior cingulate grey matter volume and white matter volume in the right posterior limb of the internal capsule suggesting progressive tissue loss (Velakoulis et al. 2002). Hietala et al. 2003 reported that long total duration of illness was associated with reduced grey matter in the left temporal lobe and right posterior region and enlarged CSF space in the left temporal lobe. Premkumar et al. (2006) compared brain structure between patients with different duration of illness, and they found that chronic patients had smaller prefrontal cortical grey matter volumes, but larger premotor cortical and putamen volumes compared to first-episode patients and matched healthy controls. However, progressive brain volume changes are not consistent; for example Whitworth et al. (2005) did not demonstrate a difference in the rate of volume changes over time between patients with schizophrenia and healthy controls for any of the brain structures measured.

The recent meta-analysis by Hulshoff Pol & Kahn (2008) included eleven longitudinal MRI or CT studies with an average duration of illness of ten years and follow-up period between 1 and 10 years. Their findings suggest continuous progressive brain tissue decrease and lateral ventricle volume increase in chronically ill patients. The extent of progressive brain tissue decrease in patients (-0.5% per year) was twice that of healthy controls (-0.2% per year). Volume loss was most pronounced in the frontal and temporal grey matter areas.

In addition to these findings of progressive brain volume changes, some studies suggest that there are morphometric brain abnormalities at the first episode,
and even before the illness onset. In a population at risk of developing psychosis Pantelis et al. (2003) found that people who developed psychosis had less grey matter in the right medial temporal, lateral temporal and inferior frontal cortex and in the cingulate cortex bilaterally compared to people who did not develop psychosis. More recent studies in these populations have identified progressive changes in superior temporal gyrus (Takahashi et al. 2009a), insula (Takahashi et al. 2009b&c) and prefrontal regions (Sun et al. 2009a&b), beginning from before illness onset. White matter changes have also been identified in individuals who were at risk and later developed psychosis: longitudinal comparison of data revealed a reduction in white matter volume in the region of the left fronto-occipital fasciculus in (Walterfang et al. 2008).

Brain imaging studies of first episode patients are many and some studies suggest that volume changes occur especially in the frontal and temporal lobes and basal ganglia. Hippocampus reduction has been reported in first-episode patients (Velakoulis et al. 1999, Velakoulis et al. 2006, Vita et al. 2006), even though the volume changes have been less consistent in this patient group (Laakso et al. 2001). Regional grey matter reductions in the first episode patients compared to controls have been reported in the temporal lobe, superior temporal gyrus, middle temporal gyrus, anterior cingulate, insula, hippocampus, parahippocampal gyrus, amygdala, frontal lobe, medial frontal lobe, prefrontal cortex, postcentral gyrus, parietal cortices, posterior region, caudate nuclei, thalamus, cerebellum; less white matter volume has been reported in the internal capsule, fronto-occipital fasciculus and greater CSF volume in the right lateral ventricle (Job et al. 2002, Kubicki et al. 2002, Hietala et al. 2003, Whitford et al. 2005, Chua et al. 2007, Fornito et al. 2008, Fornito et al. 2009d).

Longitudinal MRI studies including in first episode patients have reported baseline grey matter deficits in the frontal, temporal and parietal cortices and cerebellum, and white matter deficits in the frontal and temporal lobes as well as volumetric increases in the white matter of the frontoparietal junction bilaterally (Farrow et al. 2005, Whitford et al. 2006, Whitford et al. 2007). These studies have reported additional excessive grey matter losses relative to controls over 2-3 year follow-up in the fronto-temporal regions, left anterior cingulate gyrus and parietal cortices, and excessive white matter loss in the middle and inferior temporal cortex.

Although there is considerable evidence of progressive morphometric brain changes in schizophrenia, there is some evidence that at least some of the schizophrenic brain abnormalities are developmental in nature and that there are developmental pathways in schizophrenia that differ from non-schizophrenic
subjects. Ridler et al. (2006) have reported in NFBC 1966 that the frontal cortico-cerebellar systems that correlate with adult executive function are anatomically related to systems associated with normal infant motor development. In schizophrenia this anatomical system is disrupted and may underlie both the early developmental and adult cognitive abnormalities in schizophrenia. They found that earlier motor development in infancy was correlated with superior executive function in non-psychotic subjects. Earlier motor development was also normally associated with increased grey matter density in the adult premotor cortex, striatum, and cerebellum and increased white matter density in the frontal and parietal lobes. Adult executive function was normally associated with increased grey matter density in a fronto-cerebellar system that partially overlapped, but was not identical to, the grey matter regions normally associated with infant motor development. People with schizophrenia had relatively delayed infant motor development and impaired adult executive function in adulthood, and they demonstrated no normative associations between fronto-cerebellar structure, infant motor development or executive function.

2.3.5 Putative aetiological factors of brain abnormalities in schizophrenia

In terms of the cause of the effects in brain structures, it has been suggested that genetic or perinatal factors may be aetiology important. Children of a parent diagnosed with schizophrenia have a ten-fold increased risk of developing the disorder (Hallmayer 2000). There is some evidence of genetic mediation of structural brain abnormalities in schizophrenia. Cannon et al. (1998) reported that patients with schizophrenia and their siblings exhibited significant reductions in cortical grey matter volume and significant increases in sulcal CSF volume compared to controls. Lawrie et al. (1999) reported that people at high risk of developing schizophrenia for genetic reasons had several structural brain abnormalities, e.g. volume reduction in the amygdala–hippocampal complex and thalamus, similar to those in patients with the disorder.

In their twin-study, van Erp et al. (2004) suggested that although hippocampal volume in healthy individuals is highly affected by genetic factors, it is subject to substantially greater modulation by environmental factors in patients with schizophrenia and their relatives. Honea et al. (2008) have studied regional grey matter changes in schizophrenia patients and their siblings, and they reported that the unaffected siblings tended to share grey matter decreases in the medial frontal, superior temporal and insular cortices similar to affected siblings suggesting
weak intermediate phenotype for schizophrenia, although the findings were not significant after correction for multiple comparisons.

However, the findings have been inconsistent and some other studies report negative findings (Staal et al. 2000). In a different kind of study setting, in schizophrenia patients with a familial predisposition to psychosis, Stefanis et al. (1999) did not find hippocampal volume reduction whereas Falkai et al. (2002) did.

Perinatal complications have been found to be associated with schizophrenia. Cannon et al. (2002a) in their meta-analysis revealed three groups of complications that were significantly associated with schizophrenia: complications of pregnancy, abnormal foetal growth and development and complications of delivery. Jones et al. (1998) reported in the NFBC 1966 that low birth weight (<2500g) and the combination of low birth weight and short gestation (<37 weeks) were more common among the subjects with schizophrenia, and 4.8% of survivors of severe perinatal brain damage later developed schizophrenia. Dalman et al. (2001) reported that signs of asphyxia at birth were strongly associated with risk of schizophrenia, while Rosso et al. (2000) reported hypoxia to be associated with early onset schizophrenia. Cannon et al. (2002b) suggest that structural brain abnormalities in patients with schizophrenia or schizoaffective disorder and siblings are associated with a history of foetal hypoxia. They reported that foetal hypoxia predicted reduced grey matter and increased CSF bilaterally throughout the cortex in patients and siblings, most strongly in the temporal lobe. Hypoxia also correlated with ventricular enlargement among patients.

### 2.3.6 Structural brain abnormalities in other psychoses

The diagnostic distinctions between schizophrenia and schizophreniform or schizoaffective disorder may be artificial, as some patients with the latter disorders may later fulfil the criteria for schizophrenia. Most imaging studies have exclusively addressed schizophrenia whereas some studies also include subjects with schizophreniform or schizoaffective disorder (Velakoulis et al. 1999, Hulshoff Pol et al. 2001, Lieberman et al. 2001, Cannon et al. 2002b, Takahashi et al. 2006); bipolar disorder has been studied less often (Brambilla et al. 2002, Farrow et al. 2005). Jones et al. (1994a) demonstrated significant linear trends in association between larger lateral and third ventricle volumes in both schizophrenia and schizoaffective disorder. Temporal lobe abnormalities in the posterior region of the fusiform gyrus, superior temporal gyrus, amygdala and hippocampus have been reported in the schizophrenia spectrum (Takahashi et al. 2006).
MRI findings in bipolar disorder have been more variable, with both volumetric increases and decreases being reported across several brain regions at different illness stages (Fornito et al. 2009c). A review by Brambilla et al. (2002) reported abnormalities in hippocampus and basal ganglia in unipolar depressive disorder, and in amygdala and cerebellum in bipolar disorder. Patients with bipolar disorder have been characterized by enlargement of lateral ventricles and whole brain and prefrontal lobe volume reduction (Arnone et al. 2009). Thus, there have been abnormalities in the same areas as in schizophrenia in other psychoses, but they are less robust. These findings are not consistent; Kubicki et al. (2002) did not find significant morphometric brain differences between patients with affective psychosis and controls. However, the differences are consistent with recent meta-analyses by Bora et al. (2010) and Ellison-Wright & Bullmore (2010).

2.3.7 Rationale for epidemiological MRI studies in schizophrenia

There has been considerable variability in the results of schizophrenia MRI studies. A number of factors may contribute to this variability, including differences in analysis methods, variability in the disorder itself, and also due to variations in sampling selection and recruitment biases concerning both patient and control samples (Smith & Iacono 1986, Honea et al. 2005). Most imaging studies have been drawn from non-random samples, which can constrain generalizability of findings (Jones et al. 1994a, Haapea et al. 2007). Many studies consist of chronic or hospitalized patients, with a disproportionate number of severe cases with long duration of illness and heavy antipsychotic drug exposure. Such patients may have more prominent cerebral abnormalities.

We also know from the CT scanning literature that many effects may, in fact, be driven more by choice of control subjects rather than cases (Smith & Iacono 1986), something that an epidemiological design can address. Population-based studies are more robust against recruitment biases than other research methodologies; thus, as Lawrie & Abukmeil (1998) and Glahn et al. (2008) have previously argued, there is a clear rationale for population-based neuroimaging studies in schizophrenia. As far as we are aware, only one previous population-based sample, a Helsinki birth cohort, has reported case-control structural brain results in schizophrenia (Cannon et al. 1998): patients with schizophrenia exhibited significant reductions in cortical grey matter especially in the frontal and temporal lobes, reduction in white matter and increase in sulcal and ventricular CSF. In light of this paucity of epidemiologically principled neuroimaging...
studies in schizophrenia, the first three papers contributing to this thesis examine differences in brain structure between schizophrenia patients and controls sampled in a population-based manner.

Additionally, 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, so that the association with schizophrenia is only seen 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 computerized tomography rather than the more precise volumes that are derived from MRI.

2.3.8 Summarising earlier research

Morphometric brain abnormalities have previously been extensively reported in schizophrenia. Enlargement of lateral and third ventricles and cortical sulci, and brain volume reductions especially in the temporal and frontal lobes have been the most common findings. Morphometric brain abnormalities have been found even in first-episode patients. However, there is a lack of epidemiologically principled population-based studies, that could confirm the generalizability of these findings. Furthermore, it remains to be confirmed if the structural brain abnormalities in schizophrenia are progressive or not.

2.4 Preterm and low birth weight subjects

2.4.1 Structural brain abnormalities

Premature infants are at risk of brain injury during the neonatal period, and these persons are liable to structural brain abnormalities during infancy, childhood and adolescence. Olsén et al. (1997) reported periventricular leukomalacia on MRI among 32% of children born prematurely (birth weight less than 1750g) at the age of eight years, and it was observed in all children with cerebral palsy. In the study by Cooke & Abernethy (1999), brain MRI scans were reported abnormal in 42%
among children born very low birth at the ages 15–17 years. The findings included periventricular leucomalacia, ventricular dilatation, thinning of corpus callosum and porencephaly.

In a volumetric brain analysis study of eight-year-old preterm children, Peterson et al. (2000) reported smaller regional brain volumes in sensorimotor, premotor, midtemporal, parieto-occipital and subgenual cortices, cerebellum, basal ganglia, amygdala, hippocampus and corpus callosum, and larger volumes in the occipital and temporal horns of ventricles. Kesler et al. (2004) found disproportionately enlarged parietal and frontal grey matter, occipital horn and ventricular body, as well as reduced temporal and subcortical grey matter volumes in preterm children compared to controls at the age of 7–11 years. Nosarti et al. (2002) reported reductions in the volumes of the whole brain, cortical grey matter and hippocampus, and enlargement of lateral ventricles.

In summary, children or adolescents who were born preterm or with low birth weight have been associated with various structural brain abnormalities, e.g. periventricular leucomalasia, ventricular enlargement and loss of whole brain volume, white matter, cortical grey matter, hippocampus, caudate nuclei, corpus callosum and cerebellum in follow-up MR scans (Olsén et al. 1997, Cooke & Abernethy 1999, Melhem et al. 2000, Peterson et al. 2000, Allin et al. 2001, Nosarti et al. 2002, Abernethy et al. 2004, Isaacs et al. 2004).

### 2.4.2 Education and cognitive capacity

Difficulties in educational and professional outcomes have been reported in children, adolescents or adults among subjects who were born preterm or with low birth weight. Rantakallio (1985) reported educational subnormality, including mental retardation or some other handicap more frequently in all the birth weight percentile classes lower than the median class. It was also more frequent among preterm than term infants. Strauss (2000) reported in a cohort of subjects born small for gestational age that in adulthood they had significant differences in academic achievement and professional attainment compared with adults who were born normal weight.

Anderson & Doyle (2004) found executive dysfunction in school-aged children who were born extremely low birth weight. In a study of extremely low birth weight subjects free of major impairments, Grunau et al. (2004) reported that the subjects showed lower cognitive scores (vocabulary, block design and digit symbol) and academic skills (reading and arithmetic) at 17 years of age. Hille et
al. (2007) investigated subjects born before 32 weeks of gestation and/or with a birth weight of less than 1500g at the age of 19 years; 13% of them had moderate or severe problems in cognitive or neurosensory functioning. Additionally, twice as many young adults were poorly educated, and three times as many were neither employed nor in school at age 19 years compared to general population.

Moreover, Richards et al. (2002) have suggested that birth weight is associated with cognitive function and education in adulthood even in the full birth weight range in the normal population: birth weight was positively associated with cognition up to age 26, and with the likelihood of obtaining advanced educational qualifications in the British 1946 birth cohort study.

Brain abnormalities of subjects born prematurely or low birth weight are linked to poor neurocognitive function, and can manifest as difficulties in educational and professional contexts. There are many studies of neurocognitive function and brain structure in childhood or adolescence among subjects born preterm or low birth weight.

Olsén et al. (1998) found that the visuospatial problems were associated with periventricular leucomalacia in eight-year-old children with birth weight less than 1750g. Stewart et al. (1999) reported reading, adjustment, neurological and behavioural problems and abnormalities of ventricles, corpus callosum and white matter in subjects born before 33 gestation weeks at 14–15 years of age. Peterson et al. (2000) reported that the volumes of sensorimotor and midtemporal cortices were associated with full-scale, verbal and performance IQ scores in the volumetric brain analysis of eight-year-old preterm children.

Allin et al. (2001) found reduced cerebellar volume to be associated with poorer cognitive test scores in adolescence among subjects born before 33 gestation weeks. Abernethy et al. (2004) found lower IQ to correlate with caudate nuclei volume in seven-year-old survivors of very preterm birth. Isaacs et al. (2000) found reduced hippocampal volumes and deficits in everyday memory and numeracy in adolescents born prematurely.

In summary, focal deficits in neurocognitive function in various areas have been shown in school-aged children or adolescents who were born very preterm or with extremely low birth weight (Olsén et al. 1998, Stewart et al. 1999, Peterson et al. 2000, Abernethy et al. 2004, Anderson & Doyle 2004, Isaacs et al. 2004, Grunau et al. 2004, O’Brien et al. 2004). It has been suggested that birth weight is associated with cognitive function and education in adulthood even in the full birth weight range in the normal population (Richards et al. 2002).
2.4.3 Long-term outcome of subjects born preterm or low birth weight

However, little is known about the long-term outcome in adulthood of subjects born prematurely. Olsén et al. (1994) have investigated further education after compulsory schooling at age 24 years in subjects born with low birth weight. They concluded that low birth weight subjects’ enrolment and graduation in upper secondary education was satisfactory, except for disabled low birth weight subjects.

Allin et al. (2004) have investigated brain structure in adults who were born very low birth weight. They found enlargement of lateral ventricles, increased grey-to-white matter ratio, and widespread changes in the distribution of grey and white matter, but no differences in whole brain, grey matter, white matter or total CSF volumes compared to controls. Similarly, Fearon et al. (2004) reported increased total ventricular volume and reduction in posterior corpus callosum volume in adult survivors of very low birth weight, but no differences in whole brain, grey matter or hippocampal volumes.

Spencer et al. (2008) examined the history of low birth weight or preterm birth and brain structure in a population with special educational needs at the age of 13-22 years. They found that there was a twofold increase in prevalence of a history of low birth weight or preterm birth within this group, and grey matter deficits were observed in temporal lobe and cerebellum persisting into adolescence within the sample.

2.4.4 “Moderate” to “late” preterm subjects


However, interest has recently arisen in the consequences of ‘moderate’ to ‘mild’ preterm birth, including births after 32 and before 37 gestational weeks, since these account for the majority of preterm births (70% of all preterm births). ‘Late’ preterm births, involving subjects with 34 to 36 weeks gestational age at birth, have increased neonatal morbidity, more medical problems than their peers
(Wang et al. 2004, Raju et al. 2006, Engle et al. 2007) and inferior academic performance at school age.

Kirkegaard et al. (2006) studied gestational age after 32 completed weeks and birth weight in relation to the child’s school performance at the age of 10 years. They found reading, spelling and arithmetic disabilities in subjects born with birth weight less than 3500g or before 38 gestational weeks, with children who weighed <2500 g having the highest risks. Chyi et al. (2008) compared school outcomes between 32-33 week moderate preterm, 34–36 week late preterm and full-term infants. Moderate preterm subjects had lower test scores and teacher evaluation and higher risk for special education. Moreover, late preterm subjects had lower reading and math scores. Pietz et al. (2004) found reduced test results in language and visuo-motor abilities in low risk low birth weight children at 7 years of age.

2.4.5 Summarising earlier research

Morphometric brain abnormalities and deficits in cognitive function have been reported in children and adolescents who were born preterm or low birth weight. However, knowledge of their long-term outcome in adulthood is scarce. Additionally, previous studies have focused on the survivors of very low birth weight or gestation weeks, although late preterm babies are the majority of all preterm births.
3 Aims of the study

The Northern Finland 1966 and 1986 Birth Cohort Studies are extensive epidemiological and longitudinal research programs, which aim to promote health and well-being of the population (http://kelo.oulu.fi/NFBC). The aim of this MRI study was to investigate structural brain abnormalities in two special groups (psychiatric and paediatric) from the NFBC 1966.

We investigated if morphometric brain abnormalities exist in a truly representative sample of patients with psychosis in an epidemiological, general population based birth cohort study. First, we determined the volume differences of total brain, grey matter, white matter and CSF between subjects with schizophrenia and non-psychotic controls. Second, we investigated regional grey matter, white matter and CSF differences between subjects with schizophrenia and controls, and the effect of duration of illness on brain structure within the group of patients with schizophrenia. Third, we investigated the volumes of hippocampus and amygdala in schizophrenia or other psychoses in relation to control subjects. Furthermore, in the first and third papers, we investigated the effects of risk factors for schizophrenia (family history of psychosis and perinatal risk) on brain structure.

Deviant intrauterine growth is a risk for schizophrenia. Therefore, we wanted to explore if it is a risk for other disadvantageous outcomes in this birth cohort sample. Earlier in the Northern Finland 1966 Birth Cohort, educational capacity at age of 14 and 24 years has been investigated in subjects born preterm or with low birth weight (Rantakallio 1985, Olsén et al. 1994). In the fourth paper, we have extended the follow-up of this cohort to age 33–35 and have further explored the effects of preterm birth or low birth weight on educational, occupational, and cognitive function and structural brain development as assessed by MRI.
4 Material and methods

4.1 Study population

4.1.1 The Northern Finland 1966 Birth Cohort

The Northern Finland 1966 Birth Cohort is an unselected, general population birth cohort ascertained during mid-pregnancy. The cohort is based upon 12,068 pregnant women and their 12,058 children, representing 96% of the live-born children in the Finnish provinces of Lapland and Oulu with an expected delivery date during 1966 (Rantakallio 1969). The great majority of the cohort members were white Caucasians (Rantakallio 1988). Data on biological, socioeconomic and health conditions, living habits and family characteristics of cohort members were collected prospectively from pregnancy. The present study is based on 10,934 individuals living in Finland at the age of 16 years who did not forbid the use of their data.

4.1.2 Ethical considerations

The overall study plan of the NFBC 1966 has been accepted by the Ethical Committee of the Northern Ostrobothnia Hospital District on February 27th 2003. The research plans have been accepted by the Ethical Committee of Oulu University, Faculty of Medicine for the 31-year follow-up of the NFBC 1966 study on June 7th 1996, and for the 34-year psychiatric follow-up on March 30th 1998. Data protection has been scrutinized by the Privacy Protection Agency, as well as by the principles of the Ministry of Health and Social Affairs in 1994, when the permission to have information on the study sample was obtained.

Informed consent was inquired from all the participants. The subjects who have denied the use of their data have been excluded from the study. In this thesis participants were compared with non-participants who had not signed the informed consent. According to the Personal Data Act (No. 523/1999), however, personal data may be processed for the purposes of scientific research on terms presented in Chapter 4.1.5 of this thesis.
4.1.3 Ascertaining and sampling of people with psychosis (I–III)

The Finnish Hospital Discharge Register (FHDR) was used to identify cohort members with psychosis. FHDR covers all mental and general hospitals, as well as beds in local health centres nationwide (Miettunen et al. in press). In the FHDR, psychiatric diagnoses were coded routinely between 1969 and 1986 using ICD-8 (International Classification of Diseases), between 1987 and 1995 using ICD-9, and since 1996 using ICD-10. 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 Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised (DSM-III-R) criteria (Isohanni et al. 1997, Moilanen et al. 2003).

A total of 146 patients (84 men) with a history of one or more known psychotic episodes were invited to the present study, including two cases not recorded in the FHDR by the end of 1997 (one was treated only as an outpatient and one had onset of illness after 1997). Subjects were invited by letter to participate in the study, and 92 patients (63%; 52 men) agreed to participate. After complete description of the study to the subjects, written informed consent was obtained.

The study was conducted in 1999–2001 when the participants were aged 33–35 years. Structured Diagnostic Interview for DSM-III-R (SCID, Spitzer et al. 1989) and anamnestic information including individual hospital case notes were the main diagnostic instruments. Three subjects did not fulfil the criteria of psychosis: two cases were subsequently excluded due to revised diagnoses of developmental disorder and one due to schizotypal personality disorder. Two cases were excluded after MRI scan due to gross structural lesions (hydrocephalus). Altogether, 87 participants (49 men) with a history of any psychosis were sampled, including 61 subjects (36 men) with a diagnosis of DSM-III-R schizophrenia. A more heterogeneous category of “other psychoses” consisted of 12 people (8 men) with bipolar disorder, 7 subjects (2 men) with schizoaffective disorder, 3 subjects (2 men) with schizophreniform psychosis and 4 subjects (1 man) with other forms of psychosis including delusional disorders. Three schizophrenia subjects were hospitalized at the time of scanning (there were missing data concerning hospitalization of 2 patients).

In our analyses, we used two diagnostic groups: (1) DSM-III-R schizophrenia (I–III); and (2) all psychoses (DSM-III-R schizophrenia and other psychoses pooled) (III).
4.1.4 Sampling of comparison subjects (I–IV)

The aim was to have two sex-matched control subjects for every patient with schizophrenia. The control subjects were randomly selected from the Cohort members living in the Oulu area; they had not had a psychotic episode according to FHDR by 1997. Altogether, 187 comparison subjects were invited and 104 (62 men) consented in writing to participate in the survey. The only exclusion criterion was a psychotic episode in the history. The control subjects formed a representative sample of the general population. As they were drawn randomly from the population, there were some cases of other, non-psychotic psychiatric disorders and somatic diseases.

4.1.5 Non-participants (I–III)

Of the 146 patients with a history of psychotic episode who were invited to the present study, 54 patients (37%) did not participate, and these subjects are called “non-participants”. In psychotic subjects, compared to participants (n=92), non-participants (n=54) were more often patients with schizophrenia, had more positive psychosis symptoms during their illness course and were more often on disability pension. The non-participants had been treated longer in psychiatric hospital (median 199 days) than participants (111 days). The onset of illness had occurred at the same age in non-participants (mean 23.7 years, standard deviation [±SD] 5.5 years) as in participants (23.4 years, SD 4.5 years). Married subjects participated more often than those who were not married. (Haapea et al. 2007)

In schizophrenia subjects, the age at onset did not differ between the participants (n=61; mean 23.3 years (SD 4.4 years)) and non-participants (n=40; mean 21.8 years (SD 4.1 years)) either. The hospital treatment periods of non-participants had been longer (median 378 days) compared to participants (167 days) (Haapea et al. 2007).

The control subjects were compared with the rest of the non-psychotic cohort members. There were no major demographic differences between participating and non-participating subsets among non-psychotic subjects. None of the control subjects had been treated in psychiatric hospital, whereas 3% of the rest of the non-psychotic cohort members had received psychiatric hospital treatment for non-psychotic disorders; however, the difference was not statistically significant (chi-square test, p=0.08).
4.1.6 Preterm and low birth weight subjects (IV)

Among the total of 10,934 NFBC 1966 members, there were 715 subjects who were born either before 37 gestation weeks (n=523; mean=34.6w, SD=1.7w; mean birth weight= 2776g, SD=642) and/or whose birth weight was under 2500g (n=366; mean=2159g, SD=303g; mean gestation age= 36.4 weeks, SD=3.2), and who had not had a psychotic episode by year 1999. 175 subjects were born preterm and low birth weight. There were 10,132 cohort members in the term (≥37 gestation weeks; mean=40.3w, SD=1.5w) and normal birth weight (≥2500 g; mean=3548g, SD=472g) control group.

Of this cohort of 10,934 persons, 187 subjects, selected randomly as control subjects for psychotic subjects from the Oulu region, were invited to participate in the psychiatric field study of the Northern Finland Birth Cohort 1966 conducted in 1999-2001. The cohort members were 33-35 years of age. 104 subjects agreed to participate, referred to as “the MRI subset”. Gender-stratifying was employed in order to match a patient arm of the psychiatric study; the only exclusion criterion for recruitment was a previous history of hospitalization for psychotic illness. We analysed gender, paternal social class, family type, smoking, marital status, educational level and unemployment periods between participants (n=104) and non-participants (n=83): there were no differences between the groups on any of these factors (Haapea 2010).

Among the MRI subset of 104 subjects there were nine subjects (6 men) who were born before 37 weeks gestation (n=7; mean=34.6w; SD=1.5w; mean birth weight=2871g, SD=499) or whose birth weight was under 2500g (n=3; mean=2267g; SD=202.1 g; mean gestation age=35.5 weeks, SD=3.5). One preterm subject was born with low birth weight. One low birth weight subject had no data on gestation age. The rest of the MRI subset (n=95; 56 men) were chosen as control subjects in this study; they were born term (n=89; mean=40.2w; SD=1.4w) and normal birth weight (n=95; mean=3650g; SD=470g). There were no data on gestational age of six control subjects.

In the MRI subset one preterm case had spastic hemiplegia and unspecified borderline mental retardation (birth weight 2050g; 33 gestation weeks) and one had a history of head trauma. One control subject had perinatal brain damage. Two control subjects had epilepsy and eight control subjects had a history of head trauma.

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4.2 Magnetic resonance imaging and image analysis

The subjects were scanned using a GE Signa MRI scanner (General Electric, Milwaukee, Wisconsin) operating at 1.5 Tesla in Oulu University Hospital. T1-weighted high-resolution three dimensional spoiled gradient echo (3D SPGR) images were acquired in the coronal plane covering the whole brain (slice thickness=1.5 mm; repetition time=35 ms; echo time=5 ms; flip angle=35). Dual-echo fast spin echo (T2- and proton density-weighted (PD)) images were acquired of the whole brain in the coronal plane (slice thickness=3 mm; repetition time=4000 ms; echo time=24 ms for proton density images and 96 ms for T2 images). All subjects were scanned on the same scanner using the same protocol.

Subjects who did not consent to imaging or had images of inadequate quality were excluded from the analysis: there were seven subjects with motion artefacts, and two subjects with inadequate segmentation. The images were inspected (blind to group status) by a neuroradiologist (Juhani Pyhtinen) in order to find any major structural abnormalities. The pathologic findings were as follows (n=12): five subjects with pathological white matter signal intensity, two arachnoid cysts, medial cortex dysplasia, signal intensity change in thalamus, lacuna infarct, hypothalamus lipoma and cerebellar hypoplasia. One subject was further excluded when major pathological white matter signal intensity (multiple sclerosis) was found.

4.2.1 Voxel based morphometry: Total and regional grey matter, white matter and CSF volumes and densities (I–IV)

Adequate MRI scans for VBM-analysis were obtained from 54 schizophrenia subjects, 25 subjects with other psychosis and 100 control subjects. Two analysis methods were used to measure total brain, grey matter, white matter and CSF volumes: Phantom (unpublished data), and BAMM (brain activation and morphological mapping; I–IV). Regional grey matter, white matter and CSF differences compared to controls were analysed with BAMM (II). Regional grey matter differences were also analysed with AAL (automated anatomical labelling; IV).
Brain tissue segmentation: Phantom (unpublished data)

The dual echo MRI data were processed with a semi-automated segmentation program (Phantom) developed at the University of Oulu, Department of Radiology. The program is based on Markov random field segmentation described by Held et al. (1997). The segmentation procedure was conducted by a single radiologist (Päivikki Tanskanen) unaware of the clinical or research diagnoses. The automated segmentation program first requires manually placed training points for grey and white matter, CSF, scalp, bone, paranasal sinuses and background. The program extracts the extracerebral tissue and creates a brain mask. After iteration the automated segmentation program divides the intracranial contents into grey matter, white matter and CSF. The whole brain was included in the measurements, i.e. the cerebrum, cerebellum, pons and the ventricles and cortical sulci. Total brain volume was calculated by summing up total grey and white matter volumes. Intracranial volume (ICV) was calculated by summing up total grey matter, white matter and CSF.

Test-retest rater reliability was established by repeating the measurements twice in 15 subjects by the same rater. The intraclass correlation coefficients were high: brain volume 0.99, grey matter 0.95, white matter 0.97 and CSF 0.94.

Brain tissue segmentation: BAMM (I–IV)

The dual echo 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. 1999a). Voxels representing extracerebral tissue were automatically identified and set to 0 using a linear scale-space set of features obtained from derivatives of the Gaussian kernel (Suckling et al. 1999b). Manual editing of the segmented images was necessary only to remove the brain stem below a line parallel to the base of cerebellum. The probability of each intracerebral voxel belonging to each of 4 possible tissue classes (grey matter, white matter, CSF, or dura/vasculature) was then estimated by a modified fuzzy clustering algorithm in the 2-dimensional feature space formed by the PD and T2 intensities (Suckling et al. 1999a). The coronal in-plane voxel size was 0.86 x 0.86 mm². Total brain, grey matter, white matter and CSF volumes in millilitres were calculated from segmented images in native space. Total brain volume was calculated by summing up total grey and white matter volumes. ICV was calculated by summing up total grey matter, white matter and CSF.
Tissue classification maps were resliced in the axial orientation and coregistered with a customized template image in standard stereotactic space (Talairach & Tournoux 1988) by using an affine transformation and trilinear interpolation implemented in FSL (FMRIB Software Library) software (Jenkinson & Smith 2001, Jenkinson et al. 2002, Lancaster et al. 2007). These procedures resulted in maps of the density of grey matter, white matter, and CSF at each voxel; density is here defined as the probability that a voxel represents tissue of a particular class (Bullmore et al. 1995, Suckling et al. 1999a).

Transformed images were spatially smoothed with a standard isotropic 4-mm full-width half-maximum kernel (Suckling et al. 1999a). Voxel-level statistic maps, representing group differences in density in grey matter, white matter or CSF maps, were tested for statistical significance by using a non-parametric permutation test on the mass or sum of suprathreshold voxel. For whole-brain maps, the size of each clusterwise test was set so that the expected number of false positive tests in each map was <1: for grey and white matter maps, clusterwise equivalent p < 0.003. In order to define the cluster mass statistics t tests were performed at each voxel and measured against the null distribution, calculated from permutations of the original data set, and thresholded at p < 0.05 to form spatially contiguous clusters of suprathreshold voxels. For all observed and permuted effect maps, the sum of suprathreshold voxel statistics was calculated for each 3D spatial cluster. Critical values for these cluster mass statistics were defined by the 2.5 and 97.5 percentile values of the null distribution of cluster mass sampled from the permuted effect maps. Subthreshold clusters in the observed maps were discarded and suprathreshold clusters were retained as statistically significant (Bullmore et al. 1999).

Grey matter segmentation: AAL (IV)

The grey matter maps, segmented by using BAMM software, were resliced in the axial orientation and co-registered with the Montreal Neurological Institute (MNI) single subject high-resolution T1-weighted image (Montreal Neurological Institute; http://www.bic.mni.mcgill.ca) using an affine transformation and trilinear interpolation implemented in FSL software (Jenkinson & Smith 2001). The AAL regionally parcellated template image (Schmahmann et al. 1999, Tzourio-Mazoyer et al. 2002), also in the space of the MNI T1 image, was then used to estimate regional mean grey matter densities in each of the 116 cortical and subcortical volumes of interest for each participant. First, each hemisphere of cerebral grey
matter was divided into eight regions: pre/post-central, frontal, temporal, parietal, occipital, limbic, insular and subcortical grey matter regions. In addition each hemisphere was then divided into a further 45 grey matter regions resulting in a total of 90 grey matter areas in the cerebrum. Cerebellar grey matter was divided into 26 grey matter areas; the method of the anatomical distribution of cerebellum has been described by Schmahmann et al. (1999).

### 4.2.2 Region of interest analysis of hippocampus and amygdala (III, IV) and hippocampal shape (III)

Technically acceptable MRI data for the ROI analysis of hippocampus and amygdala were acquired from 82 patients with psychosis (56 patients with schizophrenia) and 104 comparison subjects.

The hippocampus and amygdala were measured manually from reformatted 3D SPGR-images by a single radiologist (Ulla Piippo), who was unaware of the clinical diagnosis. The images were realigned to correct for possible head tilt, and reformatted images in the coronal plane perpendicular to the axis of the hippocampus were created (with slice thickness 2.0 mm). The hippocampus and amygdala were delineated separately as described by Lehericy et al. (1994), and the number of voxels within each region of interest (ROI) was multiplied by the voxel dimensions to estimate regional volume in cm³.

The reliability (intraclass correlation coefficients) of these measurements was high: test-retest reliability was 0.99/0.99 for right/left hippocampus and 0.95/0.96 for right/left amygdala. Inter-rater reliability was 0.95/0.98 for right/left hippocampus and 0.86/0.87 for right/left amygdala.

Hippocampal shape was evaluated by estimating the cross-sectional area of the hippocampus in each 2D slice in which it was visible (Cook 1994, Laakso et al. 2001). The hippocampal percentages for the shape analysis were estimated from data of all measured slices. A weighted mean of areas of two consecutive slices was calculated to correspond to each 5% percentile.
4.3 Epidemiological data

4.3.1 Comorbid disorders and drug use (I–III)

Fourteen (17%) patients with psychosis and three (3%) comparison subjects had a history of alcohol abuse or dependence. Four (5%) patients and one (1%) comparison subject had had a developmental disorder. According to the FHDR, four (5%) patients and three (3%) comparison subjects had a history of cerebral concussion, and one (1%) comparison subject had had a cerebral contusion. Three (4%) patients and two (2%) comparison subjects had a diagnosis of epilepsy. Seven patients (four men) and eight comparison subjects (four men) were left-handed.

Fifty-seven (70%) patients with psychosis had used psychotropic medication (in most cases antipsychotic drugs) for longer than one year. During the 3-month period prior to scanning, 20 subjects with schizophrenia were taking atypical antipsychotic medication and 26 subjects typical antipsychotic medication. Seven of them had taken both atypical and typical medication. Fourteen subjects had not taken any antipsychotic medication (there were missing data concerning the medication status of one patient with schizophrenia). Three (3%) control subjects had used antidepressants for longer than one year.

An analysis of urine drug screen was performed on all subjects at the time of scanning. One subject with schizophrenia tested positive for methadone and one for opiates. Two control subjects tested positive for opiates. No patients or controls tested positive for cannabis, cocaine or amphetamine.

4.3.2 Assessment of putative aetiological factors (I–III)

The summary statistics on demographic and clinical characteristics and putative aetiological factors in subjects with adequate MRI are presented in Table 2. We used the Family Interview for Genetic Studies (FIGS; Maxwell, 1992) to investigate family history of psychosis, and divided subjects into those having a positive family history and those not having such history.

Perinatal risk is related to the development of schizophrenia in this sample (Jones et al. 1998) and was defined as one or more of the following events: low birth weight (<2500 g), short gestation (<37 weeks) or perinatal brain damage. Children were considered to have perinatal brain damage if they had 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 haemorrhage at discharge.
The onset of illness was ascertained from medical records and defined as the age when having the first evident psychotic symptoms (Räsänen et al. 1999). Mean age-at-onset of illness was 22.9 years (SD 4.2 years) in patients with schizophrenia and 23.7 years (SD 5.5 years) in all patients with psychosis. For purposes of later analysis, age at onset of illness was categorized: 20 years or less, and 21 years or more (I, III). Duration of illness was calculated in years by deducting the age at onset of illness from the age at the time of the MRI (II).

Table 2. (Table 1 in original publication III). Summary statistics on demographic and clinical characteristics in subjects with schizophrenia, other psychoses and controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Schizophrenia (N = 56)</th>
<th>All psychoses (N = 82)</th>
<th>Comparison group (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>M / F</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>58.9</td>
<td>19/14</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>41.1</td>
<td>12/11</td>
</tr>
<tr>
<td>Family history of psychosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>82.1</td>
<td>31/15</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>17.9</td>
<td>5/5</td>
</tr>
<tr>
<td>Perinatal risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>87.5</td>
<td>32/17</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>12.5</td>
<td>3/4</td>
</tr>
<tr>
<td>Handedness(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>50</td>
<td>89.3</td>
<td>37/13</td>
</tr>
<tr>
<td>Left</td>
<td>4</td>
<td>7.1</td>
<td>1/3</td>
</tr>
<tr>
<td>Age at onset of illness(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 years or less</td>
<td>20</td>
<td>35.7</td>
<td>11/9</td>
</tr>
<tr>
<td>21 years or more</td>
<td>33</td>
<td>58.9</td>
<td>20/13</td>
</tr>
</tbody>
</table>

\(^1\) One female and one male with schizophrenia with missing data.

\(^2\) Two females (one with schizophrenia) and three males (two with schizophrenia) with missing data within all psychoses group.
4.3.3 Educational and occupational data (IV)

In 1980, when children were 14 years of age, data on school performance were gathered using a questionnaire completed by the children and their parents. The categorical description of school level at age 14 was defined as 1) being at appropriate for age level or above, or 2) being below age-appropriate level or in special school. Information on children’s school marks (teacher ratings) was obtained from the national application register for upper secondary education until 16 years of age (Isohanni et al. 1998). School marks in Finland range from 4 to 10: 4 is rejected, 5–6 are poor, 7–8 satisfactory and 9–10 excellent marks.

Educational level reached by the end of 1997 was collected from Statistics Finland and was categorized into basic (9 years or less), secondary (10 to 12 years) and tertiary level (over 12 years) (Taanila et al. 2005, Haapea et al. 2008).

Occupational status was defined as “working” or “not working” for at least 50% of all days during year 2000 (Miettunen et al. 2007). Information was collected from the Central Pension Security Institute.

4.3.4 Cognitive function at age 33–35 (IV)

Cognitive tests were carried out in the entire MRI sample of 196 subjects (Murray et al. 2006). The cognitive tests of 104 non-psychotic subjects are analysed in this dissertation.

Executive Functions: categorization and categorization with working memory. The Abstraction, Inhibition and Working Memory task (AIM) is a computerized rule-abstraction/category-learning task that requires subjects to use information to group stimuli in a meaningful way, based on feedback received during the test (Glahn et al. 2000). Participants are shown five objects on the screen, two in the upper left corner, two in the upper right corner. A target object appears in the centre of the screen below the other stimuli. Subjects are required to group the target object with the left or right hand pair. In order to allow examination of category-learning performance with and without an explicit working memory component, in some trials all the objects are presented simultaneously, whilst in other trials there is a delay between the presentation of the target and other objects. Stimuli vary in color, being red, green or blue, and in shape, being modified circles, squares or triangles. The correct response for each trial is grouping on the most obvious, least complex set. Participants are given feedback for each trial.
Visuo-spatial working memory: In this computerized task 12 coloured balls (either red or blue in a 1:1 ratio, 3:1 ratio or 11:1 ratio) appear on the screen in a circular distribution. The balls disappear and a single white ball appears in the place of one of the twelve previous balls. Subjects are required to indicate whether the white ball replaced a red or a blue ball.

Visual Object Learning. The Visual Object Learning Test (VOLT) is a computerized test of visual object learning and memory (Glahn et al. 1997). Participants are shown a set of 10 visual objects - the learning set. In a forced choice paradigm, they are then required to recognize those stimuli within a group of 20 objects, 10 of which are distractors. There are 4 trials, each with novel distractors, and after each trial participants are shown the learning set. The dependent variable is the total number of correct responses in the four trials summed.

Verbal Learning. The California Verbal Learning Test (CVLT) is an auditory verbal memory test using a 16-item shopping list (the learning set) that is read to the subject five times (Delis 1983). After each trial subjects must repeat back as many items as they can remember. The dependent variable is the overall score, achieved by summing the results of the 5 trials.

4.4 Statistical analysis

4.4.1 Statistical methods in original publication I

First, mean volumes of ICV, whole brain, grey matter, white matter and CSF 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 for both 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 (20 years or less) and later age at onset of illness (21 years or more) 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.

4.4.2 Statistical methods in original publication II

The statistical analysis of processing brain images with Bamm is described above (4.2.1). The relationship between duration of illness and total brain, grey matter, white matter and CSF volumes in patients was analysed using correlation analysis. Furthermore, having established areas where brain structure differed in patients with schizophrenia and controls in this data set, we investigated the correlation between tissue density in those regions and the duration of illness.

4.4.3 Statistical methods in original publication III

Repeated-measures analysis of covariance (ANCOVA) models were used with right and left hippocampi or amygdala volumes as dependent variables, side (right or left) as a within-subject factor, gender and diagnosis as between-subject factors, and whole brain volume as a covariate. We assessed the significance of family history of psychosis, perinatal risk, handedness and age-at-onset of illness both one at a time and with all the putative mediators in the model.

Models were built separately within patient and comparison groups and for patient groups with the comparison group. The level of $p<0.05$ was considered statistically significant. The SPSS 11.5.1 was used to conduct analyses.

Hippocampus profiles were first analysed visually using profile plots. Anterior (45% of slices) and posterior (55% of slices) parts of the hippocampus were compared between patients with schizophrenia and the comparison subjects using repeated-measures ANCOVA.

4.4.4 Statistical methods in original publication IV

The data are presented separately for preterm subjects, low birth weight subjects and controls in the whole cohort. Because the MRI subset was small (9 cases), we combined the preterm and low birth weight subjects together for MRI and cognitive analyses.
Chi-square-tests were applied in the whole cohort and the MRI subset to assess the differences between preterm or low birth weight subjects and control subjects in gender, social class and family type at birth, school level at 16 years, and educational and occupational outcome in adulthood. Student’s t-tests were used to test group differences in the school marks of theoretical subjects and all subjects. Univariate and multivariate analyses were used to study the effects of preterm birth, low birth weight, gender and maternal education on educational level and employment of subjects. Maternal education was classified as low (0-4 years), intermediate (5-8 years) or high (9 years or more).

In the MRI subset, results of the cognitive tests were analysed using Mann-Whitney’s U-test because of skewed distributions. We applied a Bonferroni correction to the cognitive test analyses in order to address the problem of multiple comparisons. The mean differences in brain volumes (total brain, grey matter, white matter, grey/white matter ratio, CSF, hippocampus, amygdala and regional volume of interest measures of grey matter density) were compared between preterm or low birth weight and control subjects using Student’s t-test. SPSS version 15 was used to conduct the analyses. Effect Sizes were calculated by dividing the difference between mean scores of preterm and controls by the pooled standard deviation. Cohen’s $d$ values were used as a measure of effect size. Cohen (1992) describes $d$ values as small (0.2), as medium (0.5), and as large (0.8). Further analysis of each individual’s cognitive tests and brain structures was conducted using Z-score analysis with reference to the mean and standard deviation of the normal control grey matter densities. The Z-scores were defined from the squares of the test result in verbal learning, categorization and categorization with working memory because of skewed distributions.
5 Results

5.1 Schizophrenia and other psychoses

5.1.1 Total brain, grey matter, white matter and cerebrospinal fluid volumes (I–III)

Previously unpublished data have been added to this dissertation. The total brain, grey matter, white matter and CSF volume analysis was done with Phantom and BAMM. The results are converging with these two analysis methods: the mean brain volume was reduced by 26ml (Phantom)/31ml (BAMM); the mean grey matter volume was reduced by 14ml/15ml; the mean white matter volume was reduced by 12ml/16ml; and the mean CSF volume was increased by 21ml/12ml in subjects with schizophrenia compared to controls.

Mean volumes of whole brain, grey matter, white matter, CSF and ICV in subjects with schizophrenia, all psychoses and control subjects are shown in Table 3 (unpublished data). The distribution of CSF and whole brain volumes of each individual in the schizophrenia, all psychoses and control group are also presented graphically in Figure 1. The reduction in mean brain volume was not statistically significant in either schizophrenia (2.2%; p=0.190) or all psychoses (2.8%; p=0.058) compared to controls. The small brain volume reduction consisted of both grey (2.1%; p=0.166/2.3%; p=0.096) and white matter (2.2%; p=0.298/3.5%; p=0.065) deficits in both groups. The mean volume of CSF was significantly increased in subjects with schizophrenia (8.1%; p=0.008) and all psychoses (6.6%; p=0.014) compared to controls. The mean ICV did not differ between the groups.

The statistical analysis with tertiles of volumes (Tables 4 and 5; unpublished data) showed trends in the association between smaller brain, grey and white matter volumes and diagnosis of schizophrenia or psychosis; the subjects with psychosis were more often found in the middle or lowest tertile of brain volume, and more often in the lowest tertile of grey and white matter volumes (Figure 2). The odds ratio for the linear trend in grey and white matter became significant after adjustment for variation in intracranial volume. There was a significant linear trend in the association between increasing CSF volume and psychosis; the subjects with psychosis were more often found in the middle or highest tertile of CSF volume.
Table 3. (unpublished data). Mean volumes (±standard deviation) of brain, grey matter, white matter, CSF and ICV in subjects with schizophrenia, all psychoses and comparison subjects in relation to gender. Differences in volume (∆(%)) are calculated in both diagnostic groups contrasted to comparison group.

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>N</th>
<th>Brain</th>
<th>Grey matter</th>
<th>White matter</th>
<th>ICV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Volume</td>
<td>∆ (%)</td>
<td>Volume</td>
<td>∆ (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ml)</td>
<td>Sig.¹</td>
<td>(ml)</td>
<td>Sig.¹</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>54</td>
<td>1181±117</td>
<td>-2.2 0.190</td>
<td>647±60.5</td>
<td>-2.1 0.166</td>
</tr>
<tr>
<td>All psychoses</td>
<td>79</td>
<td>1173±124</td>
<td>-2.8 0.058</td>
<td>646±63.8</td>
<td>-2.3 0.096</td>
</tr>
<tr>
<td>Comparison group</td>
<td>100</td>
<td>1207±113</td>
<td>0.068</td>
<td>661±57.7</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>33</td>
<td>1238±105</td>
<td>-1.8 0.278</td>
<td>673±58.4</td>
<td>-1.8 0.284</td>
</tr>
<tr>
<td>All psychoses</td>
<td>46</td>
<td>1241±102</td>
<td>-1.6 0.305</td>
<td>679±57.2</td>
<td>-0.9 0.519</td>
</tr>
<tr>
<td>Comparison group</td>
<td>60</td>
<td>1261±96</td>
<td>0.147</td>
<td>685±49.3</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>21</td>
<td>1093±74</td>
<td>-2.9 0.142</td>
<td>607±37.4</td>
<td>-2.7 0.154</td>
</tr>
<tr>
<td>All psychoses</td>
<td>33</td>
<td>1078±83</td>
<td>-4.3 0.018</td>
<td>600±40.0</td>
<td>-3.9 0.025</td>
</tr>
<tr>
<td>Comparison group</td>
<td>40</td>
<td>1126±84</td>
<td>0.112</td>
<td>624±49.9</td>
<td></td>
</tr>
</tbody>
</table>

¹ Significance from the Student’s t-test.
The results did not change after adjusting the brain, grey matter, white matter and CSF tertiles for the covariates (gender, family history of psychosis, perinatal risk), i.e. the changes were independent of the effects of the covariates.

Fig. 1 The distribution of CSF and whole brain volumes of each individual in schizophrenia, all psychoses and control group (unpublished data). All psychoses = schizophrenia+other psychoses. Brain = grey+white matter. Dotted line = mean volume for control subjects
Table 4. Unadjusted odds ratios for tertiles of volumes in schizophrenia and odds ratios for linear trends, unadjusted and adjusted (unpublished data).

<table>
<thead>
<tr>
<th>Tertiles (Number of controls)</th>
<th>Brain</th>
<th>Grey matter</th>
<th>White matter</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
<td>Sig.¹</td>
<td>N</td>
</tr>
<tr>
<td>Lowest (33)</td>
<td>22</td>
<td>1.69</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Middle (34)</td>
<td>19</td>
<td>1.46</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Highest (33)</td>
<td>13</td>
<td>1.00</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Unadjusted OR for linear trend²</td>
<td>1.22 (0.81-1.84)</td>
<td>0.343</td>
<td>1.48 (0.98-2.23)</td>
<td>0.065</td>
</tr>
<tr>
<td>OR for linear trend adjusted for Intracranial volume²</td>
<td></td>
<td>2.58 (1.40-4.77)</td>
<td>0.002</td>
<td>1.93 (1.03-3.63)</td>
</tr>
<tr>
<td>Intracranial volume, gender, familial risk and obstetric risk²</td>
<td></td>
<td>2.84 (1.50-5.39)</td>
<td>0.001</td>
<td>2.10 (1.09-4.04)</td>
</tr>
<tr>
<td>Gender, familial risk and obstetric risk²</td>
<td></td>
<td></td>
<td></td>
<td>1.46 (0.86-2.50)</td>
</tr>
</tbody>
</table>

¹Significance of the OR for linear trend. ²Data are presented as OR (95% confidence interval).

Table 5. Unadjusted odds ratios for tertiles of volumes in all psychoses and odds ratios for linear trends, unadjusted and adjusted (unpublished data).

<table>
<thead>
<tr>
<th>Tertiles (Number of controls)</th>
<th>Brain</th>
<th>Grey matter</th>
<th>White matter</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
<td>Sig.¹</td>
<td>N</td>
</tr>
<tr>
<td>Lowest (33)</td>
<td>35</td>
<td>1.84</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>Middle (34)</td>
<td>25</td>
<td>1.32</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Highest (33)</td>
<td>19</td>
<td>1.00</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Unadjusted OR for linear trend²</td>
<td>1.16 (0.81-1.66)</td>
<td>0.415</td>
<td>1.39 (0.97-2.00)</td>
<td>0.071</td>
</tr>
<tr>
<td>OR for linear trend adjusted for Intracranial volume²</td>
<td></td>
<td>2.05 (1.20-3.51)</td>
<td>0.009</td>
<td>1.82 (1.05-3.16)</td>
</tr>
<tr>
<td>Intracranial volume, gender, familial risk and obstetric risk²</td>
<td></td>
<td>2.19 (1.25-3.81)</td>
<td>0.006</td>
<td>1.85 (1.06-3.25)</td>
</tr>
<tr>
<td>Gender, familial risk and obstetric risk²</td>
<td></td>
<td></td>
<td></td>
<td>1.24 (0.77-1.98)</td>
</tr>
</tbody>
</table>

¹Significance of the OR for linear trend. ²Data are presented as OR (95% confidence interval).
Brain tissue segmentation: Bamm (I)

Mean volumes of ICV, whole brain, grey matter, white matter and CSF in schizophrenia and control subjects, stratified for men and women and both unadjusted and adjusted for, are shown in Table 6. 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 thus more often statistically significant) for women than for men.

In analyses without controlling for ICV (Table 6), there were no significant between-group differences in whole-brain volume (-2.4%: schizophrenia 1266 ± 120 ml, controls 1297±117 ml [2-sample t test, df=152, t=1.55, p=0.123]), grey matter volume (-2.2%: schizophrenia 682±58 ml, controls 697±57 ml [t=1.50, p=0.136]), white matter volume (-2.7%: schizophrenia 584±67 ml, controls 600±66 ml [t=-1.46, p=0.146]) or CSF volume (+6.5%: schizophrenia 196±41 ml, controls 184±35 ml [t=-1.85, p=0.066]). After controlling for ICV, between-group differences in whole-brain volume (univariate analysis of variance, total df=153, F=8.20, p=0.005) and total CSF volume (F=8.20, p=0.005) were significant, and there were trends toward significant differences in total grey matter volume (F=3.44, p=0.066) and total white matter volume (F=3.10, p=0.080).

The statistical analysis with tertiles of volumes (Table 7) 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 volume.
Table 6. (Table 2 in original publication I). Intracranial (ICV), whole brain, grey matter, white matter and cerebrospinal fluid (CSF) volumes in subjects with schizophrenia and in control subjects in relation to gender. Differences in volume (∆ (%) are calculated in the schizophrenia group contrasted with the control group.

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>ICV</th>
<th>Whole brain</th>
<th>Grey matter</th>
<th>White matter</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Volume (ml)</td>
<td>Volume (ml)</td>
<td>Volume (ml)</td>
<td>Volume (ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>∆ (%)</td>
<td>∆ (%)</td>
<td>∆ (%)</td>
<td>∆ (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t Sig.¹</td>
<td>t Sig.¹</td>
<td>t Sig.¹</td>
<td>t Sig.¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Student's t-test</td>
<td>ANOVA</td>
<td>Student's t-test</td>
<td>ANOVA</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ</td>
<td>54</td>
<td>1462±136</td>
<td>-1.3</td>
<td>0.8</td>
<td>0.40</td>
</tr>
<tr>
<td>Controls</td>
<td>100</td>
<td>1481±135</td>
<td>1297±117</td>
<td>697±57.3</td>
<td>600±65.6</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ</td>
<td>31</td>
<td>1534±125</td>
<td>-1.0</td>
<td>0.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Controls</td>
<td>60</td>
<td>1550±114</td>
<td>1351±101</td>
<td>722±49.7</td>
<td>629±59.7</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ</td>
<td>23</td>
<td>1365±79</td>
<td>-0.9</td>
<td>0.5</td>
<td>0.59</td>
</tr>
<tr>
<td>Controls</td>
<td>40</td>
<td>1378±91</td>
<td>1215±88</td>
<td>658±45.3</td>
<td>557±48.3</td>
</tr>
</tbody>
</table>

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 7. (Table 3 in original publication). Unadjusted odds ratios for tertiles of volumes in schizophrenia and odds ratios with 95% confidence intervals for linear trends.

<table>
<thead>
<tr>
<th>Tertiles</th>
<th>Schizophrenia</th>
<th>Grey matter</th>
<th>White matter</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N OR Sig.</td>
<td>N OR Sig.</td>
<td>N OR Sig.</td>
<td>N OR Sig.</td>
</tr>
<tr>
<td>Lowest (33) N</td>
<td>24 2.18 1.00*</td>
<td>19 1.68 1.00*</td>
<td>11 1.00* 1.00*</td>
<td>18 1.00* 1.00*</td>
</tr>
<tr>
<td>Middle (34) N</td>
<td>27 2.25 1.00*</td>
<td>15 1.21 1.00*</td>
<td>12 1.00* 1.00*</td>
<td>24 1.33 1.00*</td>
</tr>
<tr>
<td>Highest (33) N</td>
<td>11 1.00* 1.00*</td>
<td>12 1.00* 1.00*</td>
<td>13 1.00* 1.00*</td>
<td>12 0.8-1.8 0.43</td>
</tr>
</tbody>
</table>

Unadjusted OR for linear trend: 1.5 (1.0-2.2) 0.08
Unadjusted OR for linear trend adjusted for Intracranial volume: 3.2 (1.2-8.6) 0.02
Unadjusted OR for linear trend adjusted for Intracranial volume, gender, familial risk and obstetric risk: 3.5 (1.3-9.7) 0.01

1 Significance of the OR for linear trend. Data are presented as OR (95% confidence interval). *Baseline odds.
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.

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).

### 5.1.2 Regional differences (II)

**Regional differences in grey matter: AAL (unpublished data)**

Previously unpublished data (AAL) have been added to this dissertation. Of the 90 grey matter regions of the cerebrum, there were decreased grey matter densities in seven gyri (Table 8): the left middle frontal gyrus, left insula and left lingual gyrus (*p*<0.01); the left inferior frontal gyrus opercular part, left calcarine fissure and surrounding cortex, right lingual gyrus and right superior temporal gyrus (*p*<0.05). Increased grey matter density was identified in the right posterior cingulate gyrus (*p*<0.01). Of the 26 regions of the cerebellum, decreased grey matter density was found in the right cerebellar lobule VIIB (*p*<0.05) and increased grey matter density in cerebellar vermis lobules IV and V (*p*<0.05).

The grey matter analysis was done with AAL and BAMM to confirm results found in more sensitive BAMM analysis. There were some similarities in the results of these methods. There were several areas with decreased grey matter density in both analysis methods: the left middle and inferior frontal gyrus, left insula, right superior temporal gyrus and bilateral lingual gyri were implicated by both levels of analysis.
### Table 8. Between group differences in parcellated grey matter volume (unpublished data).

<table>
<thead>
<tr>
<th>Anatomical description</th>
<th>Controls n=100</th>
<th>Schizophrenia n=54</th>
<th>95% confidence interval of the difference</th>
<th>2-tailed</th>
<th>df</th>
<th>Sig.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>t</td>
<td>df</td>
<td>Sig. (2-tailed)</td>
<td>Mean difference</td>
<td>Lower</td>
</tr>
<tr>
<td>Middle frontal gyrus, left</td>
<td>17.01</td>
<td>0.98</td>
<td>16.42</td>
<td>1.40</td>
<td>3.045</td>
<td>0.003</td>
<td>0.59</td>
<td>0.21</td>
</tr>
<tr>
<td>Inferior frontal gyrus, opercular part, left</td>
<td>3.40</td>
<td>0.28</td>
<td>3.29</td>
<td>0.31</td>
<td>2.233</td>
<td>0.027</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Insula, left</td>
<td>8.82</td>
<td>0.47</td>
<td>8.52</td>
<td>0.67</td>
<td>3.316</td>
<td>0.001</td>
<td>0.31</td>
<td>0.12</td>
</tr>
<tr>
<td>Posterior cingulate gyrus, right</td>
<td>0.94</td>
<td>0.14</td>
<td>1.01</td>
<td>0.16</td>
<td>-2.637</td>
<td>0.009</td>
<td>-0.06</td>
<td>-0.11</td>
</tr>
<tr>
<td>Calcarine fissure &amp; surrounding cortex, left</td>
<td>8.34</td>
<td>0.65</td>
<td>8.07</td>
<td>0.66</td>
<td>2.515</td>
<td>0.013</td>
<td>0.28</td>
<td>0.06</td>
</tr>
<tr>
<td>Lingual gyrus, left</td>
<td>8.05</td>
<td>0.47</td>
<td>7.82</td>
<td>0.54</td>
<td>2.784</td>
<td>0.006</td>
<td>0.23</td>
<td>0.07</td>
</tr>
<tr>
<td>Lingual gyrus, right</td>
<td>7.59</td>
<td>0.49</td>
<td>7.41</td>
<td>0.46</td>
<td>2.212</td>
<td>0.028</td>
<td>0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Superior temporal gyrus, right</td>
<td>11.90</td>
<td>0.69</td>
<td>11.60</td>
<td>0.79</td>
<td>2.429</td>
<td>0.016</td>
<td>0.30</td>
<td>0.06</td>
</tr>
<tr>
<td>Cerebellar VIIB, right</td>
<td>1.94</td>
<td>0.34</td>
<td>1.80</td>
<td>0.35</td>
<td>2.426</td>
<td>0.016</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td>Vermis IV,V</td>
<td>2.49</td>
<td>0.21</td>
<td>2.57</td>
<td>0.26</td>
<td>-2.041</td>
<td>0.043</td>
<td>-0.08</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

Comparison of parcellated 'Regions of Interest' between patients with schizophrenia and non-psychotic controls.

Regions listed represent a significant difference in grey matter density between patients with schizophrenia compared to healthy volunteers (p<0.05). Published with permission from K.Ridler.
**Regional differences in grey matter: BAMD (II)**

Significant grey matter density deficits were identified in patients with schizophrenia in 7 large clusters (Table 9). As several clusters span different regions, the results are also depicted graphically (Figure 3); purple and blue regions denote areas of grey matter deficit; red and yellow regions denote areas of grey matter excess in subjects with schizophrenia relative to the controls. The left side of each panel represents the right side of the brain; the z coordinate for each axial slice in the standard space of Talairach & Tournoux (1988) is given in millimetres. Clusterwise probability of type 1 error: \( p=0.003 \), at this size of test less than one false-positive test was expected over the whole map.

**Table 9. (Table 1 in original publication II). Co-ordinates of the centre of mass of the 7 clusters in which we detected deficits in schizophrenia relative to the control group.** The anatomical label of the centroid of each cluster is provided, along with Brodmann’s Area for cortical regions. Some of the clusters are very large, extending into many different regions (displayed in Figure 3, and described in the text). The maximum and minimum z-values of the clusters and size in number of voxels are listed in order to indicate the extent of the clusters.

<table>
<thead>
<tr>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Max Z</th>
<th>Min Z</th>
<th>Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>9</td>
<td>-45</td>
<td>-14</td>
<td>-8</td>
<td>-24</td>
<td>489</td>
</tr>
<tr>
<td>Left insula (BA 13)</td>
<td>-39</td>
<td>4</td>
<td>1</td>
<td>16</td>
<td>-24</td>
<td>884</td>
</tr>
<tr>
<td>Right precentral gyrus (BA 44)</td>
<td>44</td>
<td>9</td>
<td>7</td>
<td>35</td>
<td>-16</td>
<td>902</td>
</tr>
<tr>
<td>Thalamus</td>
<td>2</td>
<td>-13</td>
<td>2</td>
<td>20</td>
<td>-12</td>
<td>1065</td>
</tr>
<tr>
<td>Left middle frontal gyrus (BA10)</td>
<td>-32</td>
<td>51</td>
<td>11</td>
<td>35</td>
<td>4</td>
<td>446</td>
</tr>
<tr>
<td>Posterior cingulate gyrus (BA31)</td>
<td>-4</td>
<td>-63</td>
<td>14</td>
<td>35</td>
<td>4</td>
<td>440</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA45)</td>
<td>-46</td>
<td>16</td>
<td>21</td>
<td>35</td>
<td>4</td>
<td>248</td>
</tr>
</tbody>
</table>

Regional grey matter density deficits were found bilaterally in the cerebellum, brain stem, hypothalamus, thalamus, claustrum, middle frontal gyrus, inferior frontal gyrus, precentral gyrus, insula, superior temporal gyrus, fusiform gyrus, parahippocampal gyrus, cuneus, and lingual gyrus; in the left putamen, posterior cingulate, superior frontal gyrus, transverse temporal gyrus, precuneus, and in the right caudate and postcentral gyrus. Overall within these regions, grey matter density was reduced by 7% in subjects with schizophrenia (2-sample t test, \( t=7.990 \), \( df=152 \), \( p<0.001 \)).

Significant grey matter density excesses in subjects with schizophrenia (Figure 3) were found bilaterally in the caudate, anterior cingulate and medial orbitofrontal
cortex and in the left putamen and pallidus; density in these regions was increased by 10% (t=-7.385, df=152, p<0.00001).

Fig. 3 (Figure 1 in original publication II). Regional grey matter differences between subjects with schizophrenia and controls:
Grey matter deficits (purple/blue): bilaterally in the cerebellum, brain stem, hypothalamus, thalamus, claustrum, middle frontal gyrus, inferior frontal gyrus, precentral gyrus, insula, superior temporal gyrus, fusiform gyrus, parahippocampal gyrus, cuneus, and lingual gyrus; in the left putamen, superior frontal gyrus, posterior cingulate, transverse temporal gyrus, and precuneus; and in the right caudate and postcentral gyrus.
Grey matter excesses (red/yellow): bilaterally in the caudate, anterior cingulate and medial orbitofrontal cortex; and in the left putamen and pallidus.

Regional differences in white matter: BAMM (II)

Significant white matter density deficits were identified in subjects with schizophrenia (Figure 4) bilaterally in the cerebellum, brain stem, corpus callosum, capsula interna, corona radiata, centrum semiovale, subgyral frontal white matter, inferior frontal gyrus, medial frontal gyrus, middle frontal gyrus, cingulate, subgyral temporal white matter, superior temporal gyrus, parahippocampal gyrus and subgyral parietal white matter; in the left capsula externa and cuneus; and in the right middle temporal gyrus, transverse temporal gyrus, supramarginal gyrus and inferior parietal lobule. Density in these regions was decreased by 7% (t=8.297, df =152, p<0.00001).
Fig. 4 (Figure 2 in original publication II). Regional white matter differences between subjects with schizophrenia and controls:

White matter deficits (purple/blue): bilaterally in the cerebellum, brainstem, corpus callosum, capsula interna, corona radiata, centrum semiovale, subgyral frontal white matter, inferior frontal gyrus, medial frontal gyrus, middle frontal gyrus, cingulate, subgyral temporal white matter, superior temporal gyrus, parahippocampal gyrus, and subgyral parietal white matter; in the left capsula externa and cuneus; and in the right middle temporal gyrus, transverse temporal gyrus, supramarginal gyrus and inferior parietal lobule.

**Regional Differences in CSF: Bamm (II)**

Significant CSF density excesses were identified in patients with schizophrenia, relative to control subjects (Figure 5) bilaterally in the lateral ventricles, third ventricle, frontal interhemispheric fissure and left Sylvian fissure. These regions were increased by 13% \((t = -5.078, \text{df} = 152, p<0.00001)\). A small region of significant CSF deficit was identified in the quadrigeminal cistern. This region was decreased by 10% \((t = 2.566, \text{df} = 152, p<0.013)\).
Fig. 5 (Figure 3 in original publication II). Regional CSF differences between subjects with schizophrenia and controls:
CSF excesses (red/yellow): bilaterally in the frontal horns and bodies of lateral ventricles, atrium of the right lateral ventricle, third ventricle, frontal interhemispheric fissure and left Sylvian fissure.
CSF deficit (blue): in the quadrigeminal cistern.

Effect of duration of illness: BAMM (II)

Duration of illness was not correlated with total brain volume ($r=0.003$, $p=0.983$), grey matter ($r=-0.096$, $p=0.491$), white matter ($r=0.077$, $p=0.580$) or CSF ($r=0.151$, $p=0.276$) within the schizophrenia group. We also examined the association between duration of illness and tissue density in ROIs defined by case-control differences. Density in grey matter-deficit areas was significantly negatively correlated with duration of illness: thus, the longer the duration of illness, the less grey matter density there was in the deficit areas ($r=-0.473$, $p=0.001$, Figure 6a).

Duration of illness was also negatively correlated with bilateral white matter density deficits ($r=-0.284$, $p=0.038$, Figure 6b). Duration of illness was not correlated with grey matter density excess ($r=0.223$, $p=0.105$) or with CSF excess ($r=0.029$, $p=0.834$).
Fig. 6a (Figure 4a in original publication II). Association between duration of illness and grey matter deficits within the schizophrenia group. There was a significant correlation ($r=-0.473$, $p<0.001$) between the duration of illness and the density of deficit regions identified in the case-control comparison (see Figure 3).

Fig. 6b (Figure 4b in original publication II). Association between duration of illness and white matter deficits within the schizophrenia group. There was a significant correlation ($r=-0.284$, $p=0.038$) between the duration of illness and the density of deficit regions identified in the case-control comparison (see Figure 4).
5.1.3 Hippocampus and amygdala and shape of hippocampus (III)

Summary statistics on demographic and clinical characteristics of subjects with schizophrenia (n=56), any psychosis (n=82) and control subjects (n=104) are tabulated in Table 2. Participants in the psychotic and non-psychotic groups were well matched in terms of gender, handedness and perinatal risk. Family history of psychosis was more frequent in patients with psychosis (18% of both groups had a positive family history) than in comparison subjects (9%).

There was evidence for significant lateralization of hippocampal volume: right hippocampus was larger than the left in both diagnostic groups and in the comparison group. Hippocampal volume was greater in men than in women. There was also a main effect of diagnosis: hippocampal volume was slightly reduced in patients with schizophrenia (-2.1%), and any psychosis (-3.1%), compared to non-psychotic subjects. Whole brain volume was also reduced in patients with schizophrenia (-2.3%) and all psychoses (-2.5%) compared with non-psychotic participants (Table 10). The main effects on hippocampal volumes were attenuated by including whole brain volume as a covariate in the model, i.e. the whole brain volume reduction explained the small hippocampal reduction detected in the study (Table 11).

Within the patient groups, hippocampal volume was slightly (but not statistically significantly) larger in patients with a positive family history. There were no significant effects of perinatal risk or age-at-onset of illness (Table 11).

Profiles of hippocampal areas estimated in each slice over the entire length of the hippocampus bilaterally in patients with schizophrenia and comparison subjects are presented in Figure 7. There is slight volume reduction selectively in the anterior slices for patients with schizophrenia but this effect was not significant. The profiles were similar in the all psychoses group.

The main effect of side and gender on amygdala volume was similar to that seen in the hippocampus: right amygdala was significantly larger than the left in all groups, and men had a significantly larger amygdala than women (Table 12). Amygdala volume was not significantly reduced in patients with schizophrenia (0.9%) or in patients with any psychosis (1.3%) compared to controls. The main effect of gender was attenuated by including whole brain volume in the model. Amygdala volume was slightly (non-significantly) smaller among patients with psychosis with a positive family history. The effects of other putative risk factors were not significant (Table 11).
Table 10. (Table 2 in original publication III). Volumes of right and left hippocampus in subjects with schizophrenia, with all psychoses and in comparison subjects in relation to potential mediators. Differences in volume ($\Delta$, right and left pooled) are calculated in both diagnostic groups contrasted to comparison group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (N = 56)</th>
<th>All psychoses (N = 82)</th>
<th>Comparison group (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (mean±SD)</td>
<td>$\Delta$ $^\dagger$ (df = 1, 48)</td>
<td>Volume (mean±SD) $\Delta$ $^\dagger$ (df = 1, 70)</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>(%)</td>
</tr>
<tr>
<td>All</td>
<td>3.36±0.46</td>
<td>3.30±0.42</td>
<td>-2.1</td>
</tr>
<tr>
<td>Gender</td>
<td>3.40±0.50</td>
<td>3.36±0.43</td>
<td>-2.6</td>
</tr>
<tr>
<td>Family history of psychosis</td>
<td>3.3±0.41</td>
<td>3.24±0.39</td>
<td>-0.9</td>
</tr>
<tr>
<td>No</td>
<td>3.31±0.44</td>
<td>3.27±0.40</td>
<td>-3.1</td>
</tr>
<tr>
<td>Yes</td>
<td>3.59±0.50</td>
<td>3.48±0.46</td>
<td>1.0</td>
</tr>
<tr>
<td>Perinatal risk</td>
<td>3.35±0.48</td>
<td>3.29±0.43</td>
<td>-2.4</td>
</tr>
<tr>
<td>Handedness</td>
<td>3.43±0.35</td>
<td>3.41±0.34</td>
<td>-0.4</td>
</tr>
<tr>
<td>Left</td>
<td>3.40±0.45</td>
<td>3.33±0.42</td>
<td>-0.9</td>
</tr>
<tr>
<td>Right</td>
<td>3.18±0.50</td>
<td>3.16±0.45</td>
<td>-9.6</td>
</tr>
<tr>
<td>Age at onset of illness</td>
<td>1.4</td>
<td>0.25</td>
<td>1.4</td>
</tr>
<tr>
<td>20 y or less</td>
<td>3.23±0.49</td>
<td>3.19±0.44</td>
<td>-</td>
</tr>
<tr>
<td>21 y or more</td>
<td>3.42±0.41</td>
<td>3.36±0.35</td>
<td>-</td>
</tr>
<tr>
<td>Brain volume</td>
<td>1266±120</td>
<td>24.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^\dagger$ Repeated-measures ANCOVA with all the mediating factors in this table and brain volume forced into the models. Interactions were not significant.
(Side within schizophrenia F = 1.8, P = 0.18, within all psychoses F = 1.2, P = 0.29 and within comparison group F < 0.01, P = 0.97.)
Table 11. (Table 4 in original publication III). Selected output of repeated-measures ANCOVA for volumes of hippocampi and amygdalas. Separate models were built for subjects with schizophrenia and subjects with all psychoses together with comparison subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia and Comparison subjects</th>
<th>All psychoses and Comparison subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F  df  Sig.</td>
<td>F  df  Sig.</td>
</tr>
<tr>
<td>Hippocampus volumes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within effect: side a</td>
<td>20.3 1,160 &lt; 0.001</td>
<td>33.0 1,186 &lt; 0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>1.2 1 0.28</td>
<td>3.1 1 0.08</td>
</tr>
<tr>
<td>Gender</td>
<td>6.5 1 0.01</td>
<td>11.0 1 0.001</td>
</tr>
<tr>
<td>Within effect: side b</td>
<td>0.81 1,151 0.37</td>
<td>0.3 1,175 0.58</td>
</tr>
<tr>
<td>Covariate: total brain volume</td>
<td>35.0 1 &lt; 0.001</td>
<td>51.1 1 &lt; 0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>&lt; 0.01 1 0.89</td>
<td>0.6 1 0.43</td>
</tr>
<tr>
<td>Gender</td>
<td>0.7 1 0.41</td>
<td>1.0 1 0.32</td>
</tr>
<tr>
<td>Family history of psychosis</td>
<td>1.9 1 0.17</td>
<td>2.3 1 0.14</td>
</tr>
<tr>
<td>Perinatal risk</td>
<td>0.8 1 0.38</td>
<td>0.8 1 0.36</td>
</tr>
<tr>
<td>Handedness</td>
<td>0.3 1 0.61</td>
<td>0.2 1 0.70</td>
</tr>
<tr>
<td>Amygdala volumes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within effect: side a</td>
<td>26.8 1,160 &lt; 0.001</td>
<td>32.6 1,186 &lt; 0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.4 1 0.55</td>
<td>0.3 1 0.58</td>
</tr>
<tr>
<td>Gender</td>
<td>1.1 1 0.30</td>
<td>41.1 1 &lt; 0.001</td>
</tr>
<tr>
<td>Within effect: side b</td>
<td>0.2 1,151 0.63</td>
<td>2.1 1,175 0.15</td>
</tr>
<tr>
<td>Covariate: total brain volume</td>
<td>26.0 1 &lt; 0.001</td>
<td>34.9 1 &lt; 0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.3 1 0.61</td>
<td>0.4 1 0.56</td>
</tr>
<tr>
<td>Gender</td>
<td>3.6 1 0.06</td>
<td>4.1 1 0.05</td>
</tr>
<tr>
<td>Family history of psychosis</td>
<td>0.4 1 0.54</td>
<td>2.9 1 0.09</td>
</tr>
<tr>
<td>Perinatal risk</td>
<td>0.4 1 0.53</td>
<td>0.3 1 0.58</td>
</tr>
<tr>
<td>Handedness</td>
<td>3.4 1 0.07</td>
<td>3.9 1 0.05</td>
</tr>
</tbody>
</table>

1a N = 160: Diagnosis (Schizophrenia / Comparison) 56/104, Gender (M/F) 95/65.
1b N = 151: Diagnosis (Schizophrenia / Comparison) 51/100, Gender (M/F) 89/62,
Family history of psychosis (No/Yes) 132/19, Perinatal risk (No/Yes) 135/16, Handedness (R/L) 142/9.
2a N = 186: Diagnosis (All psychoses / Comparison) 82/104, Gender (M/F) 108/78.
2b N = 175: Diagnosis (All psychoses / Comparison) 75/100, Gender (M/F) 102/73,
Family history of psychosis (No/Yes) 151/24, Perinatal risk (No/Yes) 158/17, Handedness (R/L) 163/12.
N’s differ because of listwise handling of missing data.
Table 12. (Table 3 in original publication III). Volumes of right and left amygdala in subjects with schizophrenia, with all psychoses and in comparison group in relation to potential mediators. Differences in volume (Δ, right and left pooled) are calculated in both diagnostic groups contrasted to comparison group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (N = 56)</th>
<th>All psychoses (N = 82)</th>
<th>Comparison group (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right (mean±SD)</td>
<td>Δ (% F Sig.)</td>
<td>Right (mean±SD)</td>
</tr>
<tr>
<td>All</td>
<td>2.33±0.32</td>
<td>-0.9 0.5</td>
<td>2.32±0.35</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.43±0.34</td>
<td>-0.8 0.5</td>
<td>2.46±0.37</td>
</tr>
<tr>
<td>Female</td>
<td>2.18±0.20</td>
<td>-0.5 0.5</td>
<td>2.13±0.22</td>
</tr>
<tr>
<td>Family history of psychosis</td>
<td>0.2 0.64</td>
<td></td>
<td>3.5 0.07</td>
</tr>
<tr>
<td>No</td>
<td>2.32±0.34</td>
<td>-0.7 0.5</td>
<td>2.34±0.36</td>
</tr>
<tr>
<td>Yes</td>
<td>2.34±0.20</td>
<td>-2.2 0.5</td>
<td>2.20±0.29</td>
</tr>
<tr>
<td>Perinatal risk</td>
<td>0.2 0.70</td>
<td></td>
<td>0.3 0.57</td>
</tr>
<tr>
<td>No</td>
<td>2.33±0.33</td>
<td>-0.4 0.5</td>
<td>2.32±0.36</td>
</tr>
<tr>
<td>Yes</td>
<td>2.33±0.19</td>
<td>-2.3 0.5</td>
<td>2.30±0.20</td>
</tr>
<tr>
<td>Handedness</td>
<td>0.1 0.83</td>
<td></td>
<td>0.4 0.55</td>
</tr>
<tr>
<td>Left</td>
<td>2.34±0.30</td>
<td>0.2 0.5</td>
<td>2.33±0.34</td>
</tr>
<tr>
<td>Right</td>
<td>2.23±0.59</td>
<td>-10.0 0.5</td>
<td>2.25±0.47</td>
</tr>
<tr>
<td>Age at onset of illness</td>
<td>0.2 0.67</td>
<td></td>
<td>0.1 0.76</td>
</tr>
<tr>
<td>20 y or less</td>
<td>2.32±0.30</td>
<td>2.18±0.26</td>
<td>2.39±0.37</td>
</tr>
<tr>
<td>21 y or more</td>
<td>2.32±0.31</td>
<td>2.26±0.36</td>
<td>2.38±0.34</td>
</tr>
<tr>
<td>Brain volume</td>
<td>1266±120</td>
<td>8.2 0.007</td>
<td>1264±126</td>
</tr>
</tbody>
</table>

1 Repeated-measures ANCOVA with all the mediating factors in this table and brain volume forced into the models. Interactions were not significant. (Side within schizophrenia F = 0.1, P = 0.92, within all psychoses F = 0.5, P = 0.50 and within comparison group F = 1.2, P = 0.28.)
Fig. 7 (Figure 1 in original publication III). Profiles of right and left hippocampus within schizophrenia (N=56) and comparison subjects (N=104), genders pooled. Repeated-measures ANCOVA indicated that anterior and total volumes of hippocampi were alike, as were the effects of diagnosis, gender and side. Diagnosis, gender or side had no effect on posterior volume of hippocampus. Profiles of subjects with all psychoses and schizophrenia were alike.

5.2 Preterm and low birth weight subjects (IV)

5.2.1 Whole NFBC 1966 (n=10,847)

Children born preterm (8%) or low birth weight (13%) were below their age-appropriate level at school or were in special schools more often than controls (5%; Table 13). Their mean school marks (7.4–7.5) were slightly lower than controls’ (7.5–7.6) in theoretical subjects and in all subjects; however, the differences were small. The distributions of means of school marks did not differ between preterm or low birth weight subjects and controls, and all showed Gaussian distributions. The basic educational level in adulthood was also lower: preterm (81%) and low birth weight subjects (80%) had graduated from secondary or tertiary level of education less often than controls (85%). The low birth weight subjects (42%) were also more often unemployed than controls (31%); however, in the preterm group a similar effect was not found (34%).

We studied the effect of preterm birth, low birth weight, gender and maternal education on the educational level and employment of subjects. Significant effects
on educational level were found as follows: preterm birth, low birth weight, male gender and lower maternal education were associated with lower educational level in both univariate and multivariate analyses. The interaction between preterm birth and low maternal education was significantly associated with subject’s own educational level. If maternal education was low (<4 years) the subjects born preterm were more likely to have only basic education than if maternal education was intermediate or higher. The effect was similar for low birth weight subjects. Gender and low birth weight had significant effects on employment: males and subjects with normal birth weight were more often at work. Maternal education or preterm birth had no effect on employment (detailed data not shown).

5.2.2 MRI subset (n=104)

Our MRI subset was representative of the whole cohort in all fields but gender: men were overrepresented in the subset compared to the whole cohort; however, this applied both to preterm and low birth weight subjects (men/women 6/3) and controls (56/39) (Table 13). Significant mean differences in education or employment present in the whole cohort were not replicated within the subset.
<table>
<thead>
<tr>
<th>Variable</th>
<th>The whole cohort (n=10,847)</th>
<th></th>
<th></th>
<th>Subset with MRI and cognition –data (n=104)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (n=10132)</td>
<td>Preterm (n=524)</td>
<td>Low birth weight (n=366)</td>
<td>Controls (n=95)</td>
<td>Preterm or low birth weight (n=9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>P 1</td>
<td>N (%)</td>
<td>N (%)</td>
<td>P 1</td>
</tr>
<tr>
<td>Gender</td>
<td>Men</td>
<td>5203 (51)</td>
<td>265 (51)</td>
<td>159 (43)</td>
<td>56 (59)</td>
<td>6 (67)</td>
</tr>
<tr>
<td></td>
<td>At birth</td>
<td>0.75</td>
<td>0.003</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father’s social class</td>
<td>I</td>
<td>745 (7)</td>
<td>32 (6)</td>
<td>14 (4)</td>
<td>11 (12)</td>
<td>1 (14)</td>
</tr>
<tr>
<td></td>
<td>II-IV</td>
<td>7419 (73)</td>
<td>402 (77)</td>
<td>273 (75)</td>
<td>71 (75)</td>
<td>5 (71)</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>1937 (19)</td>
<td>87 (17)</td>
<td>75 (21)</td>
<td>13 (14)</td>
<td>1 (14)</td>
</tr>
<tr>
<td></td>
<td>Family type</td>
<td>0.001</td>
<td>0.003</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Full</td>
<td>8257 (82)</td>
<td>397 (76)</td>
<td>275 (75)</td>
<td>74 (78)</td>
<td>7 (78)</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>1875 (19)</td>
<td>127 (24)</td>
<td>91 (25)</td>
<td>21 (22)</td>
<td>2 (22)</td>
</tr>
<tr>
<td></td>
<td>At 16 years</td>
<td>0.011</td>
<td>&lt;0.001</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School level</td>
<td>Normal or upper</td>
<td>9593 (95)</td>
<td>482 (92)</td>
<td>317 (87)</td>
<td>94 (99)</td>
<td>8 (89)</td>
</tr>
<tr>
<td></td>
<td>Below normal or at special school</td>
<td>539 (5)</td>
<td>42 (8)</td>
<td>49 (13)</td>
<td>1 (1)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>School marks¹</td>
<td>Theoretical subjects</td>
<td>7.5 (0.96)</td>
<td>7.4 (0.92)</td>
<td>7.4 (0.93)</td>
<td>0.06³</td>
<td>7.7 (0.89)</td>
</tr>
<tr>
<td></td>
<td>All subjects</td>
<td>7.6 (0.96)</td>
<td>7.4 (0.92)</td>
<td>7.5 (0.94)</td>
<td>0.06³</td>
<td>7.7 (0.89)</td>
</tr>
<tr>
<td>In adulthood</td>
<td>Educational level</td>
<td>0.010</td>
<td>0.020</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basic</td>
<td>1529 (15)</td>
<td>101 (19)</td>
<td>72 (20)</td>
<td>4 (4)</td>
<td>1 (11)</td>
</tr>
<tr>
<td></td>
<td>Secondary or tertiary</td>
<td>8592 (85)</td>
<td>422 (81)</td>
<td>294 (80)</td>
<td>91 (96)</td>
<td>8 (89)</td>
</tr>
<tr>
<td></td>
<td>Employment</td>
<td>0.21</td>
<td>&lt;0.001</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at work in 2000</td>
<td>3172 (31)</td>
<td>178 (34)</td>
<td>154 (42)</td>
<td>23 (24)</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

¹ Significance from the \( \chi^2 \) test.

² School marks in Finland range from 4 (rejected) to 10 (excellent). Data are mean ± SD.

³ Significance from Student’s t-test.
Cognitive performance

Subjects born preterm or low birth weight (n=9) showed poorer performance in verbal learning (p=0.023; effect size -0.52). There were no significant between-group differences in categorization, visuo-spatial working memory or visual object learning: effect sizes ranged from small to medium (Table 14). We then applied a Bonferroni correction to the cognitive test analyses in order to address the problem of multiple comparisons. After a Bonferroni correction (compared to 0.01, i.e. significance level of 0.05 divided by 5) the difference in verbal learning was not significant.

Table 14. (Table 2 in original publication IV). Cognitive test scores in the preterm or low birth weight subjects and controls.

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>Preterm or low birth weight</th>
<th>Controls</th>
<th>Effect size</th>
<th>Sig.†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean ± SD</td>
<td>N  Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal learning</td>
<td>8  56 ± 3.8</td>
<td>89  60 ± 7.9</td>
<td>-0.52</td>
<td>0.023</td>
</tr>
<tr>
<td>Visual object learning</td>
<td>8  70 ± 4.6</td>
<td>94  68 ± 5.3</td>
<td>0.38</td>
<td>0.439</td>
</tr>
<tr>
<td>Category learning</td>
<td>9  23 ± 3.8</td>
<td>91  24 ± 2.6</td>
<td>-0.37</td>
<td>0.337</td>
</tr>
<tr>
<td>Category learning with working memory</td>
<td>9  23 ± 4.2</td>
<td>91  24 ± 3.4</td>
<td>-0.29</td>
<td>0.595</td>
</tr>
<tr>
<td>Working memory</td>
<td>9  82 ± 12.8</td>
<td>93  85 ± 6.0</td>
<td>-0.44</td>
<td>0.835</td>
</tr>
</tbody>
</table>

* Effect size: Cohen’s d, 0.2 is considered as small, 0.5 medium and 0.8 large effect
† Significance from the Mann-Whitney’s U-test.

Computational brain morphometry

There were no significant between-group differences in the mean volumes of the whole brain, grey matter, white matter, grey/white matter ratio or CSF in the preterm or low birth weight subjects compared to controls, and the effect sizes were small in all of these domains (Table 15). There were no significant differences in the mean grey matter density as measured with standard regions (Table 16) or in manually drawn regions of the hippocampus or amygdala (Table 15). Effect sizes were small in most regions.
Table 15. (Table 3 in original publication IV). Brain volumes in the preterm or low birth weight subjects and controls.

<table>
<thead>
<tr>
<th>Brain structure</th>
<th>Preterm or low birth weight</th>
<th>Controls</th>
<th>Effect size†</th>
<th>Sig.‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 9</td>
<td>n = 95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SD (ml)</td>
<td>Mean ± SD (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain*</td>
<td>1294 ± 98</td>
<td>1297 ± 119</td>
<td>-0.03</td>
<td>0.941</td>
</tr>
<tr>
<td>Grey matter*</td>
<td>696 ± 45</td>
<td>697 ± 59</td>
<td>-0.02</td>
<td>0.954</td>
</tr>
<tr>
<td>White matter*</td>
<td>599 ± 58</td>
<td>600 ± 67</td>
<td>-0.03</td>
<td>0.935</td>
</tr>
<tr>
<td>Grey/white matter*</td>
<td>1.17 ± 0.07</td>
<td>1.17 ± 0.08</td>
<td>0.00</td>
<td>0.976</td>
</tr>
<tr>
<td>CSF*</td>
<td>187 ± 53</td>
<td>184 ± 33</td>
<td>0.09</td>
<td>0.843</td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Number of controls = 91
‡ Effect size: Cohen’s d, 0.2 is considered as small, 0.5 medium and 0.8 large effect

Table 16. (Table 4 in original publication IV). Grey matter partial volume in the preterm or low birth weight subjects and controls.

<table>
<thead>
<tr>
<th>Brain structure</th>
<th>Preterm or low birth weight</th>
<th>Controls</th>
<th>Effect size†</th>
<th>Sig.‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 9</td>
<td>n = 92</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SD (ml)</td>
<td>Mean ± SD (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>26.06 ± 2.84</td>
<td>25.60 ± 1.63</td>
<td>0.26</td>
<td>0.459</td>
</tr>
<tr>
<td>Frontal</td>
<td>82.38 ± 4.72</td>
<td>82.27 ± 4.00</td>
<td>0.03</td>
<td>0.939</td>
</tr>
<tr>
<td>Temporal</td>
<td>45.90 ± 1.38</td>
<td>45.57 ± 1.91</td>
<td>0.18</td>
<td>0.617</td>
</tr>
<tr>
<td>Parietal</td>
<td>35.47 ± 2.66</td>
<td>35.41 ± 2.20</td>
<td>0.03</td>
<td>0.937</td>
</tr>
<tr>
<td>Occipital</td>
<td>41.69 ± 2.06</td>
<td>41.65 ± 2.44</td>
<td>0.02</td>
<td>0.959</td>
</tr>
<tr>
<td>Limbic</td>
<td>34.82 ± 1.76</td>
<td>34.90 ± 1.67</td>
<td>-0.05</td>
<td>0.888</td>
</tr>
<tr>
<td>Insula</td>
<td>8.19 ± 0.46</td>
<td>8.26 ± 0.47</td>
<td>-0.15</td>
<td>0.661</td>
</tr>
<tr>
<td>Subcortical grey nuclei</td>
<td>15.60 ± 1.38</td>
<td>15.84 ± 0.77</td>
<td>-0.29</td>
<td>0.421</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>24.82 ± 2.61</td>
<td>24.95 ± 1.65</td>
<td>-0.07</td>
<td>0.839</td>
</tr>
<tr>
<td>Frontal</td>
<td>82.47 ± 5.03</td>
<td>82.27 ± 3.89</td>
<td>0.05</td>
<td>0.882</td>
</tr>
<tr>
<td>Temporal</td>
<td>41.38 ± 2.24</td>
<td>41.63 ± 2.20</td>
<td>-0.11</td>
<td>0.747</td>
</tr>
<tr>
<td>Parietal</td>
<td>36.77 ± 2.57</td>
<td>36.63 ± 2.38</td>
<td>0.06</td>
<td>0.873</td>
</tr>
<tr>
<td>Occipital</td>
<td>51.07 ± 1.57</td>
<td>50.40 ± 2.76</td>
<td>0.25</td>
<td>0.476</td>
</tr>
<tr>
<td>Limbic</td>
<td>32.35 ± 1.43</td>
<td>32.69 ± 1.71</td>
<td>-0.20</td>
<td>0.563</td>
</tr>
<tr>
<td>Insula</td>
<td>8.66 ± 0.51</td>
<td>8.84 ± 0.46</td>
<td>-0.39</td>
<td>0.264</td>
</tr>
<tr>
<td>Subcortical grey nuclei</td>
<td>14.33 ± 1.39</td>
<td>14.86 ± 0.89</td>
<td>-0.56</td>
<td>0.110</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>99.64 ± 5.90</td>
<td>100.97 ± 7.54</td>
<td>-0.18</td>
<td>0.608</td>
</tr>
</tbody>
</table>

† Effect size: Cohen’s d, 0.2 is considered as small, 0.5 medium and 0.8 large effect
‡ Significance from Student’s t-test
The individual data of the MRI subset

The individual data on gender, gestation weeks, birth weight, MRI report and z-scores of cognitive tests, MRI domains and regional grey matter density measures in the preterm or low birth weight subjects are presented in Table 17 and 18. Only one subject showed a $Z < -2.5$ in bilateral pre/post central, left frontal and bilateral subcortical regions when compared to the whole control group means of the same regions. A minor abnormality was observed by the radiologist on visual inspection of the brain in this preterm subject (slightly widened cortical sulci in the frontoparietal region; the observation was confirmed by computational morphometry $Z > +2.5$ in CSF volume). However, the Z-score analysis of this subject’s cognitive testing scores revealed normal function, and attendance at a special school was not required.

Incidental MRI findings were reported in five control subjects (signal intensity change in thalamus, lacuna infarct, widened lateral ventricle and cortical sulci, hypothalamic lipoma and pathological white matter signal intensity change). Other pathological brain findings or signs of periventricular leucomalasia were not found in either group. The MR images of the case with spastic hemiplegia were reported as normal.
### Table 17. (Table 5 in original publication IV). Individual data on gender, gestation weeks, birth weight, MRI report and z-scores of MRI domains and cognitive tests in the preterm or low birth weight subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Gestation weeks</th>
<th>Birth weight (g)</th>
<th>MRI report</th>
<th>Right Brain</th>
<th>Left Brain</th>
<th>Grey matter</th>
<th>White matter</th>
<th>CSF Verbal learning</th>
<th>Visual object learning</th>
<th>Without working memory</th>
<th>With working memory</th>
<th>Working memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>female</td>
<td>-</td>
<td>2300</td>
<td>Normal</td>
<td>-0.03</td>
<td>-1.17</td>
<td>-0.30</td>
<td>-0.24</td>
<td>-0.33</td>
<td>-0.73</td>
<td>-1.57</td>
<td>-1.60</td>
<td>-1.59</td>
</tr>
<tr>
<td>2</td>
<td>male</td>
<td>33</td>
<td>2050</td>
<td>Variation</td>
<td>-1.79</td>
<td>-1.27</td>
<td>-1.30</td>
<td>-0.91</td>
<td>-1.53</td>
<td>-0.16</td>
<td>-</td>
<td>-1.79</td>
<td>-1.27</td>
</tr>
<tr>
<td>3</td>
<td>female</td>
<td>33</td>
<td>2550</td>
<td>Normal</td>
<td>+2.09</td>
<td>+1.91</td>
<td>-0.03</td>
<td>+0.19</td>
<td>-0.23</td>
<td>-0.70</td>
<td>-0.62</td>
<td>+0.68</td>
<td>+1.12</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>33</td>
<td>3270</td>
<td>Variation</td>
<td>+1.01</td>
<td>+1.93</td>
<td>+0.93</td>
<td>+0.80</td>
<td>+0.96</td>
<td>+0.20</td>
<td>-0.23</td>
<td>+0.11</td>
<td>+0.68</td>
</tr>
<tr>
<td>5</td>
<td>male</td>
<td>35</td>
<td>2800</td>
<td>Pathology</td>
<td>-0.56</td>
<td>-0.46</td>
<td>+1.04</td>
<td>+1.14</td>
<td>+0.84</td>
<td>+3.89</td>
<td>-0.62</td>
<td>-0.08</td>
<td>-1.25</td>
</tr>
<tr>
<td>6</td>
<td>male</td>
<td>36</td>
<td>2760</td>
<td>Variation</td>
<td>-0.62</td>
<td>-1.06</td>
<td>+0.56</td>
<td>+0.14</td>
<td>+0.87</td>
<td>+0.97</td>
<td>-0.49</td>
<td>+0.68</td>
<td>-0.14</td>
</tr>
<tr>
<td>7</td>
<td>female</td>
<td>36</td>
<td>3100</td>
<td>Variation</td>
<td>-1.05</td>
<td>-1.35</td>
<td>-0.99</td>
<td>-1.32</td>
<td>-0.62</td>
<td>-1.03</td>
<td>-0.62</td>
<td>+1.25</td>
<td>-0.14</td>
</tr>
<tr>
<td>8</td>
<td>male</td>
<td>36</td>
<td>3570</td>
<td>Variation</td>
<td>-0.27</td>
<td>-0.47</td>
<td>+0.41</td>
<td>+0.29</td>
<td>+0.48</td>
<td>+1.13</td>
<td>+0.04</td>
<td>+0.87</td>
<td>+0.68</td>
</tr>
<tr>
<td>9</td>
<td>male</td>
<td>38</td>
<td>2450</td>
<td>Variation</td>
<td>+2.56</td>
<td>+2.49</td>
<td>-0.52</td>
<td>-0.27</td>
<td>-0.69</td>
<td>-1.03</td>
<td>-0.87</td>
<td>+0.30</td>
<td>-0.53</td>
</tr>
</tbody>
</table>

### Table 18. (Table 5 in original publication IV). Individual data on gender, gestation weeks, birth weight, MRI report and z-scores of MRI domains and cognitive tests in the preterm or low birth weight subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Central Right</th>
<th>Frontal Right</th>
<th>Temporal Right</th>
<th>Occipital Right</th>
<th>Parietal Right</th>
<th>Limbic Right</th>
<th>Insula Right</th>
<th>Subcortical Right</th>
<th>Cerebellum Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.03</td>
<td>1.26</td>
<td>0.64</td>
<td>1.61</td>
<td>0.80</td>
<td>1.56</td>
<td>0.97</td>
<td>1.27</td>
<td>-0.46</td>
</tr>
<tr>
<td>2</td>
<td>2.63</td>
<td>1.69</td>
<td>2.04</td>
<td>1.32</td>
<td>-0.30</td>
<td>-0.25</td>
<td>0.53</td>
<td>0.86</td>
<td>1.09</td>
</tr>
<tr>
<td>3</td>
<td>1.80</td>
<td>0.39</td>
<td>0.87</td>
<td>0.47</td>
<td>1.19</td>
<td>0.85</td>
<td>1.42</td>
<td>0.79</td>
<td>1.24</td>
</tr>
<tr>
<td>4</td>
<td>-0.14</td>
<td>0.22</td>
<td>-0.62</td>
<td>-0.75</td>
<td>0.70</td>
<td>-0.69</td>
<td>0.54</td>
<td>0.00</td>
<td>-0.37</td>
</tr>
<tr>
<td>5</td>
<td>-3.24</td>
<td>-3.64</td>
<td>-2.13</td>
<td>-2.77</td>
<td>-0.34</td>
<td>-1.38</td>
<td>-2.29</td>
<td>-1.67</td>
<td>-0.95</td>
</tr>
<tr>
<td>6</td>
<td>-0.05</td>
<td>-0.69</td>
<td>-0.55</td>
<td>0.19</td>
<td>-0.69</td>
<td>-0.43</td>
<td>-0.61</td>
<td>-0.25</td>
<td>-1.02</td>
</tr>
<tr>
<td>7</td>
<td>0.92</td>
<td>0.21</td>
<td>-0.12</td>
<td>0.22</td>
<td>-0.45</td>
<td>-0.48</td>
<td>0.07</td>
<td>-0.09</td>
<td>-0.35</td>
</tr>
<tr>
<td>8</td>
<td>-1.30</td>
<td>-0.93</td>
<td>-0.49</td>
<td>-0.44</td>
<td>-0.32</td>
<td>-1.17</td>
<td>-1.34</td>
<td>-1.51</td>
<td>0.27</td>
</tr>
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6 Discussion

6.1 Schizophrenia and other psychoses (I–III)

6.1.1 Main findings

We have replicated previous results regarding structural brain abnormalities in schizophrenia, but extended the finding through the use of a general population sample of the same age. Whole brain, grey and white matter volumes were 2–3% smaller and CSF volume was 7% larger in the schizophrenia subjects compared to controls. Additionally, regional brain abnormalities were observed. In the frontal lobe, we observed bilateral grey matter deficits in the dorsal and lateral prefrontal cortex, and in the premotor and motor cortices (middle, inferior and superior frontal gyri and precentral gyri). There were grey matter deficits in the insula bilaterally and in the left posterior cingulate. In the temporal lobe, we noted some medial temporal lobe abnormalities (reductions in grey matter density in the parahippocampal gyrus bilaterally) and reductions in the superior temporal gyrus and fusiform gyrus bilaterally, and in the left transverse temporal gyrus. We also noted some deficits in the parietal (postcentral gyrus and precuneus) and occipital lobes (cuneus and lingual gyrus). There were reductions bilaterally in the cerebellum, thalamus and basal ganglia. Relative grey matter excesses were found bilaterally in the basal ganglia, medial orbitofrontal cortex and anterior cingulate cortex. There were white matter deficits in an extensive network including the inter- and intrahemispheric tracts in the frontal and temporal lobes and subcortical structures.

The whole brain volume reduction appeared to account for the non-significant reduction of hippocampal volume found in schizophrenia (2%) and all psychoses (3%) that disappeared after adjustment for whole brain volume. There were no significant differences in hippocampal shape or right-left asymmetry between subjects with psychosis and controls. In contrast to previous studies, we found no evidence for disproportionate reduction in hippocampus volume, and no evidence for disproportionate reduction in volume or abnormality of lateralization of the amygdala.

The effects concerning total brain, grey matter, white matter and CSF volumes were independent of the effect of gender, family history of psychosis, perinatal risk or the age at onset of illness. However, regional grey and white matter density differences, defined by case-control comparison, were negatively associated with duration of illness; longer duration of illness was thus associated with reduced grey and white matter density in deficit areas.
Within the psychotic groups, patients with family history of psychosis had slightly, but nonsignificantly larger hippocampal volumes than patients without family history. Perinatal risk or age at onset of illness had no effect on hippocampal volume. The putative mediating factors had no significant effects on amygdala volumes.

6.1.2 Comparison with earlier studies

Total brain, grey matter, white matter and CSF volumes (I)

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, Jones et al. 1994b), 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.

The brain volume reduction seen in our study was of similar magnitude to the meta-analysis on 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 compared to controls.

We used two statistical methods: means in Tables 3 and 6, which is rather robust and less sensitive, and the more sensitive and illustrative odds ratio analysis (Tables 4, 5 and 7), which is a standard method in epidemiological studies though less standard in imaging studies. The odds ratio analysis gave significant effects for whole brain and grey matter volume reductions. White matter reduction was not statistically significant in the odds ratio analysis based on BAMM measurements, but it was significant in the odds ratio analysis based on Phantom measurements. White matter reductions have been less robust than grey matter reductions in earlier quantitative MRI, and some studies suggest only grey matter reduction (Zipursky et al. 1992, Lawrie & Abukmeil 1998, Sullivan et al. 1998).

The CSF increase (7%) in our study was smaller than indicated by the 20–30% ventricular volume increase identified 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, as normal variation in head and ventricular size is quite large in the general population.

Regional grey and white matter volumes (II)

A meta-analysis of VBM studies by Honea et al. (2005) reported grey and white matter deficits in patients with schizophrenia relative to controls in a total of 50 brain regions; the most consistent findings were grey matter deficits in the left medial temporal lobe, superior temporal, parahippocampal, inferior and medial frontal gyri and in the right superior temporal gyrus.

Recent meta-analysis of VBM studies in schizophrenia by Ellison-Wright et al. (2008) and Fornito et al. (2009a) identified grey matter decreases in the frontal, temporal, thalamic, striatal, and thalamic regions, left uncus/amygdala, insula bilaterally, and anterior cingulate. Meda et al. (2008) reported significantly less grey matter concentration in multiple cortical and subcortical regions, some previously unreported in their recent large scale (n=400) multicentre study.

Morphometric brain abnormalities especially in the frontal and temporal lobes and basal ganglia have been observed even in first-episode patients (Job et al. 2002, Kubicki et al. 2002, Hietala et al. 2003, Whitford et al. 2005, Whitford et al. 2006, Chua et al. 2007).

We found grey matter deficits in several of these frontal and temporal regions. In the frontal lobe, we observed bilateral deficits in the dorsal and lateral prefrontal cortex and premotor cortex (middle and inferior frontal gyri, left superior frontal gyrus), and motor cortex (precentral gyri). There were grey matter deficits in the insula bilaterally. Our findings of reductions in frontal lobe gyri converge mostly with previous large VBM studies (Hulshoff Pol et al. 2001, Meda et al. 2008), a meta-analysis of ROI-based MRI studies (Shenton et al. 2001) and recent VBM meta-analyses (Honea et al. 2005, Ellison-Wright et al. 2008, Fornito et al. 2009a). Hulshoff Pol et al. (2001) found deficits in inferior, middle and superior frontal gyri, in addition to orbitofrontal deficits. Shenton et al. (2001) reported frontal reductions in 60% of the 50 reviewed MRI studies, and Honea et al. (2005) reported that 50% of studies found grey matter deficits in left inferior and medial frontal lobe gyri. Honea et al. (2005) also reported that 40% of the studies had found insular grey matter deficits, in line with our bilateral finding.

In the temporal lobe, we noted bilateral superior temporal gyrus reductions, which is in accordance with the meta-analyses by Honea et al. (2005) and Shenton et al. (2001). Additionally, we noted fusiform gyrus and left transverse temporal
gyrus reductions and some medial temporal lobe abnormalities. We observed grey matter reduction in one medial temporal lobe structure – the parahippocampal gyrus, where we found bilateral grey matter reduction, in accordance with previous studies (Wright et al. 2000, Shenton et al. 2001).

However, we did not find reductions in the hippocampus or amygdala in VBM analysis, although volume reductions in these regions have frequently been reported previously in ROI based studies (Nelson et al. 1998, Wright et al. 2000, Shenton et al. 2001). In our ROI study of the hippocampus the volume was reduced by 2%, but adjustment for total brain volume diminished the effect. In the ROI study we did not find amygdala volume changes, either. We suggest that this amounts to strong evidence against disproportionate reduction in hippocampal or amygdala volume among patients with psychosis. Contrary results in the literature may be due to lack of control for effects of whole brain volume or non-representative sampling of the population of patients with psychosis.

Even though many VBM studies and some meta-analyses have reported volume reductions in the hippocampus or amygdala (Wright et al. 1999, Hulshoff Pol et al. 2001, Job et al. 2002, Kubicki et al. 2002, Suzuki et al. 2002, Honea et al. 2005, Ellison-Wright et al. 2008) it is not a universally reported finding: for example one of the largest studies published to date, an international multi-centre study consisting of 200 patients with schizophrenia, did not find any hippocampal reductions (Meda et al. 2008). It is also possible that hippocampal reductions are only observed in severely affected patients at later illness stages, as suggested in studies by Velakoulis et al. (1999, 2006) of almost 500 subjects at different stages of psychosis and schizophrenia.

Surprisingly, besides the deficits in the prefrontal, premotor and motor cortices and posterior cingulate, we observed grey matter excesses in the medial orbitofrontal cortex and anterior cingulate, whereas many previous studies have found deficits in these regions (Honea et al. 2005, Baiano et al. 2007, Ellison-Wright et al. 2008, Fornito et al. 2009b). The interpretation of these results is challenging. One implication of this anatomical distinction is that these parts of the frontal cortex have rather different cognitive functions, the dorsal and lateral prefrontal cortex being strongly associated with executive, attentional and working memory function, while the orbitofrontal cortex plays a more critical role in affective decision making (Chudasama & Robbins 2006). Likewise, the anterior cingulate cortex has different functions according to anatomical subdivisions, with more rostral sections subtending emotional processing, and more caudal sections subserving attentional and cognitive control functions (Mohanty et al. 2007).
Our finding of subgenual anterior cingulate grey matter excess is not in direct discrepancy with the meta-analysis by Ellison-Wright et al. (2008) who reported deficits mostly in the pregenual and dorsal anterior cingulate. Additionally, anterior cingulate increases in schizophrenia are not entirely unprecedented, as at least two previous studies have reported similar findings, which have been interpreted as possibly stemming from medication effects (Kopelman et al. 2005, McCormick et al. 2005). Interestingly, albeit in non-psychotic population, greater regional grey matter volumes bilaterally in the ventral and dorsal anterior cingulate cortex were identified in subjects with intellectual disabilities in a special education group (IQ <70), (Mannerkoski et al. 2009), and intellectual disabilities are common in schizophrenia as well (Isohanni et al. 1998).

Finally, there is one more possible explanation for our anterior cingulate results; inter-individual variability in sulcal and gyral anatomy of this region has been shown in control populations as well as in schizophrenia patients (Paus et al. 1996, Yücel et al. 2002, Fornito et al. 2006). Our finding of grey matter density excess in the anterior cingulate may represent a true density difference or difference in shape, which may cause the apparent density differences in this sample.

In addition to the deficits in frontal and temporal cortices described above, we observed widespread grey matter deficits, which extended into the parietal lobe (postcentral gyri or sensory cortex and precuneus), the occipital lobe (cuneus and lingual gyri) and the cerebellum. Whilst parietal or occipital lobes have perhaps been somewhat neglected in schizophrenia research in comparison with studies focusing on frontal and temporal pathology, in fact 60% of the MRI studies of the parietal and 44% of studies of the occipital lobe have reported volume reductions (Shenton et al. 2001). Some of the more recent VBM studies and meta-analyses report volume reductions in parietal or occipital lobes (Gaser et al. 1999, Hulshoff Pol et al. 2001, Moorhead et al. 2004, Honea et al. 2005, Ellison-Wright et al. 2008, Meda et al. 2008).

Similarly, the cerebellum has rarely been a focus in schizophrenia studies, although there is ample evidence suggesting both that the cerebellum plays a critical role in higher cognitive function and that it is implicated in schizophrenia pathology (Schmahmann 1996, Andreasen 1999, Wassink et al. 1999, Ridler et al. 2006). Cerebellar volume reductions in schizophrenia have been reported by several studies (Gaser et al. 1999, Marcelis et al. 2003, Pantelis et al. 2003, Honea et al. 2005, Ellison-Wright et al. 2008), although cerebellar volume increase has also been reported (Wilke et al. 2001, Suzuki et al. 2002).
Most of the subcortical findings in our study are in agreement with previous studies. We observed bilateral thalamic volume reduction, which has also been reported in meta-analyses by Wright et al. (2000), Konick & Friedman (2001), Honea et al. (2005) and Ellison-Wright et al. (2008). In addition, we found grey matter excesses in parts of the basal ganglia (bilaterally in the caudate and left putamen) in accordance with meta-analyses by Shenton et al. (2001) and by Wright et al. (2000). It has been suggested that these basal ganglia excesses could be secondary to neuroleptic medication (Chakos et al. 1994, Chakos et al. 1998, Corson et al. 1999).

White matter reductions were bilateral and widespread in this study; deficits were observed in frontal, temporal, occipital and parietal lobes, cerebellum and brain stem. Some studies concentrate on grey matter findings e.g. seven studies included in the meta-analysis by Honea et al. (2005) had studied only grey matter whereas seven studies had explored both tissues, with only one study being restricted to white matter. Hence, the literature supporting white matter loss is not yet as strong as that documenting grey matter deficit (Lawrie & Abukmeil 1998, Wright et al. 2000). Our findings suggest that there are significant deficits in regional white matter tissue in schizophrenia, and thus white matter should not be overlooked in future morphometric studies. However, volumetric studies are not optimal for studying white matter changes, and nowadays the literature has moved towards studies based on DTI (Kubicki et al. 2007).

Hippocampus and amygdala (III)

Bogerts et al. (1985) reported reduction of hippocampal volume in an early post-mortem investigation, but more recent neuropathological studies have suggested no significant volume reduction, or change in hippocampal cell size or number in schizophrenia (Heckers et al. 1990, Heckers et al. 1991, Walker et al. 2002, Highley et al. 2003). This is similar to our current results. The non-significant volume reduction of hippocampus in schizophrenia (2%) and in all psychoses (3%) in the NFBC 1966 was less than in previous meta-analyses of imaging studies reporting significant volume reductions (Nelson et al. 1998, Wright et al. 2000, Shenton et al. 2001). This discrepancy may be explained by the preponderance of non-population-based samples in prior studies or some form of reporting bias.

In addition, inconsistent use of brain volume correction may affect the results: adjustment for total brain volume has not always been done in ROI-based studies. Some studies adjust hippocampal volume for patients’ height, head size or
intracranial volume or area (Nelson et al. 1998). The consistent finding of sulcal and ventricular enlargement in schizophrenia reflects lower brain tissue volume, either congenital or acquired, which cannot be defined by patients’ height, head size or intracranial contents. Hippocampal volume loss may thus merely reflect general brain tissue loss in psychotic patients, as our study suggests. A study by Csernansky et al. (2002) also suggests that there may not be significant volume reductions in schizophrenia after controlling for the effects on hippocampal volume of variation in total cerebral volume. Additionally, our sample may be slightly biased towards the less severe cases of psychosis with a consequent reduction in power to detect brain changes related to severity of illness. Finally, given the low use of drugs in our sample, long-term drug use may be another possible explanation for the hippocampal findings in other studies (Yücel et al. 2008).

We believe that there is no important, disproportionate difference in hippocampal volume between patients with psychosis and comparison subjects. However, it is possible that there may be more subtle differences in shape. Shape analysis is likely to be more sensitive for the study of the hippocampus than pure comparison of hippocampal volumes, and may be more informative for differentiating individuals with schizophrenia (Csernansky et al. 1998, Csernansky et al. 2002). The non-significant (3%) reduction in hippocampal volume found in our study in psychotic patients seemed on visual inspection to be located specifically in the anterior part of the hippocampus. Hippocampal volume is largest anteriorly, and the volume difference is thus most prominent there. However, anterior hippocampal volume differences did not reach statistical significance.

Recent studies have not shown consistent hippocampal shape differences; many studies suggest anterior hippocampal volume reductions or shape abnormalities (Csernansky et al. 1998, Lieberman et al. 2001, Pegues et al. 2003, Schobel et al. 2009), though some suggest posterior (Narr et al. 2001) and some diffuse hippocampal volume reductions in schizophrenia patients (Weiss et al. 2005).

It has also been suggested that there may be disturbances in the normal right-left asymmetry in schizophrenia (Fukuzako et al. 1997). Our study does not support this finding; the asymmetry in schizophrenia was similar to comparison subjects.

The question of amygdala volume reduction in schizophrenia has been even more inconsistent. Meta-analyses of MRI findings in schizophrenia (Wright et al. 2000, Shenton et al. 2001) suggest that there might be amygdala volume reductions, but a post-mortem study by Chance et al. (2002) reported no significant reduction of amygdala volume in schizophrenia. Our result is consistent with the absence of
post-mortem evidence for significant differences in the amygdala in patients with psychosis.

Effect of putative aetiological factors and duration of illness (I–III)

Total brain, grey matter, white matter and CSF volumes. 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, Cannon et al. 2002b). However, when we investigated the effects of putative factors and examine comparisons within the schizophrenia group, the number of subjects becomes smaller, which reduces the power of our study.

Age at onset of illness did not have an effect on total brain volumes in schizophrenia in our study. Early age at onset has been related to longer duration of illness in birth cohort studies. 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 the meta-analysis by Harrison et al. (2003) subjects were much older (mean age 61 years). 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.

Regional grey and white matter differences. However, our data suggest an effect of duration of illness on regional brain volumes, as the duration of illness correlated with the grey and white matter deficits in the areas identified in the case-control comparison. Increased duration of illness has previously been associated with reduced grey matter volumes in temporal or frontal cortices (Velakoulis et al. 2002, Hietala et al. 2003, Premkumar et al. 2006). Longitudinal studies have shown progressive total brain and grey matter volume loss, lateral ventricle enlargement, as well as progressive regional grey or white matter volume decreases and sulcal CSF enlargement in fronto-temporal regions (Cahn et al. 2002, Ho et al. 2003, DeLisi et al. 2004, Farrow et al. 2005, Whitford et al. 2006, van Haren et al. 2007, Hulsoff Pol et al. 2008), though negative results have also been reported (Whitworth et al. 2005).

However, there is another possible explanation for our results relating duration of illness to increased grey and white matter deficits. Given that all of our participants were the same age, duration of illness is inversely correlated with age at onset in this cohort, so that patients who had the longest duration of illness were also younger when they first became unwell. Thus, an important alternative interpretation of our findings is that patients with a younger age of onset are characterized by greater brain structural deficits. This could be interpreted as secondary to neurodevelopmental processes; namely that the putative pathological process which causes an early age of onset also causes more marked neuropathology in terms of abnormal grey and white matter density. However, it is also possible that earlier age at onset has a greater impact on regions that are continuing to develop and mature at this time, particularly frontal and temporal regions (Pantelis et al. 2005, Pantelis et al. 2009).

Finally, an additional reason contributing to the correlation of deficits with duration of illness could be the chronic effect of antipsychotic drugs, as preliminary evidence suggests that chronic exposure to haloperidol and olanzapine may decrease brain weight and volume in monkeys (Dorph-Petersen et al. 2005, Konopaske et al. 2007). Despite preliminary studies in humans (Lieberman et al. 2005), it remains unclear how antipsychotic drugs affect brain morphology in schizophrenia. The effect of drug treatment or severity of illness is not easy to disentangle in an observational study; this issue might be resolved by a randomized placebo-controlled treatment study, which could be unethical, however.

Hippocampus and amygdala. Our hypothesis that the hippocampal or amygdala volume loss would be most salient in patients with a family history of psychosis, perinatal risk or early age-at-onset of illness was not verified. Some familial studies suggest that unaffected people with a psychotic relative have structural brain differences, e.g. volume reduction in the amygdala-hippocampal complex (Lawrie et al. 1999) whereas others do not (Staal et al. 2000). Study designs similar to ours have not been used as often; Stefanis et al. (1999) did not find hippocampal volume reduction in patients with a familial predisposition to psychosis, whereas Falkai et
al. (2002) did. In the study of hippocampal volume in a group at risk for psychosis, those without a familial risk were more likely to have smaller hippocampi, which may suggest the influence of environmental factors (Wood et al. 2005).

Our finding does not suggest hippocampal volume reduction in psychotic patients with genetic liability. On the contrary, the hippocampus was slightly, but non-significantly larger in subjects with a family history of psychosis in our study (i.e. similar to the findings of Wood et al. 2005). The differences were small, as was the number of subjects within the patient group, which limits statistical power to detect group differences in hippocampus volume.

6.1.3 Strengths and limitations of the study

Epidemiological discussion

Strengths. Most of the earlier studies concerning structural brain differences in schizophrenia consist of non-randomly sampled subjects rather than epidemiologically valid designs. The generalizability of findings based on such epidemiologically unprincipled samples may be limited. Many studies have been conducted with chronic or hospitalized patients with a disproportionate number of severe cases with long duration of illness and heavy antipsychotic drug exposure. Such patients may have more prominent cerebral abnormalities. Previous studies have used mainly male patients, some have used hospital staff as comparison subjects, and the ethnic composition of the subjects or controls is reported by few investigators (Jones et al. 1994a, Lawrie & Abukmeil 1998). All these problems can lead to major bias in imaging studies, with Smith & Iancono (1986) demonstrating the vital importance of appropriate controls.

We consider that our study circumvents many of these problems. The major strength of the study is the epidemiologically representative general population sample. The subjects and controls have been drawn from a population-based birth cohort, i.e. all patients and comparison subjects are from the same geographic area, the same ethnic background and of approximately the same age, including a representative sample of women with psychosis (39%), a group often neglected (Lawrie & Abukmeil 1998). The sample of patients does not over-represent chronic or severe cases of psychosis.

The population-based nature of the research means that our study is less susceptible to sampling biases than most schizophrenia neuroimaging research. However, we studied the sampling process of our study population carefully.
(Haapea et al. 2007, Haapea et al. 2008). The controls are representative of the population from which the cases arise and are not “super-normal”, as previous evidence suggests that selection of “super-normal” control participants may have enormous influence on the results of neuroimaging studies (Smith & Iacono 1986). This is why our control participants from the Oulu region general population were selected truly at random (constrained only by gender stratification). The lifetime absence of a clinical diagnosis of any psychotic disorder in the non-psychotic group was confirmed, but as they were drawn truly randomly from the population, there were some cases of other, non-psychotic psychiatric disorders or somatic diseases (Haapea et al. 2007).

Large effect sizes from initial studies in a field often disappear in subsequent work with larger, more representative samples. The present study has these features and yet yields significant results. The epidemiological nature of the sample makes it more representative than most imaging studies, supporting generalization of the findings to the population of patients with schizophrenia.

Additionally, normal variation in head and brain size is considerable, affected both by gender and ethnic differences (Ho et al. 1980, Jones et al. 1994a). Brain volume decreases and CSF volume increases with 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). As age has previously been shown to be related to brain morphology (quite possibly differently in cases and controls) (Hulshoff Pol et al. 2002), the fact that all our subjects, being drawn from a birth cohort, are of the same age is an additional advantage, which eliminates the possibility of confounding by this factor. Additionally, we were able to exclude the effect of gender and ethnic differences because our subjects with schizophrenia and their controls were of the same ethnic background, and we had approximately two control subjects in both genders for each schizophrenia subject to strengthen the statistical power.

Illicit drug use is high in samples of schizophrenia in many countries (Barnett et al. 2007) and chronic use is known to affect brain structure (Schlaepfer et al. 2006). Patients with schizophrenia who continue to use cannabis after illness onset show larger increases in ventricular volume than schizophrenia patients who abstain from cannabis after illness onset (Rais et al. 2008). Further, recent work demonstrates the impact of cannabis use on other structures such as the hippocampus and amygdala in healthy subjects (Yücel et al. 2008). An advantage of our cohort, due to its location in Northern Finland and the time the study was conducted, is that very few patients were exposed to illicit drugs: on analysis of
urine drug screens performed on all subjects, none tested positive for cannabis, cocaine or amphetamine at the time of scanning.

**Limitations.** With a total of 186 participants (combined cases and controls), our sample is larger than most neuroimaging studies, which typically include fewer than 50 participants as noted by Meda *et al.* (2008), although it is considerably smaller than the very largest studies to date, such as those of Hulshoff Pol *et al.* (2001) (n=317) and Meda *et al.* (2008) (n=400). Additionally, our study is not large by general epidemiological standards; therefore the possibility of type 2 error remains. This seems most likely to be relevant considering of our non-significant results on the effects of several putative risk factors on brain volumes within the group of patients with psychosis. Rejection of the null hypothesis is not self-evident and large effects are probably worth considering even when results do not reach the threshold of statistical significance. In a population-based sample, a non-significant result does not prove the null hypothesis, but it may reflect either a small effect size or inadequate power (Kraemer *et al.* 2001)

Another limitation was the moderate non-participation in the psychosis group. Even though we were able to identify a total of 146 subjects with psychosis who were born in Northern Finland in 1966, our final sample of schizophrenia patients whose imaging data passed quality control standards consisted of 54 individuals. The rationale for inviting all cohort subjects with previously identified psychosis on national registers (as opposed to identifying all subjects with previously identified schizophrenia) was in order to capture individuals who had been previously misdiagnosed or who had recently converted and met criteria for schizophrenia. This approach was successful in identifying a number of additional cases of schizophrenia who would otherwise have been missed.

However, it is a limitation of our study that there were a number of schizophrenia patients who we were able to identify from the national records, but who did not agree to participate in the study or who could not be contacted. The clinical course of the participants was more advantageous than among the non-participants with psychosis (Haapea *et al.* 2007). Compared to participants, non-participants were more often patients with schizophrenia and had more psychiatric hospitalizations, they had more positive psychosis symptoms during their illness course and they were more often on disability pension. This suggests that among subjects with psychosis, particularly those who have the most severe course of illness are less willing to participate. This may lead to biased estimates when studying subjects with severe mental disorders. Our sample may, therefore, be slightly biased towards the less severe cases of psychosis with a consequent reduction in power to detect brain changes related to severity of illness.
A limitation in investigating the relationship of brain structure to illness duration is that in our study all patients were the same age, and in early middle age, typical of birth cohort studies (Welham et al. 2009). As age has been shown to be a predictor of brain abnormality in schizophrenia (Hulshoff Pol et al. 2002), this confers the advantage that age was not a confounder as regards the case-control analysis, but for the within-patients analysis it is a limitation, as there is a reciprocal relationship between illness duration and age at onset of illness. Thus, the longer the duration of illness, the earlier the age of onset; it was impossible to separate the two in this study. Moreover, the only way to truly study the course of brain structural changes in the illness is to perform repeated measurements of brain structure over time.

Technical considerations

Strengths in original publications I–II. Our study is the first VBM study of schizophrenia where cases and controls are sampled in a population-based manner. This study is the second case-control study of brain morphology in schizophrenia where all participants are drawn from a population-based birth cohort. To our knowledge, only one population-based birth cohort sample has previously reported structural brain abnormalities in schizophrenia, i.e. the study by Cannon et al. (1998). Their study was ROI-based, and most analyses from that sample have focused on genetics (sibling and twin studies) and foetal hypoxia (Cannon et al. 1998, Cannon et al. 2002b, van Erp et al. 2002, van Erp et al. 2004, Cannon et al. 2005).

When comparing the total brain, grey matter, white matter and CSF volumes measured by two different methods (Phantom and BAMM), the BAMM measures resulted in larger volumes of brain, grey matter and white matter and smaller volumes of CSF than Phantom. However, this is systematically the same in subjects with schizophrenia and controls, which is why the final results concerning both the percentage differences and the significances of the mean differences are similar. The interface between CSF and brain tissue is segmented differently by Phantom and BAMM: BAMM tends to classify the interface voxels more as grey or white matter, and Phantom as CSF. However, this does not alter the final results, and the findings of the volume differences can be considered to be confirmed by two analysis methods.

Comparing two computational morphometry methods (BAMM and AAL), there were more regions implicated by the more sensitive BAMM analysis at voxel level than by the regional analysis using AAL parcellation. There were several
areas of overlap, however: the left middle and inferior frontal gyrus, left insula, right superior temporal gyrus and bilateral lingual gyri were all implicated by both levels of analysis. The replication of the findings by two analysis methods makes them more robust. Additionally, there was no strong evidence for disproportionate reduction of hippocampus or amygdala in the ROI analysis in subjects with schizophrenia; this was confirmed by both computational morphometry analysis methods (BAMM and AAL).

An advantage of our methodology is that we employ permutation-based methods of statistical testing, which require less assumptions than parametric analyses, and also allow for the use of a smaller amount of smoothing of the original data (parametric statistics may often require greater smoothing to meet the assumptions of Gaussian random field theory) (Good et al. 2001). This is important as the amount of smoothing has been shown to be important in determining the results of morphological studies in schizophrenia research (Honea et al. 2005).

**Limitations in original publications I–II.** A technical limitation of our study relates to our scanning parameters. Although an advantage of our study is that all participants were scanned in the same magnet using the same software, a limitation is that we collected 3mm thick slices, which is less than optimal, and which could limit our sensitivity to detect small differences between groups.

**Strengths and limitations in original publication III.** Previous volumetric ROI measurements may contain systematic measurement errors that we aimed to avoid. Some studies measure the amygdala-hippocampal complex as one entity, because the boundary between the regions is difficult to define. This method can obscure subtle changes in either region. We measured the boundaries of the amygdala and hippocampus separately to avoid this. Slice thickness of more than 3 mm has been used in several earlier studies (Nelson et al. 1998). This can lead to greater variation in hippocampal volume than when using thin slices that are to be preferred (Cook, 1994). This is why we used thin slices (in original data 1.5 mm; reformatted images 2 mm).

It has been proposed that hippocampal shape analysis may be a more sensitive method in studying the hippocampus than pure comparison of hippocampal volumes. Csernansky et al. (1998) claimed that high dimensional assessment of hippocampal shape is far superior to the comparison of hippocampal volumes and it can be more informative for identifying individuals with schizophrenia. Two kinds of methods have been used in recent years. Two-dimensional shape analysis allows us to examine differences in volumes in anterior-posterior direction (Laakso et al. 2001, Velakoulis et al. 2001). Three-dimensional shape analysis makes it possible to
examine the hippocampus in lateral dimension as well (Csernansky et al. 1998, Csernansky et al. 2002) and it gives more precise information of hippocampal shape than two-dimensional studies. Three-dimensional studies require sophisticated technique and complicated software, whereas two-dimensional studies are easily performed with rather simple programming.

### 6.1.4 Theoretical discussion

*Brain development* starts antenatally and continues in childhood and adolescence, mainly stagewise (Epstein, 2001). There is lack of scientific brain-related etiological knowledge about schizophrenia even though it is essential in holistic understanding and modelling (Isohanni et al. 2009; Figure 8). This has hindered progress in identifying vulnerability genes and endophenotypes, clarifying etiopathophysiology and developing novel approaches to treatment.

Many of the mental illnesses begin in young adulthood, which is also when gender differences appear. Thus imaging studies at this age increase the knowledge of the neurobiology of the disorders. Volume differences in young subjects with schizophrenia or bipolar disorder, compared to controls, have been identified in the thalamus, nucleus accumbens, amygdala and hippocampus, possibly differently in boys and girls. (Kettunen et al. 2009)

There have been two theories about the aetiology of schizophrenia. The *neurodevelopmental theory* suggests that schizophrenia results from abnormalities in early brain development. The assumption is that normal brain development is disrupted in specific ways at critical periods resulting in the symptoms of schizophrenia, which occur in late adolescence or early adulthood.

The *neurodegenerative hypothesis* of schizophrenia, based on the evidence of morphometric brain abnormalities, suggests an ongoing neurodegenerative processes with loss of neuronal function during the course of the disease. Combined neurodevelopmental/neurodegenerative hypothesis suggest that schizophrenia may be a neurodegenerative process superimposed on a neurodevelopmental abnormality (Woods 1998).

Longitudinal studies support the hypothesis that the developmental trajectories in schizophrenia are partly different compared to controls. The NFBC 1966 study has been able to identify these developmental trajectories throughout lifespan. The subjects who later developed schizophrenia reached the early developmental motor skills (learning to stand and walk at age 1) later than subjects who did not develop the disease (Isohanni et al. 2001). Additionally, we have earlier identified structural and
Fig. 8. Descriptive life span and multilevel model of schizophrenic psychoses. Known aetiological and disease course components are presented. Hypothetical ideas on protective factors are not necessarily evidence-based. Modified from Isolainen et al. (2009). Original publications relevant to model are referred to by Roman numerals.

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**Maternal Psychological and Psychosocial Factors**
- Normal pregnancy and delivery
- Good parent-child relationship
- No drugs
- Low communication difficulties
- Aetiologic factors

**Somatic Changes in Excess Mortality**
- No disease
- Primary prevention
- Early detection and intervention
- Accurate diagnostics

**Psychiatric Treatment**
- Accurate diagnostics
- Biological treatment
- Psychosocial therapies
- Rehabilitation

**Risk Genes**
- COMT (22q11.23)
- STIP1 (16q22.3)
- BDNF (5q35.1)
- D4DR (15q21.2)
- NRGI (8p22)

**Pathophysiology of CNS Systems**
- Molecular abnormalities
- Functional polymorphisms in genes encoding neurotransmitters
- Abnormal spatial and temporal patterns of gene expression

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**Scientific Study of Schizophrenia: System Intelligence**
psychological dysfunction in a distributed network involving a fronto-striatal-cerebellar circuit in schizophrenia: brain-related early developmental deviances were demonstrated, with the normal relationship between infant development at age 1 and adult brain structure at age 34 disturbed in schizophrenia (Ridler et al. 2006).

Subjects who later developed schizophrenia in the NFBC 1966 also performed poorer than controls at school in both motor and theoretical domains at age 16 (Isohanni et al. 1998, Isohanni et al. 2004). These findings are in line with the hypothesis that a neural diathesis is present during postnatal brain development before schizophrenia onset. After the illness onset, the schizophrenia group performed significantly worse than the control group on cognitive function (Murray et al. 2006). These data support the hypothesis that developmental trajectory in the CNS through the lifespan in schizophrenia is partly different compared to controls and has less developmental plasticity. The findings amount to strong evidence for a neurodevelopmental origin of schizophrenia (Figure 8).

Current research into the course of schizophrenia has remained highly fragmented, much like the clinical heterogeneity of the disease itself. Isohanni et al. (2009) have struggled to assemble the many pieces of this puzzle. In a comprehensive theory, genetic and environmental influences in neuronal development cause functional alterations and pathophysiological changes of different neurotransmitter and circuit systems in the brain and, finally, the syndromal entity and overt illness phenotype. System theory may help integrate different types of evidence collected across many different categories and thus provide a coherent framework to guide future research. In Figure 8 a model on system view in schizophrenia is presented, with the morphological findings of original publications I–III are integrated into the model.

Endophenotypes are measurable but usually unseen neurophysiological, endocrinological, neuroanatomical, observational, self-reported, or cognitive components or a combination of these components. Endophenotypes are e.g. specific deficits in brain anatomy. The endophenotype of schizophrenia may exist even before the illness onset: morphometric brain changes in temporal and frontal cortices have been identified in the premorbid phase of psychosis (Pantelis et al. 2003). In this thesis we have shown altered brain volumes as possible endophenotypes in schizophrenia: smaller cerebral and grey and white matter volumes as well as widespread regional reductions e.g. in frontotemporal regions (Figure 8). Additionally, within the schizophrenia group, the regional grey and white matter reductions were more pronounced in subjects who had been ill
longer. These may suggest progressive effects and support the neurodegenerative hypothesis of schizophrenia. However, patients with a longer duration of illness, and thus young age of onset, were characterized by greater brain structural deficits. This could be interpreted as secondary to neurodevelopmental processes. Longitudinal imaging studies would assess possible progressive brain morphology more reliably.

6.2 Preterm and low birth weight subjects (IV)

6.2.1 Main findings

In this longitudinal birth cohort study we extended the previous findings by Rantakallio (1985) and Olsén et al. (1994), so that subjects born preterm or low birth weight showed slightly poorer school performance in adolescence, and poorer basic educational level in adulthood at age 31 years compared to full-term and normal birth weight subjects; the low birth weight subjects were also less likely to be employed. In the small MRI subset we observed a possible cognitive deficit in verbal learning, but we did not find any overall differences in brain structure or brain volumes in adulthood.

6.2.2 Comparison with earlier studies

Preterm babies are at risk of brain injury during the neonatal period as a result of hypoxia-ischaemia. Periventricular white matter is prone to hypoxic-ischaemic injury causing periventricular leukomalacia (PVL); ischaemia may also cause germinal matrix haemorrhage in the periventricular or parenchymal area. Very low birth weight (< 1500 g) babies are especially vulnerable to brain insults (Cooke & Abernethy 1999, Stewart et al. 1999, Abernethy et al. 2004, Allin et al. 2004, Isaacs et al. 2004, ).

However, at 34 gestational weeks, the total brain weight is 65% of that at term; there is still 35% of brain weight yet to be obtained to reach the term weight (Kinney 2006). Albeit rarely, both term and late preterm infants can develop periventricular leukomalacia, and their brains remain vulnerable to white matter injury (Kinney 2006). Grey matter injury is associated with periventricular leukomalasia in both very preterm and late preterm infants (Kinney 2006). However, it is not yet clear to what extent the ‘late-preterm’ infant is vulnerable to grey matter injury (Billiards et al. 2006).
Periventricular leucomalasia, ventricular enlargement and loss of white matter have been found in follow-up MR scans in childhood or adolescence in subjects who were born preterm or low birth weight (Olsén et al. 1997, Cooke & Abernethy 1999, Melhem et al. 2000). MRI studies in childhood or adolescence have shown a decrease in whole brain volume and volume decreases in a variety of areas, including cortical grey matter, hippocampus, caudate nuclei, the corpus callosum and cerebellum, and enlargement of lateral ventricles (Cooke & Abernethy 1999, Peterson et al. 2000, Allin et al. 2001, Nosarti et al. 2002, Abernethy et al. 2004, Isaacs et al. 2004).

However, little is known about their long-term outcome considering brain structure in adulthood, and there are only a few imaging studies after adolescence of survivors of preterm birth. Studies by Allin et al. (2004) and Fearon et al. (2004) did not find differences in whole brain or grey matter volumes, but lateral ventricular volume was increased at age between 17–33 years in subjects who were born very low birth weight (< 1 500 g). Total white matter was not reduced in the study by Allin et al. (2004), either. Our negative findings of whole brain, grey or white matter volumes converge with these studies, although we could not replicate their findings of increased ventricular volume. Additionally, Allin et al. (2004) found an increased ratio of grey to white matter and widespread changes in the distribution of grey matter, which we could not replicate. The subjects in their studies were the same age or younger (17–33 years) than in our study (33–35 years).

Many follow-up studies show significant brain volume changes or enlargement of lateral ventricles in adolescence (Cooke & Abernethy 1999, Stewart et al. 1999, Allin et al. 2001, Nosarti et al. 2002) or adulthood (Allin et al. 2004, Fearon et al. 2004). However, they examined the very low birth weight subjects, whereas our sample consists of moderate or mild preterm subjects. In the 1960’s only relatively preterm or low birth weight children survived while those who were very preterm or very low birth weight died. Treatment in intensive care units became common only in the 1970’s and 1980’s, as a result, smaller and more preterm babies were able to survive. Those babies are also prone to hypoxic-ischaemic or haemorrhagic injuries, and adolescents and adults born after that time have a higher probability of residual differences in brain structure. The decade of the 1990’s was notable for dramatically high survival rates of extremely preterm infants with biological risks associated with expected structural and functional brain impairments (Anderson & Doyle 2004, Hack et al. 2005).

Even though we did not find structural brain differences in moderate or mild preterm or low birth weight subjects in adulthood, we did observe an effect on educational level and a marginal effect on adult cognitive function. Neurological
and cognitive impairments have previously been reported even in the absence of imaging findings (Olsén et al. 1997, Stewart et al. 1999, Isaacs et al. 2004). Therefore, brain morphology seems to be only a coarse indicator of cognitive capability, and thorough neurological examination has been suggested to be a better predictor of later developmental problems than magnetic resonance imaging (Olsén et al. 1997). In our study, preterm or low birth weight subjects were more often behind their peers at a normal school or at a special school, had slightly lower school ratings and their basic educational level was lower than controls’ in adulthood. The low birth weight subjects had higher rates of unemployment. We had more women in the low birth weight group (57%) than in the control group (49%), and men were more likely to be employed than women. However, the risk of unemployment remained after adjustment for gender.

Focal deficits in neurocognitive function have been shown in school-aged children or adolescents who were born very preterm or with extremely low birth weight (Olsén et al. 1998, Stewart et al. 1999, Peterson et al. 2000, Abernethy et al. 2004, Anderson & Doyle 2004, Isaacs et al. 2004, Grunau et al. 2004, O’Brien et al. 2004). It has been suggested that birth weight is associated with cognitive function and education in adulthood even in the full birth weight range in the normal population (Richards et al. 2002).

In our study, the preterm subjects performed more poorly than controls on one test; i.e. verbal learning, a kind of explicit memory, also known as declarative memory, which relates to temporal and frontal lobe function, although we did not observe significant structural deficits in those (or other) brain regions. Recent findings in functional MRI studies of adults born very preterm indicate that abnormal neural function can be present in that group, something that cannot be ascribed solely to structural deficits (Narberhaus et al. 2009, Nosarti et al. 2009). The deficit in verbal learning that we observed could be due to subtle effects on brain function as a result of preterm birth that were not manifest as changes in brain volume on MR; alternatively this cognitive deficit may relate to a structural deficit that we were unable to detect due to lack of statistical power. As evidence, albeit from different (psychiatric) populations, has indicated that verbal learning is a predictor of occupational performance (Bryson et al. 1998), it is possible that such a deficit might have led to the lower educational and employment outcomes documented in our sample.

However, there might be other, non-structural, reasons for differences in cognition between the groups, such as social differences in the way the children were raised or differences in the education of the parents; this view is supported
by the finding that low maternal education was associated with subjects’ own low educational level. Finally, as the finding did not survive correction for multiple comparisons, we should remain cautious in our interpretation.

6.2.3 Strengths and limitations of the study


Many previous studies have also concentrated on survivors of very low birth weight, with weight usually less than 1 000 or 1 500 g (Cooke & Abernethy 1999, Stewart et al. 1999, Allin et al. 2001, Nosarti et al. 2002, Abernethy et al. 2004, Allin et al. 2004, Anderson & Doyle 2004, Isaacs et al. 2004, Allin et al. 2004, Fearon et al. 2004), but still the biggest group is the “late preterm” or “near term” babies born between 34–37 gestation weeks (more than 70% of all preterm births) (Allin et al. 2004, Fearon et al. 2004, Pietz et al. 2004). This group has received less attention in outcome studies, even though they are at higher risk of morbidity and mortality than full term infants (Wang et al. 2004, Raju et al. 2006, Engle et al. 2007), and there are also reports of some neurodevelopmental deficits in childhood in this group, e.g. language and visual-motor abilities (Pietz et al. 2004, Kirkegaard et al. 2006, Chyi et al. 2008).

Our group of preterm or low birth weight subjects in the whole cohort was a large unselected sample drawn from a general population. Prospective data have been collected longitudinally since pregnancy until 33-35 years of age. Although our MRI subset of 104 subjects had only a small number of premature subjects (n=9) it is a truly randomly selected sample (apart from gender stratification), making this group more representative of the general population than the majority of neuroimaging studies. Our cases and controls are the same age and ethnicity, excluding the possible effects of ageing or race on brain structure or size.

**Limitations.** The major disadvantage of our study was the small sample size considering preterm or low birth weight babies in the MRI subset (1% of the
subjects within the whole cohort), which limits statistical power to detect group differences in brain volume or neurocognitive measures. The difference in brain volumes should be large in order to be able to detect it in a small sample as ours. The cognitive tests performed in the MRI subset measure different areas of cognition, and the preterm or low birth weight subjects performed worse on verbal learning only. However, as several tests were performed, it is possible that the result may be due to chance, as suggested by further statistical analysis.

Additionally, the preterm and low birth weight subjects were born more than 40 years ago, prior to the advent of modern neonatal intensive care, so it is difficult to discern the relevance of these results to modern neonatal practices, and we cannot predict, how premature subjects born today will manage in adulthood. In addition, we do not have any information about brain morphology and possible brain insults in the neonatal period, because suitable imaging methods were not available at that time.
7 Conclusion

7.1. Schizophrenia and other psychoses

7.1.1 Main conclusions

We have replicated previous findings of brain volume differences in schizophrenia on a general population level. These results, showing frontal and temporal brain abnormalities in grey matter density, largely endorse the previous findings in the literature which have been drawn from non-population based studies. Furthermore, grey matter density deficits were observed in brain regions that have previously received less scrutiny in schizophrenia research, i.e. the cerebellum, parietal and occipital cortices; this is also true of white matter differences in which we found regional reductions. Thus our study supports evidence of widespread brain morphological abnormalities in schizophrenia. Subtle hippocampal volume reduction in psychotic patients was explained by whole brain volume reduction in this birth cohort sample. No volume differences were found in the amygdala in patients with psychosis.

Subjects with longer duration of illness and younger age at onset showed more prominent brain abnormalities, so that a longer duration of illness was associated with reduced grey and white matter density in areas defined as significantly different in case-control VBM analysis. These findings suggest either, that developmental brain deficits relate to an earlier age of onset or that brain abnormalities in schizophrenia are progressive in nature. The subjects with schizophrenia were the same age, 33–35 years, and relatively young with mean duration of illness of 10 years. They were not first episode patients, and they had differing lengths of illness. Thus we were able to study the effect of duration of illness (or the impact of earlier illness onset) on brain structure in a cross-sectional imaging study.

Perinatal events or family history of psychosis, which have been suggested to be aetiologically important in structural pathology of schizophrenia, did not have significant effects on brain structure in this study.

The main importance of our study is the epidemiological basis for the sample, which is uncommon in the neuroimaging literature. This study is the first voxel-based morphometry study of the brain in schizophrenia where cases and controls are sampled in a population based manner, and only the second case-control study of schizophrenia brain morphology where all participants are drawn from a population-based birth cohort. The only previous population-based sample was described by Cannon et al. (1998). The population based nature of the research means...
that our study is much less susceptible to sampling biases than most schizophrenia neuroimaging research. In contrast to a number of previous schizophrenia studies, chronic patients or men are not overrepresented among our cases. The controls are representative of the population from which the cases arise and are not “super-normal”, as sampling biases in control selection can have enormous influence on the results of neuroimaging studies (Smith & Iacono 1986). 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 it yields significant results. The study was population-based, and the possibility of selection bias could be assessed by consideration of psychotic cohort members who elected not to participate.

7.1.2 Clinical implications of the study

Structural brain differences are associated with schizophrenia, even in first-episode patients (Job et al. 2002, Kubicki et al. 2002, Salokangas et al. 2002), and even in the premorbid phase before illness onset (Pantelis et al. 2003). Long duration of untreated psychosis has been suggested to be associated with brain structural abnormalities (Lappin et al. 2006) with possible toxic effects on the brain (Wyatt 1991); it is therefore essential to diagnose psychosis and start treatment early. As schizophrenia is a chronic and progressive disease with poor prognosis (Lauronen et al. 2007), and as according to our study, the brain abnormalities might also be progressive, active and constant follow-up during relapses or progression of the disease is important.

**Accurate diagnosis** has major implications for short- and long-term treatment planning, and it is essential to note that diagnosis is a process rather than a one-time event. As new information becomes available about the patient and his or her symptoms, the patient’s diagnosis should be re-evaluated. Schizophrenia can be viewed as a disorder that develops in phases: premorbid, prodromal and psychotic. At present, no diagnosis-specific imaging techniques exist to help early and accurate diagnostics. Given the subtle nature of the neuropathological findings in schizophrenia, imaging studies cannot establish a diagnosis of schizophrenia after the acute psychosis. However, specific findings from MRI scanning *e.g.* ventricular enlargement, diminished cortical volume (I) may enhance the confidence of the diagnosis, and exclude major neurological diagnoses. Future research can provide information that is relevant to diagnostics, course, treatment planning and prognosis in different phases of illness, *e.g.* by utilizing another birth
High-resolution morphometric brain imaging, possibly combined with functional MRI, might offer an opportunity for early intervention. Detection of morphometric brain abnormalities in subjects with prodromal symptoms or with a high risk due to genetic reasons would identify subjects at a greater risk of developing schizophrenia (Lawrie et al. 1999, Koutsouleris et al. 2009). Close follow-up or even treatment, e.g. psychotherapy, could be focused on these subjects with altered brain volumes in this phase, which might hinder or delay the onset of acute psychosis, or improve its clinical course.

Monitoring morphometric changes in brain. It is not known whether the cross-sectional or longitudinal monitoring of the morphometric status of patients’ brains helps in treatment planning and realization. For example, if the progression of morphometric changes (II) is rapid, should active, even aggressive antipsychotic medication be applied? Future analysis of two follow-ups in 1999–2001 and 2008–2011 in the NFBC 1966 may provide new information: is morphometric status related to the outcome, medication or duration of untreated psychosis; does data on progression in brain morphology predict clinical response and influence treatment algorithms?

Antipsychotic drugs are indicated for nearly all episodes of acute psychosis in patients with schizophrenia. They relieve symptoms and prevent relapses, but have limited efficacy, especially for negative and cognitive symptoms, often causing harmful neurological and metabolic side-effects. A key unanswered question in current psychiatry is the influence and selection of antipsychotic medication (first-generation vs. second-generation drugs); what is their long-term impact on brain structure and function. Antipsychotic medications substantially reduce the risk of relapse in the stable phase of schizophrenia and are strongly recommended in most treatment algorithms and guidelines (Dixon et al. 2009, www.kaypahoito.fi). However, it is still mainly open whether antipsychotic drugs prevent or ameliorate the disease progression as also observed in this study (II). The new follow-up in 2008-2011 in the NFBC 1966 Birth Cohort may provide answers to these questions.

Psychosocial therapies. Schizophrenia is often a progressive, chronic illness that influences virtually all aspects of life of affected individuals. The morphometric changes also observed in this study (I-III) relate to cognitive deviances. Many adults with schizophrenia have cognitive deficits. These deficits lie social and occupational problems in the modern information society and vocational life. Psychosocial therapies may alleviate cognitive deviances.
7.1.3 Future research

The longitudinal changes in brain structure in midlife in schizophrenia are still not well known: whether the brain decreases develop over time, and whether they are progressive in terms of excessive reduction of brain matter particularly after the first years of onset. We know that schizophrenia progresses clinically in midlife and its outcome is unsatisfactory (Lauronen et al. 2007). Mechanisms behind this progression are mainly unknown, as is how to influence them. The effects of biological factors (e.g. brain structures and function, cognition, genes, medication) and poor treatment adherence on illness course are understudied.

The follow-up of the NFBC 1966 study is currently going on at age 43–45 (2008–2011), including interviews, cognitive tests and structural and functional MRI. We aim to investigate the progression of the morphometric abnormalities. Because the decrease of brain tissue is slow, we have a relatively long interval (8-10 years) between two scans. The brain tissue volume loss per year in schizophrenia has been estimated to be twice as much as in controls (Hulshoff Pol & Kahn, 2008). With this longitudinal data from the NFBC 1966 we might be able to answer the question of whether the brain degeneration continues over the course of schizophrenic illness.

We will also be able to study the possible decline in cognitive functions in the schizophrenia subjects, as the same cognitive tasks as before (Murray et al. 2006) will be repeated in the follow-up study. The hypothesis is that the change in brain structure and cognition will show trend in the same direction. If we detected excessive brain tissue loss and excessive decline in cognitive functions in schizophrenia subjects, it would support the Kraepelinian concept of schizophrenia being a progressive disorder.

In the NFBC 1986 the study group has recently conducted a field study aimed to detect subjects at high risk of developing schizophrenia. In the sample consisting of 314 subjects it will be possible to study brain functions (by fMRI and cognitive test battery) in such subjects. The follow-up of these members of the NFBC 1986 will give knowledge of brain functions in subjects at risk of developing schizophrenia on population level (Veijola et al. manuscript).
7.2 Preterm and low birth weight subjects

7.2.1 Main conclusions

We did not find any major structural brain differences in adult subjects who were born preterm or low birth weight; however, there were some adverse effects on educational level, occupational function and possible effects on adult cognitive function. Generally, in the largest group of preterm babies, namely ‘late-preterm’ babies, there might be a small risk of some cognitive, educational and occupational adversities in the future. In the modern information society, non-optimal education is a critical determinant of many lost later-life opportunities in the areas of occupation, economy and health (Isohanni et al. 1998).

7.2.2 Clinical implications of the study and future research

Based on our findings on cognition, education and occupation in the group of moderate to late preterm subjects, all preterm and low birth weight subjects - not only very preterm or very low birth weight subjects - should be followed with special attention prior to and at school and during secondary education.

In future research, it is important to conduct studies in the late preterm group as well, as they make up the majority of the whole preterm population. Our sample of premature subjects with brain MRI was very small, so we cannot exclude minor morphometric brain abnormalities in this group generally. MRI studies with larger samples of late preterm subjects in adulthood are needed.

7.3 Concluding remarks

First (I–III), we have confirmed previous findings of structural brain abnormalities in schizophrenia in an epidemiological population-based sample. Schizophrenia was associated with subtle alterations in the anatomy of the central nervous system in some critical areas. Our novel findings suggest that the grey and white matter deficits are widespread: besides changes in frontotemporal cortices and basal ganglia, there were deficits in parietal and occipital lobes and the cerebellum. The abnormalities were associated with duration of illness, suggesting progressive effects.

These results support the hypothesis that subtle but widespread alterations and midlife progression are key features in the postmorbid developmental trajectory.
of schizophrenia. The mechanisms behind these alterations and progression are
mainly unknown, as is how to influence them. Whether these effects are modifiable
(e.g. reversed following exposure to antipsychotics) is a key question in current
clinical psychiatry. In an ongoing second follow-up study during the years 2008-
2011 we will be able to study the possible excessive progressive changes in relation
to controls longitudinally, and also the relation between progression and potential
causal or mediating factors (e.g. medication, duration of untreated psychosis, early
development, clinical course, care).

Second (IV), premature subjects in the NFBC 1966 showed evidence of
slightly poorer educational and occupational career and cognitive function, but no
major overall changes in brain morphology in the small subsample of the NFBC
1966. We were able to study the long term effects of prematurity until adulthood in
this Cohort, which is rare as most follow-up studies of preterm births are restricted
to childhood or adolescence. The premature subjects in our sample were moderate
to mild preterm or low birth weight; in general, they make up the majority of all
preterm births. This group has received less interest in previous studies. From a
public health point of view these common, mild exposures are highly relevant.
Educational trajectory and cognitive performance are highly important in the modern
information society, and we showed that even these mild exposures were linked to
important and harmful real-world measures, such as increased unemployment.


Haapea M (2010) Non-response and information bias in population-based psychiatric research. The Northern Finland 1966 Birth Cohort study. Faculty of Medicine, Institute of Clinical Medicine, Department of Psychiatry, Institute of Diagnostics, Department of Diagnostic Radiology, Institute of Health Sciences, University of Oulu. Acta Universitatis Ouluensis D1049.


List of original publications

This dissertation is based on the following four original publications, which are referred to in the text by the Roman numerals I–IV.


The original papers have been reprinted with the permission from Elsevier (I, III, IV) and Oxford University Press (II).

Original publications are not included in the electronic version of the dissertation.


1057. Nevalainen, Jukka (2010) Utilisation of the structure of the retinal nerve fiber layer and test strategy in visual field examination


1063. Alaräisänen, Antti (2010) Risk factors and pathways leading to suicide with special focus in schizophrenia. The Northern Finland 1966 Birth Cohort Study


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Päivikki Tanskanen

BRAIN MRI IN SUBJECTS WITH SCHIZOPHRENIA AND IN ADULTS BORN PREMATURELY

THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY