Brain Plasticity, Intelligence and Schizophrenia:

Influences of genes and environment

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Brain Plasticity, Intelligence and Schizophrenia:
Influences of genes and environment

Plasticiteit van het brein, Intelligentie en Schizofrenie:
Invloeden van genen en omgeving
(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

Introduction

1.1 Introduction

The general aim of the studies conducted in this thesis is to add pieces of information to the understanding of human brain development, in schizophrenia and in health. Magnetic resonance imaging (MRI) provides us with the opportunity to study brain development within subjects over time and by using a longitudinal design, subtle changes can be identified on an individual level.

The studies presented in this thesis explore changes in brain volume and intelligence in schizophrenia and in health. Twins discordant for schizophrenia and healthy control twins (plus siblings) are used to separate the relative contributions of genetic and environmental influences on individual differences in brain volume change and its possible (genetic) relationship with intelligence.

1.2 Healthy Brain Development

There is consistent evidence for brain volume changes early and late in life. Comparison of brain weight between people at different ages has suggested that considerable volume change is taking place during development in humans. Having reached approximately 90% of its adult size around the age of six (Giedd et al., 1999), dynamic changes in brain volume continue to take place in children (Giedd et al., 1999), adolescents (Gogtay et al., 2004) as well as in adults (Bartzokis et al., 2001; Pfefferbaum et al., 2004). The most pronounced increase in brain weight occurs during the first 3 years of life (Dekaban, 1978). Between age 3 and 18 the brain increases in weight to about 5 times that of a newborn. At approximately 45 to 50 years of age a progressive decline in brain weight begins and reaches the lowest values after the age of 86. By then, it is about 11% smaller relative to the maximum brain weight attained around 19 years of age. After the age of 80 the brain mass is rapidly decreasing (Ho et al., 1980).

Cerebral gray matter volume increases in pre-adolescence (Giedd et al., 1999; Gogtay et al., 2004; Lenroot et al., 2007), after which it starts to decrease in post-adolescence, while cerebral white matter continues to increase in volume (Giedd et al., 1999) until the age of around 45 when it starts to decrease, following a quadratic curve (Bartzokis et al., 2001) . It has been suggested that GM is replaced by WM in childhood and adolescence (Giedd et al., 1999; Jernigan et al., 1991). Moreover, differences in timing and the amount of cortical

thinning or loss in gray matter density is evident across different structures. On average, throughout childhood and adolescence, changes in cortical gray matter appear to occur first in primary cortical areas (e.g., sensory-motor cortex), followed by secondary, and eventually the multimodal cortical areas (Sowell et al., 2002; Gogtay et al., 2004).

1.2.1 | Influence of Genetic and Environmental Factors

Variation in global brain volumes is to a large extent explained by genetic factors (around 70-80%) in children and adolescents (Wallace et al., 2006; Peper et al., 2009; Yoon et al., 2010; van Soelen et al., 2013) and in adults (Baaré et al., 2001; Kremen et al., 2010). Heritability by age effects have been suggested indicating that the influence of genetic and environmental factors varies with age and brain region (Wallace et al., 2006; Giedd et al., 2007; Peper et al., 2009). To what extent genetic and environmental influences act during the development of brain structures is not completely understood. Identifying the actual genes that are involved in the changes of brain structure is of profound importance since brain structure is coupled with brain functioning. Finding the genes for healthy brain changes might yield important information for genes contributing to psychiatric diseases, such as schizophrenia.

1.3 Schizophrenia

Schizophrenia is a severe and disabling mental disorder characterized by a disruption in the perception of reality and abnormalities of thought processes and feelings. It usually strikes in late adolescence or early adulthood with earlier onset containing a worse prognosis. The relatively young age of onset implies not only great suffering for the patient themselves but also involves important social implications. Due to a large variety in symptoms, severity, course and outcome of the illness, the clinical presentation differs from one patient to another.

1.3.1 | History

Emil Kraepelin (1856-1926) was the first to differentiate the illness into what he called “dementia praecox” (dementia from the young) from manic depressive psychosis (Kraepelin, 1913). The symptoms were clustered into one syndrome by Kraepelin, underpinning both the clinical deterioration that characterize the course of the illness and the relatively young age of onset. Shortly thereafter, Eugen Bleuler (Bleuler, 1923) renamed the syndrome into “schizophrenia” which is derived from the Greek words: “schizo”, which means split, and

“phren”, meaning mind. Bleuler emphasized that the illness was not a single entity but he described it as “the group of schizophrenias”. According to Bleuler, the core symptoms are ambivalence, disturbance of affect and associations plus a preference for fantasy over reality. He claimed that these symptoms are present in all patients, at all stages of the illness, and are hence diagnostic of schizophrenia. Since that time, numerous articles and books have been published on schizophrenia and many attempts have been made at formalizing the definition of schizophrenia. In fact, psychiatry has produced more than 40 definitions of schizophrenia (Jansson and Parnas, 2007). These attempts on diagnostic categorizations have resulted in two major classifications systems: the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (see Table 1 for schizophrenia criteria) and the International Classification of Diseases, 10th Revision (ICD-10). In research, criteria according to the DSM-IV are mostly used. In May 2013, DSM-V was released. Two changes were made to DSM-IV Criterion A for schizophrenia. One is the elimination of bizarre delusions and Schneiderian first-rank auditory hallucinations (e.g., two or more voices conversing) due to poor reliability in distinguishing bizarre from nonbizarre delusions. The second change is the addition of a requirement in Criterion A that the individual must have at least one of these three symptoms: delusions, hallucinations and disorganized speech.

Table 1 | Diagnostic criteria for schizophrenia, according to DSM-IV

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. Delusions
2. Hallucinations
3. Disorganized speech (e.g., frequent derailment or incoherence)
4. Grossly disorganized or catatonic behavior
5. Negative symptoms, i.e., affective flattening, alogia, or avolition

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal (symptomatic of the onset) or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either: 1) no major depressive episode, manic episode, or mixed episode have occurred concurrently with the active-phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

(Adapted from Diagnostic and Statistical Manual of Mental Disorders, 4th ed.)

1.3.2 | Symptoms and Classifications

The first symptoms of schizophrenia typically occur in adolescence or early adulthood and are preceded by a decline in functioning before the onset of the first psychotic episode. Schizophrenia is a psychiatric illness characterized by different clusters of symptoms which are well defined. Usually a distinction between positive and negative symptoms is made. Positive symptoms, such as hallucinations (hearing voices), persistent abnormal beliefs (delusions), disorganized behavior and speech (rapid changes of subject and odd associations) reflect an excess of normal functioning. Negative symptoms, such as avolition (lack of motivation), flat affect (lack of emotional response) and withdrawal, refer to a reduction or loss of normal functioning. Furthermore, cognitive deficits are also consistently seen in patients with schizophrenia, including problems with attention, executive functioning (planning and organization of behavior), working memory, speed and concentration.

The DSM-IV provides several diagnostic subtypes of schizophrenia (paranoid, disorganized, undifferentiated, residual and catatonic). The validity of these categorical distinctions is a matter of debate. For instance, differences between the diagnostic subtypes of schizophrenia have not been well reported (Carpenter et al., 2009). These subtypes are therefore excluded in the new edition (DSM V). Instead a dimensional approach to rating severity for the core symptoms of schizophrenia is included.

1.3.3 | Etiology and Risk Factors

The etiology of schizophrenia remains largely unknown. The illness generally manifests on average earlier and more frequently in men (20-25 years) than in women (25-30 years) (Aleman et al., 2003). Moreover, there is a second smaller peak in females after age 45 (Goldstein and Levine, from Castle et al., 2000).

Family, twin and adoption studies indicate that genetic factors play an important role and the heritability to develop schizophrenia is estimated to be around 80% (Sullivan et al., 2003). The prevalence of schizophrenia worldwide appears to be slightly less than 1%, but the incidence of schizophrenia is much higher in first-degree relatives of schizophrenic patients; indicating that the closer the level of genetic relatedness, the greater the likelihood that a relative will also suffer from the illness (Gottesman et al., 1991; McGuffin et al., 1995). Figure 1 shows the lifetime expectancy of incidence of schizophrenia, which is the chance of being affected during an entire lifetime. As a first-degree relative (sibling or parent) of a patient with schizophrenia, the risk is about 9 percent. The risk is greater if several family members are

affected. In dizygotic (fraternal) twins, the risk increases to approximately 17 percent for the co-twin of a patient and most strikingly, the risk increases to about 48 percent for monozygotic co-twins of a patient (Gottesman, 1991; McGuffin et al., 1995; Cardno and Gottesman, 2000). Despite the strong and consistent evidence for genetic influence, the role of environmental (non-genetic) factors is clear from the fact that monozygotic twins have less than 100 percent concordant rates of schizophrenia.

Environmental factors such as cannabis use and viral infections have been associated with schizophrenia susceptibility (Torrey, 1988; Semple et al., 2005). Other suggested environmental factors involved in the development of schizophrenia are: obstretic complications (Cannon et al., 2002), severe nutritional deficiency (Hulshoff Pol et al., 2000), (pre- and perinatal) stress factors such as foetal hypoxia (Khashan et al., 2008; Norman and Malla, 1993), urbanicity, migration and social factors, such as (parental) socioeconomic status, separation or death during childhood (Cantor-Graae, 2007). Moreover, older paternal age at conception together with maternal infections and birth during late winter or early spring have been linked to an increased risk of developing schizophrenia (Kaplan and Sadok, 2009). However, the specific contributions of environmental factors remain unclear. Previously, genetic and environmental risk factors were considered separately to clarify the vulnerability for schizophrenia. Now, it is well accepted that they both act together in concert in the etiology of schizophrenia (van Os and Murray, 2008).

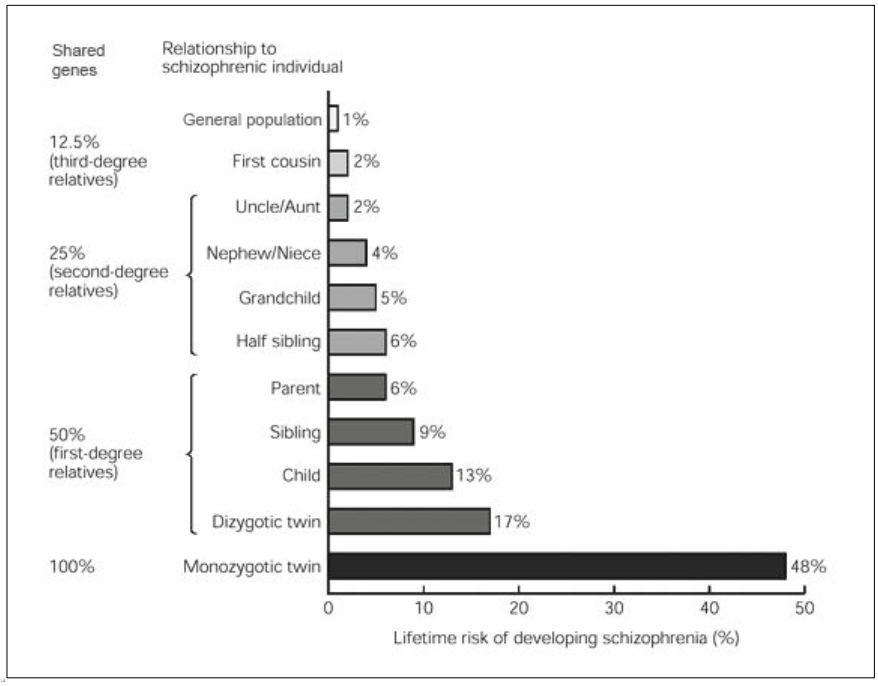

Figure 1 | The lifetime risk of developing schizophrenia (source: Gottesman, 1991)

1.4 Brain Imaging

1.4.1 | History

The history of neuroimaging started more than a century ago, in the early nineteen-hundreds with techniques called pneumo-encephalography and ventriculography. Brain abnormalities and (progressive) atrophic cerebral changes in patients with schizophrenia were reported in studies (Haug et al., 1962). In pneumo-encephalography, air was injected by lumbar spinal punction to enter the cerebral ventricles and cerebrospinal fluid compartments. In ventriculography, X-ray images of the ventricular system were obtained by injection of filtered air directly through holes drilled in the skull. These techniques resulted in unpleasant side effects, such as headaches and nausea, and were very painful. Therefore, healthy controls were scarcely included.

Computerized axial tomography (CAT), later called computer assisted tomography, was introduced in the early 1970s. With this technique it became possible to obtain more detailed anatomical images and to visualize the brain non-invasively and safely.

A great improvement came with the introduction of modern imaging technique, such as Computed Tomography (CT). In CT, series of X-ray images was analyzed with a computer. Increased lateral ventricle volume in patients with schizophrenia as compared to controls was for the first time reported by Johnstone and colleagues in the 1970's using CT (Johnstone et al., 1976).

1.4.2 | MRI Techniques

Magnetic Resonance Imaging (MRI) vas developed in the early 1980s. Initially, MRI was referred to as nuclear magnetic resonance (NMR), since it is based on the sensitivity of certain anatomic nuclei to magnetic fields. Shortly, by using a strong magnetic field and a radio transmitter, MRI scanners are capable of creating three-dimensional images of the brain based on the physical qualities of hydrogen protons in brain tissues. Approximately 60-70% of the human brain consists of water, which means plentiful hydrogen nuclei (protons) that can be aligned in a strong magnetic field. Therefore, different tissue types lead to differences in MR signal depending on their water content. MRI has been very useful in revealing subtle structural brain abnormalities and one of the main advantages of MRI is that brain scans are acquired in vivo without exposure to radiation, making repeated scanning possible. Moreover, with MRI it is possible to quantify the gray and white matter of the brain since the image resolution of MRI allow for a greater contrast. Gray matter consists largely of neurons (or cell bodies) and the neighboring white matter consists of myelinated fiber connections between the neurons.

After the scans are acquired, the procedure of processing them start with specific in-house developed software. Different brain areas can be segmented and partitioned into meaningful structures (e.g., intracranium, whole brain, gray and white matter, lateral and third ventricles, cerebellum) to obtain a quantification of the volume in the different structures (Schnack et al., 2001a, 2001b; Brouwer et al., 2010).

The majority of the MRI studies in schizophrenia employ a volumetric ROI (Region Of Interest) approach (e.g., see Lopez-Garcia et al., 2006). An anatomical ROI is usually

defined *a priori* in structural brain imaging by a manual or semi-automated delineation procedure. Although the anatomical validity is high in these measurements, this type of analysis is often tedious and time-consuming as well as they are sensitive to individual decision on anatomical boundaries of the ROI, which in turn may lead to a higher risk of unreliable measurements.

Another technique examines the localization of focal brain abnormalities by quantifying the thickness of the gray matter in specific regions of the cerebral cortex, such as the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm (Kim et al., 2005). Cortical thickness is determined of the density, size and arrangement of neurons, neuroglia and nerve fibers. Since cell types and amount of cortical layers can be region-specific, cortical thickness measures can provide important clues about pathological brain changes. Moreover, cortical surface area can be determined by taking the mid-area between the white matter (i.e., inner surface) and the gray matter (i.e., outer surface). Brain volume is defined by the product of cortical thickness and surface area (Winkler et al., 2010), each influenced by their own genetic factors, which may have a separate etiology (Panizzon et al., 2009; Winkler et al., 2010). Therefore, surface area can reveal important clues about pathophysiological processes, otherwise not found in cortical thickness.

Other MRI techniques, such as diffusion tensor imaging (DTI) and functional MRI, can provide additional important information about the human brain. However, these techniques lie beyond the scope of this thesis.

1.4.3 | MRI Studies in Schizophrenia

Many of the MRI studies that have been conducted in schizophrenia suffer from small sample sizes, different brain regions measured, and have been conducted in different type of subjects. Therefore, the interpretation of the available data is complicated. A recent meta-analysis in over 18,000 subjects (Haijma et al., 2012) reported the largest effect sizes for gray matter structure decrease (d=-0.4 on average) in patients relative to control subjects. Intracranial and total brain volume were significantly decreased in patients by 2.0% and 2.6% respectlvely as compared to controls. Total CSF, lateral ventricles and especially third ventricle (d=0.60) volumes were increased in patents as compared to controls. Relative to healthy subjects, the volume reduction in caudate nucleus and thalamus seemd more pronounced in antipsychotic naïve patients than in medicated patients (Haijma et al., 2012).

In addition, evidence for regional pathology indicates lower volumes in the prefrontal and temporal lobes (especially in the superior temporal gyrus) and part of the limbic system (including hippocampus, parahippocampus gyrus and amygdala) which are reduced in schizophrenia patients as compared to healthy controls (Wright et al., 2000; Shenton et al., 2001). Finally, white matter has been reported to be reduced with approximately 1% (Wright et al., 2000 and Haijma et al., 2012).

Several studies focused specifically on the cortex, i.e., cortical thickness and cortical surface area. Cortical thinning, primarily in the frontal and temporal cortices has been reported in chronic (Kuperberg et al., 2003) and in first-episode (Narr et al., 2005) schizophrenia patients as compared to healthy control subjects. These findings have been replicated in larger samples of patients in childhood onset (Greenstein et al., 2006), chronic (Nesvag et al., 2008) and in a sample of patients across the adult range (van Haren et al., 2011).

Longitudinal studies further indicate progressive tissue loss in multiple brain structures in high risk, first-episode and chronically ill schizophrenia patients (DeLisi et al., 1995; Pantelis et al., 2005; Hulshoff Pol and Kahn, 2008), particularly in the frontal (Ho et al., 2003) and temporal (Kasai et al., 2003) lobe. This tissue loss can mainly be attributable to gray matter volume decrease (Cahn et al., 2006; van Haren et al., 2008). Moreover, patients with the poorest outcome have been reported to have the largest brain volume decrease (Davis et al., 1998; Cahn et al., 2002; van Haren et al., 2008).

1.5 Intelligence

1.5.1 | Intelligence in Schizophrenia

Cognitive deficits have been reported as a key feature of schizophrenia since its first description by Kraepelin (1893). In particular, deficits in global measures of cognition are commonly reported in patients with schizophrenia, such as lower intelligence quotient (IQ) (Aylward et al., 1984; Heinrichs and Zakzanis, 1998). Individuals with schizophrenia show mean IQ scores of about 90, or 2/3 of a standard deviation below healthy controls (Aylward et al., 1984). Lower premorbid IQ has been found to be associated with increased risk to develop schizophrenia spectrum disorders (Zammit et al., 2004; Reichenberg et al., 2006) and already years before the onset of psychotic symptoms the mean IQ-scores are below that of healthy controls (Woodberry et al., 2008). Not only is a lower IQ associated with the

development of schizophrenia, a *decline* in global cognitive functioning has been suggested to predict the onset of psychotic symptoms in young children (Kremen et al., 1998) and in adolescents (Fuller et al., 2002; Reichenberg et al., 2005). Moreover, intelligence and schizophrenia susceptibility have been shown to have overlapping genes (Toulopoulou et al., 2007; but see Fowler et al., 2012).

1.5.2 | Intelligence in Health

Intelligence quotient (IQ) is remarkably stable across the lifespan (Deary et al., 2000) and has a high predictive value for several outcome factors in life, such as health, lifespan, educational attainment and income. An intriguing aspect of the aetiology of general cognitive ability is the increase of genetic influences with increasing age, while the influence of common environmental influences decrease (Deary et al., 2009).

Several studies have shown that total brain volume (Thompson et al., 2001; Posthuma et al., 2002), but also focal gray (Thompson et al., 2001; Frangou et al., 2004; Hulshoff Pol et al., 2006) and white (Hulshoff Pol et al., 2006) matter densities are positively related to the level of intelligence and that these associations are mediated by common genetic factors (Boomsma et al., 2002; Posthuma et al., 2002; Wright et al., 2002; Toga and Thompson, 2005; Hulshoff Pol et al., 2006). Furthermore, results have shown that adults with a higher intelligence show attenuated cortical thinning and more excessive cortical thickening over time than subjects with average or below average IQ (Brans et al., 2010). Recently an increase in gray matter density in certain focal areas was positively associated with an increase in IQ in young individuals (Ramsden et al., 2012). Thus, genes involved in individual variations in intelligence (Plomin and Spinath, 2004) overlap with genes for brain volume (Posthuma et al., 2002) and with cortical thickness change (Brans et al., 2010) although the causality underlying this association remains to be determined.

1.6 The Role of Genes and Environment

1.6.1 | Twin Design

Twin studies provide a powerful model to quantify the relative influences of genetic and environmental factors on individual differences in traits and behaviors. Twins have been employed for more than a century as a natural experiment where the resemblance of monozygotic (MZ) twins is compared to the resemblance of dizygotic (DZ) twins. Twins are a

valuable source for observation because their genes and family environments tend to be similar. More specifically, MZ twins, also called identical twins, derive from one fertilized egg (zygote), and thus share 100% of their genes which means that most of the variation in their traits (measured height, intelligence, depression, etc.) is due to their unique experiences. DZ or fraternal twins are developed from separately fertilized eggs and share, like other full siblings, on average 50% of their genes. Both types of twins tend to share many aspects of their familiar environment (e.g., parenting style, education) by virtue of being born at the same place and time. However, both of them also experience unique environmental influences (e.g., unique life-events).

The basic logic of the twin study can be understood with very little mathematics. The classical twin study begins with assessing the variance of a trait in a large group of MZ and DZ twins and then estimating how much of this is due to: genetic effects (heritability), shared environment (e.g., events that happen to both twins and affect them equally) and unique (or unshared) environment (e.g., events that are unique to one twin). These three parts are typically called A (additive genetics), C (common environment) and E (unique environment) which together make up the acronym “ACE”.

Any differences between MZ twins raised in the same family are due to unique environment, since they share 100% of their genes and all of the common environment. The correlation of the MZ twins provides an estimate of the proportion of the variance that can be attributed to genetic and common environmental factors (A+C)/(A+C+E). DZ twins share on average 50% and all of the common environment so the correlation between DZ twins is an estimate of (½A+C)/(A+C+E). The twin-pair correlations (respectively rMZ and rDZ for the correlation within MZ and DZ pairs) reflect the resemblance between the twin pairs where:

$$rMZ = (A+C)/(A+C+E)$$
$$rDZ = (½A+C)/(A+C+E)$$

Therefore, heritability (i.e. the proportion of variance that can be attributed to genetic factors) can be expressed as twice the difference between identical and fraternal twin correlations (A/(A+C+E) = 2(rMZ-rDZ); Falconer’s formula). The proportion of variance attributable to common environment can be estimated by the MZ correlation minus the estimate of heritability (C/(A+C+E)= rMZ - A/(A+C+E)). Therefore, the proportion of variance that is not

shared between MZ twins, (unique environmental factor, which also include measurement error: E/(A+C+E)=1-rMZ) (Fulker and Jinks, 1970; Plomin et al., 2001).

The classical twin model can be extended to include siblings of twins in a so-called twin-sibling design. By including siblings of twins, the statistical power to detect the influences of common environmental factors shared by family members is enhanced (for instance, a family of DZ twins and a sibling gives three correlations among first-degree relatives, a family with only two DZ twins gives only one correlation) (Posthuma et al., 2000).

Univariate twin models are applied for assessing the aetiology of one trait (see below on structural equation modeling of a more elaborate way of implementing the rationale of the twin design). By extending the univariate model to a multivariate design where more than one phenotype per person is included, the causes of associations between traits can be investigated (Boomsma et al., 2002). Multivariate modeling allows for the estimating the associations between traits (i.e., the phenotypic, or observed correlation, r_{ph}). By applying bivariate models one can tell whether either genetic or environmental factors (or both) are shared between the two traits and hence contribute to the phenotypic correlation. These partitioned correlations provide information regarding the extent to which genetic (r_g), shared environmental (r_c) and unique environmental (r_e) effects in one phenotype (e.g., liability for schizophrenia) correlate with another trait (e.g., brain volume change). Decomposition is based on the cross-twin/cross-trait correlations where for instance, schizophrenia liability in twin 1 is correlated with brain volume change in twin 2 where twin 1 and twin 2 represent a twin pair (see Figure 2 for bivariate model). If the value of the cross-twin/cross-trait correlation is larger in MZ twins than in DZ twins, a shared genetic factor influencing both phenotypes is suggested.

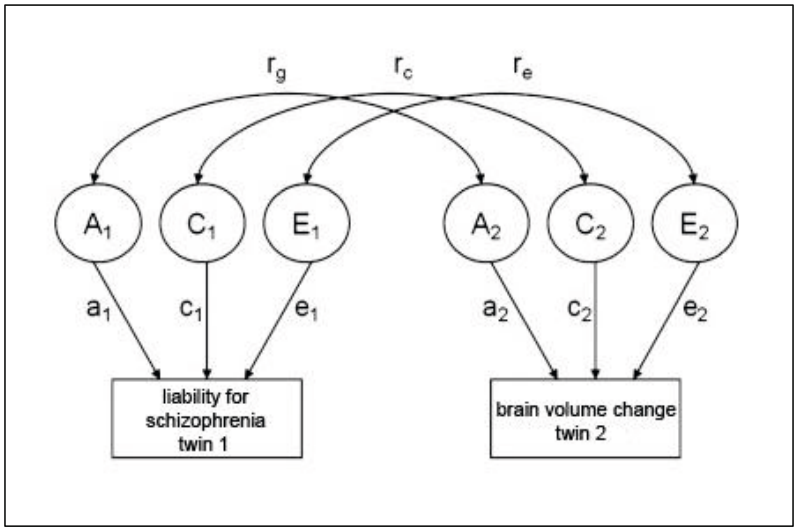

Figure 2 | Example of a bivariate twin model. A = Additive genetic factors, C = Shared or common genetic factors, E = Nonshared or unique environmental factors, r_g = Genetic correlation, r_c = Shared environmental correlation, r_e = Unique environmental correlation. Lower case a, c and e represent the parameter estimates for the corresponding variance components.

1.6.2 | Structural Equation Modeling

Structural Equation Modeling (SEM) or model fitting involve fitting a model that best describes the observed data. The advantage of SEM is that it can model multivariate data and incorporate many different types of family structure. Models get presented as path diagrams, structural equations and covariance matrices, and it is possible to translate one into the other. Model fitting allows different types of models to be explicitly tested and compared to a saturated model and it facilitates the estimation of confidence intervals around the parameter estimates. SEM programs estimate model parameters by minimizing a goodness-of-fit statistic between observed and predicted covariance matrices. One of the most common criteria used to test goodness-of-fit is the maximum-likelihood. By iteratively adjusting the values of the unknown parameters one can maximize the log-likelihood. This procedure, called optimization or minimization, is carried out until parameter estimates are obtained that maximize the log-likelihood (i.e., smallest discrepancies between the model and the data). The differences between two nested (i.e., one model is a submodel of the other model) models can be tested by the -2*differences in log-likelihoods and the differences in degrees of freedom. Minus 2 times the differences in log-likelihood is X^2 distributed. A non-

significant X^2 value ($p>0.05$) means that the simpler model is consistent with the data, whereas a significant X^2 value implies that the simpler model gives a poor fit to the data and can hence be rejected. Components (path coefficients) can be tested to see whether they significantly differ from zero (i.e., are present). For instance, one can compare an AE model with an ACE model to see if the common environmental component is significant. If not significant, then the simpler model (i.e., AE) is preferred since it provides a more parsimonious explanation of the observed data (Neale and Cardon, 1992; Sham, 1998).

1.7 Aim and Outline of the Thesis

The general aim of this thesis is to examine changes in brain volume and intelligence over time in schizophrenia and in health. I conducted two studies comprising healthy individuals only. The other studies examine schizophrenia patients compared with healthy controls. Three out of five studies are conducted in twins making it possible to separate the relative contributions of genetic and environmental influences of individual differences in the examined phenotypes (i.e., liability of schizophrenia and cortical thickness/surface area change plus brain volume change/surface area change and intelligence).

In Chapter, 2 I perform a systematic review of fifty-six longitudinal MRI studies on global brain volume change in healthy individuals. This review makes it possible to investigate the extent of brain volume change across the life-span, from childhood to the age of 90.

In Chapter 3, I compare change in intelligence quotient during a 5-year interval in chronically ill schizophrenia patients, their discordant co-twins and healthy control twins. By using a twin design, I explore whether these (possible) changes in intelligence are of genetic or environmental origin.

In Chapter 4 I conduct a meta-analysis to determine the magnitude and extent of IQ-change over time in schizophrenia patients compared to healthy control subjects. One of the major advantages of a meta-analysis is that it allows for the estimation of an effect-size statistic, which represents the quantitative findings of the studies included in a standardized form. This, in turn, permits meaningful comparison across the studies (Lipsey and Wilson, 2001). In this analysis, I also want to investigate whether several confounding factors (e.g., duration of illness, age of onset, follow-up duration) explain the overall effect size.

In Chapter 5, I compare cortical thickness and surface area change between twins discordant for schizophrenia and healthy control twins over a five-year interval. I aim to disentangle the relative contributions of genetic and environmental influences on cortical thickness and surface area change and whether these brain phenotypes and liability for schizophrenia share common genes. This study uses a ROI approach to examine in which part of the brain changes are most pronounced. Moreover, I will report the heritability of cortical thickness and surface area change over time.

In Chapter 6, I use a longitudinal extended twin design with siblings including 176 adult individuals from 86 twin families between 19-56 years of age, to study the influences of genes and environment on brain plasticity and intelligence. Including siblings of the twins increases the power of the statistical analyses. The heritability of brain volume change and surface area change in adulthood will be estimated. Moreover, by using a bivariate design in structural equation modeling, I aim to investigate whether intelligence and brain volume change are associated and whether these (possible) associations are genetic in origin.

Chapter 7 provides a brief summary and an overview of the main results, including implications for future research.

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Chapter 2

Human Brain Changes Across the Life Span: a review of 56 longitudinal magnetic resonance imaging studies

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Abstract

There is consistent evidence that brain volume changes in early and late life. Most longitudinal studies usually only span a few years and include a limited number of participants. In this review we integrate findings from 56 longitudinal magnetic resonance imaging studies on whole brain volume change in healthy individuals. The individual longitudinal MRI studies describe only the development in a limited age-range. In total, 2,211 participants were included. Age at first measurement varied between 4 and 88 years of age. The studies included in this review were performed using a large range of methods (e.g., different scanner protocols and different acquisition parameters). We applied a weighted regression analysis to estimate the age-dependency of the rate of relative annual brain volume change across studies.

The results indicate that whole brain volume changes throughout the lifespan. A wave of growth occurs during childhood/adolescence, where around 9 years of age a 1 percent annual brain growth is found which levels off until at age 13 a gradual volume decrease sets in. During young adulthood, between approximately 18 and 35 years of age, possibly another wave of growth occurs or at least a period of no brain tissue loss. After age 35 years a steady volume loss is found of 0.2% per year, which accelerates gradually to an annual brain volume loss of 0.5% at age 60. The brains of people over 60 years of age show a steady volume loss of more than 0.5%.

Understanding the mechanisms underlying these plastic brain changes may contribute to distinguishing progressive brain changes in psychiatric and neurological diseases from healthy aging processes.

Introduction

Comparison of brain weight between people at different ages has suggested that considerable volume change takes place during development in humans. It has been shown in an autopsy study that included more than 4,000 individuals across the full age range that the most pronounced increase in brain weight occurs during the first 3 years of life (Dekaban, 1978). Between age 3 and 18 the brain increases in weight to about 5 times that of a newborn. At approximately 45 to 50 years of age a progressive decline in brain weight begins and reaches the lowest values after the age of 86. By then it is about 11% smaller relative to the maximum brain weight attained around 19 years of age. Another post-mortem study suggests that it is after the age of 80 that the brain mass is rapidly decreasing (Ho et al., 1980). Cross-sectional studies suggest a linear decline in cerebral volume throughout adulthood (Raz et al., 2004) with an estimated volume loss of an average of 14% at age 90 (Jernigan et al., 2001).

Magnetic Resonance Imaging (MRI) provides us with the opportunity to study brain development within subjects *over time*. In longitudinal studies participants can serve as their own control and therefore subtle changes can be identified on an individual level. Longitudinal studies have revealed that brain changes occur in childhood, and in adulthood including in old age. However, to date, individual longitudinal MRI studies describe only the development in a limited age-range as scanning subjects across their whole life span requires a very long interval. While having shown that brain changes occur during the whole life span, each of these studies provides a key-hole representation of these changes at a limited age span. Specifically, these studies do not allow for a direct comparison between childhood and adult changes and between young adult and old adult changes. It is during these transitions that important changes may take place. Therefore, we reviewed and integrated the findings of longitudinal MRI studies in healthy subjects throughout the lifespan on whole brain volume change.

Methods

Data Sources

A systematic search was conducted to identify magnetic resonance imaging (MRI) studies that quantitatively examined longitudinal whole brain volume changes in healthy individuals with at least two MRI scans at different time points. These studies were obtained through the computerized database PUBMED for English-language articles published until January 1st 2010. The keywords combinations used in the computerized search were *"MRI and longitudinal and "whole brain"", "Brain volume change(s) and longitudinal and MRI and healthy subjects".* Articles were examined to investigate whether papers reached the inclusion criteria (see below). Additional studies were obtained by hand search of cross-references in already identified papers. From the studies that were found, those that also reported on volume change over time in gray matter (GM) and/or white matter (WM) volume were identified.

Study Selection

Studies were included if they (1) were longitudinal MRI studies with at least two MRI scans, (2) investigated healthy individuals, (3) provided quantitative measures of whole brain volume change, and (4) were published in the English language in scientific peer-review journals.

Statistical Analysis and Data Extraction

Whole brain, GM and WM volume change in percent-change per year (Q) was extracted from the studies. The formula for this calculation was:

$$Q = \Delta V/(V1*\Delta t)*100\%$$

with ΔV= V2-V1 representing the volume change between volume (V1) at baseline (t1) and volume (V2) at follow-up (t2) and Δt=t2-t1 representing the time between t1 and t2. For each study, mean age of the sample was defined as the mean age halfway the interval. It was measured based on either mean age at t1 or t2 in years (dependent on what was available) and the interval of the longitudinal measurement in years as follows: [t1 + (follow-up interval)/2] or [t2 – (follow-up interval)/2].

For whole brain volume change regression analysis in the form of a locally-weighted running-line smoother (Cleveland and Devlin, 1988; Hastie and Tibshirani, 1990) was used to obtain the dependence of Q on age. Software for these analyses was developed in house (van Haren et al., 2008). First, the data were split into two age ranges based on the mean age of the sample, i.e., from 7 to 19 years and from 19 to 84 years. This was done because there are only a limited number of studies available covering the age range between 18 and 21 years, preventing us from making a reliable connection between development during childhood and adolescence and development during the adult age range. The degrees of freedom of the fits was set to a conservative value of 3, the lowest number allowing some curvature in the fits, since there is no (statistical) support for higher values.

Smoothed Q was numerically integrated to obtain volume as a function of age: Volume(age) = Volume(age0) * exp(Integrate[Q(age')/100, {age', age0, age}]). The division by 100 is beause Q is given in %; the 'exp' is because integration of Q leads to the log of Volume, since Q is a relative measure. Age0 and Volume(age0) are taken from the study of 9 year olds by Peper et al. (2009)*;* the endpoint of the integration of the younger age group was the starting point of the integration of the older age group (19 year).

For GM and WM volume change percent change per year was calculated according to the same procedure as described previously. For those studies in the adult age range (> 19 years) we smoothed the GM and WM data using the locally-weighted running-line smoother (3 dfs). The studies in childhood and adolescence were excluded from the smoothing procedure as there were too few studies that provided data on GM/WM changes.

Results

Fifty-six studies were identified as suitable for our review. Table 1 lists the included articles. DeLisi et al. (1992) published the first longitudinal study that included healthy controls. The number of participants per study ranged from 7 (Henley et al., 2006) to 228 (Lenroot et al., 2007). Minimum interval between the MRI scans was 29 days (Pfefferbaum et al., 1995) while the maximum interval was 10 years (DeLisi et al., 2004).

Table 1 | Overview of the longitudinal studies on whole brain volume change in healthy individuals

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
DeLisi et al. 1992	N=33	28.0 (6.3)	29.0	2	cerebrum corrected for baseline brain volume	1.5T GE, spin echo pulse sequence, 5-mm slice thickness with 2-mm gap in coronal and sagittal plane	manual	no information
DeLisi et al. 1995	N=5, completely overlapping with DeLisi et al., 1992	28.2 (6.0)	30.2	4	cerebrum corrected for baseline brain volume	1.5T GE, spin echo pulse sequence, 5-mm slice thickness with 2-mm gap in coronal, axial and sagittal plane	manual	no information
Pfefferbaum et al. 1995	N=58	45.3 (14.2)	45.4	0.1	cerebrum corrected for baseline brain volume	1.5T GE, spin echo sequence, 5-mm slice thickness with 2.5 -mm gap in axial plane	semi-automated	no information
Fox et al. 1996	N=11	51.3 (5.9)	51.8	1.07	whole brain	1.5T GE, SPGR, 1.5-mm slice thickness	semi-automated	Q=-0.05
DeLisi et al. 1997	N=20	26.5 (5.0)	28.7	4.3 (1.1)	cerebrum, corrected for sex and baseline hemispheric volume	1.5T GE, spin echo pulse sequence, 5-mm slice thickness with 2-mm gap	manual	Q=-0.70
Gur et al. 1998	N=17	31.9 (8.9)	33.3	2.7	whole brain corrected for baseline volume	1.5T GE, multiecho sequence, 5-mm slice thickness in transaxial plane	automated	no information

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Mueller et al. 1998	N=46 A:N=11 B:N=15 C:N=20	A: 87.0(2.2) [85.1-93.1] B: 81.1 (2.8) [75.7-84.8] C: 70.4 (2.4) [66.6-73.7]	A: 72.4 B: 82.8 C: 88.5	A:3.10 (1.21) [3-6] B:3.47 (1.25) [3-6] C:4.09 (0.83) [3-5]	cerebrum corrected for IC	1.5T, multiecho, multiplanar image acquisition, contiguous slices with 4-mm slice thickness in coronal plane. 14 scans acquired in the first year had a 2.5-mm gap	semi-automated	A: Q=-0.44 B: Q=-0.39 C: Q=-0.32
Fox et al. 1999a	N=15, completely overlapping with Fox et al., 2000	55.3 (14.0)	56.2	1.7 (1.2)	whole brain	1.5T GE, SPGR, 1.5-mm slice thickness in coronal plane	semi-automated (BBSI)	Q=-0.40 (0.70)
Fox et al. 1999b	N=26	no information		approx 1	cerebrum	1.5T, T1-weighted 1.5-mm slice thickness	semi-automated (BBSI)	median Q=-0.20
Giedd et al. 1999a	N=36, complete overlap with Lenroot et al., 2007	13.6 (2.6)	14.6	approx. 2	cerebrum, corrected for age	1.5T GE, SPGR, 1.5-mm slice thickness in axial plane	semi-automated	trajectory
Giedd et al. 1999b	N=65, complete overlap with Lenroot et al., 2007	4.2 - 21.6, N=145		approx. 2	cerebrum corrected for sex	1.5T GE, SPGR, 1.5-mm slice thickness in axial plane	semi-automated	trajectory
Fox et al. 2000	N=18	65.0 (10.5) [52-84]	65.5	0.89	cerebrum corrected for baseline volume	1.5T GE, SPGR, 1.5-mm slice thickness in coronal plane	semi-automated (BBSI)	Q=-0.41 (0.47)

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Chan et al. 2001	N=27	59.6 (11.7)	60.2	1.06	whole brain corrected for sex	1.5T GE, SPGR, 1.5-mm slice thickness	semi-automated (BBSI)	Q=-0.47 (0.40)
Cohen et al. 2001*	N=25, female only	weighted mean: 59.8	60.8	2	cerebrum corrected for IC	1.5T GE, 3D gradient echo sequence with RF spoiling, 1.5-mm slice thickness	semi-automated	weighted mean: Q=-0.19
Hu et al. 2001	N=10	71.6 (9.5)	72.4	1.59	whole brain	1.0T Picker, 3D, slice-thickness 1.6-mm in sagittal plane	semi-automated	Q=-0.06 [-0.61-0.34]
Liu et al. 2001	N=20, complete overlap with Liu et al., 2003	median: 35 (18-81)	36.8	median: 3.5	whole brain corrected for baseline volume	1.5T GE, IR-SPGR, 1.5-mm slice thickness	automated	Q=-0.11
Tang et al. 2001	N=66	78.4 (2.9) [74-87]	80.6	4.4 (3-5)	cerebrum corrected for baseline volume	1.5T GE, T2-weighted images with 5-mm slice thickness and 1.5-mm gap in axial plane	manual with Cavalieri principle	Q=-2.10 (1.6)
Wood et al. 2001	N=26	23.8 (7.9)	24.9	2.2 [0.86-4.18]	whole brain corrected for IC	1.5T GE, SPGR, 1.5-mm slice thickness	semi-automated	no information

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Cahn et al. 2002	N=36, N=35 overlap with van Haren et al., 2008	24.5 (5.8) [17-40]	25.0	1.04	whole brain corrected for IC, age and sex	1.5T Philips, FFE, 1.2-mm slice thickness in coronal plane	automated	Q=+0.95
James et al. 2002	N=16	16.0 (2.0)	16.9	1.7 (0.5)	whole brain	1.5T GE, spin echo, 5-mm slice thickness in sagittal plane and volumetric T1-weighted SPGR with 3-mm slice thickness in coronal plane	semi-automated	no information
Cardenas et al. 2003	N=16	76.0 (5.0)	77.3	2.6 (1.0)	whole brain	1.5 T Siemens, MP-RAGE, 3-mm slice thickness	semi-automated (BBSI)	Q=-0.20 (0.10)
Ho et al. 2003	N=23	26.9 (5.3) [16-35]	28.6	3.39 (1.60) [0.92 - 6.67]	whole brain corrected for sex, height, age and interval duration	1.5T GE, spoiled GRASS, 1.5-mm slice thickness in coronal plane	manual	Q=+0.12
Liu et al. 2003	N=90 A: N(<35y)=44 B: N(35-54y) =37 C: N(>54y)=9	A: 24.5 (6.6) [14-34] B: 44.5 (5.7) [35-53] C: 67.9 (6.4) [57-77]	A: 26.3 B: 46.3 C: 69.7	A: 3.57 B: 3.53 C: 3.52	whole brain corrected for baseline MRI-volume and sex	1.5T GE, IR-SPGR, 1.5-mm slice thickness in coronal plane	automated	A: Q=-0.06 B: Q=-0.18 C: Q=-0.38

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Resnick et al. 2003	N=92	70.4 (7.0) [59-85]	72.4	2	cerebrum corrected for baseline volume, age and sex	1.5T GE, SPGR, 1.5-mm slice thickness	semi-automated	Q=-0.5
Rusinek et al. 2003	N=32	68.2 (5.1)	69.2	2.2	whole brain corrected for baseline volume, age, sex and education	1.5T GE, SPGR, 1.3-mm slice thickness in coronal plane	automated	Q=-0.58 (0.42)
Scahill et al. 2003	N=39 A:N=8 B:N=10 C:N=10 D:N=6 E:N=5	weighted mean: 52.4y [31-84] A: 36.1 (2.5) B: 45.6 (2.9) C: 53.9 (3.5) D: 62.7 (2.3) E: 76.8 (5.5)	53.3 A: 36.9 B: 46.5 C: 54.9 D: 63.7 E: 77.3	weighted mean: 1.72 A: 1.57 B: 1.83 C: 1.91 D: 2.07 E: 0.98	whole brain corrected for IC, sex and age	1.5T GE, 1.5-mm slices thickness in coronal plane	semi-automated (BBSI)	Total: Q=-0.32 [-0.10 - -0.54] A: Q=-0.29 B: Q=-0.35 C: Q=-0.26 D: Q=-0.46 E: Q=-0.55
Sporn et al. 2003	N=43, complete overlap with Lenroot et al., 2007	14.8 (2.2)	16.6	3.6 (1.6)	cerebrum corrected for baseline brain volume	1.5T GE, SPGR, 1.5-mm slice thickness in axial plane	automated	Q=-0.26
Thompson et al. 2003	N=14	71.4 (0.9)	72.7	2.6 (0.3)	cerebrum, corrected for age and sex	2T Bruker Medspec, 3D MP-RAGE in oblique plane	automated	Q=-0.88 (0.15)

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
DeLisi et al. 2004	N=10, complete overlap with DeLisi et al., 1997	at follow-up: 35.5 (5.38) [24 -43]	30.5	10	cerebrum, corrected for sex and baseline volume	1.5T GE, spin echo pulse sequence, 5-mm slice thickness with 2-mm gap	manual	Q=-0.41
Ezekiel et al. 2004	N=22	76.7 (8.1)	77.7	2.0 (0.7)	whole brain	1.5T Siemens, MP-RAGE, 1.4-mm slice thickness	semi-automated (BBSI)	Q=-0.49 (0.39)
Gogtay et al. 2004	N=38, complete overlap with Lenroot et al., 2007	13.3 (3.1)	14.6	2.6 (0.8)	cerebrum	1.5T GE, SPGR, 1.5-mm slice thickness in axial plane	automated	Q=-0.17
Jack Jr et al. 2004	N=40	79 (56 - 93)	81.2	4.3 (2.5-5.2)	whole brain corrected for baseline MRI-volume	1.5T GE, SPGR, 1.6-mm slice thickness	automated	median, Q=-0.4 [-0.5-0.2]
Blumberg et al. 2005	N=8	15.3 (2.8) [11-19]	16.3	2.0 (0.6)	whole brain	1.5T GE, SPGR, 1.2-mm slice thickness in sagittal plane	automated	no information

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Fotenos et al. 2005	N=38	at baseline N=94 78.0 (8) [65 - 95]	78.9	1.8 (0.5) [1.1 - 3.9]	whole brain corrected for IC, age and sex	1.5T Siemens, MR-RAGE, 1.25-mm slice thickness	automated	Q=-0.45 (0.53)
Goldstein et al. 2005	N=121 A:N=62 B:N=59	66.2 (6.0) A: [55-66] B: [67-79]	68.7	4.9 (0.63)	whole brain corrected for IC	1.5T Picker, transverse asymmetrical dual spin-echo Carr-Purcell-Meiboom-Gill sequence, interleaved 3-mm slice thickness in axial plane	manual	weighted mean: Q=-0.62 A: Q=-0.50 B: Q=-0.73
Lieberman et al. 2005	N=44	25.5 (4.1) from the baseline sample with 62 participants.	26.0	1.00	whole brain corrected for IC	1,5T GE and Philips, IR-SPGR, 1.5-mm slice-thickness in axial plane	automated	Q=+0.60
Schott et al. 2005	N=19	69.3 (7)	70.3	1.00	whole brain	1.5T GE, spoiled fast GRASS, 1.5-mm slice thickness	semi-automated (BBSI) and manual	BBSI: Q=-0.72 manual: Q=-0.97
Whitworth et al. 2005	N=20	at follow-up: 31.5 (4.9) y	29.7	3.70 (1.63)	whole brain corrected for age and height	1.5T Siemens, MP-RAGE, 0.9-1.4-mm slice-thickness in sagittal plane	semi-automated	Q=+0.13

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Henley et al. 2006	N=7	40.7 (10.5)	40.9	0.48	whole brain corrected for IC, age and IQ	1.5T GE, IR prepared fast spoiled GRASS sequence, 1.5-mm slice thickness in coronal plane	semi-automated (BBSI)	Q=-0.26 (0.54)
Paviour et al. 2006	N=18	66.8 (5.4) [56-74]	67.2	0.69	whole brain corrected for baseline MRI volume	1.5T GE, SPGR, 1.5-mm slice thickness	semi-automated	Q=-0.4 (0.5)
Ridha et al. 2006	N=25	46.5 (10)	47.3	1.5 (0.8)	whole brain corrected for IC and sex	1.5 T GE, SPGR, 1.5-mm slice thickness in coronal plane	semi-automated (BBSI)	Q=-0.01 (0.57)
Chen et al. 2007**	N=36 (ApoE e4)	weighted mean: 56.8	57.9	weighted mean: 2.17	whole brain corrected for IC and sex	1.5T GE, SPGR, 1.5-mm slice thickness	semi-automated (BBSI)	weighted mean: Q=-0.11
Lenroot et al. 2007	N=228	at follow-up: 13.0 (3.9)	12.3	1.5	cerebrum, corrected for IC and age	1.5T GE, SPGR, 1.5-mm slice thickness in axial plane	automated	different developmental trajectories for boys and girls
Autti et al. 2008	N=12	12.6 (0.9)	15.9	6.5 (0.5)	whole brain, corrected for IC and sex	1.5T Siemens, MP-RAGE, 1.0-mm slice thickness	automated	Q=-0.20 (0.5)

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Brans et al. 2008a ***	N=54 twins, N=29 overlap with van Haren et al., 2008	weighted mean: 35.4	37.8	weighted mean: 4.81	whole brain corrected for IC, age and sex	1.5T Philips, FFE, 1.2-mm slice thickness in coronal plane	automated	Q=-0.07
Brans et al. 2008b	N=33, N=32 overlap with van Haren et al., 2008	40.2 (8.2)	42.7	5.02 (0.39)	whole brain corrected for IC, age and sex	1.5T Philips, FFE, 1.2-mm slice thickness in coronal plane	automated	Q=-0.04
Fisher et al. 2008	N=17	41.6 (8.1) [32-56]	43.6	4	BPF (Brain Paraenchymal Fraction)	1.5T, T1-weighted spin echo image with and without contrast, 5-mm slice thickness and T2-weighted FLAIR	automated	no information
Fotenos et al. 2008	N= 33, complete overlapping with Fotenos et al., 2005	weighted mean: 77.3	79.5	weighted mean: 4.35 [3.1 - 6.5]	whole brain corrected for IC, age and sex	1.5T Siemens, MP-RAGE, 1.25-mm slice thickness	automated	weighted mean: Q=-0.53
Rais et al. 2008	N=31, N=29 overlap with van Haren et al., 2008	24.7 (6.7) [16.7-40.2]	27.3	5.21 (0.18) [4.78 - 5.50]	whole brain corrected for IC, age and sex	1.5T Philips, FFE, 1.2-mm slice thickness in coronal plane	semi-automated	Q=-0.07

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Silbert et al. 2008	N=104	85.1 (5.6) [64.6-88.2]	88.2	1.3 (0.7) [0.9-5.5]	cerebrum	1.5T, multiecho sequence, 4-mm slice thickness in sagittal plane	automated	Q=-0.67
Sluimer et al. 2008a	N=23	66 (9)	67.0	1.9 (1.0)	whole brain corrected for age and sex	1.0T Siemens, MP-RAGE, 1.5-mm slice thickness in coronal plane	automated	Q=-0.6 (0.6)
Sluimer et al. 2008b	N=10	69 (7)	70.2	2.3 (0.5)	whole brain corrected for age and sex	1.0T Siemens, MP-RAGE, 1.5-mm slice thickness in coronal plane	automated	Q=-0.50 (0.5)
Van Haren et al. 2008	N=113	35.3 (12.3) [16.8-56.3]	37.8	4.94 (0.32)	whole brain corrected for IC, age and sex	1.5T Philips, FFE, 1.2-mm slice thickness in coronal plane	automated	Q=-0.15
Driscoll et al. 2009	N=120, partly overlapping with Resnick et al., 2003	70.6 (6.1) [64-86]	73.6	6.02 (2.91) [1-10]	cerebrum corrected for IC, age and sex	1.5T GE, SPGR, 1.5-mm-slice thickness	semi-automated	Q=-0.77 , MRI baseline volume was read from a graph

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Brain region	Acquisition protocol	Method of analysis	Relative Rate of % Brain Volume Change/Year (mean (SD) [range])
Ment et al. 2009	N=20	8.6 (0.7)	10.4	3.5	whole brain, corrected for age, sex and interval	1.5T GE, SPGR, 1.5-mm slice thickness in axial plane	automated	Q=+0.98
Reig et al. 2009	N=34	15.8 (1.4) [13-18]	16.8	2.02	whole brain, corrected for IC	1.5T Philips, gradient echo sequence with 1.5-mm slice thickness	semi-automated	weighted mean: Q=-0.17 Boys: Q=-0.29 Girls: Q=+0.01

Abbreviations: N=Number of subjects, SD=standard deviation, yrs=years, IC=Intracranial volume, GE=General Electrics, T=Tesla, SPGR=Spoiled Prepared Gradient Recalled Echo sequence, IR=Inversion Recovery, MP-RAGE=Magnetization Prepared Rapid Gradient Echo, GRASS=Gradient Recalled Acquisition in Steady State, FFE=Fast Field Echo, FLAIR=Fluid Attenuated Inversion Recovery

*9 APOE-e4 allele negative and 16 APOE-e4 allele positive subjects. Age and relative rate of brain volume change per year are weighted in relation to the population frequency of ApoE-e4 carriers (Cumming and Robertson, 1984)
**10 homozygote for ApoE e4, 10 heterozygote for ApoE e4 and 16 noncarriers. Age, follow-up period and relative rate of brain volume change per year are weighted in relation to the population frequencies for ApoE-carriers (Hill et al., 2007)
***Age, follow-up period and relative rate of brain volume change are weighted for healthy controls in monozygotic and dizygotic group.
“no information” in the column for “Relative rate of % Brain Volume Change/Year” indicates that there was no information available to extract percentage brain volume change per year. These studies were excluded from the smoothing analysis.

Out of these 56, nine studies provided data on GM and WM matter volume change over time and one study provided data on only GM volume change. Table 2 lists the articles with GM and WM volume change. Whenever it states “no results” in the tables for the column(s) “Relative rate of % Brain/GM/WM Volume Change/Year” it means that there was no information available to extract percentage change per year. These studies were left out from the smoothing analysis.

MRI Acquisition and Processing Specifics

The majority of the Magnetic Resonance Imaging studies acquired T1-weighted images (SPGR, FFE, or MPRAGE depending on manufacturer being GE, Philips or Siemens respectively) on a 1.5 Tesla scanner. Brain scans were obtained in either axial, sagittal or coronal plane with slice thickness ranging from 0.9 mm to 5 mm. Images were segmented using manual, semi-automated, or automated procedures or with a combination of these. For details see Table 1.

Study Specific Details

Several studies published data on totally or partly overlapping samples. To prevent bias these studies were identified and the study with the highest number of participants (usually the most recent study) was included in the regression plots (see Table 1).

One study included only female subjects (Cohen et al., 2001) and two studies included only male subjects (Withworth et al., 2005; Pfefferbaum et al., 1995). Eighteen studies measured cerebrum volume and the remainder of the studies (N=38) measured whole brain volume.

Table 2 | Overview of the longitudinal studies for GM and WM volume changes in healthy individuals

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Relative Rate of % WB Volume Change/Year (mean, SD, range)	Relative Rate of % GM Volume Change/Year (mean, SD, range)	Relative Rate of % WM Volume Change/Year (mean, SD, [range])
Ment et al. 2009	N=20	8.6 (0.7)	10.4	3.5	Q=+0.98	Q=-2.73	Q=+7.51
Lenroot et al. 2007	N=228	at follow-up: 13.0 (3.9)	12.3	1.5	different developmental trajectories for boys and girls	different developmental trajectories for boys and girls	different developmental trajectories for boys and girls
Autti et al. 2008	N=12	12.6 (0.9)	15.9	6.5 (0.5)	Q=-0.20 (0.5)	Q=-0.30 (0.60)	Q=+0.80 (0.70)
Reig et al. 2009	N=34	15.8 (1.4) [13-18]	16.8	2.0	weighted mean: Q=-0.17 Boys: Q=-0.29 Girls: Q=+0.01	weighted mean: Q=-0.74 Boys: Q=-1.01 Girls: Q=-0.30	weighted mean: Q=+1.03 Boys: Q=+1.26 Girls: Q=+0.65
Lieberman et al. 2005	N=44	25.5 (4.13) from the baseline sample with 62 participants.	26.0	1.0	Q=+0.60	Q=+0.59	Q=+0.62

Authors, year	Subjects	Age at baseline (yrs: mean(SD)[range])	Age in between scans (yrs: mean)	Interval (yrs: mean (SD) [range])	Relative Rate of % WB Volume Change/Year (mean, SD, range	Relative Rate of % GM Volume Change/Year (mean, SD, range	Relative Rate of % WM Volume Change/Year (mean, SD, [range])
Van Haren et al. 2008	N=113	35.3 (12.3) [16.8-56.3]	37.8	4.9 (0.3)	Q=-0.15	Q=-0.15	Q=+0.30
Liu et al. 2003	N=90 A: N(<35y)=44 B: N(35-54y)=37 C: N(>54y)=9	A: 24.5 (6.6) [14-34] B: 44.5 (5.7) [35-53] C: 67.9 (6.4) [57-77]	26.3 46.3 69.7	A: 3.6 B: 3.5 C: 3.5	A: Q=-0.06 B: Q=-0.18 C: Q=-0.38	A: Q=-0.11 B: Q=-0.02 C: Q=-0.26	A: Q=+0.06 B: Q=-0.43 C: Q=-0.57
Driscoll et al. 2009	N=120, partly overlapping with Resnick et al., 2003	70.6 (6.1) [64-86]	73.6	6.0 (2.9) [1-10]	Q=-0.77 , MRI baseline volume was read from a graph	Q=-0.50, MRI baseline volume was read from a graph	Q=-1.07, MRI baseline volume was read from a graph
Thompson et al. 2003	N=14	71.4 (0.9)	72.7	2.6 (0.3)	Q=-0.88 (0.15)	Q=-0.91 (0.92)	Q=-2.72 (1.44)
Cardenas et al. 2003	N=16	76.0 (5.0)	77.3	2.6 (1.0)	Q=-0.20 (0.10)	Q=-0.90 (1.40)	no information

Abbreviations: N=Number of subjects, SD=standard deviation, yrs=years, WB=Whole Brain, GM=Gray Matter, WM=White Matter, “no information” in the column for “Relative rate of % Brain Volume Change/Year” indicates that there was no information available to extract percentage brain volume change per year. These studies were excluded from the smoothing analysis.

As we were interested in relative brain volume change this was not a problem in this study. Findings from twenty studies were corrected for intracranial volume (ICV) and 17 studies for baseline brain volume. Seventeen studies reported brain volume change after correcting for age and sex. An additional four studies only corrected for age while another six studies corrected only for sex. Here, the rate of change for whole brain, gray and white matter volumes is based on the uncorrected data (if present). In the study by Lieberman et al. (2005), the follow-up interval with 52 weeks with N=44 was used in the review, but baseline volumes of N=52 were used to calculate the rate of change per year.

Two studies were designed to investigate the effect of Apolipoprotein Epsilon e4+ (ApoE e4+) on whole brain volume change (Cohen et al., 2001;Chen et al., 2007). Groups were either defined as ApoE e4+ carrier or non-carrier (Cohen et al., 2001) or subjects were divided in three groups being either homozygous (non-carriers or carriers) or heterozygous for ApoE e4+ (Chen et al., 2007). The frequency of ApoE e4+ carriers in the total population of white Caucasians is 15% (Cumming and Robertson, 1984). In addition, the frequency of being homozygous or heterozygous for ApoE e4+ is approximately 2% and 26.5% respectively (Hill et al., 2007). Weighted means of rate of whole brain volume change per year were calculated using these known frequency distributions. For ApoE e4+ carriers (Cohen et al., 2001) the formula is as follows: (0.15 * Q in ApoE 4+ carriers) + (0.85 * Q in ApoE e4+ non-carriers). The formula for the study by Chen et al. (2007) is as follows: (homozygous: 0.02 * Q) + (heterozygous: 0.27 * Q) + (non-carriers: 0.71 * Q). Schott et al. (2005) compared two segmentation methods, i.e., Brain Boundary Shift Integrals (BBSI) and manual segmentation. Here, the findings from the manual segmentation were chosen as this is still considered to be the golden standard. One study included monozygotic (MZ) and dizygotic (DZ) twin pairs and reported whole brain volume change for each group separately (Brans et al., 2008a). For our purpose, relative rate of volume change per year was weighted according to the number of dizygotic and monozygotic twins.

In Figure 1 all studies for which relative rate of brain volume change per year was calculated are shown (N=33). Eight studies did not present sufficient information to extract relative rate of whole brain volume change per year. Fifteen studies were excluded as they reported on overlapping samples. Several studies reported results for different age-groups (Mueller et al., 1998; Liu et al., 2003; Scahill et al., 2003) and these individual age-groups are depicted separately. As a result 41 data points are shown. Two studies reported their data as non-

linear trajectories (Lenroot et al., 2007; Van Haren et al., 2008) and their respective trajectories are also shown here.

Figure 2 shows the relative rate of brain volume change per year for each individual study as circles. The area of the circle scales with the number of included subjects. One study is excluded from this analysis since it deviates from all the other studies (Tang et al., 2001). Therefore, fits were based on 32 studies, including 1,393 participants.

In Figure 3 whole brain volume is presented as a function of age, obtained by integration of the fits from Figure 2 with respect to age. As starting volume mean whole brain volume was used from a study of N=210 nine year old twins (Peper et al.,2009).

The results indicate that a wave of growth in whole brain volume occurs during childhood and adolescence, i.e., around 9 years of age a 1 percent annual brain growth is found which levels off until at age 13 a gradual volume decrease sets in. During young adulthood, between approximately 18 and 35 years of age, possibly another wave of growth occurs or at least a period of no brain tissue loss. After age 35 years a steady volume loss is found of 0.2 percent per year, which accelerates gradually to an annual brain volume loss of 0.5 percent at age 60.

Figure 4a and 4b shows the relative rate of GM and WM volume change per year for each individual study as circles. The area of the circle scales as the number of included subjects. A decrease is found in percent GM volume per year in all studies except for one (Lieberman et al., 2005). Those studies that included individuals below the age of approximately 45 years show an increase in percent WM volume per year while studies with subjects older than 45 years of age show decreases. Two studies provided age-related trajectories of GM and WM changes with age (Lenroot et al., 2007; Van Haren et al., 2008). These are added to Figure 4a and 4b.

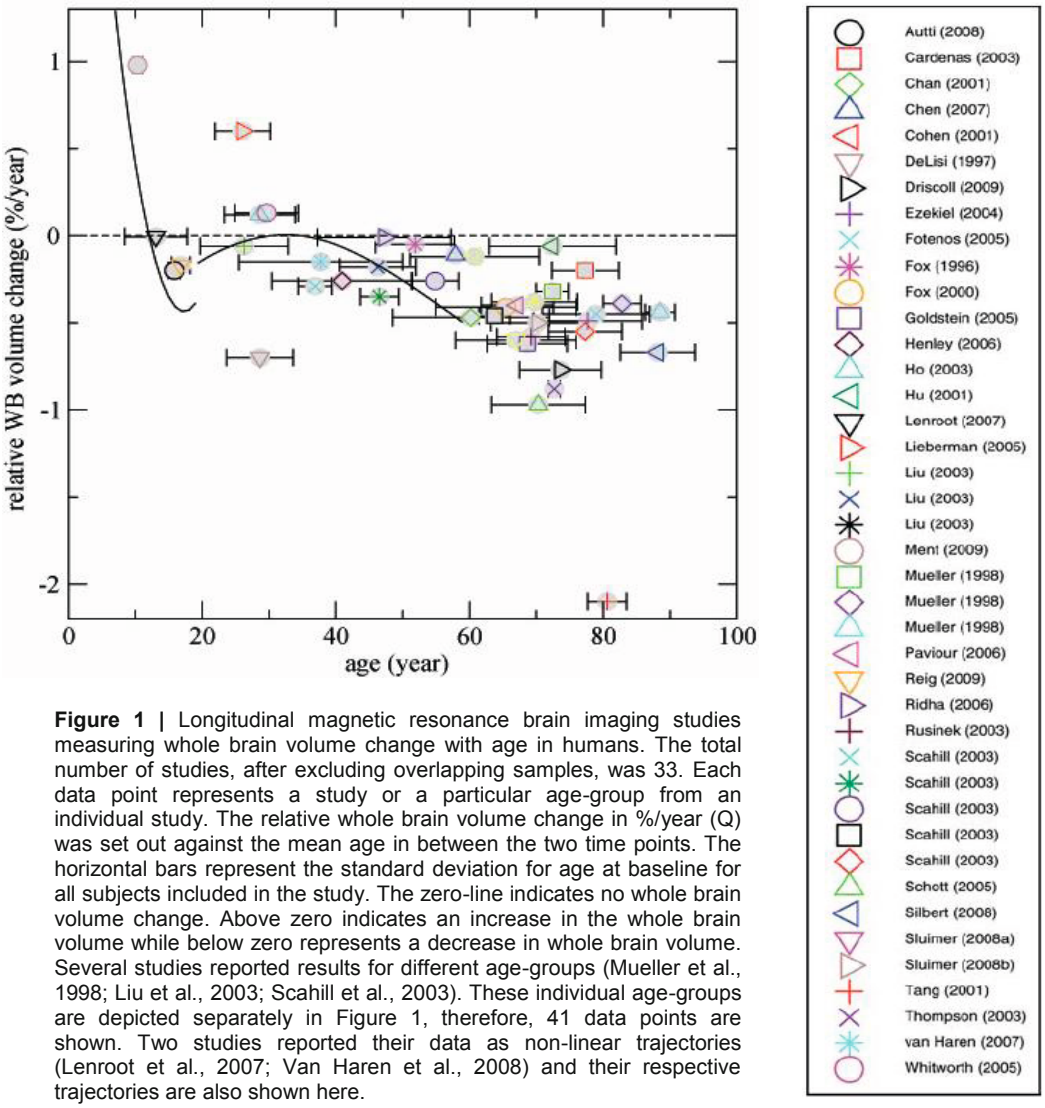


Figure 1 | Longitudinal magnetic resonance brain imaging studies measuring whole brain volume change with age in humans. The total number of studies, after excluding overlapping samples, was 33. Each data point represents a study or a particular age-group from an individual study. The relative whole brain volume change in %/year (Q) was set out against the mean age in between the two time points. The horizontal bars represent the standard deviation for age at baseline for all subjects included in the study. The zero-line indicates no whole brain volume change. Above zero indicates an increase in the whole brain volume while below zero represents a decrease in whole brain volume. Several studies reported results for different age-groups (Mueller et al., 1998; Liu et al., 2003; Scahill et al., 2003). These individual age-groups are depicted separately in Figure 1, therefore, 41 data points are shown. Two studies reported their data as non-linear trajectories (Lenroot et al., 2007; Van Haren et al., 2008) and their respective trajectories are also shown here.

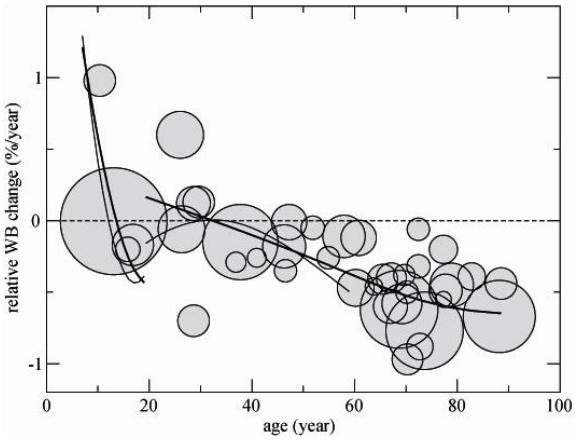


Figure 2 | Fits that show the association between relative rate of whole brain volume change and age. Whole brain volume change data from the individual studies are shown as circles. The area of the circles scales with the number of subjects in the study (a larger area of the circle corresponds to more participants). Fits (with 3 degrees of freedom) were calculated to the data below and above age 19 separately (thick lines). Two studies reported their data as trajectories (Lenroot et al., 2007; Van Haren et al., 2008) and these are made visible (thin lines).

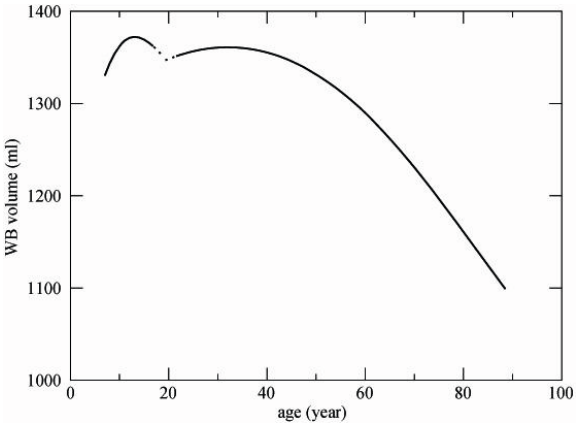
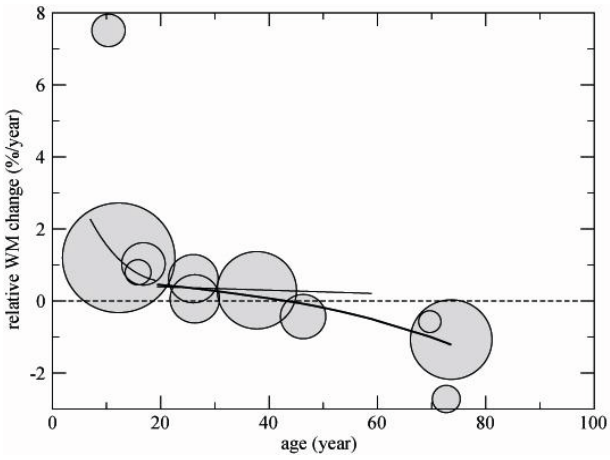
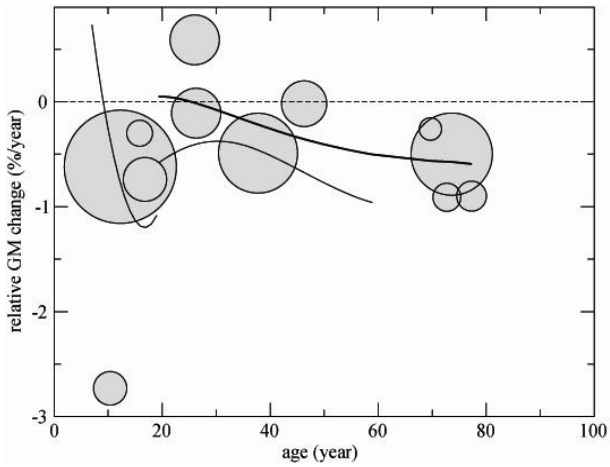


Figure 3 | Whole brain volume across the life span between 4 and 88 years of age. Whole brain volume as a function of age is obtained by numerical integration of the whole brain volume change fits with respect to age from Figure 2. As starting volume the mean whole brain volume from a study of N=210 nine year old twins was used (Peper et al., 2009). The curves are dashed around age 18-21, indicating the uncertainty in this area, since only few data were available for fitting this age range. Two separate fits were calculated for the younger (<19 years) and older (>19 years) group.



(a)



(b)

Figure 4a and 4b | GM and WM volume change with age. Total number of studies that presented data on GM (after excluding overlapping studies) was 10 while 9 studies presented data on WM. The relative GM and WM volume change in %/year (Q) was set out against the mean age in between the two time points. The zero-line indicates no volume change. Above zero indicates an increase in the volume while below zero represents a decrease in volume. The area of the circles scales as the number of subjects in the study. Fits for both GM and WM with age (with 3 degrees of freedom) were calculated to the data above age 19 (thick line). Two studies reported their GM and WM data as trajectories (Lenroot et al., 2007; Van Haren et al., 2008) and these are made visible (thin lines). Liu et al., 2003 reported results for different age-groups. These individual age-groups are depicted separately, therefore, 12 data circles are shown for GM while 11 data circles are shown for WM.

Discussion

In this review findings from longitudinal MRI studies on whole brain volume change in healthy individuals over the full lifespan are integrated. Fifty-six studies were selected including a total of 2,211 healthy individuals. We find that brain volume changes throughout life, not only in childhood and adolescence but also in adulthood. More specifically, the results indicate that brain volume increases during childhood and young adolescence until the age of approximately 13 years. After age 13 years a decrease in whole brain volume sets in. The main finding from the current study is that we provide evidence for a possible second wave of brain volume growth or at least a stable period in early adulthood preceding a brain volume decrease from the age of 35 years with accelerating tissue loss occurring with increasing age.

As is shown in Figure 1, there are three studies that show brain growth in young adulthood (age 20-30 years; Ho et al., 2003; Lieberman et al., 2005; Whitworth et al., 2005; symbols above zero) and two studies showing a decrease (DeLisi et al., 1997; Liu et al., 2003; symbols below zero). Fitting the data from these studies suggests that brain volume slightly increases over time in this age range, but, given the fact that there is no agreement between the different studies, we interpret this result with caution and suggest a possible growth or a plateau period where no change in volume takes place.

Most likely these whole brain volumes changes are a net consequence of many different factors such as focal growth and shrinkage of gray and white matter. Until now, only a limited number of studies have investigated GM and WM volume change over time in longitudinal studies. Our findings suggest an increase in gray matter volume in childhood after which a decrease sets in, while WM increases till the age of approximately 45 years and thereafter starts to decrease.

Indeed, the NIMH group showed that cerebral gray matter volume increases in pre-adolescence (Giedd et al., 1999a; Giedd et al., 1999b; Sporn et al., 2003; Gogtay et al., 2004; Lenroot et al., 2007), after which it starts to decrease in post-adolescence, while cerebral white matter continues to increase in volume (Giedd et al., 1999b). It has been suggested that GM is replaced by WM in childhood and adolescence (Giedd et al., 1999b; Jernigan et al., 1991). In line with our findings, others have suggested that gray matter shows a linear age-related decrease in adulthood but an increase in white matter until midlife which

started to decrease after that in an inverted U-shaped curve (Taki et al., 2009; Van Haren et al., 2008). If indeed there is subtle brain growth in young adulthood as is suggested by the plots in the current review, this might then be explained by white matter increasing more than gray matter is decreasing.

Most studies did not provide sufficient data to investigate differential effects between males and females while those that did report inconsistent findings. One study showed a greater decline in cerebral volume in girls as compared to boys in cerebral volume during the 2nd decade of life (Lenroot et al., 2007). The developmental trajectories suggest that brain volume in girls peaked at 10.5 years while that in boys peaked at 14.5 years. One study, however, was not able to replicate this in children between the ages of 8 to 12 years (Ment et al., 2009). In older age a significant sex difference with more pronounced volume loss in males relative to females has been reported (Driscoll et al., 2009). However, most studies suggested that in adulthood and old age rate of change in whole brain volume is similar in males and females (Autti et al., 2008; Chan et al., 2001; DeLisi et al., 2004; Fotenos et al., 2005; Fotenos et al., 2008; Liu et al., 2003; Ridha et al., 2006; Resnick et al., 2003; Scahill et al., 2003; Tang et al., 2001). Here, we focus on volume change in global measures such as whole brain or gray and white matter. Males do indeed have larger brains, but the available literature in adults on gender differences suggests that males and females have similar rates of change in global brain volume measures.

As to the mechanisms underlying the brain changes throughout life we can only speculate at this point. Our finding of brain changes over the entire life-span suggests continuous brain plasticity throughout life. Brain plasticity can be referred to as the changing of neurons, the reorganization of their networks, and their change in function as a consequence of new experiences. Obviously and fortunately, experiencing new events does not stop at reaching adulthood. In the aging brain it has been proposed that cell shrinkage, degeneration of key neurons and circuits could explain the age-related decrease in brain volume (Morrison & Hof, 1997). We recently found that genes are implicated in brain structure changes in adulthood (Brans et al., 2010). In contrast, there is no evidence that it is synaptic density that explains the adult volume change since a post-mortem study showed that the synaptic density is constant throughout adult life (ages 16-72 years) (Huttenlocher, 1979). Disentangling the processes underlying brain plasticity is important for healthy development and also provides

insight into what may be arrested in brain disorders that have their first symptoms at a particular age.

There are several limitations to the study that have to be considered when interpreting its findings. A limited number of studies were available covering the age range between 18 and 21 years, preventing us from making a reliable connection between development during childhood and adolescence and development during the adult age range. For this reason the data were split in two age ranges. However, since the (mathematical) integration was determined over the full age range, and only the integrand (i.e., the rate of change) was derived from two separate regressions, we can conclude that after the growth wave during childhood and adolescence a second wave of growth or at least a plateau period occurs in young adulthood. Since there remains some uncertainty as to what exactly happens between 18 and 21 years this finding requires confirmation from longitudinal study in subjects between 16 and 25 years.

A few studies did not fit the regression line well and can be considered as outliers. One study included subjects over the age of 80 years and found remarkable losses in brain volume of 2.1 percent per year (Tang et al., 2001). An explanation for this finding may be that it is the only study that used the Cavalieri method to estimate the whole brain volume. One study included subjects with a mean age of approximately 25 years and reported a relatively large decrease of -0.70% per year (DeLisi et al., 1997). Consideration mentioned by the authors was possible artifacts in the scanner over time (see DeLisi et al., 1997).

The differences in acquisition methods and study design may have affected the results, specifically the regression lines. Studies with high resolution scans are expected to be more sensitive to brain volume changes than studies using thicker MRI slices. The high/low resolution studies were more or less evenly distributed over the age range. Studies with large age ranges have to be dealt with carefully, since they tend to average out the change-rate-per-age values. In our analysis, we assume that the scan intervals are short enough (<=6.5 year) so that between the first and the last scan the rate of change will not differ much. For rapidly changing rates and for large age ranges this assumption is violated. In two studies this assumption could be violated (Lenroot et al., 2007; Van Haren et al., 2008). However, these two studies applied an age-dependent analysis, which we incorporated in full in our analysis. Another 6 studies that had an age-range >20 years: (Fox et al., 2000; Liu et al.,

2003; Fotenos et al., 2005; Goldstein et al., 2005; Silbert et al., 2008 and Driscoll et al., 2009). After inspection, these studies do not seem to violate the assumption of piece-wise constant change-rate.

Another issue concerns the definition of “healthy individual” which differed between studies. Some studies excluded participants with a psychiatric history or hypertension, while others did not obtain this information or performed population based studies. In addition, even when using the same scale (such as the MMSE) as a screening, the cutoff for inclusion differed between studies (e.g., 24 for the MMSE in two studies (Mueller et al.,1998; Silbert et al., 2008) and 28 for one other study (Rusinek et al., 2003). Finally, with increasing age the incidence of hypertension, diabetes, white matter hyperintensities (WMH) and cognitive decline most likely increases, so that the inclusion of healthy participants at an older age may be limited to a shrinking population of people that remain (extremely) healthy throughout life. As can be seen from Figure 2 there appears to be a flattering of the decrease in brain volume after the age of 75 years. This might be explained by the inclusion bias mentioned. It is likely that extremely healthy participants are selected in the age-range over 75 years of age. Only those who are physically healthy (can) participate while functionally impaired subjects cannot.

When interpreting longitudinal follow-up studies using complex techniques such as MRI one always has to take into consideration that noise is introduced by changes in the measurement over time. However, it is unlikely that such limitations of the study significantly influenced the results of our analysis. Because of the large number of studies that were included one would expect noise to be largely leveled out. We were able to plot the trajectories of whole brain volume change with age that were present in two studies onto our plot based on all studies. Comparison of these fits with the overall fit shows that both trajectories, i.e. one during childhood and adolescence (Lenroot et al., 2007) as well as one in adulthood (Van Haren et al., 2008), agree nicely with the brain volume change based on all the included longitudinal MRI studies.

In conclusion, we reviewed and integrated the findings of 56 studies investigating longitudinal whole brain volume change. The results indicate that whole brain volume change is an ongoing process throughout the full lifespan with increasing brain volume in childhood and adolescence in the age of approximately 13 years after which a rapid volume decrease sets

in. We found suggestive evidence of a second period of growth or at least stability in brain volume. It is only after the age of 35 years the brain starts to decrease in adulthood. Longitudinal studies that include subjects between 15 and 25 years of age are needed to confirm our finding of a stable or growing whole brain volume during this possibly critical stage of brain development. The results may help in understanding the mechanisms of normal brain changes, and may contribute to distinguishing psychiatric and neurodegenerative diseases from healthy aging processes.

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Chapter 3

Is there change in IQ in chronically ill schizophrenia patients? A longitudinal study in twins discordant for schizophrenia

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Abstract

Intellectual deficits are commonly found in schizophrenia patients. These intellectual deficits have been found to be heritable. However, whether the intellectual deficits change over time and if so, whether the change is related with an increased genetic risk for the disease is not known.

We investigated change of intelligence (IQ) in a twin sample of chronically ill schizophrenia patients, the discordant co-twins and healthy controls during a follow-up period of 5 years. A total of fifty-two twins (9 patients [3 monozygotic (MZ)/ 6 dizygotic (DZ)], 10 unaffected co-twins [3MZ/7DZ] and 33 healthy control twins [21MZ/12DZ]) completed two IQ assessments.

A significant interaction effect over time was found between IQ measurement and illness ($F=4.22$, $df=1$, $p<0.05$), indicating that change in IQ over time is significantly different between the groups. A stable course in IQ over time was found in the patients with schizophrenia (mean IQ from 109.78 at baseline to 108.44 at follow-up) relative to both the healthy control twins who showed a small increase (from 114.61 at baseline to 119.18 at follow-up) ($t=2.06$, $p<0.05$) and the unaffected co-twins (from 111.60 to 117.60; $t=-2.32$, $p<0.05$). IQ change in the unaffected co-twins of schizophrenia patients was comparable to that in healthy control twins ($t=-0.49$, $p=0.63$).

Patients with schizophrenia in the chronic phase of the disease, but not the discordant co-twins, show a lack of increase in IQ, which is likely due to environmental (non-genetic) factors related to the disease.

Introduction

Cognitive deficits are one of the key features of schizophrenia (Kraepelin,1919). In particular, deficits in global measures of cognition, such as intelligence quotient (IQ) or general cognitive ability composite scores (g) are common in patients with schizophrenia (Keefe & Fenton, 2007; Irani et al., 2010). IQ has been shown to be highly heritable in adulthood (Posthuma et al., 2001) and interestingly, genes for schizophrenia partly overlap with genes for intelligence (Toulopoulou et al., 2007).

Cross-sectional studies suggest that there is little evidence for change in IQ during the course of illness suggesting that the lower IQ found in schizophrenia patients is a stable trait (Mockler et al.,1997; Hijman et al., 2003). However, longitudinal studies are more informative as they provide the opportunity to compare the level of IQ within subjects over time. Unfortunately, many longitudinal studies did not include an unaffected control sample (Haywood & Moelis, 1963; Smith,1964; Hamlin, 1969; Klonoff et al., 1970; Russel et al., 1997; Gold et al., 1999; Bedwell et al., 1999; Sheitman et al., 2000; Stirling et al., 2003; Gochman et al., 2005; Van Winkel et al., 2006; Cervellione et al., 2007; Zipparo et al., 2008; Carter et al., 2010). In fact, some studies that do use healthy controls show that patients do not benefit from practice effects as much as controls do (Hoff et al., 2005; Jepsen et al., 2010; but see Hoff et al., 1999; Heaton et al., 2001).

The aim of this study was to investigate the change in IQ over time in a twin sample with chronically ill schizophrenia patients and in unaffected co-twins of patients and to compare these IQ changes with those found in healthy control twins over a follow-up period of five years.

Table 1 | Demographics of the twins

	Twin-sample			
Subjects, N	**Patients (9[1])**	**Co-twins (10[1])**	**Controls (33[2])**	**Statistics**
Follow-up period, years mean (SD)	4.86 (0.79) [4.24-6.56]	4.79 (0.74) [4.24-6.51]	4.80 (0.31) [4.02-5.56]	F=0.06, p=0.94
Sex, M/F, No	6/3	7/3	19/14	X^2=0.62, p=0.78
Age, years mean (SD) [range]	39.94 (11.74) [24.74-57.01]	40.14 (13.09) [20.85-57.01]	34.94 (10.59) [19.44-55.84]	F=1.24, p=0.30
Education, years completed, mean (SD)	11.33 (2.18)	12.20 (2.90)	12.64 (2.55)	F=0.93, p=0.40
Parental education years completed, mean (SD)	12.44 (3.09)	10.60 (3.17)	10.88 (2.03)	F=1.68, p=0.20
Age (y) at first psychotic symptoms, means (SD) [range]	22.11 (5.69) [14-29]			
Duration of illness, y (SD) [range]	17.83 (8.12) [3.23-29.01]			
Type of medication (typical/atypical/both), nr Cumulative haloperidol equivalents, mean (SD)	2/3/2[a] 10363.79 (5844.94)[a]			
IQ time 1, mean (SD)	109.78 (13.10)	111.60 (15.06)	114.61 (12.58)	F=0.57, p=0.57
IQ time 2, mean (SD)	108.44 (13.54)	117.60 (19.77)	119.18 (11.11)	F=2.25, p=0.12
IQ-change, mean (SD)	-1.33 (5.61)[*]	6.00 (7.82)	4.58 (8.06)	F=4.22, p<0.05
PANSS positive symptom score time 1, mean (SD)	11.89 (4.01)			
PANSS negative symptom score time 1, mean (SD)	11.44 (3.54)			
PANSS general symptoms score time 1, mean (SD)	24.78 (6.76)			
PANSS total symptom score time 1, mean (SD)	48.11 (13.45)			
PANSS positive symptom score time 2, mean (SD)	11.44 (3.36)			
PANSS negative symptom score time 2, mean (SD)	9.22 (3.11)			
PANSS general symptoms score time 2, mean (SD)	24.22 (4.47)			
PANSS total symptom score time 2, mean (SD)	44.89 (7.27)			
Total change PANSS positive symptoms score, mean (SD)	0.44 (2.51)			
Total change PANSS negative symptoms score, mean (SD)	-2.22 (3.27)			
Total change PANSS general symptoms score, mean (SD)	-0.56 (6.17)			
Total change PANSS total symptoms score, mean (SD)	-3.22 (9.77)			

[1] 2 complete MZ discordant twin pairs and 4 complete discordant DZ twin pairs . 1 singleton MZ patient, and 2 singleton DZ patient. 1 singleton MZ co-twin and 3 singleton DZ co-twins [2] 6 complete unaffected MZ twin pairs and 5 unaffected complete DZ twin pairs. 9 singleton MZ controls and 2 singleton DZ controls. [a] Information on antipsychotic medication intake was missing in 2 patients * Patients differed significantly in IQ-change compared to healthy controls (p<0.05) and to the unaffected to-twins (p<0.05), where patients slightly decreased and healthy controls and co-twins both increased.

Methods

Participants

From a large cohort of discordant twins and their control twins (Baare et al., 2001; Hulshoff Pol et al., 2004, 2006) we included those individuals (N=52; 9 patients, 10 unaffected co-twins and 33 healthy controls) who were tested twice at a mean interval of approximately 5 years (Brans et al., 2008) and had completed IQ tests at both measurements. Baseline IQ data were available in 21 patients, 18 co-twins, and 53 control twins (mean (SD) patients: 108.67 (14.22), co-twins: 116.78 (13.46), healthy controls: 116.40 (13.17). When we compared those patients who did undergo a second WAIS measurement (and were included in the current study) with those patients who did not we did not find a significant difference between the two groups (109.78 and 107.83 respectively, p=0.77). Thus, we conclude that IQ of the subgroup of patients whom we included in the present study was representative for the entire twin sample that we have been following over the past years. The discordant twins sample in this study consisted of two MZ pairs and four DZ pairs, one MZ patient, two DZ patients, one MZ unaffected co-twin and three DZ unaffected co-twins. The control twins sample consisted of six MZ pairs and five DZ pairs, nine MZ controls and two DZ controls. Data were collected between 1994 and 2006. No significant differences were found between the groups on age, sex, follow-up duration, education, parental education and baseline IQ. For demographic information see Table 1.

Assessment of Intelligence

Four subtests of the Dutch version of the WAIS (Stinissen et al., 1970) were used as a proxy for IQ. Subtests that were administered were vocabulary, block design, picture arrangement and comprehension. To estimate a proxy for IQ we summarised the scaled scores corrected for age and sex from each subtest, divided by 4 and multiplied with 11 for the final total scaled score (for method see Hijman et al., 2003). Total IQ-score can then be derived from the total scaled score in tables from WAIS (Stinissen et al., 1970).

Analyses

Repeated measures analysis of variance (ANOVA) was performed with measurement (IQ at baseline and at follow-up) as within subjects factor and dummy-coded variables with discordant twins (discordant twin pair = 1 or healthy control twin pair = 0), illness (patient = 1, co-twins and healthy control = 0), and zygosity (dizygotic=0 and monozygotic =1) as

between-subjects factor, as applied before (Hulshoff Pol et al., 2004, 2006; Baare et al., 2001).

Change in IQ was determined by subtracting the total IQ score on follow-up from the total IQ score at baseline. The IQ change scores were used to investigate the planned comparisons pair-wise analyses using independent samples t-tests to detect the source of significance.

Pearson correlation analyses were used to investigate the association between change in IQ with cumulative medication in haloperidol equivalents during the interval, symptom level at baseline and follow-up measured with the PANSS (Positive and Negative Syndrome Scale; Kay et al., 1987), and change in symptom level measured with the PANSS.

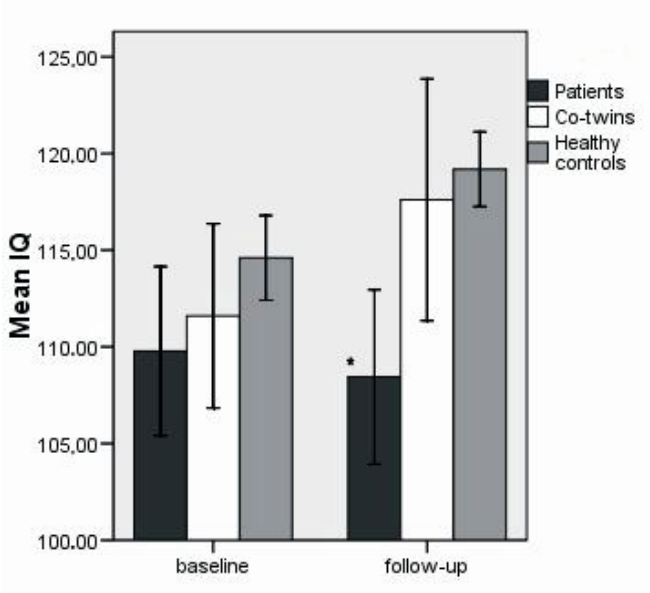

Figure 1 | IQ at baseline and follow-up for patients, unaffected co-twins and controls. *At follow-up, patients had a significantly lower IQ than healthy controls ($p<0.05$). Patients differed significantly from healthy controls and co-twins in IQ-change (both $p<0.05$) in that co-twins and healthy controls increase over time while patients did not. Error bars are showing +/- 1 SE.

Results

A significant interaction effect over time was found between IQ measurement and illness ($F=4.22$, $df=1$, $p<0.05$), indicating that change in IQ over time is significantly different between the groups. Planned comparisons with independent samples t-tests indicated a stable course in IQ over time in patients relative to both the healthy control twins ($t=2.06$, $p<0.05$) and the unaffected co-twins ($t=-2.32$, $p<0.05$) who both showed a slight increase in IQ (Figure 1). No significant difference was found between the unaffected co-twins and the healthy controls ($t=-0.49$, $p=0.63$). For individual IQ-change over time for each group see Figure 2.

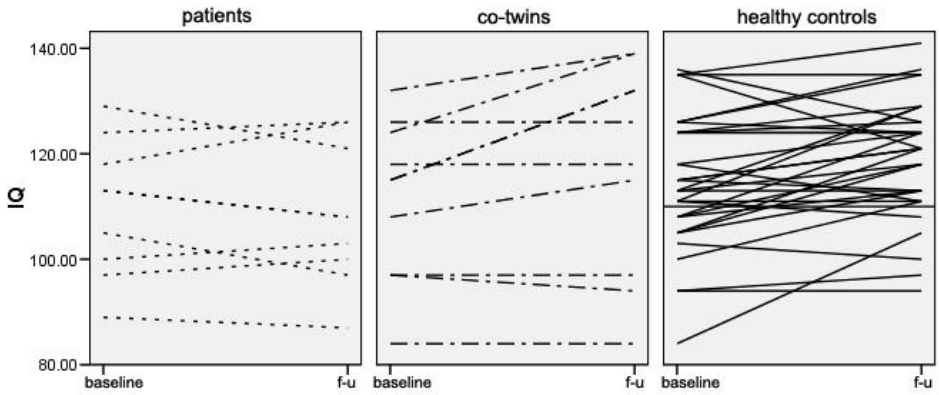

Figure 2 | IQ change over time. For each group, the individual IQ change over time is shown. There are two patients and two co-twins who have the same IQ at baseline and at follow-up, therefore only 8 lines are visible for the patients and 9 lines for the co-twins. f-u=follow up

Cumulative antipsychotic medication intake during the follow-up period did not correlate with change in IQ ($r=0.06$, $p=0.91$). Change in IQ correlated significantly with PANSS total symptom score at follow-up ($r=-0.68$, $p<0.05$) indicating that those patients with a higher symptom load at follow-up showed the largest decline in IQ over time. Change in IQ did not correlate significantly with PANSS scores at baseline, or change in PANSS scores during the interval.

Discussion

In this study we measured change in global intelligence over a 5-year interval in chronically ill patients with schizophrenia from discordant twin pairs (3MZ/6DZ individuals) and unaffected co-twins (3MZ/7DZ individuals). We found that IQ in patients failed to increase over time whereas IQ in unaffected co-twins and matched healthy controls (21MZ/12DZ individuals) did. Our results show that change in IQ in unaffected co-twins of patients with schizophrenia did not differ significantly from control twins. The mean IQ increase was even slightly higher in co-twins relative to control twins, although this difference did not reach significance. Since the lack of increase in IQ was limited to the patients, and not present in co-twins of patients, we could argue that the lack of changes in IQ found in patients with schizophrenia is associated with the illness or illness-related factors. Indeed, our findings suggests that in chronically ill patients environmental (non-genetic) factors implicated in the disease are most likely to be associated with the lack of IQ improvement over time.

Our results in patients are in line with other controlled longitudinal studies in early-onset schizophrenia (Jepsen et al., 2010) and first-episode schizophrenia (Hoff et al., 2005) where patients showed less increase in IQ over time as compared with healthy controls. A lack of increase in IQ might be explained by an abnormal slow acquisition of new skills and intellectual information in patients (Hoff et al., 2005; Jepsen et al., 2010). In addition, it might be that patients with schizophrenia do not benefit from practice effects, while both the unaffected co-twins and healthy control twins do (Salthouse, 2010). Another explanation could be that the patients are not influenced by the Flynn effect (i.e. an increase in average scores on intelligence tests) (Hiscock, 2007) in contrast to the unaffected co-twins and healthy controls. While interpreting the findings from our and the above mentioned studies it is important to keep in mind that the reported changes are small (i.e., a few IQ points) and are not necessarily clinically relevant.

Previously, it was shown that intelligence is decreased in unaffected co-twins of patients suggesting that a lower IQ in schizophrenia can to some extent be explained through common genes (Toulopoulou et al., 2007). Our findings suggest that the subsequent lack of IQ increase on repeated testing in patients is more likely to be non-genetic since unaffected co-twins did not significantly differ from healthy control twins. However, it is important to note that we were not able to take zygocity into account, due to the small numbers in our study.

One of the disease-associated factors that could have influenced the lack of IQ change in the patients with schizophrenia is the intake of antipsychotic medication. However, we found no evidence for an influence of antipsychotic medication on IQ change. This could be due to the diversity in types of antipsychotic medication intake in our sample (typical N=2, atypical N=3, or both N=2). The effect of antipsychotic medication on cognitive functioning is still debated, with the general consensus that both first and second generation antipsychotics provide small but positive effects on cognition (Keefe et al., 2007; Davidson et al., 2009). This has been shown in either short term studies, i.e, 3 and 6 months of treatment (Rollnick et al., 2002; Davidson et al., 2009) or long term studies: more than 2 years (Green et al., 2002). Should a positive effect of antipsychotic medication on cognitive functioning indeed exist, then this could imply that without medication, patients would not show a lack of improvement but perhaps even a decline in IQ over time during the course of illness.

Research on the developmental course of specific cognitive functions in schizophrenia patients (i.e. using a longitudinal design) show no differences between patients and controls, despite the lower performance in patients, on various neuropsychological domains such as abstraction, attention, verbal and spatial memory, language, initiation/preservation, spatial, sensory and motor abilities (Cencits et al., 1997; Savla et al., 2006) as well as in measures such as the Clinical Dementia Rating (CDR) scale and the Mini Mental State Examination (MMSE) (Friedman et al., 2001). However, it might be that in chronically institutionalized older patients (> 65 years of age) an excessive decline over time in cognitive functioning (i.e., CDR and MMSE) is present (Friedman et al., 2001). In addition, higher incidence of develop dementia in older patients with schizophrenia compared with healthy controls have been reported (Brodaty et al., 2003; Kørner et al., 2009). In first-episode schizophrenia significantly less improvement over time relative to that of healthy controls has been found in verbal memory (Hoff et al., 1999)

This study has several limitations that have to be taken into consideration when interpreting its findings. One, this is a preliminary study and the results must be interpreted with caution given the small sample size. Because of the small sample size we were not able to measure effects of changes in IQ while taking zygosity into consideration - let alone do more advanced statistical analysis such as structural equation modelling to determine the extent to which the lack of IQ increase in schizophrenia was due to environmental and/or genetic influences. Two, our patients had a baseline IQ of on average 109.78, which was comparable with that in co-twins of patients and control twins. However, we cannot exclude

that in particular our patient sample is at the high end of the IQ distribution (which is in line with the higher parental education of the parents of the patients). Therefore, we have to consider that the follow-up IQ assessment in patients was unchanged due to regression to the mean effects. In other words, patients were less likely to improve even further at follow-up as compared to co-twins and controls. However, considering that all three groups had comparable baseline IQ levels makes it unlikely that a regression to the mean explained the differences in change in IQ between our groups. Moreover, positive influences of a higher baseline IQ on follow-up IQ have also been suggested (i.e., the rich get richer) (Rapport et al., 1997).

In conclusion, we suggest that a lack of increase in IQ over time in chronically ill patients relative to unaffected co-twins and healthy controls might be due to environmental (non-genetic) factors related to the disease.

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Chapter 4

IQ change over time in schizophrenia and healthy individuals: A meta-analysis

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Abstract

Cognitive deficits have been recognized as a key feature of schizophrenia, since the first description of this illness by Kraepelin. More specifically, lower intelligence is considered a core feature of the disorder and may represent a risk factor for its development. However, whether global intelligence decreases over time in schizophrenia is not known. The aims of this quantitative meta-analysis are to gather, integrate and estimate the overall mean effect size of *IQ change* over time in schizophrenia as compared to healthy individuals.

A systematic search was conducted to identify relevant studies. Longitudinal studies with at least two intelligence assessments in schizophrenia cohorts were retrieved. Studies had to report sufficient data on IQ-change and include data from healthy comparisons for computation of effect sizes. For each study, the Cohen *d* was calculated as well as an combined mean effect size.

Fourteen studies were identified. Eight studies with a total of 280 patients and 306 healthy controls were suitable to be included. The mean weighted IQ at baseline was 97.20 for patients and 109.26 for controls. The mean weighted IQ-point change per year was +0.33 for patients and +2.08 for controls. The combined effect size for the studies included was Cohen's *d*=-0.48, p=0.01.

A global cognitive deficit is present in patients with schizophrenia expressed as a lower test score increase over repeated testing as compared to healthy subjects possibly due to the lack of practice effects in patients. Thus, schizophrenia is characterized by a relative lack of gain in global cognitive abilities over time.

Introduction

Cognitive deficits have been recognized as a key feature of schizophrenia since its first description by Kraepelin over a century ago (Kraepelin, 1893). In particular, deficits in global measures of cognition are commonly reported in patients with schizophrenia, such as lower intelligence quotient (IQ) (Aylward et al., 1984; Heinrichs and Zakanis, 1998) or general cognitive ability factor (Dickinson et al., 2008). Moreover, schizophrenia and intelligence show overlapping genetic influences (Toulopoulou et al., 2007; but see Fowler et al., 2012).

In addition, in population-based studies lower premorbid IQ was found associated with an increased risk to develop schizophrenia and schizophrenia spectrum disorders (Zammit et al., 2004; Reichenberg et al., 2006). Meta-analysis has confirmed that mean IQ-scores are below that of healthy comparison individuals years before the onset of psychotic symptoms in individuals who later develop schizophrenia (Woodberry et al., 2008; Dickson et al., 2011).

Not only is a lower IQ associated with the development of schizophrenia, a *decline* in global cognitive functioning has been suggested to predict the onset of psychotic symptoms in young children (between 4 and 7 years old) (Kremen et al., 1998) and adolescents (Fuller et al., 2002; Reichenberg et al., 2005).

It is not clear whether IQ declines – or continues to decline - in patients relative to controls *after* illness onset, despite the fact that numerous studies measuring IQ change in schizophrenia have been conducted. The reason is that results of many of these longitudinal IQ studies are difficult to interpret because they lack a (healthy) control group (for references see supplementary material). Consequently, the failure of most of these studies to find a decline in global cognitive functioning in schizophrenia may have been due to the fact that IQ changes over time in patients were not contrasted to those in healthy subjects. Fortunately, several longitudinal studies did include healthy controls. Therefore, we decided to gather, integrate and estimate the overall mean effect size of *IQ change* in all longitudinal studies in schizophrenia samples that included healthy individuals.

Materials and Methods

Literature Search

A systematic search was conducted to identify IQ change in schizophrenia samples that were examined in a longitudinal design and were compared with healthy controls. The literature search included an online PubMed database search for papers published until July 1, 2011. The keyword combination used in the computerized search included the following: (*"IQ" or "intelligence" or "IQ-change(s)" or "change(s) in intelligence" or "cognition" or "neurocognitive" or "neuropsychological" or "course of intelligence") and "longitudinal" and ("schizophrenia" or "psychosis").* Titles and abstract were carefully examined and evaluated to see whether they fulfilled the inclusion criteria (see Figure 1 for flowchart). Additional studies were obtained by hand search in cross-references.

Study Selection

Inclusion criteria were the following: 1) longitudinal studies with at least two intelligence assessments in schizophrenia cohorts, 2) compared patients with a healthy control group (having no history and family history of psychosis or mental-illness), 3) provided quantitative measures of IQ change, 4) patients had to have a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder at follow-up under the criteria of DSM, ICD, or RDC, 5) use of standardized psychometric IQ with at least 2 subtests from Wechsler adult intelligent scale (WAIS, WAIS-R, WAIS-III and WAIS-IV) or Wechsler intelligent scale for children (WISC, WISC-R, WISC-III and WISC-IV) as a proxy for IQ at one of the two assessments and 6) published in English in scientific peer-review journals. Exclusion criteria were as follows: 1) reporting data on overlapping sample and 2) reporting insufficient data to obtain the effect size (Cohen's *d*) for IQ change, with each study required to have one of the following combinations: means, standard deviations, number of subjects for each group; either a t of F score and the number of subjects or the degree of freedom for this statistic; or group differences expressed in a z-score unit or a standard deviation.

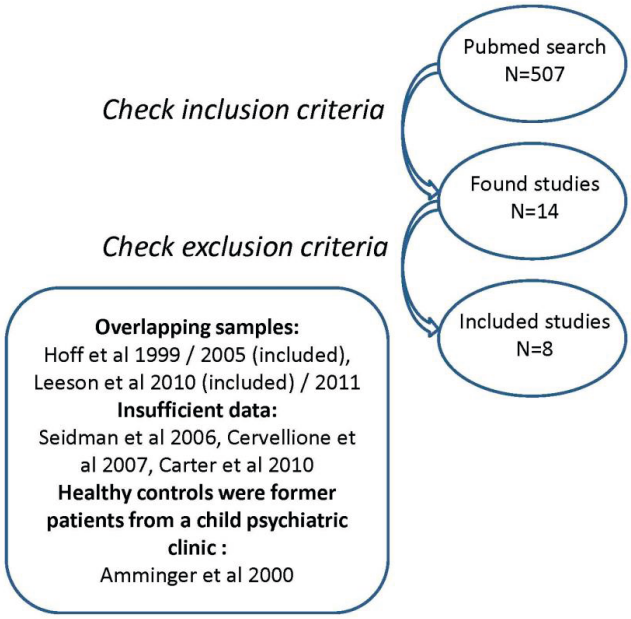


Figure 1 | Flowchart of inclusion and exclusion criteria

Fourteen articles published between 1999 and 2011 fulfilled inclusion criteria for this meta-analysis. (see Table 1). The numbers of patients per study varied between 9 and 81 and the number of healthy controls varied between 8 and 86. Follow-up interval varied between 1 and 28 years. Age at baseline ranged between 12 and 51 years. After applying the exclusion criteria (see flow chart, Figure 1), eight studies were included in the calculation of an overall effect size for IQ change in schizophrenia patients compared to healthy controls, including 280 patients and 306 healthy controls (see Table 1, the studies indicated with *).

Table 1 | Overview of longitudinal studies measuring the change in intelligence in schizophrenia patients and healthy individuals

Author	Subjects	Age, mean (SD) [range]	Illness onset/Status of disease/Duration of illness at baseline[b]	Follow-up duration, mean (SD)	Tests	Group differences	Medication	Baseline IQ/Change in IQ mean (SD)
Hoff et al., 1999	42 first hospitalized patients 16 HC	baseline; P: 26.3 (7.4) y HC: 26.1 (5.3) y	mean age at first hospitalization for patients was 26.7 (7.2)	P and HC had yearly measurements. mean time f-u; P: 3.6 (0.7) y HC: 3.8 (0.9) y	first measurement and f-u: Pro-rated WAIS-R (information, vocabulary and similarities) as a proxy for verbal IQ	age (ns), sex (ns), education (p<0.0001)	first measurement: typical N=39 naïve N=3 f-u: typical N=30 atypical N=4 naïve N=8	no information
Amminger et al., 2000 prospective study	13 Sz-related psychosis 31 HC	baseline; P: 14.5 (3.5) y HC: 12.2 (3.1) y	mean age when subjects reached diagnostic criteria: 18.9 (1.9)	P: 17 y HC: 18.1 y	first measurement: full-scale WISC (under the age of 16) or full scale WAIS f-u: full scale WAIS	age (p<0.05) sex (ns), WISC/WAIS ratio (ns)	no information	no information
Heaton et al., 2001[a*]	81 chronically ill Sz patients 86 HC	baseline; P: 47.6 (15.7) y (taken from baseline sample N=142), HC: 51.7 (20.1) y (taken from baseline sample N=208)	age at illness onset: 28.2 (14.0) y (from N=142). duration of illness: 18.8 (14.3) y (from N=142)	P and HC had yearly measurements. mean time f-u; P: 18.1 (11.7) m (from N=142), HC: 15.6 (5.3) m (from N=208)	first measurement and f-u: full scale WAIS-R	age (p=0.04), sex (ns), education (P<0.001)	mean daily dose: 993.1 (1742) of chlorpromazine equivalent. 25% used atypical medication at some time point (from N=142)	baseline IQ; P: 94.73 (13.08), HC: 112. 14 (11.13) change in IQ-points; P: +2.21 (5.54), HC: + 3.66 (6.00)
Hoff et al., 2005* (overlapping sample with Hoff et al., 1999)	21 FE 8 HC	f-u: FE: 37.9 (5.7) y HC: 39.4 (5.8) y	age at illness onset: 26.40 (8.3) y. duration of illness: 1.5 y	10 y (yearly measurement in the first 5 years)	first measurement and f-u: pro-rated WAIS-R (information, vocabulary and similarities) as a proxy for verbal IQ	age (ns), sex (ns), education (p=0.002)	First measurement: typical N=21 f-u: typical N=3 atypical N=13 naïve N=2 lithium only N=3	baseline IQ; P: 97.7 (13.6), HC: 106.1 (12.1) change in IQ-points; P:+3.9 (13.2), HC: +7.6 (8.9)
Albus et al., 2006[a*]	71 FE 71 HC	f-u: FE: 29.74 (9.13) HC: 29.9 (9.2)	age at illness onset: 24.9 duration of illness: 0 y	approx. 5 y	first measurement and f-u: WAIS-R; information and similarities as a proxy for verbal IQ and block design and picture completion as a proxy for performance IQ	age (ns), sex (ns), education (ns), handedness (ns) and SES (ns)	first measurement: typical N=71 f-u: typical N=16 atypical N=40 naïve N=15	baseline IQ; no information change in IQ in z-score units; P:+0.32 (0.64), HC: +0.38 (0.64)

Author	Subjects	Age, mean (SD) [range]	Illness onset/Status of disease/Duration of illness at baseline[b]	Follow-up duration, mean (SD)	Tests	Group differences	Medication	Baseline IQ/Change in IQ mean (SD)
Bilder et al., 2006* prospective study	39 FE 24 HC	f-u: FE: 26.5 (6.7) y HC: 23.1 (5.1) y	age at illness onset:: 24.3 (6.5) y. duration of illness at f-u: 2.2 y	approx. 8 y	first measurement: SAT/PSAT, math and verbal grades which together was converted into IQ-equivalents f-u: full scale WAIS-R	age (ns), sex (ns), education (ns),handedness (ns), SES (p=0.001) and baseline IQ (p=0.001)	no information	baseline IQ; P: 103.0 (9.5), HC: 111.0 (11.4) change in IQ-points; P: -11.5 (9.9), HC: -0.1 (7.9)
Seidman et al., 2006 prospective study	27 chronically ill Sz patients 60 HC	f-u: P: 36.2 (2.5) HC: 34.8 (2.4)	no information	approx. 28 y	first measurement: full scale WISC f-u-up: estimated IQ using the vocabulary and block-design subtest of WAIS-R	sex (ns), ethnicity (p=0.007), SES (ns), full-scale IQ (p=0.005)	no information	baseline IQ; P: 96.5 (14.3), HC: 105.3 (13.2). change in IQ-points; P: -5.3, HC: -3.1
Cervellione et al., 2007	26 EOS 26 HC	baseline; EOS: 16.0 (2.2) y HC: 15.6 (2.1) y	age at illness onset:: 13.1 (3.8) y duration of illness: 33.7 (31.3) m	EOS:14.2 (9.8) m HC:15.5 (10.5) m	first measurement and f-u: WISC-III (age<16), WAIS-III (age>16) (subtests: similarities, arithmetic, block design, digit span, and digit symbol)	age (ns), sex (ns), handedness (ns), SES (ns) ethnicity (ns)	first measurement: mean chlorpromazine (CPZE) equivalent; 324.3 (224.6) f-u: mean CPZE; 266.2 (185.4)	no information
Frangou et al., 2008[a*]	20 EOS 20 HC	baseline; EOS:15.58 (2.27) y HC: 15.98 (0.75) y	age at illness onset: 14.10 (2.1) y. duration of illness: 1.48 y	4.00 (1.08) y	first measurement and f-u: full scale WISC-III to participants aged 13-16 y, and full scale WAIS-R to those older than 16 y WAIS-R scores were converted into WISC-III equivalents derived from 16-year-olds tested with both instruments	age (ns), sex (ns), handedness (ns), SES (ns)	first measurement: typical N=3 atypical N=17 f-u: typical N=2 atypical N=18	baseline IQ; P: 92.53 (17.97), HC: 101.74 (15.63) change in IQ-points; P: +6.79 (12.03) HC: +1.11 (11.10)
Carter et al., 2010 prospective study	34 patients with psychosis 99 HC	f-u: average age for P and HC: 24 y	no information	10 y	first measurement: full-scale WISC f-u: short version of WAIS as a proxy for IQ (vocabulary, similarities, block design and object assembly)	no information	no information	no information

Author	Subjects	Age, mean (SD) [range]	Illness onset/Status of disease/Duration of illness at baseline[b]	Follow-up duration, mean (SD)	Tests	Group differences	Medication	Baseline IQ/Change in IQ mean (SD)
Jepsen et al., 2010*	10 EOS 35 HC	baseline; EOS: 15.5 (1.9) y, HC: 15.7 (1.5) y	age at illness onset:: 11.9 (3.6) y. duration of illness: 3.6 y	EOS: 5.6 (0.6) y HC: 5.6 (0.3) y	first measurement and f-u: full scale WISC-III	age (ns), sex (ns), education (ns), SES (p=0.002) and f-u interval	first measurement: typical/atypical N=9 naïve N=1 f-u: typical/atypical N=5 naïve N=5	baseline IQ; P: 87.4 (14.5), HC: 110.1 (12.0) change in IQ-points; P: +5.7 (10.8), HC: +14.8 (7.1)
Leeson et al., 2010[a*]	29 recent-onset psychosis patients 29 HC	baseline; P: 26.77 (7.75) (from N=53) HC: 26.49 (6.70) (from N=53)	age at illness onset:: 25.17 (0.63). duration of illness: 1.6 y	1 y	first measurement and f-u: 4 subtests of WAIS-III as a proxy for IQ (information, arithmetic, block design and digit symbol)	age (ns), sex (ns) and baseline IQ (ns)	first measurement: typical N=2 atypical N=48 naïve N=3 (from N=53)	baseline IQ; P: 98.62 (11.75) HC:98.24 (11.82) change in IQ-points; P: -1.52 (7.72), HC: +3.83 (6.84)
Leeson et al., 2011 (partly overlapping sample with Leeson et al., 2010)	78 FE at 1 y f-u and 60 FE at 3 year f-u 27 HC at 1 y f-u and at 3 year f-u	no information (divided the patients into subgroups depending on their current IQ)	age at illness onset: N=78: 24.59 (8.03), N=60: 24.31 (8.02)	1 y and 3 y	first measurement and f-u: 4 subtests of WAIS-III as a proxy for IQ (information, arithmetic, block design and digit symbol)	no information	no information	baseline IQ; no information change in IQ-points; P (1 y): +2.23 (8.83), HC: +5.33 (5.04), P (3y): +4.42 (8.83), HC: +10.26 (8.46)
Hedman et al., 2012*	9 chronically ill Sz patients 33 HC	baseline; P: 39.94 (11.74) y HC: 34.94 (10.59) y	age at illness onset: 22.11 (5.69) y duration of illness: 17.83 (8.12) y	P: 4.86 (0.79) y HC: 4.80 (0.31) y	first measurement and f-u: 4 subtests of WAIS-III as a proxy for IQ (vocabulary, block design, picture arrangement and comprehension)	age (ns), sex (ns), education (ns), SES (ns), f-u interval (ns) and baseline IQ (ns)	mean cumulative haloperidol equivalents during the interval: 10363.79 (5844.94), medication were missing for 2 P	baseline IQ; P: 109.78 (13.10) HC:114.61 (12.58) change in IQ-points; P:-1.33 (5.61), HC:+4.58 (8.06)

Abbreviations: Sz=Schizophrenia, HC=Healthy Controls, FE=First Episode, EOS=onset of psychotic symptoms by age 17 (defined in study by Frangou et al., 2008) and 18 (defined in study by Jepsen et al., 2010), P=Patients, HC=Healthy Controls, y=year, m=month, f-u=follow-up, ns=non significant, SES= Socio-Economic Status, no information = information on the variable of interest was missing in the article

WAIS; Wechsler Adult Intelligent Scale

WAIS-III; Wechsler Adult Intelligent Scale third edition

WAIS-R; Wechsler Adult Intelligent Scale Revised

WISC; Wechsler Intelligent Scale for Children

WISC-III; Wechsler Intelligent Scale for Children third edition

WISC-R; Wechsler Intelligent Scale for Children Revised

SAT; Scholastic Aptitude Test, PSAT; Preliminary Scholastic Aptitude Test

[a] complete data not available in reported study but provided upon request

[b] if not otherwise stated *study included in the meta-analysis

Statistics and Data Extraction

This meta-analysis was performed to examine the difference in change in IQ between patients with schizophrenia and healthy controls (Lipsey and Wilson, 2001). First, the mean weighted IQ at baseline was calculated as follows:

$$\sum(\text{Baseline IQ}*\text{Nstudy})/\text{Total N}$$

where baseline IQ stands for the IQ at baseline patients or controls had for each study, Nstudy defines the total number of participants (patients or controls) in each study, and Total N reflect all participants (patients or controls) in all studies together. Next, the mean weighted IQ-point change per year was calculated as follows:

$$\sum(\Delta\text{IQ/y}*\text{Nstudy})/\text{Total N}$$

where ∆IQ/y is the change in IQ per year for either patients or controls in each study, Nstudy defines the total number of participants (patients or controls) in each study, and Total N is the number of all participants (patients or controls) in all studies together.

Then, the effect size statistic Cohen's *d* was calculated for each study representing the difference between the mean of the experimental group and the mean of the comparison group divided by the pooled standard deviation. After calculating individual effect sizes (*d*) for each study, a combined effect size (*d*) was obtained, indicating the magnitude of the association across all studies (Hedges and Olkin, 1985). Subsequently, a *t*-test on the null hypothesis that the combined effect size *d*= 0.00 was performed, indicating no significant differences between the patient and the control populations. According to Cohen (Cohen, 1988), *d*-values of 0.2 represent small effects, *d*-values between 0.4 and 0.6 represent moderate effects, and *d*-values of 0.8 or higher represent large effects. In addition, we computed the combined effect size for verbal and performance IQ-change for those studies that provided data on change in verbal and performance IQ.

All analyses were performed with a random-effects model using the statistical package Comprehensive Meta-Analysis V2 (Borenstein and Rothstein, 1999). The assumption of a random-effects model is that the estimated effect size by different studies varies among studies not only because of a coincidence but also because of differences in paradigms or

samples and that the effect sizes have a normal distribution (DerSimonian and Laird, 1986). If there is significant heterogeneity the variation between the effect sizes of the individual studies is larger than would be expected by chance alone. In case of significant heterogeneity the random-effects model will give wider confidence intervals than the fixed effects models (DerSimonian and Laird, 1986; DerSimonian and Kacker, 2007). A test of homogeneity (Cochran's Q test) was performed to test whether the studies could be assumed to share a common population effect size. A significant Q statistic indicates heterogeneity of the individual study effect sizes, limiting a reliable interpretation of the results. If significant heterogeneity was found, meta-regression analyses were performed of experimental variables to explore the effect of potential sources of heterogeneity and to identify possible outliers. Meta-regressions in this study were performed by regressing effect sizes against the follow-up duration, the percentage of males in the patient group, age of illness onset, duration of illness and mean baseline age in patients and controls. To examine the possibility of publication bias, we computed a fail-safe number of studies (Orwin, 1983; Rosenthal, 1991; Lipsey and Wilson, 2001). Publication bias can pose a threat to the stability of the obtained effect size as it implies that studies with no effect may not be published. Additionally, I^2 was calculated to provide another, perhaps more interpretable measure of the consistency between the studies (Higgins et al., 2003; Huedo-Medina et al., 2006). The I^2 statistics can be seen as the percentage of the total variability in a set of effect sizes due to true heterogeneity, i.e. between-studies variability. The I^2 gives a percentage between 0 and 100% with a larger percentage indicating an increased heterogeneity. The fail-safe number of studies indicates the number of unpublished studies with null effects that must reside in file drawers to reduce the observed effect size to a negligible level. The file-safe number statistics can be calculated as follows:

$$K*((ESk/Esc) -1)$$

where K is the number of studies, Esk, the mean weighted effect size of all studies included in the meta-analysis; and Esc, the criterion effect size which allow the researcher to select a value that would represent the smallest effect deemed to be clinically important and how many missing studies it would take to bring the combined effect below this point (which we set at a value of -0.10).

Study specific details (see supplementary material)

Results

The meta-analysis on IQ-change in schizophrenia patients as compared to healthy controls included eight studies with a total of 280 patients and 306 healthy controls. The mean weighted IQ at baseline was 97.20 for patients and 109.26 for controls. The mean weighted IQ change per year was +0.33 for patients and +2.08 for controls, with a combined effect size (Cohen's *d*) of the difference in IQ change between the groups of -0.48 (p=0.01) (Figure 2). This suggests a medium-sized deficit for IQ-change in patients, and is attributable to a failure of test score increase in patients on repeated testing relative to healthy controls. When leaving out the early onset studies (i.e., Jepsen et al., 2010; Frangou et al., 2008), we still find a significant overall effect size of -0.29 (-0.11 to -0.48; p=0.0016).

The effect size for IQ-change was moderately heterogeneous (Q=26.85, p<0.001, I^2 =73.93). No significant heterogeneity was found for any of the moderator variables (i.e. follow-up duration, percentage of males in the patient group, age at illness onset, duration of illness, baseline age; see Supplementary figures).

No significant differences were observed for change in verbal or performance IQ between patients and controls, i.e., Cohen's *d*=-0.19, p=0.10 and Cohen's *d*=-0.16, p=0.39 respectively (Figure 3a-b).

A leave-one-out analysis to assess the extent to which the effect could be driven by one specific study, revealed that Cohen's *d* remained significant, implicating that the effect was driven by multiple studies in the meta-analysis, i.e., 7 out of 8 studies reported a lower IQ increase in in patients than in controls. The fail-safe number was 30, large enough to lend credence to our findings.

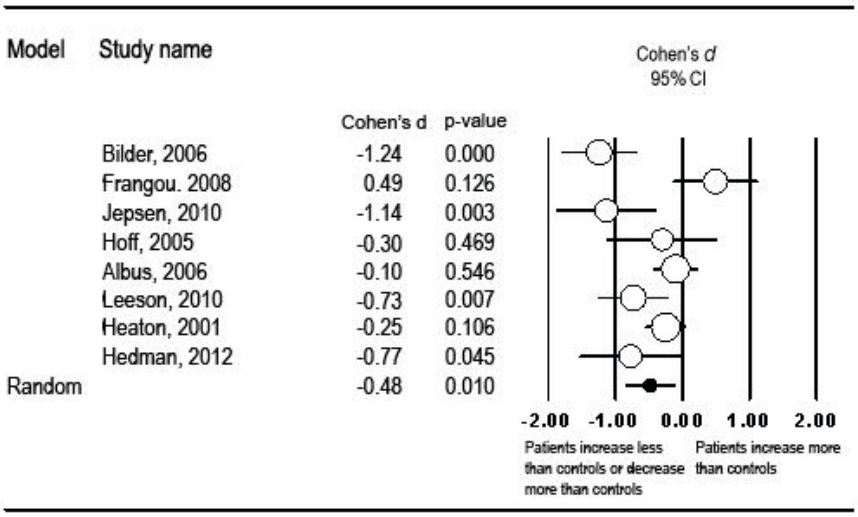
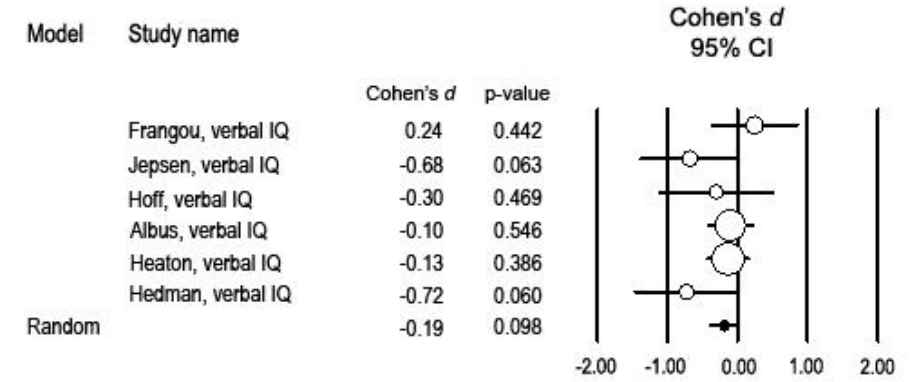


Figure 2 | Meta-analysis on IQ change in schizophrenia patients as compared to healthy controls. Displayed on the x-axis are the Cohen's *d*, 95% confidence interval and p-value per study. The y-axis gives the included studies ordered according to stage of the disease, , i.e., Bilder et al. (2006) is from premorbid to morbid, Frangou et al. (2008) and Jepsen et al. (2010) in early onset schizophrenia, Hoff et al. (2005), Albus et al. (2006) and Leeson et al. (2010) in first-episode and Heaton et al. (2001) and Hedman et al. (2012) in chronically ill schizophrenia. The size of the circles is proportional to the study's weight in the meta-analysis. The combined Cohen's *d* for the random effects model is: -0.48 (p=0.01).



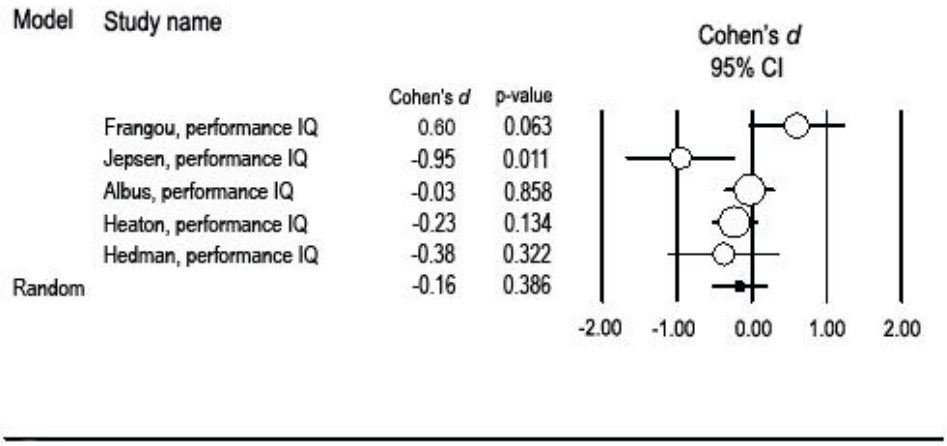


Figure 3a | Meta-analysis on verbal IQ change in schizophrenia patients as compared to healthy controls. Displayed are the Cohen's *d* and 95% confidence interval per study. The size of the circles is proportional to the study's weight in the meta-analysis. The combined Cohen's *d* for the random effects model is: -0.19 (p=0.10). Full-scale verbal IQ measures were applied in the studies by Frangou et al. (2008) Jepsen et al. (2010) and Heaton et al. (2001). The verbal IQ estimate in Hoff et al. (2005) was based on 3 subtests of the WAIS for verbal IQ. The IQ estimate in Albus et al. (2006) and Hedman et al. (2012) were based on 2 subtests of the WAIS. **b.** Meta-analysis on performance IQ change in schizophrenia patients as compared to healthy controls. Displayed are the Cohen's *d* and 95% confidence interval per study. The size of the circles is proportional to the study's weight in the meta-analysis. The combined Cohen's *d* for the random effects model is: -0.16 (p=0.39). Performance IQ estimates were based on full-scale performance IQ in the study by Frangou et al. (2008), Jepsen et al. (2010) and Heaton et al. (2001), and on 2 subtests from the WAIS in Albus et al. (2006) and in Hedman et al. (2012).

Discussion

To the best of our knowledge, this is the first meta-analysis on longitudinal studies investigating IQ change over time in schizophrenia patients as compared to healthy individuals. We report a significant difference with a moderate effect size (Cohen's *d*=-0.48) between the groups. This effect is attributable to an attenuated test score increase in patients (+0.33 IQ points per year) relative to that in healthy controls (+2.08 IQ points per year). Thus, after the onset of the disease patients do not benefit from repeated cognitive testing to increase general intelligence level.

Thus, the attenuated IQ increase over time in patients with schizophrenia does not appear to reflect an *absolute* intellectual deterioration since we find the direction of change in patients to be (marginally) positive over time (+0.33 IQ points per year). The diminished improvement in IQ more likely represents a sub-normal learning of new information and skills in schizophrenia patients. The literature has been inconsistent regarding the stability of specific cognitive domains over the course of the illness. Many of these studies tend to show improvement in most cognitive tasks in patients with controls showing similar or larger improvements (Granholm et al., 2010; Harvey et al., 2010, see Szöke et al., 2008 for meta-analysis); but others report no differences between the groups (Cencits et al., 1997; Gold et al., 1999; Crespo-Facorro et al., 2009). In a meta-analysis where each test metric was included separately, improved test scores over time were found for several tests in controls, whereas no significant improvement was found in patients (Szöke et al., 2008), thus corroborating our findings on IQ change. Our finding of minimal IQ change in schizophrenia is also in line with numerous studies on intellectual change in schizophrenia that did not include a control group (see supplementary material). However, the conclusion of most of these studies implies that intellectual functioning is normally stable in schizophrenia is unwarranted since longitudinal findings in patients were not compared to healthy subjects. Without a control group a relative lack of intellectual gain in patients cannot be found because of the design of the study. Indeed, subtle increases in IQ over time have been found in healthy subjects (McCaffrey RJ et al., 2000; Kaufman, 2001; Ramsden et al., 2011).

Both verbal and performance IQ might have contributed to the lack of IQ improvement over time in patients with schizophrenia. Cohen's *d* for a difference in change in verbal (-0.19, p=0.10) and performance IQ (-0.16, p=0.39) between groups was not significant. This might be a type-II error due to lack of statistical power to detect the contribution of verbal and

performance IQ to general IQ since not all studies included provided data on change in verbal and performance IQ over time.

Importantly, several studies suggest that IQ decline in schizophrenia presents (years) before the onset of the illness,. Bilder et al. (2006) showed a remarkable drop in cognitive ability in subjects with a relatively high level of functioning prior to disease onset, suggesting that those with higher cognitive abilities demonstrate a more pronounced loss in cognitive function after illness onset (Bilder et al., 1988; 1992). Other prospective studies assessing global cognitive functioning prior to disease onset (using draft board psychometric tests), and again after disease transition, reported a significant decline in patients as compared with controls (Lubin et al., 1962; Caspi et al., 2003). In sum, the relative decline in IQ in schizophrenia may be (most) pronounced prior to, or at the time of disease transition, but continues to change throughout the course of the illness.

How can we explain the relative lack of repeated test score improvement in patients? One obvious explanation is that patients cannot benefit as much from practice as controls do, and that this possibly reflects some underlying cognitive disability. Alternatively, patients may benefit normally from practice but less so than controls because of their lower cognitive abilities as part of a continuing cognitive decline. Indeed, baseline IQ was consistently lower in patients than in controls (in those studies that reported baseline IQ scores). Longitudinal IQ-studies assessing healthy participants suggest that a higher IQ at baseline is associated with more practice effects later, i.e., “the rich get richer” (Rapport et al., 1997; Rabbitt et al., 2008). This would imply that the patients in our meta-analysis show a less prominent increase in test scores because of their lower initial IQ as compared to the controls. Unfortunately, we could not reliably disentangle initial IQ from IQ change test scores because not all studies reported data on baseline IQ. Practice effects have also been found to be more prominent at a younger age and less pronounced in older age groups (Rabbitt et al., 2008; Catron and Thompson, 1979). Finally, practice effects are more pronounced with shorter follow-up periods (Catron and Thompson, 1979). However, these explanations are less likely to have influenced our findings since follow-up periods and age were similar between patients and controls. Moreover, we did not find significant associations with baseline age and follow-up duration, although this might partly be due to the limited number of studies. Assuming that practice is important, one critical piece of information would be whether the test scores change per unit of time, or per repetition of time. If the patient deficit

reflects relative progressive cognitive deterioration compared to that of healthy controls, it should depend on elapsed time. On the other hand, if it reflects a failure to profit from practice, it should depend more on the number of tests. Unfortunately, making the distinction between relative progressive decline and a failure to profit from practice effects was not feasible because of the limited number of studies. Also, we have to consider the Flynn Effect, which refers to the well-established finding that IQ tests scores have been increasing in all industrialized countries for the past 50 years or more. One consequence of this is that people will obtain a higher score on an older test than on one more recently standardized (Flynn, 1998). Should the Flynn Effect explain the overall increase in test scores, this would imply that patients with schizophrenia have a relative decrease in overall cognitive functioning over time.

An alternative explanation of the diminished improvement in patients is that it reflects abnormal intellectual development as a functional expression of abnormal brain development in patients. Interestingly, changes in IQ in healthy adolescents were recently found to be associated with local structural and functional brain development (Ramsden et al., 2011). Considering that progressive brain tissue loss in patients with schizophrenia at different stages of the disease (see reviews; Pantelis et al., 2005: Hulshoff Pol and Kahn, 2008) the lack of normal age-related changes in IQ may be directly linked with these progressive brain changes.

It is important to consider the potential limitations of this meta-analysis and its possible generalizability when interpreting its findings. First, there were only a limited number of suitable longitudinal case-control IQ studies that could be included in the meta-analysis, and hence the number of subjects was relatively low (280 patients, 306 controls). Second, the degree of variability on important variables such as sample size, age, follow-up interval, age of illness onset, pre and post-test assessment and duration and severity of illness should not be underestimated despite the statistical methods used to ensure that these variables were considered. Differences between childhood and adult onset schizophrenia are likely to be influenced by differences in developmental and educational status. Unfortunately, we did not have data available for each individual study to correct for these measures more carefully. Moreover, change in IQ per year during the interval assumes that IQ change is linear, which is a (inevitable) simplification of reality. However, after excluding studies with early onset schizophrenia patients (Jepsen et al., 2010; Frangou et al., 2008) in a post-hoc analysis the

findings did not change. Thus, while much of the evidence suggests that cognitive decline happens before or around the start of the illness (Woodberry et al., 2008; Leeson et al., 2011; Seidman et al., 2006), adult-onset (chronically ill) patients significantly contributed to the diminished improvement in IQ over time. Importantly, medication intake was not reported in all studies and for those studies that did report data on medication, the measures varied (e.g., some included data on cumulative medication, others did not, see Table 1). Therefore, we could not test medication type and dose as moderator variables in meta-regression. However, both typical and atypical antipsychotic medication have shown small to moderate improvements in cognitive function (Keefe et al., 2007; Davidson et al., 2009). Thus, if anything, antipsychotic medication intake may have resulted in an underestimation of the actual IQ-change deficit occurring in schizophrenia since all patients were medicated. Another important issue is that many (if not all) of the studies included in this meta-analysis suffered from attrition bias. The subjects included in the current analysis were only those that were able or willing to participate more than once in a longitudinal study. Indeed, Heaton et al. (2001) reported that those not included at follow-up were older at baseline than those included at follow-up and Bilder et al. (2006) reported that those without achievement test scores were higher educated. Hoff et al. (2005) and Albus et al. (2006) find no evidence for attrition bias. The remaining studies either provided no information (Frangou et al., 2008; Leeson et al., 2010; Hedman et al., 2012) or only lost one patient (Jepsen et al., 2010). Finally, not all studies used the same tests (Bilder et al., 2006) or versions (Frangou et al., 2008) for IQ at baseline and follow-up complicating interpretation of the findings. However, excluding either one of them did not alter the findings considerably.

In conclusion, this meta-analysis reporting on global IQ change over time in schizophrenia patients and healthy controls finds a less prominent improvement in test scores over time in IQ in patients, with a moderate effect size. Although the cause of this relative lack of intellectual gain is presently unclear, the finding is consistent with the notion that relative cognitive decline is at the core of the illness that Kraepelin coined dementia praecox (Kraepelin, 1893).

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Supplementary Material

References (without a control group)

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Calculations of individual effect sizes (references are in the main text)

- Hoff et al. (2005): The effect size for change (Δ) was estimated using Cohen's *d*:

$$(M_1+M_2)/\text{square root } ([(n_1-1)(SD_1)2+(n_2-1)(SD_2)2]/[n_1+n_2-2])$$

  where M_1 and M_2 is the mean of the Δ for each group, and n_1 and n_2 are the number of participants in each group respectively. SD_1 and SD_2 is the standard deviation of Δ for each group respectively.

  Albus et al. (2006): see Hoff et al. (2005). For the mean weighted effect size we use the verbal IQ from the study by Albus et al. (2006). When verbal IQ was substituted with performance IQ by the same study the result yielded a combined effect size of -0.47 (p=0.013).
- Bilder et al. (2006): see Hoff et al. (2005).
- Frangou et al. (2008): see Hoff et al. (2005).
- Jepsen et al. (2010): see Hoff et al. (2005).
- Leeson et al. (2010): see Hoff et al. (2005).
- Hedman et al. (2012): see Hoff et al. (2005).
- Heaton et al. (2001): The Δ in IQ was derived as (IQ time 2 - IQ time 1). The standard deviation for Δ was not provided but the intra-class correlation as a degree for consistency between measurements was provided (McGraw and Wong, 1996). We used the intra-class correlation (ICC) as a proxy for Pearson's correlation. The intra-class correlation is dependent on the ratio of within and between variances between two measurements. If the intra-class correlation is high – the Pearson's correlation must also be high, but if the intra-class correlation is low – the Pearson's correlation can be high or low. In this case the intra-class correlation for the patients (ICC=0.92) and the controls (ICC=0.85) were both high, indicating that Pearson's correlations also must be high. Therefore we used these ICC correlations as a proxy for the Pearson's correlations. By applying the rules of variances and covariances for Δ we could derive the varience in Δ for each group (i.e., patients and controls) with this formula:

$$SD_1^2 + SD_2^2 - 2SD_1*r* SD_2$$

where SD_1 is the standard deviation for the first measurement, SD_2 is the standard deviation for the second measurement, and r is the correlation between the two measurements. The SD for the Δ was derived by taking the square root from the variance in Δ. Finally, the effect size for Δ was estimated using Cohen's *d*, see Hoff et al. (2005).

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Study Specific Details

One study assessed patients prior to disease onset at baseline (Scholastic Aptitude Test (SAT), Preliminary Scholastic Aptitude Test (PSA), math and verbal grades, were combined converted into IQ-equivalents) and again at follow-up after they had become ill (full-scale WAIS) (Bilder et al., 2006). Jepsen et al. (2010) assessed participants that were diagnosed with childhood-onset schizophrenia. Frangou et al. (2008) included individuals with early onset schizophrenia (defined as onset before the age of 17 years) at baseline measurement. In three studies, first-episode schizophrenia patients were included at baseline (Hoff et al., 2005; Leeson et al., 2010; Albus et al., 2006) and in two studies chronically ill schizophrenia patients were included at baseline (Heaton et al., 2001; Hedman et al., 2012).

Baseline IQ from one study (Albus et al., 2006) was not provided but mean z-score unit change (SD) in IQ and a proxy for premorbid IQ (SD) were. Therefore, this study was included in the meta-analysis but left out from the data-descriptives (i.e., mean weighted IQ at baseline and weighted mean IQ-point change per year). Definition of age at illness onset differed slightly between the included studies: in two studies the age at which the first psychotic symptoms occurred was used (Bilder et al., 2006; Hedman et al., 2012), in one study the age at which the first unspecified symptoms occurred (Albus et al., 2006), another paper used the age at which psychotic symptoms had fully developed (Jepsen et al., 2010), while in one study (Heaton et al., 2001) age at illness onset information was provided in a table from a sample with 142 patients while only 81 patients were assessed longitudinally. In studies that did not report the duration of illness, age at illness onset was subtracted from the age at first IQ assessment, except for one study where age at first IQ assessment was based on assessment done prior to the disease onset (Bilder et al., 2006). Therefore, this study

(Bilder et al., 2006) was excluded from the moderator-analysis with duration of illness as regression variable.

The studies in this meta-analysis assessed IQ with the WAIS or with the WISC at least at one time-point since the WAIS and WISC are highly validated IQ tests with population norms and the most frequently used tests for assessing IQ. In three of the included studies full-scale IQ was measured based on WAIS-R (Heaton et al., 2001), WISC-III and WAIS-R (Frangou et al., 2008) and WISC-III (Jepsen et al., 2010); in the study of Hoff et al. (2005) only verbal IQ was measured (WAIS-R based on subtests information, vocabulary and similarities); in the study by Albus et al. (2006) verbal IQ (WAIS-R subtests information and similarities) and spatial ability (WAIS-R subtests block design and picture completion, which we here used as a proxy for performance IQ) were assessed separately, but not combined; in two studies a shortened version of WAIS-III (Leeson et al., 2010) and WAIS (Hedman et al., 2012) was used as a proxy for IQ. In addition, the composition of subtests (information, arithmetic, block design and digit symbol) used in the study by Leeson et al. (2010) had been validated in schizophrenia samples to account for a high percentage of the overall variance in full-scale IQ (Blyler et al., 2000). Finally, the composition of subtests (vocabulary, block design, picture arrangement and comprehension) used in the study by Hedman et al. (2012) has been applied earlier in a schizophrenia sample (Hijman et al., 2003). While shortened versions of the WAIS and WISC have been reported to overestimate IQ scores (Crawford, 1992), this is likely not relevant for change in IQ.

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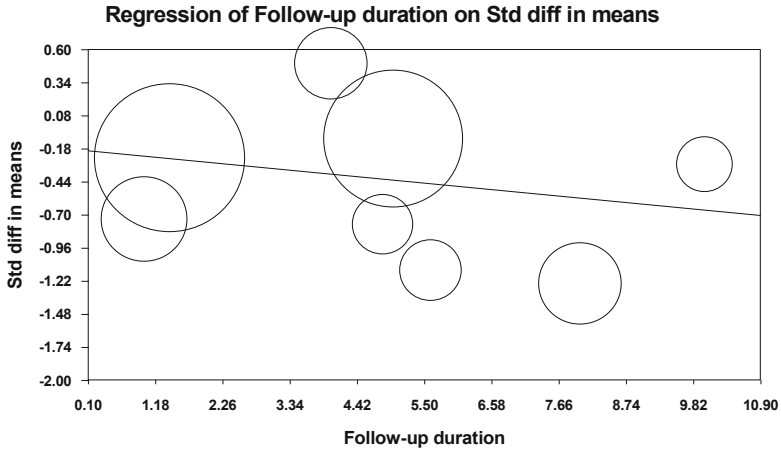
Regression of Follow-up duration on Std diff in means
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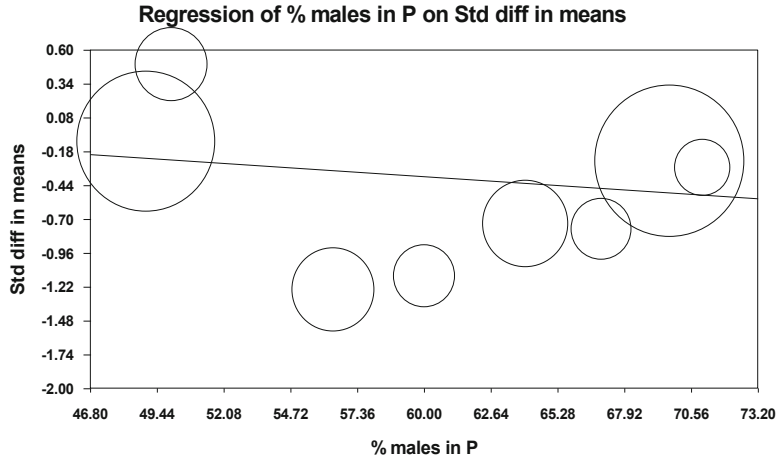
Regression of % males in P on Std diff in means
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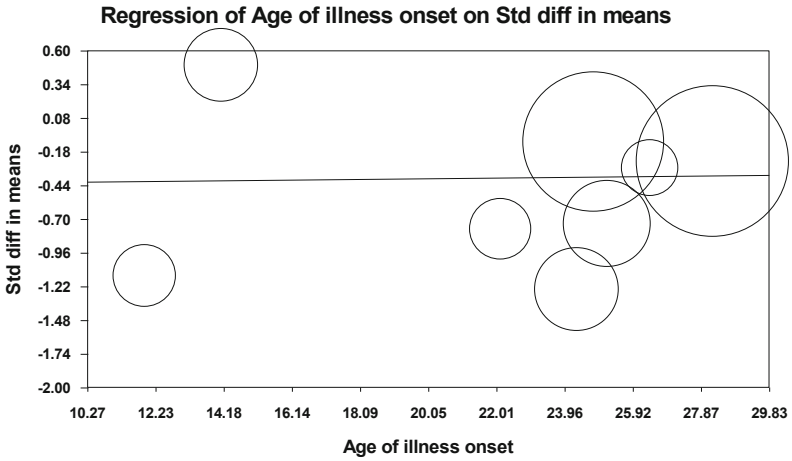
Regression of Age of illness onset on Std diff in means
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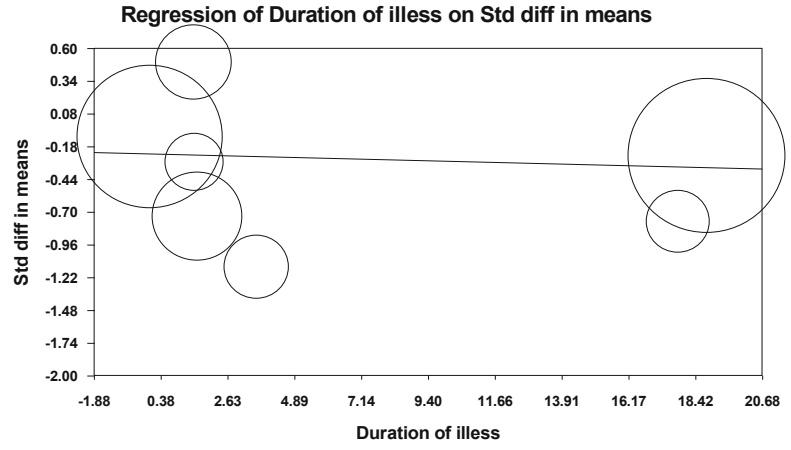
Regression of Duration of illess on Std diff in means
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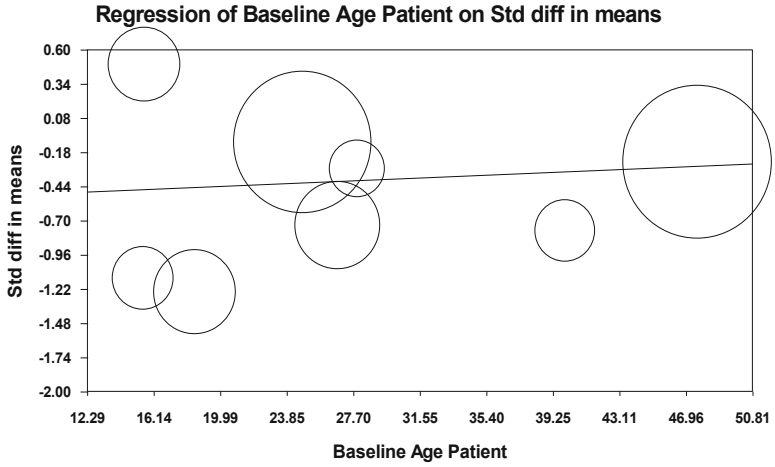

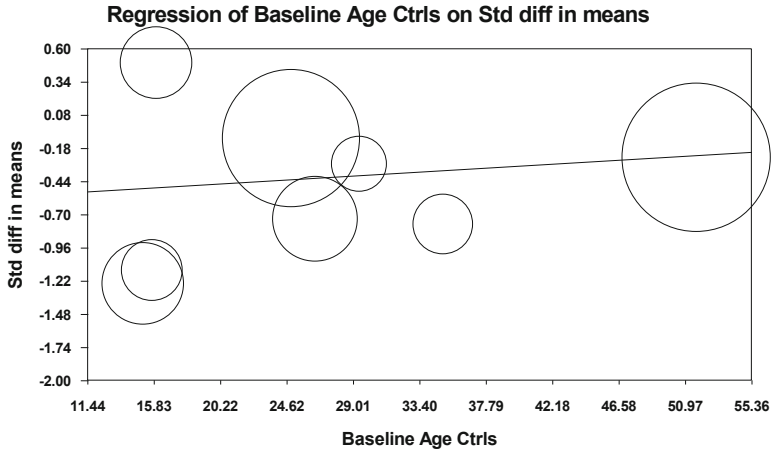

Supplementary Figures | Moderator variables in meta-regression. When significant heterogeneity is found, meta-regressions of experimental variables was performed to investigate potential sources of heterogeneity and to identify possible outliers (i.e., follow-up duration, percentage of males in the patient group, age of illness onset, duration of illness and mean baseline age in patients and controls). The size of the circles is proportional to the study's weight in the meta-analysis None of these moderators reached significance. Std diff in means = Cohen's *d.*

Chapter 5

Heritability of cortical thickness changes over time in twin pairs discordant for schizophrenia

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Hugo G. Schnack | René S. Kahn | Hilleke E. Hulshoff Pol

(submitted for publication)

Abstract

Cortical thickness and surface area changes have repeatedly been found in schizophrenia. Whether progressive loss in cortical thickness and surface area are mediated by genetic or disease related factors is unknown. Here we investigate to what extent genetic and/or environmental factors contribute to the association between change in cortical thickness and surface area and liability to develop schizophrenia.

Longitudinal magnetic resonance imaging study over a 5-year interval. Monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for schizophrenia were compared with healthy control twin pairs using structural equation modeling. Twins discordant for schizophrenia and healthy control twins were recruited from the twin cohort at University Medical Centre Utrecht, The Netherlands. A total of 90 individuals from 46 same sex twin pairs were included: 9 MZ and 10 DZ discordant for schizophrenia and 14 MZ and 13 (11 complete and 2 incomplete) DZ healthy twin-pairs. Age varied between 19-57 years. Higher genetic liability for schizophrenia was associated with progressive thinning of the cortex, particularly of the left superior temporal cortex. Higher environmental liability for schizophrenia was associated with attenuated thinning of the cortex. Cortical surface area and surface area change were heritable, but not associated with higher genetic (or environmental) liability for schizophrenia.

Excessive cortical thinning, particularly of the left superior temporal cortex, but not surface contraction, may represent a genetic risk marker for schizophrenia.

Introduction

Schizophrenia is characterized by structural brain abnormalities that appear to progress with longer illness duration (Pantelis et al., 2005; DeLisi et al., 2008; Hulshoff Pol & Kahn, 2008; van Haren et al., 2008; Kempton et al., 2010; Olabi et al., 2011; Andreasen et al., 2011). One of the brain areas in which progressive structural brain abnormalities have been implicated in schizophrenia is the cerebral cortex. Excessive thinning of the cortex, particularly of the fronto-temporal cortices, has been reported in childhood onset (Thompson et al., 2001; Greenstein et al., 2006), recent onset (Ziermans et al., 2012), first episode (Rais et al., 2010), as well as in more advanced stages of schizophrenia (Rimol et al., 2010; van Haren et al., 2011). At first blush, one would assume that these data suggest that the progressive cortical thinning in schizophrenia is related to the (effects of the) illness. However, schizophrenia is highly heritable (Sullivan et al., 2003), and brain volume is predominantly influenced by genes (Peper et al., 2007). Moreover, progressive brain volume loss in schizophrenia, particularly of the frontal and temporal lobes, is at least partially heritable through genes implicated in the illness (Brans et al., 2008). Thus, it is reasonable to hypothesize that the cortical thickness changes observed in schizophrenia could be related to the genetic risk to develop the illness. Interestingly, while several imaging studies in (twin) siblings of schizophrenia patients have been done (Moran et al., in press), this has not been studied. What is known is that, *cross-sectionally*, a thinner cortex in schizophrenia can in part be attributed to genes conferring risk to develop the disorder (Hulshoff Pol et al., 2012). That *progressive* cortical thinning in schizophrenia may indeed be (partially) attributable to schizophrenia risk genes as well is suggested by a study where increased familial risk was related to excessive thinning of prefrontal and temporal cortices in childhood schizophrenia (Gogtay et al., 2007). However, since so far twins have not been studied, it remains unresolved whether the reported progressive cortical thinning is related to the effects of (increased) genetic burden or whether it is attributable to the environment.

In addition to changes in cortical thickness, reduced cortical surface area has also been found in schizophrenia (Rimol et al., 2012; Palaniyappan et al., 2011; Hartberg et al., 2011). Since brain volume is represented by combined aspects of cortical thickness and surface measures (Winkler et al., 2010), each of which are influenced by their own genetic factors (Winkler et al., 2010; Panizzon et al., 2009), it is therefore possible that genes for schizophrenia are differentially associated with changes over time in cortical thickness or surface area in schizophrenia. Localised surface area contraction has been reported to occur

in patients (Palaniyappan et al., 2011) and may be related to the risk to develop schizophrenia (Prasad et al., 2010). However, these studies did not include twins, and therefore cannot resolve the issue of whether cortical surface area (contraction) is associated with the genetic liability to develop schizophrenia. The purpose of the current study was to establish the relative contributions of genetic and environmental (disease-related) factors to progressive changes in cortical thickness and surface area over time in schizophrenia.

Methods

Subjects

Participants were recruited from the twin-pair cohort at the University Medical Centre Utrecht (Brans et al., 2008). A total of 109 twins completed the baseline study. In the baseline sample discordant twins were matched to control twins for zygosity, age, gender, birth order, handedness, socioeconomic status of their parents, and follow-up duration. A total of nine MZ and ten DZ twin-pairs discordant for schizophrenia and 14 MZ and 11 DZ healthy comparison twin-pairs plus two singletons DZ healthy controls (i.e. from incomplete pairs) completed the longitudinal MRI study (total N=90 subjects) after an interval of approximately five years (T5) (mean=4.86 years; SD=0.57), see Table 1. All twins participated after written informed consent was obtained. Zygosity was determined by DNA fingerprinting using either the polymorphic markers D06S474, D07S1804, D07S1870, D12S811, D13S119, D13S126, D13S788, D20S119, D22S683, DXS1001 and ELN, or D13S317,VWA, D74520, D35158, TH01, TP0X, CSF1P0, and D55818. The study was approved by the medical ethics committee for research in humans of the University Medical Centre Utrecht, the Netherlands and was carried out according to the directives of the “declaration of Helsinki” (amendment of Edinburgh, 2000). All participants underwent extensive psychiatric assessments at baseline and at follow-up using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992).

Table 1 | Demographic characteristics of MZ and DZ patients with schizophrenia, their co-twins and healthy control twin pairs

	Monozygotic Twins				Dizygotic Twins			
Characteristic	**Patients**	**Co-twins**	**HC 1**	**HC 2**	**Patients**	**Co-twins**	**HC 1**	**HC 2**
No	9	9	14	14	10	10	12	12
Age, m (SD), y	40.2 (12.2)	40.2 (12.2)	35.5 (11.8)	35.5 (11.8)	37.1 (11.9)	37.2 (11.9)	34.0 (9.9)	36.3 (10.6)
Sex, M/F, No	4/5	4/5	9/5	9/5	6/4	6/4	7/5	8/4
Follow-up duration, m (SD), y	4.88 (1.02)	4.83 (0.98)	4.80 (0.22)	4.78 (0.21)	4.98 (0.59)	4.92 (0.69)	4.91 (0.43)	4.83 (0.41)
Handedness, right/left/both, No	8/1/0	8/0/1	11/1/2	10/3/1	9/1/0	9/1/0	10/2/0	10/1/1
Parental education m (SD), y*	12.44 (2.65)	12.44 (2.65)	10.93 (2.43)	10.93 (2.43)	11.90 (2.51)	11.90 (2.511)	10.92 (2.61)	10.92 (2.57)
Education, m (SD), y**	11.56 (3.05)	12.00 (2.83)	12.36 (2.41)	12.93 (3.10)	10.40 (2.27)	13.20 (3.01)	12.83 (2.53)	12.75 (2.56)
Medication nr typical/atypical/both	4/3/2				3/3/3[a]			
Cumulative Haloperidol Eq., m (SD)	10427 (6477)				8606 (6931)[a]			
Age at illness onset, m (SD), y	22.78 (5.54)				22.50 (6.10)			
Duration of illness, m (SD), y	17.41 (11.82)				14.63 (8.73)			
PANSS positive score at t0 m (SD)	15.17 (7.39)[b]				14.30 (5.50)			
PANSS negative score at t0 m (SD)	17.33 (10.61)[b]				13.20 (5.98)			
PANSS general score at t0 m (SD)	35.17 (13.27)[b]				27.80 (8.23)			
PANSS total score at t0 m (SD)	67.67 (29.49)[b]				55.30 (16.44)			
PANSS positive score at f-u m (SD)	13.00 (5.96)				11.70 (3.95)			
PANSS negative score at f-u m (SD)	13.22 (8.98)				12.20 (6.91)			
PANSS general score at f-u m (SD)	24.56 (5.15)				26.10 (9.91)			
PANSS total score at f-u m (SD)	50.78 (14.99)				50.00 (18.51)			

a= data was missing for one individual
b= data was missing for three individuals
t0=baseline
f-u=follow up
m=mean

*Parental education differed significantly between the discordant twin pairs and the healthy control twin pairs (t_{88}=-2.37, $p<0.05$), with parents of discordant twin pairs having longer parental education relative to control twin pairs.
**Education differed significantly between patients, co-twins, and control twins ($F_{2, 87}$=3.21, $p<0.05$). Pairwise analyses revealed that this was due to a significant difference between patients and controls, with controls having longer education.

Age at onset of illness was defined as the first time the patients experienced psychotic symptoms. Duration of illness was defined as time between age of first symptoms and age at first MRI scan. The Positive and Negative Syndrome Scale (Kay et al., 1987) was used to evaluate severity of symptoms. In the co-twins of the schizophrenia patients and the matched healthy comparison twin-pairs, the Schizophrenia and Affective Disorder Schedule–Lifetime version (SADS-L) (Endicott & Spitzer, 1987) and the Structured Interview for DSM-IV Personality (SIDP-IV) (Pfohl et al., 1995) were completed.

See supplemental information on diagnosis (patients, co-twins and controls) and medication information.

Brain Imaging

The magnetic resonance brain scans were acquired on a Philips NT scanner (Philips Medical Systems, Best, the Netherlands) operating at 1.5 T in all participants. T1-weighted three-dimensional fast-field echo (3D-FFE) scans with 160 to180 contiguous coronal slices (echo time/repetition time, 4.6 ms/30 ms; flip angle = 30°; voxel dimension, 1 x 1 x 1.2 mm^3) and T2-weighted dual-echo turbo-spin-echo scans with 120 contiguous coronal slices (echo time 1 /echo time 2/repetition time, 14 ms/80 ms/6350 ms; flip angle, 90°; voxel dimension, 1 x 1 x 1.6 mm^3) of the whole head were used for quantitative measurements. In addition, T2-weighted dual-echo turbo-spin-echo scans (echo time 1/echo time 2, 9 ms/100 ms; flip angle, 90°; in plane voxel dimension, 0.98 x 0.98 mm^2) with 19 axial 5-mm slices and 1.2-mm gap of the whole head were used for clinical neurodiagnostic evaluation.

Processing was done on the neuroimaging computer network from the Department of Psychiatry, University Medical Center Utrecht,The Netherlands. All images were coded to ensure blindness of participant identification and diagnoses. Scans were manually put into Talairach frame (no scaling) for segmentation purposes and corrected for inhomogeneities in the magnetic field (Sled et al., 1998). Intensity histogram analysis on the T1 image yielded thresholds for separating brain tissue from cerebrospinal fluid and, within the brain, gray matter (GM) from white matter (WM); GM and WM segments were created by applying these thresholds to the images (Schnack et al., 2001).

To estimate the cortical thickness, we used the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm designed at the McConnell Brain Imaging Centre of

the Montréal Neurological Institute (MacDonald et al., 2000; Kabani et al., 2001; Kim et al., 2005). A 3-dimensional surface consisting of 81,920 polygons was fitted to the WM-GM interface. This defined the inner surface of the cortex, which was then expanded to fit the GM–cerebrospinal fluid interface, thereby creating the outer cortical surface (MacDonald et al., 2000; Kim et al., 2005). Cortical thickness was estimated by taking the distance between the two surfaces such that each polygon vertex on the outer surface had a counterpart vertex on the inner surface.

This analysis involved two stages. First, a vertex-by-vertex analysis was carried out to estimate the phenotypic correlation between liability for schizophrenia and cortical thickness change at each vertex on the brain. Each subject's thickness measurements were smoothed across the surface using a 20 (FWHM) mm surface-based blurring kernel as was done before (Brouwer et al., 2010; Brans et al., 2010). This method of blurring improves the chances of detecting population differences, but also follows the curvature of the surface to preserve any anatomical boundaries within the cortex (Chung & Taylor, 2007). It should be noted that the area defined as the parahippocampal gyrus comprises parts of the perirhinal, entorhinal, and parahippocampal cortex, and those parts of uncus and hippocampus proper that are on the cortical surface in the medial temporal lobe (Lerch et al., 2008). The surfaces of the participants were registered to an average surface created from 152 individuals (International Consortium for Brain Mapping) (Lyttelton et al., 2007), allowing comparison of cortical thickness locally between subjects both at baseline as well as follow-up measurement. For each person, the change in cortical thickness was calculated for each of the 81,924 vertices.

Second, the automated anatomical labelling atlas (AAL) (Tzourio-Mazoyer et al., 2002) was used to define 78 regions of interest (ROIs; 39 in each hemisphere) on the unsmoothed individual thickness change measurements. For each person, the mean change in cortical thickness per ROI was calculated. The mid-area between the white matter (i.e., inner surface) and the gray matter (i.e, outer surface) was used for this study as a measure of surface area and surface area change.

Statistical Analyses

Overall and ROI cortical thickness and surface area (change) data were prepared using regression analysis to control for the effects of age, sex, and handedness. Unstandardized residuals were saved for further statistical analysis.

For statistical analysis of the data, the approach was two-fold (see also Brans et al., 2008; Hulshoff Pol et al., 2012). Multiple repeated-measures univariate analyses of covariance were applied to baseline and change in cortical thickness as well as baseline and change in cortical surface area plus all the ROIs for cortical thickness change and surface area change. This procedure did not separate genetic and environmental influences but made the findings comparable with earlier studies. In repeated-measures univariate analysis of covariance, the unstandardized residuals corrected for age sex and handedness of baseline and change in cortical thickness/surface area, plus change in cortical thickness/surface area in predefined ROIs were entered one by one as dependent variables. Twin (twin 1=patient with schizophrenia or healthy control, twin 2=co-twin of patient or healthy control) was entered as within-subjects factor. Between-subjects factors were Group (discordant twin pair, healthy twin pair) and Zygosity (MZ, DZ). A Bonferroni correction was applied to control for multiple comparisons for those ROIs that showed a significant main effect for Group. This was done to explore whether there were differences in cortical thickness/surface area *change* between healthy twins and those with a genetic liability to develop the illness (i.e., patients and co-twins). The threshold for significance was set by dividing the alpha value by the total number of ROIs for each hemisphere separately (0.05/39), which resulted in a p-value of $1.28*10^{-3}$. We chose to correct for multiple comparisons for each hemisphere separately to compensate for the overly conservative procedure that results from a Bonferroni correction for multiple comparison correction with dependent data. Next, for genetic model fitting, structural equation modelling (SEM) was performed to further investigate the relative contributions of genetic and environmental factors to all brain measures and their associations with the risk for schizophrenia. In addition, we performed SEM on the baseline measure for those changes in cortical thickness/surface areas ROIs that survived the Bonferroni correction for multiple comparisons (please note that the analyses for baseline cortical thickness overlap with those reported for twins discordant for schizophrenia in (Hulshoff Pol et al., 2012)). Genetic model fitting was based on the twin model. See supplemental information for the twin model.

Post-hoc bivariate correlations were done on unstandardized residuals to examine the potential influence of cumulative haloperidol equivalents in patients and change in cortical thickness/surface area and change in the significant ROIs.

Results

Discordant twins differed significantly from the healthy twins on parental education ($t_{(88)}$=-2.37, p<0.05), with parents of discordant twins having a higher level of education level as compared with parents of control twins. A significant difference in subject's level of education was found between control twins, patients and co-twins ($F_{(2,87)}$=3.21, p=0.045). Pairwise comparisons showed that controls had a significantly higher level of education relative to patients (p<0.05) while level of education between controls and co-twins of patients did not differ significantly (Table 1).

Cortical Thickness, Surface Area and ROI at Baseline

A significant main effect of Group was found for baseline cortical thickness, due to discordant twin pairs having a thicker cortex than the control twin pairs ($F_{(1,40)}$=4.39; p=.04) (Table 2, Figure 1). Furthermore, a significant main effect of Twin was found for baseline cortical thickness due to the co-twins and HC 2 having a thicker cortex relative to the patients and HC 1 ($F_{(1,40)}$=8.58; p=.01). Since also a significant Twin*Group*Zygosity interaction was found ($F_{(1,40)}$=8.23; p=.01), due to co-twins having a thicker cortex than the patients in the MZ but less pronounced in DZ discordant twin pairs (while this pattern seemed reversed in the control twin pairs), the effect could largely be explained by a thinner cortex in the MZ patients and a thicker cortex in the MZ discordant co-twins. No significant main or interaction effects were found for surface area at baseline (Table 2, Figure 1).

Table 2 | Cortical thickness and surface area change in twins discordant for schizophrenia and control twins

	MZ Twins				DZ Twins			
Total	Pat	Co-twins	HC 1	HC 2	Pat	Co-twins	HC 1	HC 2
Baseline cortical thickness (mm)	2.99 (0.16)	3.09 (0.16)	2.99 (0.14)	3.00 (0.15)	3.04 (0.07)	3.04 (0.12)	3.02 (0.08)	3.01 (0.08)
Follow-up cortical thickness (mm)	2.97 (0.21)	3.00 (0.17)	2.98 (0.13)	2.99 (0.10)	2.95 (0.17)	2.98 (0.12)	3.02 (0.06)	3.00 (0.10)
Cortical thickness change (mm)	-0.03 (0.11)	-0.09 (0.04)	-0.01 (0.08)	-0.01 (0.09)	-0.08 (0.15)	-0.06 (0.07)	0.00 (0.08)	-0.01 (-0.06)
Cortical thickness change (%)	-0.87 (3.74)	-2.83 (1.30)	-0.28 (2.58)	-0.14 (3.10)	-2.81 (4.80)	-1.82 (2.29)	0.05 (2.51)	-0.23 (-1.89)
Baseline surface area (cm^2)	1779 (157)	1790 (184)	1882 (134)	1865 (155)	1851 (161)	1850 (172)	1877 (133)	1819 (131)
Follow-up surface area (cm^2)	1774 (159)	1783 (188)	1872 (144)	1854 (136)	1831 (142)	1841 (161)	1859 (136)	1801 (132)
Surface area change (cm^2)	-5.77 (27.71)	-7.12 (20.80)	-10.42 (21.17)	-10.79 (24.40)	-19.81 (33.05)	-9.08 (24.10)	-17.19 (22.96)	-17.73 (24.40)
Surface area change (%)	-0.32 (1.62)	-0.42 (1.22)	-0.58 (1.14)	-0.49 (1.80)	-0.99 (1.63)	-0.44 (1.26)	-0.93 (1.26)	-0.97 (1.31)

	MZ Twins				DZ Twins			
Left Superior Temporal	Pat	Co-twins	HC 1	HC 2	Pat	Co-twins	HC 1	HC 2
Baseline thickness (mm)	2.94 (0.18)	3.08 (0.15)	2.93 (0.15)	2.97 (0.17)	3.05 (0.12)	3.08 (0.15)	2.98 (0.16)	3.02 (0.15)
Follow-up thickness (mm)	2.93 (0.23)	2.98 (0.18)	2.96 (0.15)	2.95 (0.14)	2.94 (0.14)	2.94 (0.25)	3.00 (0.13)	3.01 (0.19)
Cortical thickness change (mm)	-0.01 (0.13)	-0.10 (0.09)	0.03 (0.09)	-0.02 (0.12)	-0.12 (-0.10)	-0.15 (0.14)	0.03 (0.11)	-0.01 (0.12)
Cortical thickness change (%)	-0.33 (4.56)	-3.23 (3.14)	1.01 (3.29)	-0.60 (4.03)	-3.78 (3.29)	-4.84 (4.73)	0.96 (3.76)	-0.28 (3.94)
Baseline surface area (cm^2)	31.82 (2.42)	29.46 (4.93)	31.79 (3.95)	31.61 (3.33)	29.21 (5.41)	31.55 (3.99)	32.03 (3.26)	29.50 (3.91)
Follow-up surface area (cm^2)	31.57 (2.81)	28.87 (4.40)	32.93 (4.18)	31.70 (3.45)	29.43 (5.01)	30.39 (3.61)	32.40 (3.20	28.75 (3.47)
Surface area change (cm^2)	-0.26 (3.84)	-0.59 (1.70)	1.13 (3.62)	0.08 (1.95)	0.22 (2.10)	-1.17 (2.96)	0.37 (1.22)	-0.74 (3.03)
Surface area change (%)	-0.22 (12.29)	-1.56 (6.00)	4.07 (10.75)	0.39 (6.00)	1.21 (6.91)	-3.25 (8.83)	1.23 (3.82)	-1.93 (9.64)

Pat=Patients
MZ=Monozygotic
DZ= Dizygotic
HC=Healthy Controls

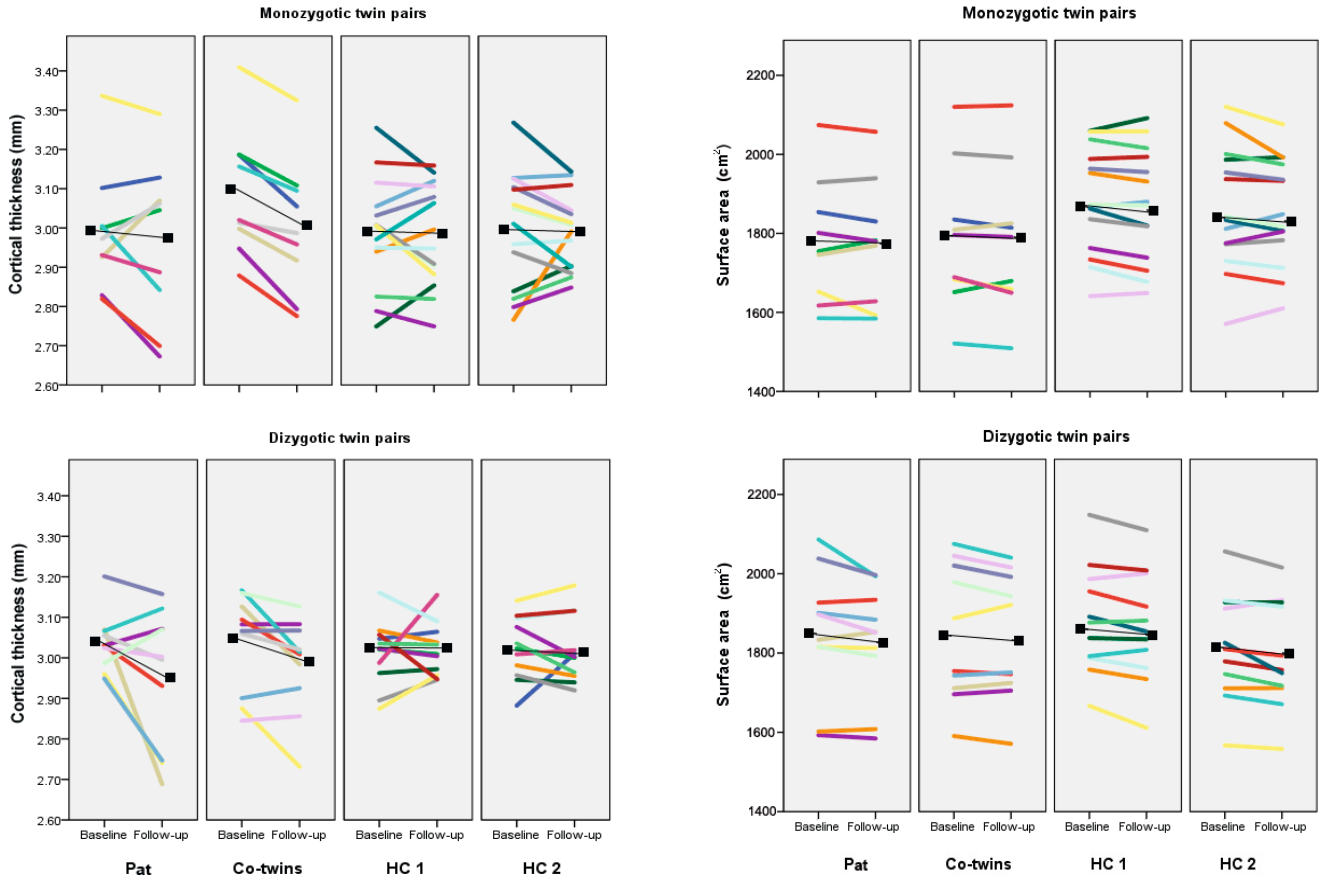

Figure 1 | Individual changes in cortical thickness and area surface over time. Brain changes in monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for schizophrenia and control twin-pairs over the 5-year interval are represented through color-coding. The average for each group is represented in black squares. Raw data are shown.

ROI analysis based on the selected region of change over time (see findings below over the five-year interval) revealed a significant main effect of Group for left superior temporal cortical thickness at baseline ($F_{(1,40)}$=7.20; p=.01) in that the patients and their co-twins had a thicker cortex in the left superior temporal cortex compared to healthy control twin pairs (Table 2). In addition, a significant Twin*Group*Zygosity interaction was found ($F_{(1,40)}$=4.54; p=.04), with MZ co-twins having a thicker left superior temporal cortex than the DZ co-twins while MZ patients had a thinner cortex at baseline in the same ROI than the DZ patients. This interaction effect was not found in the healthy control twin pairs.

Change over the Five-Year Interval

Over time, patients and their co-twins combined showed an overall progressive decrease in cortical thickness as compared with healthy control twins expressed as a significant main effect of Group ($F_{1, 40}$=7.46; p=.01) (Table 2). No significant main or interaction effects were found for change in surface area (Table 2).

ROI analyses for cortical thickness change revealed significantly more pronounced cortical thinning over time in discordant twin pairs as compared with healthy control twins (i.e., main effect of Group) in the left superior temporal cortex ($F_{1,40}$=13.65; p=.001). This finding remained significant following Bonferroni correction for multiple comparisons ($p<1.28*10^{-3}$) (Table 2).

None of the ROIs analyses of surface area change survived Bonferroni correction.

Genetic Modelling

At baseline, genetic liability for schizophrenia was significantly associated with a thicker cortex (phenotypic association through common genes, $r_{ph\text{-}a}$=.36); and with a thicker left superior temporal cortex ($r_{ph\text{-}a}$=.25) (Table 3, Figure 2).

Over time, genetic liability for schizophrenia was significantly associated with more pronounced cortical thinning (phenotypic association through common genes, $r_{ph\text{-}a}$=-.20); particularly for the left superior temporal cortex ($r_{ph\text{-}a}$=-.25) (Table 3, Figure 2). No significant associations between genetic liability for schizophrenia and cortical surface area (change) were found (Table 3).

At baseline, environmental factors implicated in schizophrenia were significantly associated with a thinner cortex (phenotypic association through unique environmental factors, $r_{ph\text{-}e}$=-.17), including a thinner left superior temporal cortex ($r_{ph\text{-}e}$=-.18).

Over time, environmental factors implicated in schizophrenia were significantly associated with less prominent cortical thinning ($r_{ph\text{-}e}$=.10), including less prominent left superior temporal thinning ($r_{ph\text{-}e}$=.13). Environmental factors implicated in schizophrenia were not significantly associated with cortical surface area change.

The phenotypic correlations, representing the sum of the influences of genetic and environmental risk factors for schizophrenia on cortical thinning/surface contraction (r_{ph}=$r_{ph\text{-}a}$+ $r_{ph\text{-}e}$), were largely negative but did not reach significance (Table 3, Figure 3).
These findings remained essentially the same after correcting for parental education.
Irrespective of disease, at baseline, heritability significantly influenced cortical thickness (62%), left superior temporal cortical thickness (37%), and cortical surface area (83%). Irrespective of disease, heritability significantly influenced cortical thickness change over time (25%), left superior temporal cortical thickness change (50%), and cortical surface area change (52%).

Cumulative antipsychotic medication dose (in haloperidol equivalents) was not significantly associated with change in cortical thickness or surface area or with change in the left superior temporal cortex in patients.

Table 3 | Estimates of genetic and environmental influences on cortical thickness and surface change in schizophrenia

Total	h^2	r_g	r_e	r_{ph}	$r_{ph\text{-}a}$	$r_{ph\text{-}e}$
Baseline cortical thickness	**62 (33 to 78)**	**0.51 (0.15 to 0.96)**	**-0.96 (-1.00 to -0.65)**	0.21 (-0.20 to 0.51)	**0.36 (0.01 to 0.62)**	**-0.17 (-0.22 to -0.13)**
Baseline cortical thickness L	**68 (32 to 84)**	**0.29 (0.14 to 0.53)**	**-0.98 (-1.00 to -0.68)**	0.06 (-0.08 to 0.25)	**0.21 (0.03 to 0.44)**	**-0.16 (-0.22 to -0.12)**
Baseline cortical thickness R	**52 (20 to 71)**	**0.44 (0.16 to 0.91)**	**-0.88 (-1.00 to -0.35)**	0.12 (-0.06 to 0.29)	**0.29 (0.10 to 0.45)**	**-0.17 (-0.23 to -0.12)**
Change cortical thickness	**25 (1 to 52)**	**-0.45 (-1.00 to -0.06)**	0.42 (-0.07 to 0.79)	-0.10 (-0.28 to 0.07)	**-0.20 (-0.37 to -0.02)**	**0.10 (0.03 to 0.17)**
Change cortical thickness L	**22 (1 to 49)**	**-0.44 (-1.00 to -0.03)**	0.38 (-0.11 to 0.76)	-0.09 (-0.27 to 0.08)	**-0.19 (-0.36 to -0.01)**	**0.10 (0.02 to 0.16)**
Change cortical thickness R	**27 (1 to 55)**	**-0.40 (-1.00 to -0.02)**	0.31 (-0.21 to 0.74)	-0.12 (-0.29 to 0.06)	**-0.19 (-0.36 to -0.01)**	**0.07 (0.01 to 0.14)**
Surface area baseline	**83 (65 to 92)**	-0.04 (-0.27 to 0.19)	-0.09 (-0.67 to 0.51)	-0.05 (-0.24 to 0.15)	-0.03 (-0.22 to 0.16)	-0.01 (-0.08 to 0.07)
Surface area baseline L	**84 (69 to 92)**	-0.03 (-0.26 to 0.20)	-0.30 (-0.85 to 0.38)	-0.06 (-0.25 to 0.13)	-0.02 (-0.21 to 0.09)	-0.03 (-0.10 to 0.05)
Surface area baseline R	**82 (63 to 92)**	-0.07 (-0.24 to 0.17)	0.01 (-0.56 to 0.56)	-0.06 (-0.25 to 0.14)	-0.05 (-0.24 to 0.14)	0.01 (-0.07 to 0.08)
Surface area change	**52 (25 to 70)**	0.07 (-0.23 to 0.37)	-0.05 (-0.53 to 0.46)	0.03 (-0.15 to 0.22)	0.04 (-0.15 to 0.23)	-0.01 (-0.11 to 0.09)
Surface area change L	24 (0 to 49)	0.05 (-1.00 to 1.00)	0.16 (-0.36 to 0.62)	0.07 (-0.11 to 0.24)	0.02 (-0.16 to 0.20)	0.04 (-0.09 to 0.16)
Surface area change R	**62 (37 to 77)**	0.01 (-0.26 to 0.29)	-0.23 (-0.69 to 0.32)	-0.04 (-0.22 to 0.15)	0.01 (-0.18 to 0.20)	-0.04 (-0.13 to 0.06)
Left Superior Temporal	h^2	r_g	r_e	r_{ph}	$r_{ph\text{-}a}$	$r_{ph\text{-}e}$
Baseline cortex	**37 (6 to 60)**	**0.45 (0.12 to 1.00)**	**-0.81 (-0.98 to -0.34)**	0.07 (-0.11 to 0.24)	**0.25 (0.07 to 0.41)**	**-0.18 (-0.23 to -0.13)**
Change cortex	**50 (25 to 68)**	**-0.39 (-0.73 to -0.11)**	**0.65 (0.19 to 0.90)**	-0.12 (-0.30 to 0.06)	**-0.25 (-0.41 to -0.07)**	**0.13 (0.08 to 0.17)**
Baseline surface	0 (0 to 29)	0 (0 to 0.11)	0.18 (-0.23 to 0.70)	0.05 (-0.17 to 0.19)	0 (-0.25 to 0.12)	0.05 (-0.07 to 0.20)
Change surface	0 (0 to 34)	0 (0 to 0.11)	0.09 (-0.33 to 0.68)	0.03 (-0.21 to 0.15)	0 (-0.27 to 0.11)	0.03 (-0.09 to 0.19)

h^2 = heritability (percentages of additive genetic effects of the total variance)
r_g = genetic correlation showing the extent to which two traits share the same genetic effects
r_e = unique environmental correlation showing the extent to which two traits share the same unique environmental effects
r_{ph} = phenotypic correlation showing the association between schizophrenia and cortical thickness baseline/change or surface baseline/change
$r_{ph\text{-}a}$ = part of the phenotypic correlation that can be attributed to genetic influences
$r_{ph\text{-}e}$ = part of the phenotypic correlation that can be attributed to unique environmental influences
CI (Confidence Interval) is 90% for h^2 and 95% for r_g, r_e, r_{ph}, $r_{ph\text{-}a}$ and $r_{ph\text{-}e}$
L = Left, R = Right,
In **bold** = significant estimates

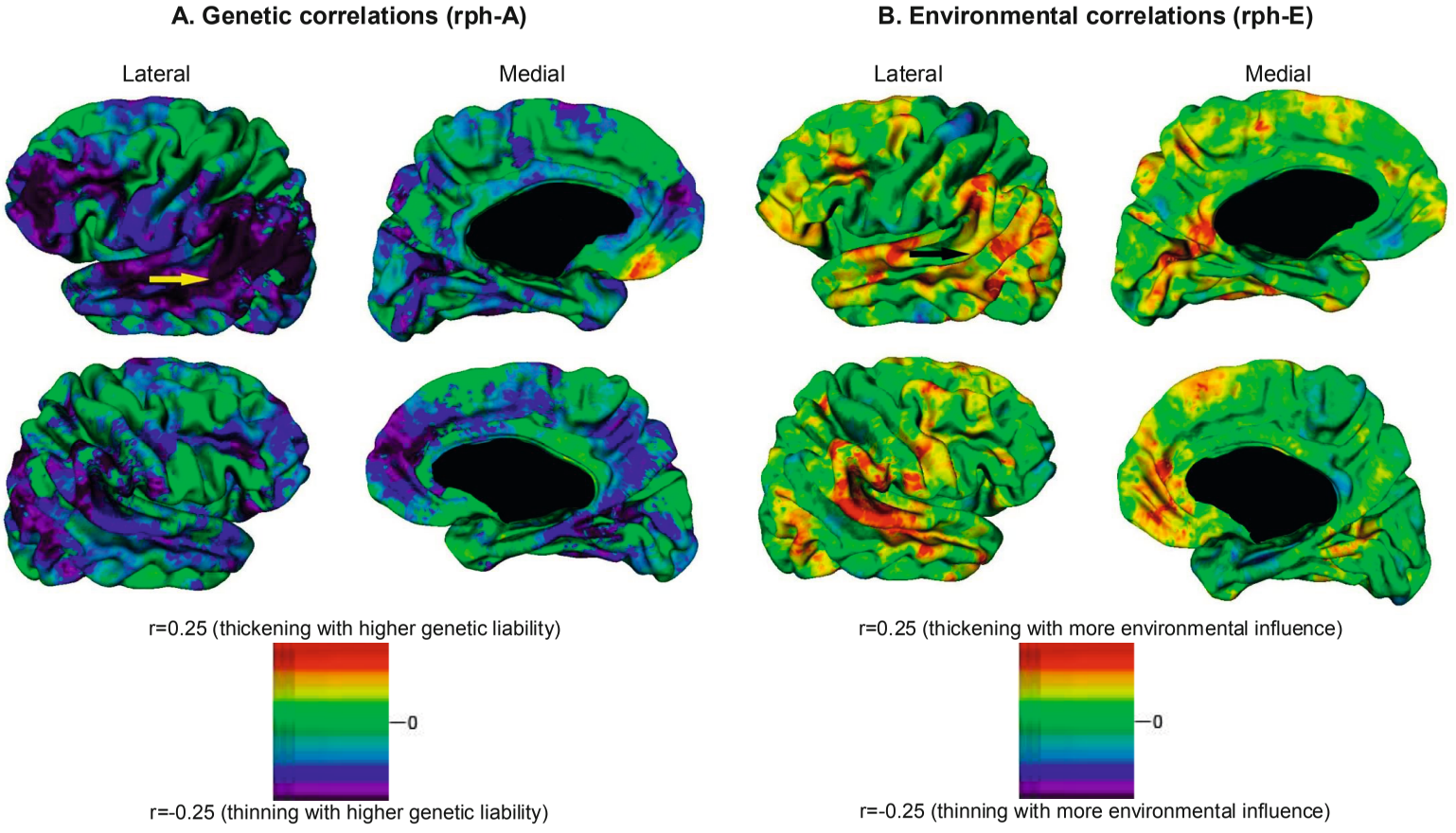

Figure 2 | Genetic and environmental liability for schizophrenia and cortical thickness change over time. Higher genetic ($r_{ph\text{-}a}$) and environmental ($r_{ph\text{-}e}$) correlations between liability for schizophrenia and cortical thinning over the 5-year interval is represented by negative correlations (up to blue/purple), cortical thickening by positive correlations (up to orange/red). Arrow shows left superior temporal cortex ($p<1.28*10^{-3}$).

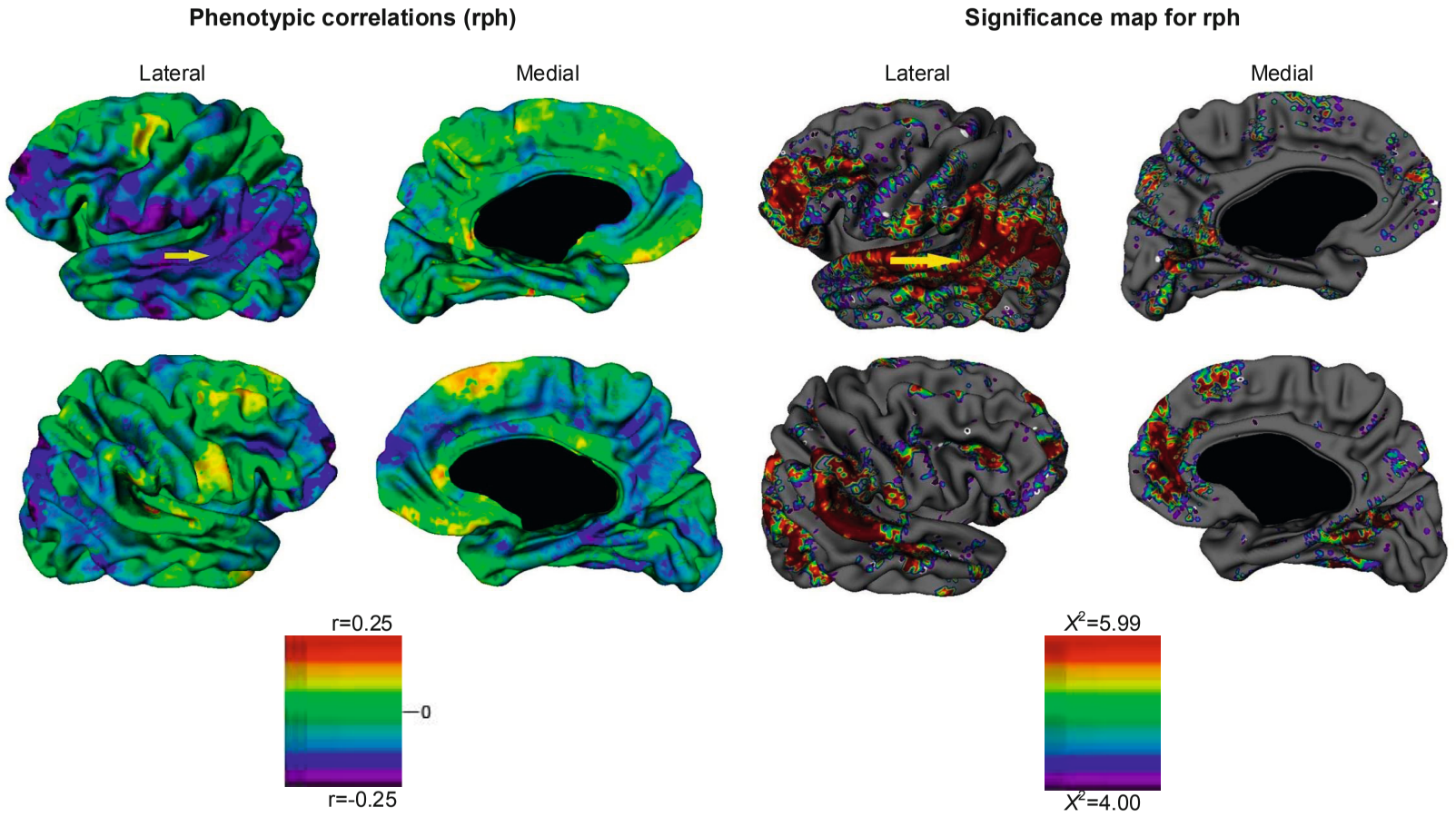

Figure 3 | Cortical thickness change over time and liability for schizophrenia. Cortical thickness change over the 5-year interval is shown as phenotypic correlations (r_{ph}) with liability for schizophrenia and their significance (X^2 map). Cortical thinning associated with higher disease liability in blue/purple (negative correlations), cortical thickening/less pronounced cortical thinning in yellow/red (positive correlations).

Discussion

To our knowledge, this is the first longitudinal study measuring change in cortical thickness and surface area over time in twin pairs discordant for schizophrenia. We find increased genetic liability for schizophrenia to be associated with excessive cortical thinning, particularly of the left superior temporal cortex. In addition, unique environmental influences associated with the illness may attenuate cortical thinning in patients. Moreover, while individual variation in cortical surface area contraction over time was found to be highly heritable irrespective of disease, we did not find significant associations with increased genetic or environmental liabilities for schizophrenia. Thus, excessive cortical thinning of the cortex, particularly of the left superior temporal cortex, may be a genetic marker for schizophrenia.

We find increased genetic risk for the disease to be significantly implicated in the progressive cortical thinning in schizophrenia. Thus, the excessive cortical thinning found in several studies in schizophrenia (Thompson et al., 2001; Greenstein et al., 2006; Ziermans et al., 2012; Van Haren et al., 2011; Cobia et al., 2012) can be attributed, at least in part, to genes implicated in the disease. This implies that disease-related factors such as medication cannot fully explain the progressive cortical thinning in patients. Our results are in line with and extend previous findings of excessive cortical thinning as a familiar risk marker for schizophrenia (Gogtay et al., 2007; Prasad et al., 2010). Here we add that excessive cortical thinning in schizophrenia is not only familial, it is of genetic origin.

In contrast, we find that total cortical surface (contraction) is not significantly associated with increased genetic (or environmental) liability for schizophrenia. This finding differs from the report that cortical surface contraction may be familial in schizophrenia (Prasad et al., 2010). However, this study examined offspring of affected patients, who carry a different genetic risk than do twins (Gottesman, 1991); clearly their environments differ as well. Therefore their results are difficult to compare with ours. This may suggest that the cortical surface contraction in offspring of patients reflects a non-genetic, familial, aspect of being a child of a parent with schizophrenia. Based on our findings we conclude that cortical surface area (change) is not significantly associated with the genetic risk for schizophrenia.

Irrespective of disease, we find that cortical thickness (h^2=62%), thickness change over time (h^2=25%), cortical surface area (h^2=83%), and surface change (h^2=52%), are all highly

heritable. These findings are in line with previous findings on cortical thickness (Thompson et al., 2001; Rimol et al., 2010; Goldman et al., 2009), thickness change (Chung & Taylor, 2007; van Soelen et al., 2012) and surface area (Winkler et al., 2010; Panizzon et al., 2009; Eyler et al., 2011). We are not aware of any earlier studies on heritability of cortical surface area change over time. Thus, our findings suggest that, while both cortical thickness and surface area changes are clearly influenced by genes, increased genetic liability for schizophrenia is primarily associated with excessive cortical thinning.

Excessive cortical thinning was found throughout the cortex, but was predominantly associated with increased genetic liability for schizophrenia in the superior temporal cortex of the left hemisphere. In addition, the left frontal pole and right medial temporal cortex seemed to be thinning excessively in patients and their co-twins, although, in contrast to the left superior temporal cortex, these areas did not survive the Bonferroni correction for multiple comparisons. Interestingly, Kraepelin already mentioned left superior temporal cortex involvement in schizophrenia, based on clinical observations (Kraepelin, 1893). Moreover, early brain imaging studies reported the left posterior superior temporal gyrus to be significantly decreased in volume and associated with the severity of thought disorder in schizophrenia (see e.g., (Shenton et al., 1992)). Here we show that individual variation in progressive thinning of the left superior temporal cortex can be explained – at least partly - by genes implicated in schizophrenia. This finding is particularly interesting in light of the superior temporal gyrus being specialised in processing of voices (Belin et al., 2000), a specialisation that develops in infancy (Grossman et al., 2010).

Unique environmental influences implicated in schizophrenia also contributed to the cortical thickness change over time in schizophrenia although this effect was considerably smaller than the genetic one. Interestingly, increased environmental risk for schizophrenia was associated with *less* prominent cortical thinning. There are several potential explanations for this finding. Possibly, after having already lost a considerable amount of cortical tissue in this chronic phase of the disease, cortical thinning in the patients may have reached a so-called floor effect, resulting in less prominent progressive loss when compared with their co-twins. Alternatively, antipsychotic medication may have attenuated cortical thinning. Indeed, in patients, atypical antipsychotic medication has been shown to be associated with less prominent progressive brain tissue loss ((van Haren et al., 2011, Lieberman et al., 2005; DeLisi et al., 2006); but see (Ho et al., 2011)), including less cortical thinning (van Haren et

al., 2011). We found no significant association between cumulative haloperidol equivalents and cortical thickness change in the current study. However, we have to emphasize that the number of patients (N=19) left us statistically underpowered to address this question appropriately.

We can only speculate about the physiological mechanisms underlying excessive cortical thinning associated with increased genetic risk for schizophrenia in the absence of surface contraction. Changes in cortical thickness could reflect several processes, including synaptogenesis, neurogenesis, glio-genesis, altering vasculature and an interplay between these factors (Zatorre et al., 2012). Cortical thinning has been associated with a two- to three-fold reduction in synapses during adolescence and young adulthood based on post-mortem research of normal development (Huttenlocher, 1979; Petanjek et al., 2011). A delayed development would be consistent with the thicker cortex of the discordant twin pairs at baseline, and (faster) thinning at a later age than normal, at least in some areas. This is what we found for overall cortical thickness and left superior temporal cortex in the discordant twin pairs (see also Hulshoff Pol et al., 2012). Thus, increased liability for schizophrenia could reflect a stunted dynamic reorganization of the synaptic circuitry. Our findings could also represent a progressive loss of the extra-neuronal space encompassing perineuronal nets. Perineuronal nets are involved in neuronal development and plasticity (Wang et al., 2012), and may be implicated in schizophrenia (Berretta, 2012). Moreover, with recent large multicentre studies showing linkage between specific genes with human brain structure through genome-wide associations (Stein et al., 2012), identification of genes implicated in (aberrant) brain plasticity is becoming feasible.

That we do not find progressive cortical surface contraction despite cortical thinning in schizophrenia patients and their co-twins suggests that pathophysiological processes occur within (one or more layers of) the vertical cortical columns rather than in the number of columns (Mountcastle, 1997; Rakic, 1988). The cortex is organized horizontally into six laminae (I-VI), and vertically into groups of cells linked synaptically across the horizontal laminae. Vertically grouped cells have migrated serially in time in a radial column and originate from the same locus of the ventricular and sub-ventricular zones, together forming an ontogenetic unit. The surface area of the cortex is determined by the number of its ontogenetic units, set by the number of symmetric divisions of progenitor cells in the neural epithelium before migration begins (Rakic, 1988). Indeed, one extra symmetric division will

double the number of ontogenetic units, and thus double the area of the neocortex (Mountcastle, 1997). Thus, the cortical surface area seems to predominantly reflect early (prenatal) developmental processes. Based on our data it is not likely that prenatal developmental processes (expressed as cortical surface) are associated with increased genetic risk for schizophrenia. In fact later aberrations in brain development (expressed as cortical thickness) are more likely to be implicated.

Our findings have to be interpreted in light of some limitations. One, excessive cortical thinning, while showing significant correlations with increased liability for schizophrenia through shared genetic influences (r_{ph-a}) did not show an overall significant phenotypic correlation (r_{ph}); This was due to the significant genetic (r_g) and environmental (r_e) correlations being in opposite directions, cancelling each other out (by combining r_g with heritability h^2 of each trait the part of the phenotypic correlation that is attributable to shared genetic influences r_{ph-a} can be estimated). Two, the applied regions of interest analysis and stringent Bonferroni correction may not have captured several other relevant areas, in addition to the left superior temporal cortex, such as the left frontal pole, and right medial temporal cortex. Three, with parental education (as a proxy for social economic status) being higher in discordant twins than in healthy twins, the influence of increased genetic and environmental liabilities for the disease may have been underestimated. Four, power-issues refrained us from measuring possible contributions from gene-by-environment interactions.

In conclusion, we found significant contributions of genetic factors to excessive cortical thinning in schizophrenia, particularly in the left superior temporal cortex. Progressive thinning of the left superior temporal cortex may therefore represent a promising target for genetic studies in schizophrenia.

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Supplemental Information

Diagnosis and Medication

Sixteen probands met criteria for schizophrenia and three met criteria for schizoaffective disorder. Furthermore, co-twins of the probands met diagnoses of schizoid personality disorder (one MZ), schizotypical personality disorder (two MZ), cannabis abuse (one DZ), conduct disorder (one MZ) and major depressive disorder (in remission: one MZ and one DZ). In two healthy participants, diagnoses of adjustment disorder with depressed mood (one DZ) and major depressive disorder (in remission: one MZ) were made. At follow-up, two co-twins of probands had developed a major depressive disorder (in remission: two DZ) and one a depressive disorder not otherwise specified (one DZ). Four healthy participants (three MZ and one DZ) developed major depressive disorders (in remission). Except for one control twin pair that was separated at 12 years of age when both their parents died, all twins were reared together.

A table from the Dutch National Health Service (Commissie Farmaceutische Hulp, 2002) was used to calculate the cumulative dosage of typical antipsychotics during the scan interval and to derive the haloperidol equivalents. For atypical antipsychotics, the respective pharmaceutical companies suggested how to convert dosage into haloperidol equivalents (clozapine,40:1; olanzapine,2.5:1; risperidone,1:1; sulpiride,170:1; quetiapine,50:1; sertindole,2:1 and aripripazole,2:1). During the scan-interval, six patients had been taking atypical antipsychotic medication (including clozapine, olanzapine and aripripazole) exclusively and seven patients were taking typical medication exclusively. Five patients switched between typical and atypical antipsychotics during the scan interval. From one patient, we did not have reliable information about medication intake. None of the co-twins (with the exception of one co-twin who had used antipsychotic medication for a short period) had ever used antipsychotic medication. Five co-twins (three MZ, two DZ) as well as two healthy participants (two MZ) used antidepressants. Commissie Farmaceutische Hulp van het College voor Zorgverzekeringen. (2002): Farmacotherapeutisch Kompas [in Dutch], Amstelveen, the Netherlands.

Twin Model

The twin model relies on the fact that monozygotic or identical twins share (almost) all their genetic makeup while dizygotic or fraternal twins share on average half of their genetic resemblance (rMZ = 1, rDZ = 0.5). If MZ twins resemble each other more than DZ twins, genetic factors are important for that particular trait. The presence of shared environmental influences is suggested when correlations in MZ twin pairs are less than double the correlations in DZ twin pairs. Unique environmental influences are present if the MZ correlation is less than 1 (Boomsma et al., 2002).

SEM can estimate the contribution of additive genetic (A), common (or shared) environmental (C) and unique environmental (E) factors to the variance in one trait by minimizing a goodness-of-fit statistic between the observed and predicted covariance matrices. Genetic model-fitting was carried out in each trait (i.e., baseline and change in cortical thickness/surface area, baseline and change in predefined ROIs that differed significantly between discordant and control pairs. The analyses were performed using the package Mx software for statistical modeling (Michael Neale, Department of Psychiatry, Virginia Commonwealth University, Richmond; http://www.vcu.edu/mx). Because simultaneous analyses of dichotomous and continuous data could not be performed, the standardized residuals, (corrected for age, sex, and handedness) were ordinalized into five equal classes. Each class would cover 20% of the data following a normality distribution. The dichotomous variable schizophrenia was assumed to represent an underlying continuous liability with a mean (SD) of 0 (1) with both affected and unaffected individuals assumed to be part of the same distribution of liability. The disorder is thought to occur only when a certain threshold of liability is exceeded. The heritability and the critical threshold for schizophrenia were not based on our sample since data were from twin pairs selected for schizophrenia. Instead, we constrained the heritability of schizophrenia (h^2) at 81%, the shared environmental influence (c^2) at 11% and the unique environmental influences (e^2) at 8% according to point estimates of a meta-analyses (Sullivan et al., 2003) and the prevalence to 1% (resulting in a critical threshold at 2.33). Effects of genes and familiar background were tested by fitting different models to the data. Via likelihood ratio tests (-2 Log-Likelihood- difference which is χ^2 distributed), nested models are compared against a saturated model and against each other (e.g. the latent factors A, C or both can be removed from the basic ACE twin model to generate submodels i.e. AE, CE and E) resulting in the most parsimonious model. A χ^2 larger than 3.84 (1 df) indicates a significant difference at

alpha= .05, indicating that the discarded parameters cannot be left out without seriously deteriorating the goodness of fit. Chi-squares can be relaxed because tests of variance components constrained to be non-negative correspond to tests of parameters on the boundary of the parameter space and in such situations the standard test procedure provides too large *p*-values; these p-values have to be halved, resulting in a critical value of the χ^2=2.71 (1 df) at alpha=.05 (Dominicus et al., 2006). For this reason we report on 90% confidence interval (CI) instead of 95% CI for the heritabilities (h^2). A previous study on change in cortical thickness did not show evidence for influences of shared environment (c^2) (Brans et al., 2010). Subsequent (bivariate) analysis in this study were based on models containing additive genetic (A) and unique environmental (E) influences only (AE-model), however, for schizophrenia, $c^2$was fixed to 11% (Sullivan et al., 2003).

By applying bivariate genetic models, SEM can tell whether either genetic or environmental related factors or both explain the correlation between e.g., schizophrenia liability and cortical thickness change. These correlations provide information regarding the extent to which the same genetic (rg) and unique environmental (re) effects in one trait (risk to develop schizophrenia) correlate with a second trait (e.g. cortical thickness change). Decomposition of these sources is based on the cross-trait/cross-twin correlations for MZ and DZ twins, the correlation between a trait (e.g., schizophrenia liability) of twin 1 with another trait (e.g. cortical thickness change) of twin 2 (twin 1 and twin 2 are representing a twin-pair). If the absolute value of the correlation between risk for schizophrenia in twin 1 and cortical thickness change in twin 2 is larger in MZ twins than in DZ twins, this indicates that genes influencing schizophrenia risk and e.g., cortical thickness change (at least partly) overlap. The extent of the overlap is reflected by the magnitude of the genetic correlation (rg). It is possible for a large genetic correlation to explain a small part of the observed co-variation between two traits since the rg and re correlations do not take the heritability of either trait into account. By combining the information from the heritabilities h^2 and e^2 with the rg and re correlations, the influence of genetic and unique environmental parts of the total phenotypic correlation between schizophrenia liability and e.g., cortical thickness change could be established. Specifically, the part of the phenotypic (r_{ph}) correlation (within-twin cross-trait) between risk to develop schizophrenia and e.g., cortical thickness change that is accounted for by a common genetic factor ($r_{ph\text{-}a}$) is counted as the square root of the heritability of schizophrenia (h_x^2) times the genetic correlation (r_g) times the square root of the heritability of cortical thickness change (h_y^2); $r_{ph\text{-}a}= \sqrt{h_x^2}* r_g*\sqrt{h_y^2}$. This method has been described in detail

elsewhere (Rijsdijk & Sham, 2002; Toulopoulou et al., 2007) and applied before (Brans et al., 2008). To estimate the genetic correlation (rg) and the unique environmental correlation (re) a critical chi-square larger than χ^2>3.84 (1 df) was set. To calculate the phenotypic correlation (r_{ph}) a critical chi-square larger than χ^2>5.99 (2 df) was set.

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Chapter 6

Heritability of brain volume change and intelligence

(to be submitted)

Abstract

Variation in human brain volume is highly heritable, and has been associated with general cognitive functioning. It is also known that brain volume changes throughout adult life. Although part of the association between volume and cognition is genetic, it is unknown whether brain volume changes in young adults are under genetic control and related to general cognitive functioning. Also, it is not known whether cortical surface area change is heritable and associated with cognition. We measured change in brain volume and surface area during a 5-year interval in 176 monozygotic and dizygotic twins and their siblings using magnetic resonance imaging. Results show that change in volumes of total brain (mean=-6.4 ml; -0.5% loss), cerebellum (1.4 ml, 1.0% increase), cerebral white matter (4.4 ml, 0.9% increase), lateral ventricles (0.6 ml; 4.8% increase) and in surface area (-19.7 cm2, -1.1% contraction) are heritable (h2=43%; 52%; 29%; 31%; and 33%, respectively) between age 19 and 56. Moreover, genes involved in the variation in change in total brain volume seem to overlap in part with genes involved in intelligence. Thus, dynamic changes in brain structure are heritable and may have cognitive significance in young adulthood.

Introduction

Human brain volume is highly heritable in children (Wallace et al., 2006; Lenroot et al., 2009; Peper et al., 2009) and in adults (Pfefferbaum et al., 2000; Baaré et al., 2001; Thompson et al., 2001; Wright et al., 2002), with heritability estimates exceeding the 90 percent (Peper et al., 2007). This suggests that genetic influences on overall brain size are established early in life and remain important in adulthood. However, it is well known that brain volume is far from static and changes throughout life. Having reached approximately 90% of its adult size around the age of six (Giedd et al., 1999), dynamic changes in brain structure continue to take place in children and adolescents (Giedd et al., 1999; Gogtay et al., 2004; Shaw et al, 2006; van Soelen et al., 2012a), and on the other side of the age spectrum in older adults over 60 years of age (Bartzokis et al., 2001; Liu et al., 2003; Pfefferbaum et al., 2004; Raz et al., 2005; for review see Hedman et al., 2012). However, in young adulthood, and particularly between 20 and 40 years of age, a period or relative stability in total brain volume is found (for review see Hedman et al., 2012), despite focal changes in cortical thickness (Brans et al., 2010). Indeed, while several of these changes in brain structure were found to be heritable (van Soelen et al., 2012a, b; Brans et al., 2010; Pfefferbaum et al., 2004), particularly at both extremes of the age spectrum, it is not known whether genes are implicated in total brain volume and cortical surface area change in young adulthood.

Several studies have shown that level of intelligence is positively correlated with total brain volume (Thompson et al., 2001; Posthuma et al., 2002), focal gray (Thompson et al., 2001; Frangou et al., 2004; Haier et al., 2004; Hulshoff Pol et al., 2006) and white (Hulshoff Pol et al., 2006) matter densities, and that these associations are mediated by common genetic factors (Boomsma et al., 2002; Posthuma et al., 2002; Wright et al., 2002; Toga and Thompson, 2005; Hulshoff Pol et al., 2006). It must be noted that the genetic correlation between the two traits does however not imply causality, since a significant bivariate heritability can indicate causality in one direction or the other.

Moreover, young adults with a higher intelligence show attenuated cortical thinning and more pronounced cortical thickening over time than subjects with average or below average intelligence (Brans et al., 2010). In adolescents, cortical maturation has been associated with intelligence (Shaw et al, 2006), as well as with changes in intelligence over time (Ramsden et al., 2011). Thus, genes involved in individual variations in intelligence (Plomin and Spinath,

2004) overlap with those for individual variations in brain volume (Posthuma et al., 2002), and with local cortical thickness change (Brans et al., 2010).

However, it is unknown whether genes influence brain volume change in adulthood. Moreover, it is unclear whether brain volume change is associated with intelligence and if common genes are implicated in the association. Therefore, we examined whether changes in brain volume and surface area over time are related to intelligence and if so, whether genes common to both influence this relationship. This was investigated in a large longitudinal magnetic resonance imaging (MRI) study in 176 adult individuals from 86 twin families between 19-56 years of age, with a 5-year interval between scans.

Methods

Subjects

Twins and their siblings were from the twin-pair cohort at the University Medical Centre Utrecht and from the Netherlands Twin Registry, VU University Amsterdam, as have been described in (Brans et al., 2010). At baseline assessment, a total of 242 participants from 106 twin families were assessed. Average age was 29. After 5-years 176 participants from 86 families (51 monozygotic (MZ) males, 41 dizygotic (DZ) males, 23 MZ females, 39 DZ females, and 22 siblings (11 males and 11 females)) participated again (Table 1). All participants gave written informed consent. DNA testing using polymorphic markers determined zygosity. Except for one twin pair, all twins and their siblings were reared together. Two twin pairs were born by caesarean section delivery. The study was carried out according to the directives of the “declaration of Helsinki” (amendment of Edinburg, 2000) and was approved by the medical ethics committee for research in humans (METC) of the University Medical Centre Utrecht, the Netherlands.

Table 1 | Demographics of the twins and their siblings

	MZ	DZ	Siblings
Sex, male/female	51/23	41/39	11/11
Age at time of the first scan, y*	31.09 (9.02) [19.45 to 55.88]	28.21 (5.98) [19.07 to 51.58]	28.01 (3.07) [20.22 to 31.34]
Height, cm	177.12 (8.97)	177.14 (8.81)	174.32 (11.97)
Handedness, r/l/ambidextrous	57/15/2	67/7/6	17/4/1
Level of education, y	13.69 (12.90)	13.41 (2.56)	12.73 (3.18)
Parental level of education, y	12.22 (2.64)	12.08 (2.76)	12.05 (2.79)
Follow-up duration, y*	5.13 (0.56)	5.51 (0.69)	5.41 (0.55)
Total IQ**	105.12 (16.24)	104.74 (8.50)	106.37 (12.57)
Verbal IQ**	103.56 (16.64)	104.87 (8.77)	109.64 (16.12)
Performance IQ**	106.75 (14.59)	106.07 (10.83)	101.99 (8.81)

*Age differed significantly between the groups (i.e., MZ, DZ and siblings); $F_{2,173}$=7.10, p=0.001, post-hoc analysis for multiple comparisons revealed that this was due to MZ twins having significantly higher age than DZ twins. F-u duration differed significantly between the groups: $F_{2,173}$=3.54, p=0.031, post hoc analysis for multiple comparisons revealed that this was due to DZ twins having significantly longer f-u duration than MZ twins. ** Total, Verbal and Performance IQ was available in 101 participants that had repeated MRI scans.

Brain Imaging

Magnetic Resonance Imaging brain scans were acquired on a Philips NT (Best, the Netherlands) scanner on 1.5 T in all subjects. T1-weighted three-dimensional fast field echo (3D-FFE) scans with 160–180 contiguous coronal slices scans (TE = 4.6 ms, TR = 30 ms, flip angle = 30°, 1 x 1 x 1.2 mm3 voxels), and T2-weighted dual-echo turbo-spin-echo (DE-TSE) scans with 120 contiguous coronal slices (TE1 = 14 ms, TE2 = 80 ms, TR = 6350 ms, flip angle = 90°, 1 x 1 x 1.6 mm3 voxels) of the whole head were used for quantitative measurements. In addition, T2-weighted dual-echo turbo-spin-echo (DE-TSE) scans (TE1 = 9 ms, TE2 = 100 ms, flip angle = 90°, 0.98 x 0.98 mm2) with 19 axial 5-mm slices and 1.2-mm gap of the whole head were used for clinical neurodiagnostic evaluation.

Processing was done on the neuroimaging computer network of the Department of Psychiatry at the University Medical Center Utrecht. All images were coded to ensure blindness for subject identification and diagnoses, scans were manually put into Talairach frame (no scaling) for segmentation purposes, and corrected for inhomogeneities in the magnetic field (Sled et al., 1998). Our automatic processing pipeline was used for segmentation of total brain, gray (GM) and white matter (WM) of the cerebrum (Brouwer et al., 2010). In short, pure GM and WM intensities were directly estimated from the image. The

amounts of pure and partial volume voxels were modeled in a non-uniform partial volume density, which is fitted to the intensity histogram. Expected tissue fractions, based on the pure intensities and the partial volume density, were subsequently computed in each voxel within the cerebrum. Intracranial, whole brain, ventricle and cerebellum segmentations were checked after measurement and corrected manually if necessary (Schnack et al., 2001).

The frontal, parietal, temporal, and occipital lobes were segmented based on transformations to a model brain onto which the lobes had been manually demarcated (Hulshoff Pol et al., 2002). Brain images were registered to the model brain through the Automatic Nonlinear Image Matching and Anatomical Labeling (ANIMAL) algorithm (Collins et al., 1995) to remove global differences in size and shape of individual brains. The inverse of the transformation process registered the manual segmentations of the model brain to all participants' brain images.

To estimate the cortical surface, we used the CLASP (Constrained Laplacian Anatomic Segmentation Using Proximity) algorithm designed at the McConnell Brain Imaging Centre of the Montréal Neurological Institute (MacDonald et al., 2000; Kabani et al., 2001; Kim et al., 2005). A 3-dimensional surface consisting of 81,920 polygons was fitted to the WM-GM interface. This defined the inner surface of the cortex, which was then expanded to fit the GM–cerebrospinal fluid interface, thereby creating the outer cortical surface (MacDonald et al., 2000; Kim et al., 2005). The surfaces of the participants were registered to an average surface created from 152 individuals (International Consortium for Brain Mapping: Lyttelton et al., 2007) allowing comparison of cortical surface locally between subjects both at baseline as well as follow-up measurement. The mid-areas between the white matter (i.e., inner surface) and the gray matter (i.e., outer surface) at baseline and follow-up measurement were subtracted to obtain a measure of surface area change.

Cognitive Assessment

Total IQ (WAIS-III, 1997) measured at baseline was available for 129 participants (48 MZ (23 complete pairs), 62 DZ (28 complete pairs) and 19 siblings. For 101 of the participants from 49 twin families (33 monozygotic (14 complete pairs), 51 dizygotic (22 complete pairs) and 17 siblings) repeated MRI measurements were available. We also estimated verbal and performance IQ in these participants.

Statistical Analyses

To estimate the relative contribution of genetic and common and unique environmental factors on the variation of brain volume change and surface area change, the extended twin-sibling model was applied. This model is based on the fact that MZ twins are genetically identical and DZ twins share on average 50% of their genes. Both types of twins share their familial environment. Therefore, if MZ twins resemble each other more than DZ twins, genetic factors are important for that trait. The presence of shared environmental factors is suggested when correlations in DZ twins are larger than half the MZ correlation. Unique environmental influences are present if the MZ correlation is less than 1 (Boomsma et al., 2002). By including siblings, the statistical power to detect the influences of common environmental factors shared by family members is enhanced, because, similar to DZ twins, a twin and its non-twin sibling also share 50% of their genes on average and share the familial environment (Posthuma et al., 2000).

Brain volume change/surface area change per year during the interval was corrected for age and sex with a linear regression analysis. The unstandardized residuals were saved and used for further analysis. For genetic model fitting, structural equation modeling (SEM) was performed to investigate the relative contributions of genetic and environmental factors of brain volume change and surface area change. SEM can estimate the contribution of additive genetic (A), common (or shared) environmental (C) and unique environmental (E) factors to the variance in one trait by minimizing a goodness-of-fit statistic between the observed and predicted covariance matrices. Because brain volumes / surface area and intelligence in adulthood show little evidence for influences of shared environment (C), analyses incorporating change measures and IQ were based on models containing additive genetic (A) and unique environmental (E) influences only. To determine whether change over time was significantly different from zero, we first computed change values per year, corrected for age and sex using a linear regression model, and then tested whether the mean was zero in a univariate model. All available data was entered in the model estimating heritability of brain volume change/surface area change, also subjects for which IQ measures were not available.

The bivariate genetic analysis yielded an estimate of the phenotypic correlations (r_{ph}) between brain volume change/surface area change and IQ, which can result from a common set of genes or common set of environmental factors represented by genetic (r_g) and

environmental correlations (r_e) respectively. Decomposition of these sources was based on the comparison of cross-trait/cross-twin correlations for MZ and DZ twins, i.e., the correlation between a trait (e.g., brain volume change) of twin 1 with another trait (e.g., IQ) of twin 2, where twin 1 and twin 2 represent a twin-pair. If the absolute value of the correlation between brain volume change of twin 1 and IQ of twin 2 is larger in MZ twins than in DZ twins, this indicates that genes influencing brain volume change (partly) overlap with genes that influence IQ. The extent of the overlap is reflected by the magnitude of the genetic correlation r_g. Likewise, r_e represents the extent of overlap of environmental factors influencing the traits. The extent, to which either of these correlations explains the observed correlation between two traits, also depends on the etiology of the traits. For example, a genetic correlation between two traits may exist, but when the traits themselves show a low heritability, this genetic correlation may only explain the observed correlation to a small extent. We therefore also computed the $r_{ph\text{-}a}$ and $r_{ph\text{-}e}$ (Toulopoulou et al., 2007), which is defined by the genetic (environmental, respectively) covariance, divided by the standard deviations of the two traits. These represent the observed correlation when only the genetic or unique environment is taken into consideration.

It was tested whether an AE model fits as well as an E model, taking the simplest model explaining the data best. A Chi-squared larger than χ^2 =3.84 (1 df) (Neale et al., 2003) indicates a significant difference at alpha=0.05, which means that the reduced model provides a significantly worse fit to the data and indicates that the discarded effect (e.g. additive genetic influence) cannot be left out of the model without seriously deteriorating the goodness of fit. When estimating heritabilities, this Chi-square criterion can be relaxed because tests of variance components constrained to be non-negative correspond to tests of parameters on the boundary of the parameter space. In such situations the standard test procedure provides too large p-values; these p-values have to be halved, resulting in a critical value of the Chi-squared χ^2=2.71 (Dominicus et al., 2006).

Results

Changes in Brain Volumes and Surface Area

Over the 5-year interval, whole brain volume decreased [mean (SD)=-6.40 (19.97) ml; percent change = -0.51 (1.58) %], with 66% of the adult participants showing whole brain volume loss (See Table 2 for details). Cerebral volume decreased [-7.67 (18.79) ml; percent change = -0.70 (1.69)%] with 67% of the participants showing cerebral volume decrease. Cerebral white matter volume increased [4.38 (16.57) ml; percent change = 0.91 (3.27)%], with 64% of the participants showing cerebral white matter volume increase. Cerebral gray matter volume decreased [-12.05 (12.35) ml; percentage change = -1.97 (1.99)%], with 86% of the adult participants showing a decrease in gray matter volume over the 5-year interval. Cerebellum volume increased [1.43 (3.33) ml; percentage change= 1.04 (2.44)%], with 64% of adult participants having an increase. Lateral ventricles increased [0.61 (1.23) ml; percent change = 4.76 (9.14)%] with 69% of the participants showing an increase in lateral ventricles over the 5-year interval. Surface contracted [-19.69 (25.84) cm2; percentage change= -1.05 (1.37)%] with 78% of the participants showing surface contraction. Decreases and increases described above were also seen when considering left and right hemisphere separately. Moreover, lobar gray matter volumes all decreases over time (Table 2). All brain structures decreased/increased significantly, except for third ventricles.

We found no significant sex effects on change. A significant age effects on cerebral GM change (total; $p=0.005$, right; $p<0.001$) in that a higher age at baseline was associated with a smaller decrease for total and right cerebral GM. Cerebral WM change resulted in a significant age effect (total; $p=0.002$, left; $p=0.008$, right; $p<0.001$) where those with a higher age at baseline had a larger decrease/smaller increase in cerebral WM. Furthermore, a significant age effect was found for change in the ventricles (total; $p<0.001$, left; $p<0.001$; right; $p<0.001$) in that higher age at baseline was associated with larger increase in the ventricles. However, to exclude possible effects on heritability estimates, we chose to correct all change measures for age at baseline and sex and entered the corrected values in the twin model.

Heritability of Brain Volume and Surface Area Change

Heritabilities of brain volume change and surface area change over time are listed in Table 2. See Supplemental Table for twin-correlations on all variables (i.e., change in brain structure and IQ). Additive genetic effects accounted for 43% (95% CI = 17 to 62%) of the variance in

whole brain volume change (Figure 1), and 48% (95% CI = 22 to 67%) in cerebrum (whole brain excluding the cerebellum and brain stem) volume change. Cerebral GM volume change was not significantly influenced by genetic factors, nor were the gray matter volumes in the lobes separately. In contrast, cerebral WM volume change showed a significant heritability of 29% (95% CI = 2 to 52%). Cerebellum volume change showed significant heritability with additive genetic effects accounting for 52% (95% CI = 34 to 66%) of the total variance (Figure 1). Change in lateral and third ventricle volumes showed significant heritabilities of 31% (95% CI = 9 to 51%) and 29% (95% CI 8 to 48%) respectively. Total surface area change showed a significant heritability with genetic factors accounting for 33% (95% CI = 8 to 54%) of the total variance. Overall, genetic influences reached somewhat higher estimates in the left as compared to the right hemisphere.

Heritability of Intelligence

Within twin-pair correlations for monozygotic twins were 0.85 (95% CI 0.72 to 0.92), 0.78 (95% CI 0.60 to 0.88) and 0.73 (95% CI 0.52 to 0.84) for total, verbal and performance IQ respectively. Dizygotic/twin-sib correlations were 0.48 (95% CI 0.18 to 0.68), 0.54 (95% CI 0.29 to 0.72) and 0.25 (95% CI -0.08 to 0.52) for total, verbal and performance IQ respectively. Heritability of total, verbal and performance IQ were estimated at 86% (95% CI = 76 to 91), 79% (95% CI = 66 to 85) and 74% (95% CI = 57 to 84), respectively.

Table 2 | Heritability of brain volume and surface area changes

Structure	h^2 of change* (CI)	Change**	Change %
Whole brain	**0.43 (0.17 to 0.62)**	**-6.40 (19.97)**	-0.51 (1.58)
Cerebrum	**0.48 (0.22 to 0.67)**	**-7.67 (18.79)**	-0.70 (1.69)
Cerebrum GM	0.10 (0.00 to 0.35)	**-12.05 (12.35)**	-1.97 (1.99)
Cerebrum WM	**0.29 (0.02 to 0.52)**	**4.38 (16.57)**	0.91 (3.27)
Cerebellum	**0.52 (0.34 to 0.66)**	**1.43 (3.33)**	1.04 (2.44)
Lateral ventricles	**0.31 (0.09 to 0.51)**	**0.61 (1.23)**	4.76 (9.14)
Third ventricles	**0.29 (0.08 to 0.48)**	0.03 (0.15)	4.24 (17.80)
Cortical volume	0.03 (0.00 to 0.28)	**-12.51 (17.33)**	-2.44 (3.42)
Frontal GM	0.02 (0.00 to 0.28)	**-6.76 (8.70)**	-3.23 (4.29)
Temporal GM	0.15 (0.00 to 0.39)	**-1.62 (4.35)**	-1.14 (3.15)
Parietal GM	0.17 (0.00 to 0.40)	**-2.85 (4.52)**	-2.53 (4.11)
Occipital GM	0.01 (0.00 to 0.26)	**-1.53 (3.11)**	-2.96 (6.32)
Surface	**0.33 (0.08 to 0.54)**	**-19.69 (25.84)**	-1.05 (1.37)
Left hemisphere	**h^2 of change* (CI)**	**Change****	**Change %**
L brain	**0.45 (0.19 to 0.65)**	**-2.09 (11.77)**	-0.32 (1.87)
L cerebrum	**0.52 (0.24 to 0.70)**	**-3.01 (10.29)**	-0.54 (1.85)
L cerebrum GM	0.10 (0.00 to 0.36)	**-5.19 (7.32)**	-1.68 (2.36)
L cerebrum WM	0.23 (0.00 to 0.48)	**2.18 (8.62)**	0.91 (3.33)
L cerebellum	0.13 (0.00 to 0.35)	**0.90 (2.51)**	1.32 (3.62)
L lateral ventricles	**0.28 (0.03 to 0.49)**	**0.32 (0.66)**	4.77 (9.45)
L cortical volume	0.03 (0.00 to 0.28)	**-6.10 (9.10)**	-2.42 (3.70)
L frontal GM	0.00 (0.00 to 0.27)	**-3.56 (4.27)**	-3.46 (4.30)
L temporal GM	0.09 (0.00 to 0.32)	**-0.78 (2.39)**	-1.09 (3.45)
L parietal GM	**0.27 (0.02 to 0.49)**	**-1.16 (2.41)**	-2.11 (4.59)
L occipital GM	0.00 (0.00 to 0.00)	**-0.54 (1.75)**	-1.96 (6.82)
L surface	**0.36 (0.13 to 0.55)**	**-9.21 (13.65)**	-0.98 (1.45)
Right hemisphere	**h^2 of change* (CI)**	**Change****	**Change %**
R brain	0.14 (0.00 to 0.36)	**-4.31 (11.30)**	-0.69 (1.79)
R cerebrum	**0.31 (0.05 to 0.53)**	**-4.66 (10.05)**	-0.85 (1.80)
R cerebrum GM	0.16 (0.00 to 0.38)	**-6.86 (6.86)**	-2.26 (2.25)
R cerebrum WM	**0.28 (0.02 to 0.51)**	**2.19 (8.45)**	0.93 (3.42)
R cerebellum	0.00 (0.00 to 0.20)	**0.53 (2.67)**	0.80 (3.92)
R lateral ventricles	**0.30 (0.09 to 0.48)**	**0.28 (0.62)**	4.83 (9.76)
R cortical volume	0.07 (0.00 to 0.31)	**-6.59 (8.84)**	-2.55 (3.48)
R frontal GM	0.00 (0.00 to 0.24)	**-3.01 (4.45)**	-2.81 (4.25)
R temporal GM	0.25 (0.00 to 0.49)	**-0.81 (2.43)**	-1.13 (3.53)
R parietal GM	0.06 (0.00 to 0.30)	**-1.66 (2.37)**	-2.83 (4.13)
R occipital GM	0.22 (0.00 to 0.49)	**-1.00 (1.57)**	-4.12 (6.66)
R surface	0.24 (0.00 to 0.46)	**-10.47 (13.93)**	-1.11 (1.48)

In **bold** = significant, h^2 = heritability (the percentage additive genetic effect of the total variances) Whole brain = cerebrum + cerebellum + brain stem, GM = Gray Matter, WM = White Matter, CI = Confidence Interval * Univariate heritability estimates were based on the data corrected for age and gender. Performing the analysis on the uncorrected data showed similar results ** mean (SD) raw change in volumes (ml), surface area (cm^2) over a 5 year interval. Significance testing of change is based on values per year corrected for age and gender.

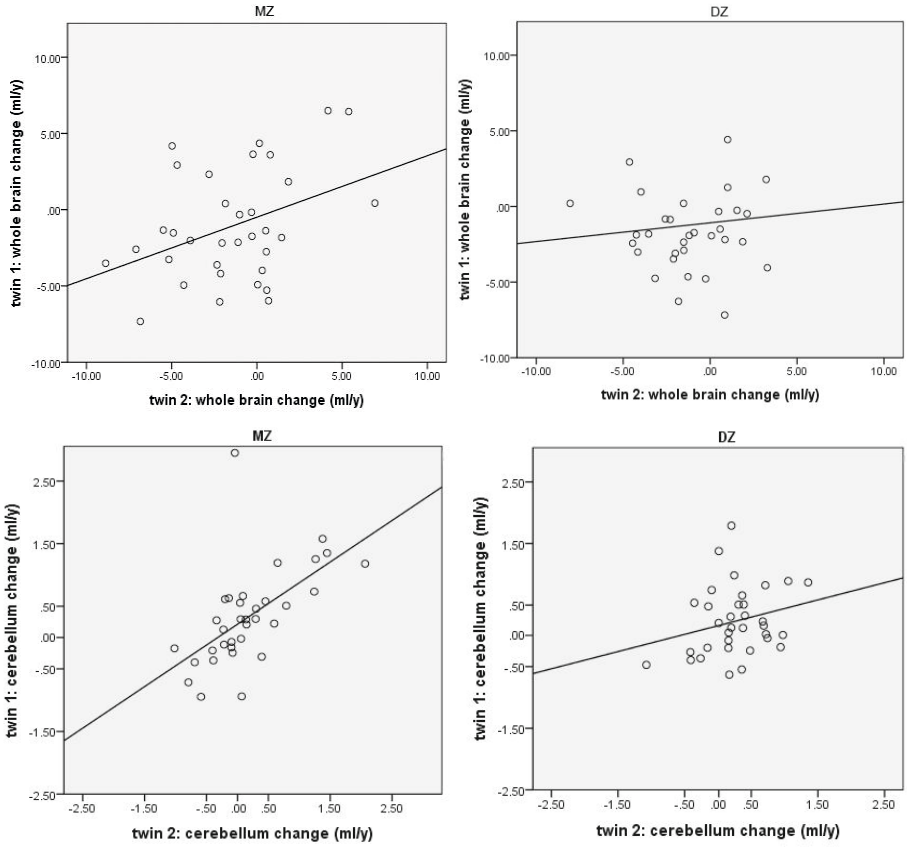

Figure 1 | MZ and DZ twin correlations. Correlations for volume change in whole brain (top) and cerebellum (bottom) between MZ twin pairs (rMZ) and DZ twin pairs (rDZ) are shown. For visualization purposes, two points in the scatterplot on whole brain change (DZ twins) are excluded (these fell outside the visible range, but are included in the statistical analyses; their values are; twin 1: 13.0 ml/y, twin 2: -1.01 ml/y and twin 1: 2.22 ml/y, twin 2: 12.44 ml/y respectively). Regression lines are shown in black.

Associations between brain volume change/surface area change and intelligence

Significant phenotypic correlations (r_{ph}) were found between total IQ and volume change in total, left and right whole brain (r_{ph}=0.39, r_{ph}=0.29, and r_{ph}=0.29) (Figure 2) and total, left and right cerebrum (r_{ph}=0.40, r_{ph}=0.36, and r_{ph}=0.29) (Table 3). Genes influencing both IQ and brain volume change drove all these correlations (r_g around 0.5, see Table 3), except for the correlation between IQ and right whole brain volume change.

Significant phenotypic associations (r_{ph}) were found between verbal IQ and change in total, left and right whole brain (r_{ph}=0.43, r_{ph}=0.32, and r_{ph}=0.36), total, left, and right cerebrum (r_{ph} =0.45, r_{ph} =0.40, and r_{ph}=0.38), and total and right frontal GM (r_{ph}=0.20; r_{ph}=0.20). Genes implicated in both verbal IQ and total/left brain volume change and total/left cerebrum volume change explained part of these associations with significant r_g around 0.5 (see Table 3 and Figure 2). For the other brain change measures that showed a significant phenotypic correlation with verbal IQ, the genetic or environmental influences on the associations between verbal IQ and brain change could not be disentangled (Table 3). Performance IQ was not significantly associated with brain volume change or surface area change.

Table 3 | Brain volume change and IQ (total and verbal IQ) with significant phenotypic (r_{ph}) correlation

Change in structure	Total IQ				
	r_{ph} (95%CI)	r_g (95%CI)	r_e	r_{ph-a} (95%CI)	r_{ph-e} (95%CI)
Whole brain	**0.39 (0.14 to 0.57)**	**0.58 (0.21 to 0.88)**	-0.06 (-0.57 to 0.50)	**0.40 (0.13 to 0.59)**	-0.01 (-0.11 to 0.13)
Cerebrum	**0.40 (0.14 to 0.59)**	**0.59 (0.23 to 0.87)**	-0.16 (-0.62 to 0.43)	**0.42 (0.16 to 0.61)**	-0.03 (-0.12 to 0.10)
L whole brain	**0.29 (0.05 to 0.49)**	**0.48 (0.12 to 0.80)**	-0.24 (-0.63 to 0.32	**0.33 (0.08 to 0.53)**	-0.04 (-0.14 to 0.07)
R whole brain	**0.29 (0.05 to 0.49)**	0.58 (-0.15 to 1.00)	0.29 (-0.48 to 0.76)	0.22 (-0.07 to 0.46)	0.07 (-0.12 to 0.32)
L cerebrum	**0.36 (0.12 to 0.56)**	**0.54 (0.19 to 0.82)**	-0.19 (-0.59 to 0.33)	**0.39 (0.14 to 0.59)**	-0.03 (-0.11 to 0.07)
R cerebrum	**0.29 (0.03 to 0.50)**	**0.52 (0.01 to 1.00)**	-0.07 (-0.69 to 0.63)	**0.31 (0.01 to 0.53)**	-0.01 (-0.18 to 0.20)

Change in structure	Verbal IQ				
	r_{ph} (95%CI)	r_g (95%CI)	r_e	r_{ph-a} (95%CI)	r_{ph-e} (95%CI)
Whole brain	**0.43 (0.19 to 0.61)**	**0.54 (0.10 to 0.85)**	0.32 (-0.23 to 0.69)	**0.35 (0.05 to 0.56)**	0.09 (-0.06 to 0.30)
Cerebrum	**0.45 (0.20 to 0.63)**	**0.58 (0.17 to 0.85)**	0.24 (-0.30 to 0.65)	**0.39 (0.10 to 0.60)**	0.06 (-0.07 to 0.26)
L whole brain	**0.32 (0.08 to 0.52)**	**0.47 (0.05 to 0.79)**	0.01 (-0.44 to 0.51)	**0.31 (0.03 to 0.53)**	0.01 (-0.12 to 0.19)
R whole brain	**0.36 (0.13 to 0.55)**	0.38 (-0.68 to 1.00)	0.58 (-0.02 to 0.83)	0.13 (-0.16 to 0.39)	0.23 (-0.00 to 0.51)
L cerebrum	**0.40 (0.16 to 0.58)**	**0.55 (0.18 to 0.83)**	0.04 (-0.41 to 0.50)	**0.39 (0.12 to 0.59)**	0.01 (-0.10 to 0.17)
R cerebrum	**0.38 (0.12 to 0.57)**	0.39 (-0.33 to 1.00)	0.48 (-0.16 to 0.80)	0.21 (-0.11 to 0.47)	0.17 (-0.05 to 0.44)
Frontal GM	**0.20 (0.01 to 0.37)**	0.99 (-1.00 to 1.00)	0.30 (-0.20 to 0.64)	0.09 (-0.14 to 0.30)	0.11 (-0.07 to 0.29)
R Frontal GM	**0.20 (0.01 to 0.37)**	0.99 (-1.00 to 1.00)	0.21 (-0.27 to 0.59)	0.11 (-0.11 to 0.33)	0.08 (-0.10 to 0.27)

In **bold** = significant, L = left, R = right, CI = Confidence Interval, r_g = genetic correlation, r_e = environmental correlation, r_{ph} = phenotypic correlation, r_{ph-a} = correlation when only genetic factors are taken into account, r_{ph-e} = correlation when only environmental factors are taken into account

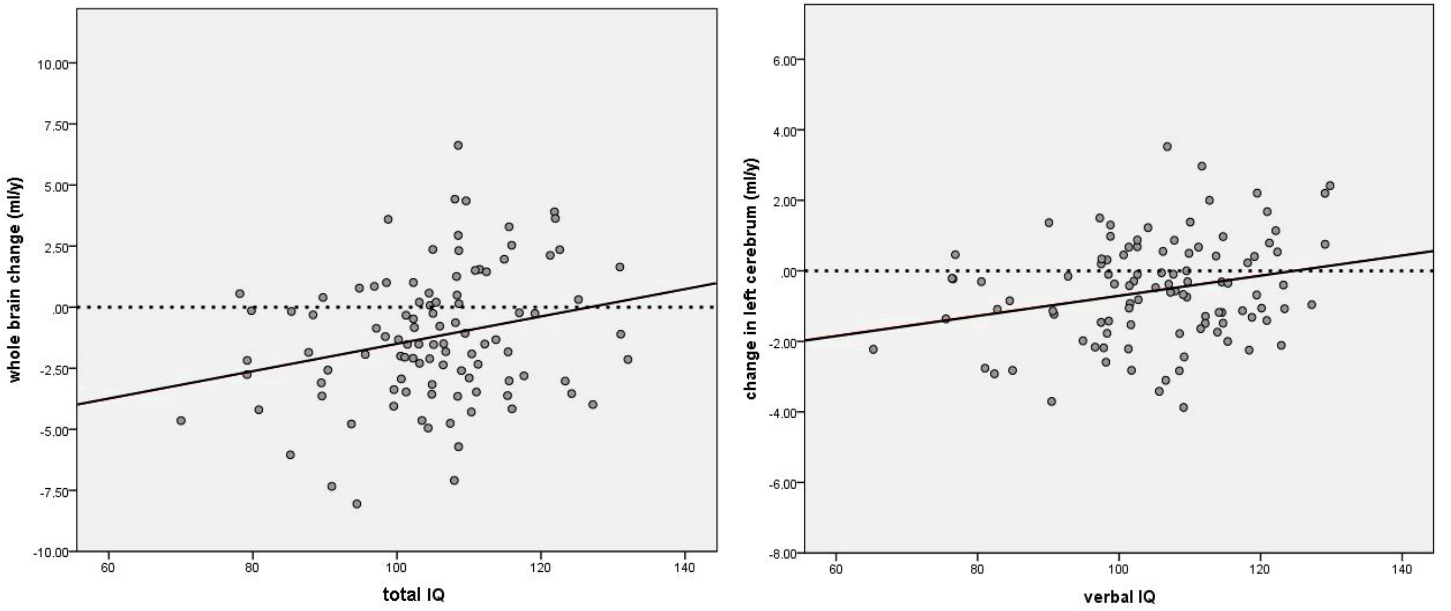

Figure 2 | Associations between change in brain volume and total IQ and between left cerebrum change and verbal IQ in individual twins and siblings. The correlation between total IQ (X-axis) and whole brain volume change (Y-axis) and between verbal IQ (X-axis) and left cerebrum change (Y-axis) are shown. Regression lines are shown as unbroken black lines and the black dotted lines in the middle show zero change. Phenotypic correlations; r_{ph}=0.39 (95% CI; 0.14 to 0.57) and r_{ph}=0.40 (95% CI; 0.16 to 0.58).

Discussion

Here we report that dynamic changes in total brain volume and cortical surface area take place in young adulthood and that these changes are heritable. Moreover, brain volume changes in the young adult brain are positively related to intelligence and this association is mediated through genes common to both intelligence and brain volume change.

Specifically, we found significant heritability estimates for changes in total brain, cerebrum, cerebellum, white matter and lateral and third ventricle volumes in young adults that were considerable, with values of h^2 equal to 43%, 48%, 52%, 29%, 31% and 29%. Also, for the first time we found evidence for significant change in surface area, with additive genetic effects accounting for 33% of the total variance. Thus, genes are not only involved in the absolute brain volume (Pfefferbaum et al., 2000; Baaré et al., 2001; Thompson et al., 2001; Wright et al., 2002), surface area (Winkler et al., 2010; Panizzon et al., 2009; Eyler et al., 2011), and total brain volume change on the verge of adolescence (Van Soelen et al., 2012), but genes are also involved in total brain volume change and surface area change in young adulthood. The extent to which genes explain individual differences in brain changes ranges from 27 to 52%. This leaves room for environmental influences also shaping these changes in brain structure. Thus, changes in brain volume may represent (plastic) changes as a result of an interaction between genetic background and environmental influences. Future studies on gene by environmental interactions may reveal how these factors may help shape individual brains over time. This may have implications, not only for physiological pathways leading to brain volume change, but also to cognitive functioning (Shaw et al., 2006; Van Soelen et al., 2012; Brans et al., 2010; Ramsden et al., 2011).

We found that intelligence is positively associated with change in brain volume and that this association may be in part driven by genes in young adulthood. In particular, we report for the first time that a higher IQ is significantly associated with more total brain volume increase or attenuated decrease (r_{ph}=0.39, 95% CI=0.14 to 0.57). Our data suggest that common genes may be in part be implicated in this association ($r_{ph\text{-}a}$ =0.40, 95% CI=0.13 to 0.59). Interestingly, when separating out verbal and performance IQ in these twins, a higher verbal IQ was significantly associated with more increase or attenuated decrease in total brain volume and cerebrum volume (total brain excluding the cerebellum and brainstem) and this association was due to genes common to both, particularly in the left hemisphere. No significant phenotypic associations between performance IQ and any of the brain volume

changes were found. Previously, level of intelligence has been associated with thickness changes in particular areas of the cortex in childhood and adolescence (Shaw et al., 2006) and in adulthood (Brans et al., 2010). Also change in intelligence has been associated with volume changes in particular areas of the cortex in adolescents (Ramsden et al., 2011). Here, we add that total brain volume change in adulthood is positively associated with intelligence, and that this association could be partly heritable.

There may be several interpretations for the finding that young adults with a higher IQ show a more pronounced increase in brain volume or attenuated decrease in brain volume over time while a higher IQ is not reflected in cortical surface area change. This finding suggests that intelligence level is associated rather with change in cortical thickness (Brans et al., 2010), subcortical volume, and connecting white matter, than with change in cortical surface area. Also, the association between intelligence and brain volume change is mostly driven by verbal IQ rather than by performance IQ. Interestingly, there is increasing evidence for a relationship between intelligence and brain networks, with more efficiency of the structural (Chiang et al., 2009) and the functional (van den Heuvel et al., 2009) connectivity being positively associated with intelligence. Future studies may reveal to which extend intelligence is associated with dynamic changes in brain networks. We found that genes for intelligence are overlapping with genes for total brain volume change. These overlapping genes may directly influence both intelligence and brain volume change, and/or be represented through even more complicated pathways in which more intelligent people seek out mentally challenging activities that may increase their brain volume (Plomin & Kosslyn, 2001). There is evidence for changes in volume in particular areas of the brain after training on difficult tasks such as juggling (Draginski et al., 2004).

Finding genes and environmental influences implicated in brain volume change and IQ will ultimately help to unravel the relationship between cognition and brain structure. Identification of genes implicated in brain volume change seems one of the logical next steps to obtain this goal. Importantly, in a genome-wide meta-analysis a significant association with hippocampus volume and intracranial volume were recently revealed, as well as a suggestive association with total brain volume within DDR2, which encodes a receptor tyrosine kinase involved in cell growth and differentiation (Stein et al., 2012). With combined efforts to combine imaging and genetics data, such as is evidenced from the ENIGMA consortium (Stein et al., 2012), we may be able to identify genes for brain volume change.

Finding genes and environmental influences implicated in brain volume change may have important potential consequences not only for healthy adults but also for physiological pathways involved in schizophrenia and depression, diseases that are accompanied by (heritable) progressive brain tissue loss (Brans et al., 2008; Frodl et al., 2008).

This study has several limitations that have to be taken into consideration when interpreting its findings. One, while considerable in size, considering the inclusion of 176 individuals from 86 twin families with follow-up MRI brain scans, the number of inclusions is of limited statistical power when concerning changes in brain volumes with lower heritability. However, we did find significant and considerable heritability for total brain volume change as well as for several of its sub-structures. Two, we did not measure change in intelligence and could therefore not associate this with brain volume changes in adulthood. Three, our data allowed for application of the additive genetic model, but not for modeling of possible gene-by-environment interactions. Four, the heritability estimates for brain volume change were considerable (up to 50%) but not in the order of e.g., 90% such as has been reported for brain volume itself (Peper et al., 2007).

In conclusion, we find that brain volume changes and surface area change in the healthy human brain are heritable. Moreover, individuals with a higher intelligence show continued brain expansion or attenuated decrease of brain tissue, but not surface area change, in adulthood, and genes are implicated in this process.

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Supplemental Table: Twin-correlations

Structure	MZ (95%CI)	DZ (95%CI)	Twin/Sib (95%CI)
Whole brain	**0.38 [0.08 to 0.62]**	0.11 [-0.30 to 0.48]	0.14 [-0.24 to 0.46]
Cerebrum	**0.39 [0.08 to 0.62]**	0.15 [-0.31 to 0.54]	0.10 [-0.29 to 0.43]
Cerebrum GM	0.28 [-0.10 to 0.58]	0.08 [-0.25 to 0.40]	**-0.41 [-0.62 to -0.09]**
Cerebrum WM	0.15 [-0.20 to 0.46]	0.05 [-0.40 to 0.47]	0.30 [-0.01 to 0.55]
Cerebellum	**0.57 [0.30 to 0.75]**	0.30 [-0.08 to 0.59]	**0.45 [0.10 to 0.68]**
Lateral ventricles	0.31 [-0.02 to 0.58]	0.14 [-0.17 to 0.42]	0.08 [-0.24 to 0.38]
Third ventricles	**0.34 [0.03 to 0.59]**	0.21 [-0.12 to 0.49]	0.01 [-0.34 to 0.37]
Cortical volume	0.05 [-0.31 to 0.39]	0.21 [-0.11 to 0.49]	-0.22 [-0.53 to 0.21]
Frontal GM	-0.03 [-0.38 to 0.33]	0.21 [-0.12 to 0.49]	-0.22 [-0.55 to 0.25]
Temporal GM	0.22 [-0.11 to 0.51]	0.15 [-0.17 to 0.43]	-0.12 [-0.40 to 0.20]
Parietal GM	0.22 [-0.15 to 0.53]	0.19 [-0.13 to 0.47]	-0.04 [-0.47 to 0.40]
Occipital GM	0.13 [-0.24 to 0.46]	-0.02 [-0.34 to 0.31]	-0.19 [-0.46 to 0.16]
Surface	**0.34 [0.01 to 0.61]**	-0.06 [-0.42 to 0.33]	0.25 [-0.13 to 0.52]
Left hemisphere	**MZ (95%CI)**	**DZ (95%CI)**	**Twin/Sib (95%CI)**
L brain	**0.46 [0.16 to 0.68]**	-0.08 [-0.45 to 0.32]	0.22 [-0.20 to 0.52]
L cerebrum	**0.46 [0.16 to 0.67]**	-0.02 [-0.44 to 0.41]	0.16 [-0.24 to 0.48]
L cerebrum GM	**0.36 [0.02 to 0.62]**	0.03 [-0.29 to 0.35]	**-0.52 [-0.68 to -0.27]**
L cerebrum WM	0.07 [-0.28 to 0.40]	0.03 [-0.41 to 0.45]	0.31 [-0.01 to 0.55]
L cerebellum	0.26 [-0.06 to 0.53]	-0.09 [-0.40 to 0.24]	0.13 [-0.25 to 0.44]
L lateral ventricles	**0.34 [0.01 to 0.59]**	0.07 [-0.23 to 0.36]	-0.05 [-0.38 to 0.31]
L cortical volume	0.05 [-0.30 to 0.39]	0.22 [-0.11 to 0.50]	-0.36 [-0.62 to 0.10]
L frontal GM	-0.02 [-0.39 to 0.36]	0.25 [-0.08 to 0.53]	-0.37 [-0.62 to 0.08]
L temporal GM	0.18 [-0.15 to 0.48]	0.25 [-0.06 to 0.51]	-0.26 [-0.53 to 0.09]
L parietal GM	0.35 [-0.00 to 0.62]	0.22 [-0.10 to 0.49]	-0.06 [-0.52 to 0.43]
L occipital GM	-0.01 [-0.35 to 0.33]	-0.14 [-0.44 to 0.20]	-0.19 [-0.45 to 0.14]
L surface	**0.39 [0.07 to 0.63]**	-0.09 [-0.44 to 0.28]	**0.32 [0.03 to 0.54]**
Right hemisphere	**MZ (95%CI)**	**DZ (95%CI)**	**Twin/Sib (95%CI)**
R brain	0.19 [-0.13 to 0.47]	0.05 [-0.33 to 0.41]	-0.10 [-0.38 to 0.23]
R cerebrum	0.27 [-0.05 to 0.53]	0.23 [-0.23 to 0.59]	-0.03 [-0.38 to 0.33]
R cerebrum GM	0.30 [-0.07 to 0.59]	0.03 [-0.30 to 0.36]	-0.11 [-0.41 to 0.22]
R cerebrum WM	0.18 [-0.17 to 0.49]	0.06 [-0.40 to 0.49]	0.25 [-0.08 to 0.53]
R cerebellum	0.19 [-0.14 to 0.48]	-0.26 [-0.54 to 0.09]	-0.16 [-0.39 to 0.14]
R lateral ventricles	0.25 [-0.09 to 0.54]	0.26 [-0.06 to 0.53]	0.17 [-0.13 to 0.43]
R cortical volume	0.04 [-0.32 to 0.38]	0.21 [-0.11 to 0.49]	0.01 [-0.37 to 0.37]
R frontal GM	-0.06 [-0.39 to 0.29]	0.19 [-0.14 to 0.48]	0.06 [-0.36 to 0.41]
R temporal GM	0.31 [-0.02 to 0.58]	-0.00 [-0.33 to 0.32]	0.07 [-0.26 to 0.37]
R parietal GM	0.03 [-0.34 to 0.38]	0.17 [-0.15 to 0.45]	0.10 [-0.31 to 0.45]
R occipital GM	0.36 [-0.04 to 0.64]	0.10 [-0.22 to 0.41]	-0.15 [-0.48 to 0.26]
R surface	0.24 [-0.10 to 0.53]	-0.01 [-0.39 to 0.37]	0.03 [-0.38 to 0.41]

In bold=significant; CI=Confidence Interval; Twin/Sib represents the correlation between the sibling and a twin; All variables are corrected for age and sex.

Chapter 7

Concluding Words

7.1 Summary and Discussion

The research conducted in this thesis explored changes in brain volume and intelligence over time in healthy individuals, in patients with schizophrenia, and in their non-affected first-degree family members. Twins, and their siblings were examined to disentangle the relative contributions of (shared) genetic and environmental influences on these phenotypes of interests.

In this final chapter, a summary and brief discussion of the main findings is provided. Moreover, possible directions and implications for future research are suggested.

In Chapter 2, I describe a systematic review on longitudinal MRI studies reporting on global brain volume change in healthy individuals. In this review, the extent of brain volume change across the life-span was investigated. For this purpose, a search in the PubMed database was done to identify relevant longitudinal structural MRI studies that examined whole brain volume change in healthy subjects.

Fifty-six studies were identified as suitable for the inclusion, including 2,211 participants. Age at first measurement varied between 4 and 88 years of age. A weighted regression analysis was applied to estimate the age dependency of the rate of relative annual brain volume change across studies. The results indicate that whole brain volume changes throughout the life span. A wave of growth was found during childhood/adolescence, which levels off at age 13 when a gradual volume loss sets in. Possibly another wave of growth occurs during young adulthood or at least a period of no brain tissue loss. After age 35 years, a steady volume decrease takes place with accelerating tissue loss occurring with increasing age. The trajectories of whole brain volume change with age that were present in two studies were plotted onto our plot that was based on all reviewed studies. Comparison of these fits with the (weighted regression) overall fit shows that both of the trajectories, one during childhood and adolescence (Lenroot et al., 2007) as well as one in adulthood (van Haren et al., 2008) agree nicely.

I concluded that the human brain is dynamic throughout the life span. The main finding was that there is evidence for a possible second wave of brain volume growth, or at least a stable period in early adulthood preceding a brain volume decrease from the age of 35 years.

Longitudinal studies focusing on healthy subjects between the age of 15 and 25 years are needed to confirm this finding of a possible second wave of growth.

The study described in Chapter 3 compared change in intelligence quotient (IQ) during a five-year interval in chronically ill schizophrenia patients, their discordant co-twins and healthy control twins. A total of 52 twins completed two assessments of IQ (9 patients, 10 co-twins and 33 healthy controls). This study suggests that patients with schizophrenia in the chronic phase of the disease show a lack of increase in IQ whereas the discordant co-twins of the patients and the healthy controls show a small increase. Since the lack of increase in IQ was limited to the patients, and not present in the co-twins of patients, it was argued that the lack of changes in IQ found in patients with schizophrenia is associated with the illness or illness-related factors. The findings reported in Chapter 3 in patients are in line with other controlled longitudinal studies in early-onset schizophrenia (Jepsen et al., 2010) and first-episode schizophrenia (Hoff et al., 2005) where patients showed less increase in IQ over time as compared with healthy controls. A lack of IQ increase might be explained by an abnormal slow acquisition of new intellectual information and skills in patients (Jepsen et al., 2010; Hoff et al., 2005), or it might be that patients do not benefit from practice effects, while both the unaffected co-twins and healthy controls do (Salthouse, 2010). Another explanation might be that the schizophrenia patients are not influenced by the Flynn effect (i.e., an increase in average scores on intelligence tests) (Hiscock, 2007).

I went beyond my findings of IQ change in schizophrenia twins by gathering all studies published on IQ-change in schizophrenia patients compared to healthy controls. In Chapter 4, I describe a meta-analysis to determine the magnitude and extent of IQ-change over time in schizophrenia patients. I conducted a PubMed search to identify relevant studies that examined differences in IQ-change over time in schizophrenia patients and healthy control subjects.

I identified fourteen studies of which eight fulfilled all criteria, including a total of 280 patients and 306 healthy controls. The findings of this meta-analysis suggest that patients show diminished improvement in IQ over time compared to healthy controls. In line with the results from Chapter 4 are many longitudinal studies that tend to show improvement in cognitive tasks in patients with healthy controls showing similar or larger improvements (Granholm et al., 2010; Harvey et al., 2010; see Szöke et al., 2008 for meta-analysis). A significant decline

in global cognitive functioning over time has been reported in patients as compared to controls when assessed prior to disease onset and again after disease transition (Lubin et al., 1962; Caspi et al., 2003). The relative decline in IQ in schizophrenia may be (most) pronounced prior to, or at the time of disease transition, but continues to change throughout the course of the illness.

From Chapter 4 it was concluded that a less prominent improvement in IQ in patients as compared to controls is present throughout the disease and may be due to the lack of practice effects in patients.

The study that is described in Chapter 5 involves the comparison of cortical thickness and surface area change over a five-year interval between twins discordant for schizophrenia and healthy control twins. Cortical thickness and surface area changes have repeatedly been found in schizophrenia (Rais et al., 2010; Rimol et al., 2010; van Haren et al., 2011; Palaniyappan et al., 2011). Whether progressive loss in cortical thickness and surface area are mediated by genetic or disease related factors was unknown. A total of 90 individuals from 46 same- sex twin pairs were included. Age varied between 19-57 years. The findings from this study suggest that a higher genetic liability for schizophrenia was associated with progressive thinning of the cortex, and particularly of the left superior temporal cortex. Higher environmental liability for schizophrenia was associated with attenuated thinning of the cortex. In addition, cortical surface area and surface area change were heritable, but not associated with higher genetic (or environmental) liability for schizophrenia.

Our results are in line with and extend previous findings of excessive cortical thinning as a familiar risk marker for schizophrenia (Gogtay et al., 2007; Prasad et al., 2010). In Chapter 5 it was added that excessive cortical thinning in schizophrenia is not only familiar, it is of genetic origin. Interestingly, Kraepelin already mentioned left superior temporal cortex involvement in schizophrenia, based on clinical observations (Kraepelin, 1983). Moreover, early brain imaging studies reported the left posterior temporal gyrus to be significantly decreased in volume and associated with the severity of thought disorder in schizophrenia (Shenton et al., 1992). Indeed, it was shown that individual variation in progressive thinning of the left superior temporal cortex can be explained - at least partly - by genes implicated in schizophrenia.

In contrast to another study in which surface area in schizophrenia was examined (Prasad et al., 2010), we did not find that total surface area (contraction) associate significantly with increased genetic (or environmental) liability for schizophrenia. However, in that study (Prasad et al., 2010) offspring of affected patients was examined, including individuals who carry a different genetic risk than do twins (Gottesman, 1991), and clearly their environments differ as well.

In conclusion, Chapter 5 emphasized that excessive cortical thinning, particularly of the left superior temporal cortex, but not surface contraction, may represent a genetic risk marker for schizophrenia.

In Chapter 6, I examined healthy twins and their siblings in an extended twin design. The heritability of brain volume and surface area change during a five-year interval was estimated. Furthermore, it was examined whether intelligence and change in brain volume /surface area are associated and whether these (possible) associations have genes in common. By applying a bivariate design using Structural Equation Modeling, I could separate the relative influence of genetic and environmental factors of the association between intelligence, and brain volume/surface area change.

Chapter 6 shows that brain volume change and surface area change in adults in the 3rd to 6th decade of life is heritable. Thus, genes are not only involved in the absolute brain volume (Pfefferbaum et al., 2000; Baaré et al., 2001; Thompson et al., 2001; Wright et al., 2002) and surface area (Winkler et al., 2010; Panizzon et al., 2009; Eyler et al., 2011) but to a large extent also determine brain volume/surface area change over time. Moreover, genes involved in cerebral volume change over time overlap with genes involved in intelligence. Previously, focal changes in cortical thickness have been found associated with level of intelligence in childhood and adolescent (Shaw et al., 2006) and in adulthood (Brans et al., 2010). Here, these findings are extended by showing that intelligence is associated with global volumetric brain changes in adulthood. Participants with a higher IQ show diminished loss of brain volume. In addition, absolute brain volume has been reported to share genes with intelligence (Posthuma et al., 2002). In Chapter 6 it is shown that brain volume *change* has overlapping genes with intelligence.

Based on these findings it can be concluded that brain volume change and surface area change in the adult human brain are at least in part heritable. Moreover, individuals with a higher intelligence show continued brain expansion or less pronounced loss of brain tissue, but not surface area change, in adulthood. Genes, common to both may be implicated in this process.

7.2 Methodological Considerations

There are some methodological considerations or limitations in this thesis which need to be taken into account when interpreting the results of the studies. First, in the systematic review described in Chapter 2 differences in acquisition methods and study design between studies may have affected the results, specifically the regression lines. Studies with high-resolution scans are expected to be more sensitive to brain volume changes than studies using thicker MRI slices. However, in the review, the high/low-resolution studies were more or less evenly distributed over the age range, making it an unlikely explanation for the findings.

In the meta-analysis that in Chapter 4, a diminished IQ increase in patients with schizophrenia was compared to healthy controls. One difficulty in interpreting the results of this meta-analysis, however, is that studies were included where schizophrenia patients were in different stages of the disease (i.e., early-onset schizophrenia, first-episode and chronically ill schizophrenia). Differences between childhood and adult-onset schizophrenia are likely to be influenced by differences in developmental and educational status. Moreover, the degree of variability on important variables such as sample size, age, follow-up interval, age of illness onset, pre and post-test assessment and duration and severity of illness should not be underestimated despite the statistical methods used to ensure that these variables were considered.

A few aspects relate to the twin design in general. The twin design is often criticized for some of its assumptions. One of these is the “equal environmental assumption” which implies that MZ and DZ twins treated the same way, although it has been shown that MZ twins do experience a more similar environment than DZ twins. However, cases of mistaken zygosity and studies that investigate twins reared apart have suggested that the more similar environment is a consequence of their greater phenotypic similarity instead of the cause (Kendler et al., 1993). Furthermore, concerns have been raised regarding generalization of findings towards the singleton population. However, reliable estimates of heritabilities have

been demonstrated in studies comparing MZ and DZ twin pairs with their siblings, at least with respect to brain structure (Hulshoff Pol et al., 2002) and intellectual abilities (Posthuma et al., 2000). Finally, the term “heritability” is sometimes wrongly interpreted. The word “inherited” does not equal heritability although the literature sometimes uses the words interchangeably. Heritability is a statistic that describes the contribution of genetic differences to observed (phenotypic) differences among individuals in a particular population at a particular time. Thus, heritability refers to the genetic contribution in individual differences (variance) and not to the phenotype of a single individual (Plomin et al., 2008). According to twin methodological standards the twin sample discordant for schizophrenia is relatively small which gives room for possible chance variations between the subgroups. Furthermore, it was not always possible to separate the relative influence of genetic and environmental factors on a given trait. Therefore, when confidence intervals are large, the genetic or environmental influences should be interpreted cautiously.

7.3 Final Remarks and Conclusions

Taken together, the studies presented in this thesis show plasticity in the adult human brain. In the review of longitudinal MRI studies in healthy individuals, we showed how the brain changes across the lifespan. Moreover, results from the meta-analysis indicate that IQ slightly increases over time in health. Interestingly, genes involved in brain volume changes in healthy adults overlap with genes for intelligence, which is shown in the study on healthy twins. Thus, it appears that continued dynamic brain changes in adulthood and intelligence act together in concert, and both are mediated by common genes.

Regarding the cortical thickness change in schizophrenia, we concluded that the progressive loss that we observe in the left superior temporal cortex both in schizophrenia patients and their unaffected co-twins during a 5-year interval is at least partly attributable to genes involved in the disease. Cortical surface area and surface area change were heritable, but not associated with higher genetic (or environmental) liability for schizophrenia. In addition, compared to controls and co-twins, schizophrenia patients show diminished improvement in IQ over time which is indicated in the meta-analysis of IQ change.

As a next step, one could investigate whether changes in brain volume and (changes in) intelligence overlap with a third trait (e.g., disease liability) in a trivariate model (SEM), and whether these associations are driven by overlapping genes. In addition, the left superior temporal cortex may represent a promising target for genetic studies in schizophrenia which would be interesting to explore.

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Chapter 8

Nederlandse Samenvatting

Samenvatting en Discussie

De studies beschreven in dit proefschrift onderzochten veranderingen in hersenvolume en intelligentie over de tijd bij gezonde personen en bij patiënten met schizofrenie en hun niet-aangedane eerstegraads familieleden. Tweelingen, en broers en zussen van tweelingen, werden onderzocht om de relatieve bijdragen van (gedeelde) genetische en omgevingsinvloeden op deze fenotypes te ontrafelen.

In hoofdstuk 2 beschrijf ik een systematische review over longitudinale MRI studies naar hersenvolume veranderingen in gezonde individuen. In dit overzicht werd de omvang van hersenvolume veranderingen onderzocht door het leven heen. Hiertoe deed ik een zoekopdracht in de PubMed database om relevante longitudinale structurele MRI studies die totaal hersenvolume veranderingen bij gezonde individuen onderzochten te identificeren.

Zesenvijftig studies werden geïdentificeerd als geschikt voor de meta-analyse, met een totaal van 2,211 deelnemers. Leeftijd bij de eerste meting varieerde tussen 4 en 88 jaar. De resultaten laten zien dat hersenvolume blijft veranderen gedurende het hele leven. Een groeigolf werd gevonden tijdens de kindertijd en adolescentie, waarna vanaf ongeveer 13 jaar een afname in volume plaats vind. Een eventuele nieuwe golf van groei treedt op tijdens de jonge volwassenheid. In ieder geval is gedurende de volwassenheid sprake van een periode van stabiliteit in hersenvolume. Na de leeftijd van 35 jaar vindt een gestage volumedaling plaats, die bij toenemende leeftijd gaat versnellen.

Ik concludeerde dat het menselijk brein dynamisch is gedurende het hele leven. De belangrijkste bevinding was dat er aanwijzingen zijn voor een mogelijke tweede golf van volumegroei van de hersenen, of op zijn minst een stabiele periode, in de vroege volwassenheid voorafgaand aan een hersenvolume daling vanaf de leeftijd van 35 jaar. Longitudinale studies gericht op gezonde proefpersonen tussen de leeftijd van 15 en 25 jaar zijn nodig om deze bevinding van een mogelijke tweede golf van de groei te bevestigen.

De studie in hoofdstuk 3 vergeleek veranderingen in het intelligentie quotiënt (IQ) in chronisch zieke schizofrenie patiënten, in hun discordante co-tweelingen en in gezonde controle tweelingen over een periode van vijf jaar. In totaal 52 tweelingen voltooiden twee evaluaties van IQ (9 patiënten, 10 co-tweelingen en 33 gezonde controles). Dit onderzoek suggereert dat patiënten met schizofrenie in de chronische fase van de ziekte een gebrek

aan toename in IQ vertonen terwijl de niet-aangedane co-tweelingen van de patiënten, evenals de gezonde controles, een geringe stijging in IQ laten zien over de periode van 5 jaar. Aangezien het uitblijven van een stijging in het IQ beperkt bleef tot de patiënten, en niet in de co-tweeling van de patiënten werd gevonden, suggereert dit een associatie met ziekte of ziekte - gerelateerde factoren.

Ik heb, naast de studie naar IQ verandering bij schizofrenie tweelingen, alle studies verzameld die gepubliceerd waren over IQ verandering bij schizofrenie patiënten in vergelijking met gezonde controles. In hoofdstuk 4 beschrijf ik resultaten van mijn meta-analyse naar de omvang en reikwijdte van de IQ veranderingen bij schizofrenie. Ik identificeerde hiervoor in de PubMed literatuur database relevante studies die verschillen in IQ veranderingen over de tijd bij schizofreniepatiënten en gezonde proefpersonen onderzochten.

Ik geïdentificeerde veertien studies, waarvan acht studies met in totaal 280 patiënten en 306 gezonde controles geschikt waren om te worden opgenomen in de meta-analyse. De bevindingen van deze meta-analyse suggereren dat patiënten ten opzichte van gezonde controles een verminderde verbetering in hun IQ laten zien over de tijd. De relatieve daling in IQ bij schizofrenie is het meest uitgesproken vooraf gaand aan - of op - het tijdstip van de transitie naar ziekte, maar de relatieve daling is ook aanwezig in meer chronisch zieke patiënten.

Uit hoofdstuk 4 werd geconcludeerd dat een minder prominente verbetering in IQ bij patiënten vergeleken met controles gedurende de hele ziekte aanwezig is en mogelijk te wijten is aan een verminderde invloed van oefening bij de patiënten.

Het onderzoek dat wordt beschreven in Hoofdstuk 5 betreft de vergelijking van de corticale dikte en oppervlakte veranderingen over een periode van vijf jaar tussen tweelingen die discordant zijn voor schizofrenie en gezonde controle tweelingen. Corticale dikte en hersenoppervlakte veranderingen zijn herhaaldelijk gevonden bij patiënten met schizofrenie. Of progressief verlies in corticale dikte en oppervlakte worden gemedieerd door genetische of ziekte-gerelateerde factoren was onbekend. Een totaal van 90 personen, bestaande uit 46 tweelingparen van hetzelfde geslacht, werd geïncludeerd in de studie. De leeftijd varieerde tussen de 19 en 57 jaar. De bevindingen van deze studie suggereren dat een hoger

genetisch risico op schizofrenie geassocieerd is met een progressieve verdunning van de cortex; met name van de bovenste winding van de linker temporaalkwab. Ziekte-gerelateerde factoren waren geassocieerd met een kleinere verdunning van de cortex gedurende het interval. Daarnaast werd gevonden dat het corticale oppervlakte en veranderingen in het corticale oppervlakte erfelijk waren, maar niet geassocieerd met een hogere genetisch (of omgevings-) risico op schizofrenie.

Concluderend , hoofdstuk 5 benadrukt dat overmatige corticale verdunning, met name van de bovenste winding van de linker temporaalkwab, maar niet corticale oppervlakte contractie, een marker voor het genetische risico op schizofrenie vertegenwoordigt.

In hoofdstuk 6 onderzocht ik gezonde tweelingen en hun broers en zussen met behulp van het uitgebreide tweeling design. De erfelijkheid van de verandering in hersenen volume en oppervlakte over een periode van vijf jaar werden geschat. Verder werd onderzocht of intelligentie samenhangt met veranderingen in hersenvolume en/of corticaal oppervlakte en of beiden genetische factoren delen.

Op basis van de bevindingen kan worden geconcludeerd dat hersenenvolume verandering en corticaal oppervlakte verandering in de volwassen menselijke hersenen tenminste gedeeltelijk erfelijk zijn. Bovendien was bij diegenen met een hogere intelligentie sprake van meer hersengroei dan wel van minder uitgesproken verlies van hersenweefsel. Er werd geen associatie tussen corticale oppervlakte verandering en intelligentie gevonden. Genetische factoren die zowel bij intelligentie als bij hersenvolume verandering betrokken zijn, zijn mogelijk betrokken bij deze samenhang.

Slotopmerkingen en Conclusies

Samenvattend, laten de studies in dit proefschrift zien dat er sprake is van plasticiteit in de hersenen van volwassenen. In het overzicht van longitudinale MRI studies bij gezonde individuen toonde ik aan in welke mate het volume van het brein verandert gedurende het hele leven. Bovendien blijkt uit de resultaten van de meta-analyse dat de intelligentie bij gezonde mensen iets toeneemt in de tijd. De hersenenvolume veranderingen bij gezonde volwassenen zijn ten minste gedeeltelijk erfelijk. Ook lijken sommige hersenvolume veranderingen samen te hangen met intelligentie, mogelijk door overlappende genetische factoren. Het blijkt dus dat er in de volwassenheid dynamische veranderingen plaatsvinden

in de hersenen, die ten dele erfelijk zijn en die ten dele samenhangen met het cognitief functioneren.

Wat betreft de corticale dikte veranderingen bij schizofrenie, concludeer ik dat het progressieve verlies in de bovenste winding van de linker temporaalkwab zowel bij schizofreniepatiënten als ten dele bij hun niet aangedane co-tweelingen optreedt gedurende een vijf jaar interval. Deze progressieve veranderingen kunnen ten minste gedeeltelijk toegeschreven worden aan genen die betrokken zijn bij de ziekte. Corticale oppervlakte en corticaal oppervlakte verandering waren beiden erfelijk, maar niet geassocieerd met een hoger genetisch of omgevings-risico op schizofrenie in het onderzochte tweeling-cohort. In vergelijking met controles en co-tweelingen , lieten schizofrenie patiënten een verminderde verbetering in hun IQ zien over de tijd - en dit bleek ook uit de meta-analyse naar IQ verandering.

Als volgende stap is het zinvol om te onderzoeken of veranderingen in hersenvolume en (veranderingen in) intelligentie gezamenlijk (genetisch) samenhangen met het risico op schizofrenie in een tri-variaat model. Daarnaast kan de linker superieure temporale cortex een veelbelovend uitgangspunt vormen in de zoektocht naar genen die betrokken zijn bij schizofrenie.

List of Publications

Journal Articles

Hedman AM, **van Haren NE, Schnack HG, Kahn RS, Hulshoff Pol HE**. (2012): Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. Hum Brain Mapp 33:1987-2002.

Hedman AM, **van Haren NEM, van Baal GCM, Brans RGH, Hijman R, Kahn RS, Hulshoff Pol HE**. (2012): Is there change in IQ in chronically ill schizophrenia patients? A longitudinal study in twins discordant for schizophrenia. Psychol Med 42:2535-2541.

Hedman AM, van Haren NEM, van Baal GCM, Brans RGH, Kahn RS, Hulshoff Pol HE. (2013): IQ change over time in schizophrenia and healthy individuals: a meta-analysis. Schizophr Res 146:201-208.

Hedman AM, **van Haren NEM, Schnack HG, van Baal GCM, Brans RGH, Kahn RS, Hulshoff Pol**. Heritability of cortical thickness changes over time in twin pairs discordant for schizophrenia. (submitted for publication)

Hedman AM et al. Heritability of brain volume change and intelligence. (in preparation)

Abstracts and Conference Proceedings

Hedman AM, van Haren NE, Schnack HG, Kahn RS, Hulshoff Pol HE. Human brain volume changes across the lifespan. (2010): A review and non-linear regression analysis of 56 longitudinal magnetic resonance imaging studies. *Poster presented at the Schizophrenia International Research Society (SIRS) Meeting. Florence, Italy. April 10-14, 2010.*

Hedman AM, van Haren NE, Schnack HG, Kahn RS, Hulshoff Pol HE. Human brain changes across the life span. (2011): A review of 56 longitudinal magnetic resonance imaging studies. *Poster presented at the EU Marie Curie Satellite Meeting, Torino, Italy. July 1-2, 2010.*

Hedman AM, van Haren NEM, van Baal GCM, Brans RGH, Hijman R, Kahn RS, Hulshoff Pol HE. (2011): Is there progressive decline in IQ for schizophrenia patients? A longitudinal study in twins discordant for schizophrenia and meta-analysis for IQ-change in schizophrenia compared to healthy controls. *Oral presentation at the U-Miami International Congress Cognition in Schizophrenia Satellite Meeting, The Broadmoor. Colorado-Springs, USA. April, 1-2, 2011.*

Hedman AM, van Haren NE, Schnack HG, Kahn RS, Hulshoff Pol HE. (2011): Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. *Poster presented at the International Congress of Schizophrenia Research (ICOSR) Meeting. Colorado-Springs, USA. April, 2-6, 2011.*

Hedman AM, van Haren NEM, van Baal GCM, Brans RGH, Kahn RS & Hulshoff Pol HE. (2012): IQ change over time in schizophrenia and healthy individuals: a meta-analysis. *Poster presented at the Schizophrenia International Research Society (SIRS) Meeting. Florence, Italy. April, 14-18, 2012.*

Hedman AM, van Haren NEM, Schnack HG, van Baal GCM, Brans RGH, M Bohlken, Kahn RS, Hulshoff Pol. (2012): Quantitative genetic modeling of cortical thickness change in twin pairs discordant for schizophrenia: a longitudinal study. *Poster presented at the XXth World Congress of Psychiatric Genetics (WCPG) Meeting. Hamburg, Germany. October, 14-18, 2012.*

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Curriculum Vitae

Curriculum Vitae

Anna Margareta Hedman was born the 27th of January 1975 in Skellefteå, Västerbottens county, Sweden. In 1994 she received her diploma from Anderstorps Gymnasium, ”naturvetenskaplig linje”, in Skellefteå. Anna started to study Forest Management, ”jägmästarutbildningen”, at the Swedish University of Agricultural Sciences, but later switched to study psychology at Umeå University. She worked as a research assistant at Aging Research Center (ARC), Karolinska Insitutet, Stockholm, before she started as a PhD student. In 2008 she started as promovenda at the Rudolf Magnus Institute of Neuroscience, department of Psychiatry at the Universitair Medisch Centrum (UMC) Utrecht. During her first two and a half years she was involved in a Marie Curie EUTwins network with young researchers from several universities in Europe all investigating twins discordant for schizophrenia. Anna has conducted her studies in the neuroimaging group under supervision of Prof. dr. H.E. Hulshoff Pol and Prof. dr. R.S. Kahn which has led to this thesis.