Structural brain changes in adolescents at risk for psychosis

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Abstract

Objectives: The onset of psychosis is often preceded by prodromal signs and symptoms. The precise neurobiological changes and time course underlying the prodromal phase are not yet known and have been studied intensively by several research centers. The aim of this review was to summarize the findings from the various structural MRI studies in order to investigate potential neurobiological markers preceding the onset of a first psychotic episode in individuals at increased risk of developing psychosis.

Methods: We conducted a search using the electronic database PubMed to identify publications on structural neuroimaging in subjects at risk of developing psychosis. Three approaches were used to search for studies, which investigated neurobiological precursors of psychosis. Clinical high risk studies are based on help-seeking individuals who come to a clinic because of the experience of prodromal symptoms. Familial liability of psychotic disorders is a second approach that investigates subjects with affected family members. The third approach studies patients with a genetic disorder (Klinefelter syndrome or velo-cardio-facial syndrome). As psychosis normally occurs at young adulthood and prodromal symptoms occur up to five years before that, the neurobiological changes underlying the prodromal phase should be identifiable during adolescence. Therefore, we restricted the search by only including studies that concentrated on adolescents at risk for psychosis (mean age range of 10-24 years).

Results: A total of 50 studies using structural MRI met inclusion criteria and were included for this review. Across the three high risk approaches, the majority of studies predominantly found gray matter decreases in various brain regions for the high risk subjects as compared to healthy controls, and for the at risk subjects who subsequently developed psychosis as compared to at risk subjects who did not. There is a great variety in brain regions that are found to be reduced, although the most frequently observed is a smaller total brain for the at risk subjects. Further frequently reported reduced brain volumes were found for the prefrontal cortex, the superior temporal lobe and the anterior cingulate gyrus.

Conclusions: In this review, despite methodological limitations and inconclusive results, we tentatively postulate that structural GM reductions in prefrontal cortex, superior temporal gyrus and anterior cingulate cortex could be regarded as precursors for the onset of psychosis.

Keywords: Psychosis; Adolescent; High-risk; Clinical high-risk; Heritability; Genetic risk; VCFS; Klinefelter's syndrome; Prodromal; Transition; Brain changes; Structural magnetic resonance imaging (sMRI)

Contents

1. Introduction

Psychosis refers to a state of mind in which individuals experience an abnormal reality, thereby lacking insight in the deviant nature of their experiences (Kaplan et al. 1994). It may consist of positive, negative and disorganized symptoms, such as hallucinations and delusions, stupor and disorganized cognitive and behavioural functions. Psychotic disorders cause severe disruptions in the normal functioning and psychosocial development of an individual, and are associated with increased mortality. Not only the patient's life but also that of their caring relatives are often affected (Heckers, 2009; McGrath et al., 2008; Phillips et al., 2002; Salokangas and McGlashan, 2008). Lifetime prevalence of psychosis is approximately 3% (Perälä et al., 2007).

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), psychosis is often a feature of psychotic disorders, such as schizophrenia and schizoaffective disorder (American Psychiatric Association, 1994). However, they may also occur in isolation and other psychiatric disorders, such as affective disorders, pervasive developmental disorders (Van Engeland and Van der Gaag, 1994), velo-cardio-facial syndrome (VCFS, also known as 22q11.2 deletion syndrome) (Tan et al., 2009; Zinkstok and van Amelsvoort, 2005), Klinefelter (karyotype 47,XXY) syndrome (Van Rijn et al., 2006), and personality disorders (American Psychiatric Association, 1994).

Although there is considerable variability among patients in long-term course of psychotic disorders, as well as the ultimate outcome (Heckers, 2009), most of these disorders have a common onset in late adolescence or early adulthood (Phillips et al., 2002; Salokangas and McGlashan, 2008). Various genetic and environmental factors contribute to this baseline risk and can accumulate, thereby significantly increasing the risk for a given individual (Murphy, 2005). For example, up to 30% of individuals with VCFS are diagnosed with schizophrenia, making VCFS the third highest risk factor for developing schizophrenia. Only individuals with either two affected parents or identical twins diagnosed with schizophrenia appear to be at higher risk (Debbané et al., 2006; Murphy, 2005).

A psychosis, in general, develops in a gradual manner (Häfner et al., 1993). The development of behavioural abnormalities in schizophrenic individuals long before the

onset of a first psychotic episode has also been acknowledged by psychologists from the previous century (e.g. Bleuler, 1911; Sullivan, 1927). Sullivan (1927) even argued that by identifying individuals who experience sub-threshold psychotic symptoms, the possibility is created to intervene in the development of the psychosis, which in the ideal situation might stop the emergence of more symptoms and improve the disorder outcome (Phillips et al., 2002; Sullivan, 1927). The belief of a critical pre-psychotic phase is still shared and supported by several authors and recent studies (reviewed by Marshall et al. 2005; e.g. Yung et al., 2010). This critical pre-psychotic phase is referred as 'prodrome' (McGorry et al. 2008), and is used to describe the premorbid phase in which symptoms and signs are noticeable before the definitive diagnosis of psychosis is determined (Hecker, 2009; Salokangas and McGlashan, 2008). The prodromal phase needs to be clearly distinguished from the premorbid phase, in which there are no symptoms or signs present, and the diagnosis of a first episode of psychosis (McGorry et al. 2003).

Several retrospective studies have demonstrated that the onset of psychosis is often preceded by such a prodromal phase. Symptoms include behavioural and cognitive changes, social decline and subthreshold psychotic symptoms (e.g. Hafner et al. 1999; Schothorst et al. 2006; Yung and McGorry, 1996). As the first psychotic episode typically occurs at 20-25 years of age, a gross number of studies focused on this age range (Kessler et al., 2007). However, the prodromal phase has to be present even earlier in life, as the earliest subthreshold psychotic signs occur in general 4,8 years before psychosis is diagnosed (Häfner and Maurer, 2006). Therefore, in childhood, adolescence and young adulthood, there may already be an abnormal development of neurobiological processes that eventually increase the risk of developing a psychotic disorder (Phillips et al., 2002). This also implicates that antipsychotic treatment and psychotherapy should be started during the prodromal phase, leading to an attenuation of psychotic symptoms and eventually a better outcome (Cannon et al., 2008; Salokangas and McGlashan, 2008).

In the last decade, the focus of research has therefore shifted to the prodromal phase of a psychotic disorder, causing an exponential growth in studies attempting to disentangle the neurobiological processes underlying the onset of psychosis (Cornblatt et al., 2001; Phillips et al., 2002). In order to study the prodromal phase, it became necessary to identify individuals who have an increased risk of developing psychosis.

A family history of psychotic illnesses drastically increases the lifetime prevalence rate of developing psychosis. About 80% of the variance in susceptibility to the disorder is explained by genetic factors (Asherson et al., 1995). The number of relatives diagnosed with schizophrenia in fact increases this risk. If one sibling or parent is affected, the risk is approximately 9%, if both a sibling and a parent have the disorder, the risk further increases to 16%. The risk is highest when both parents are affected: 46% (McGuffin et al., 1995). This has lead to the traditional inclusion of asymptomatic individuals, regardless of age, who have a family history of psychotic illness in prodromal research, e.g. prospective studies of the offspring of schizophrenic parents. However, disadvantages of such a study design are low transition rates to full-blown psychosis, the need of large numbers of subjects, the long period required for transition and the difficulties in correct classification of the outcome. There are some studies which succeeded to follow the offspring of schizophrenic parents until adulthood, providing data on key questions of the prediction of psychosis (Cannon et al., 2003; for review, see Niemi et al., 2003).

However, the majority of researchers switched to alternative methods to search for individuals at risk for psychosis (Owens and Johnstone, 2006). In general, there are three of such alternative approaches: One approach relies on clinical symptoms, the second approach focuses only on an age restricted, familial liability (Pantelis et al., 2009, 2007; Smieskova et al., 2010), and a third approach investigates patients with a genetic disorder.

The approach used by McGorry & colleagues from the Melbourne group is an example of assessment based clinical symptoms. Their approach is based on the ideas by Bell (1992), who proposed that individuals must meet multiple conditions before high-risk inclusion criteria are met, termed “multiple-gate screening”. This contradicts with the traditional OSP approach, in which a single criterion is used. Furthermore, Bell argued that in order to decrease false-positive rates, a shortening of the period of follow-up is needed. Therefore, he concentrated the follow-up to the period in which transition to psychosis is most likely to occur, the age of maximum incidence of psychotic disorders. Besides these methodological issues, Bell advocated for using signs of behavioural difficulties in

adolescence as inclusion criteria, which would lead to a more clinical approach in stead of the traditional OSP approach (McGorry et al., 2003).

Adolescents who experience sub-threshold psychotic symptoms seek help in a clinic facility, in order to cope better with these symptoms. These help-seeking individuals are then screened for research-purposes, providing the research group the opportunity to select a cohort of adolescents who have an increased risk for developing psychosis (Wood et al., 2008). This cohort is termed 'Ultra High-Risk' (UHR) or 'At Risk Mental State' (ARMS). Screening of help-seeking adolescents by the Melbourne Group is performed using a list of operational criteria. Subjects (aged 14-30 years) must meet inclusion criteria such as the experience of subthreshold attenuated psychotic symptoms during the past year, the experience of brief episodes of psychotic symptoms, or the combination of a first degree psychotic relative and a significant decrease in functioning, operationalized by a 30% reduction on the Global Assessment of Functioning (GAF) score (McGorry et al., 2003). These criteria can be assessed with structured or semi-structured interviews. Often used assessment tools are the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung and McGorry, 1996) of the Melbourne group, the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al. 2001; Miller et al. 2003) and the semi-structured Bonn Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P; Gross et al., 1997; Schultze-Lutter, 2009).

The majority of studies implementing the familial liability approach are from Edinburgh, UK, and are called the Edinburgh High Risk Studies (EHRS) (Hodges et al., 1999, Johnstone et al., 2000). They do not merely focus on the offspring of schizophrenic parents such as the traditional approach but use a set of criteria to include participants. They only included participants within the age-range of 16- to 25- years old, which is the period of maximum risk of illness onset. Furthermore, their participants should have more than one affected family member, which increases the chance of illness conversion progressively (Murphy et al., 2005; Owens and Johnstone, 2006).

The third approach consists of studies including patients with a genetic disorder. The advantage of investigating these patient groups is twofold. On the one hand, the exact genetic defect is known and on the other hand, for some genetic disorders the incidence

of schizophrenia and other psychotic disorders is high. Combining these two advantages provides a unique opportunity to link behaviour to genetic makeup and derive macroscopic neurobiological abnormalities. For instance, as mentioned before, up to 30% of individuals with VCFS are diagnosed with schizophrenia, making VCFS the third highest risk factor for developing schizophrenia (Murphy et al., 2005). Additionally, Klinefelter syndrome has been associated with an increased risk (hazard ratio 4.7) for being hospitalized with a psychotic disorder (Bojesen et al., 2006). Also, Klinefelter syndrome is found to be more prevalent among patients with schizophrenia as compared to the prevalence in the general population (DeLisi et al., 1994).

Regardless of the high risk approach used (clinical symptoms, familial liability or genetic disorders) it is worth noting that individuals with an increased risk will not inevitably develop a subsequent psychosis (Phillips et al., 2002). Therefore, transition rates were calculated; the ratio of at risk subjects who did develop a psychosis versus the proportion of subjects at risk who did not convert into a psychosis. Using a transition rate, one can evaluate the predictive validity of the assessment instruments used to originally discriminate a high risk individual from the general population (Cannon et al. 2007). The predictive validity of various assessment-tools used in the clinical approach was reported promisingly high, with transition rates of 16-54% within 12 months (e.g. Cannon et al. 2008, 2007; Miller et al. 2002; Pantelis et al., 2007; Wood et al., 2008; Yung et al., 2007b, 2004, 2003. See Haroun et al., 2006 for review). However, more recent studies report lower rates, such as the follow-up study by Yung et al. (2008), who reported a transition rate of 16% after a period of two years. It is not clear whether this reduction is explained by more effective treatment, earlier detection of high risk individuals, or more false positive inclusions, considerations that were postulated by Yung et al. (2007a, 2008).

Besides the differences in approach to identify subjects at risk, there are also several approaches to study the underlying neurobiological predictors of psychosis, such as structural brain changes and genetic risk factors. However, they all aim to elucidate the precursors of disease onset, thereby facilitating the development of more effective and efficient therapeutic tools (Cannon et al., 2003). Another aim of high risk research is to improve the ability to accurately identify individuals at high risk, thereby facilitating

early intervention in order to improve the disease outcome (McGlashan et al. 2003; McGorry et al. 2002). A beneficial side-effect is that costs of public health services for effective treatment will decline (Phillips et al., 2002).

To summarize, psychosis is a devastating feature that can occur in a wide variety of disorders. A psychotic disorder, in general, is characterised with a gradual development and an average onset during late adolescence and young adulthood. The period in which the gradual increase of subthreshold psychotic symptoms is recognized and precedes the onset of a full blown psychosis, is termed prodromal phase. The existence of this prodromal phase implicates that behavioural signs and underlying neuropathology must be detectable in childhood and adolescence. Intervention strategies applied during the prodromal phase could possibly attenuate psychotic symptoms and eventually lead to a better illness outcome. This notion has lead to an exponential growth in prodromal research, and with this growth, also the need for accurate identification of individuals at increased risk of developing psychosis. There are three high approaches toward the identification of high risk individuals: The first is based on clinical symptom recognition, further operationalized by the Melbourne Group, the second is the familial liability approach, based on the presence of familial history of psychotic disorders, and a third approach including patients with a genetic disorder, such as VCFS and Klinefelter syndrome.

One direction of research has focused on brain changes, using magnetic resonance imaging (MRI). Using this technique, the anatomy, function and connectivity of the brain and its local areas can be imaged. Furthermore, MRI can be used to compare groups and trace brain development over time. Therefore, the usage of MRI in the research towards prodromal signs aids to the ongoing research in discovering neural correlates of developing psychosis (Keshevan et al., 2007; Pantelis et al., 2009). Several reports of premorbid changes in the neuroanatomy of the brain exist, but the chronological path of these changes has not yet been established, nor has it been investigated if these changes are actual causes of the disease onset or merely have a correlational relationship (Pantelis et al., 2009).

1.1. Aim of the study

The overall aim of this review is to investigate potential neurobiological markers that precede the onset of psychosis. We focus on studies that used structural MRI, either in a cross-sectional or longitudinal design.

As described before, prodromal symptoms often first occur in adolescence. In order to track the developmental neurobiological pathway to psychosis, it is necessary to instigate tracking these changes when they first occur, with the onset of symptoms. This review therefore focuses on adolescent populations with a mean age range of 10 – 24 years.

There have been several reviews focussing on this same issue (for example, see Smieskova et al., 2010), however, to our knowledge, there has not yet been published a review focussing on adolescence and including genetic disorder high risk groups as well.

There are multiple approaches to elucidate these biomarkers, and comparison of the results of various techniques is complicated. However, by doing so, we hope to find a synergistic effect that potentially could provide new insights in, and give future directions to prodromal research.

2. Methods

A search was conducted using the electronic database PubMed. Studies that reported structural MRI data in adolescents at risk for psychosis and unaffected controls were included up to January 2010.

Search terms used to identify the studies included: 'Risk for Psychosis', 'Risk for Mental State', '22q11DS', 'Klinefelter syndrome' and related terms, in combination with 'Magnetic Resonance Imaging' or 'Brain Imaging'. The search was complemented by a manual and bibliographic crossreferencing. No restrictions for year of publication were set.

Inclusion criteria were:

1. The focus of the study had to be in line with the research question of this review
2. Patient groups were at increased risk of developing psychosis. No restriction was set on whether the sample was termed Ultra High-Risk, Genetic High-Risk, At Risk Mental State or whether the increased risk was due to a genetic disorder, e.g. Klinefelter syndrome or VCFS
3. Imaging technique was structural MRI (e.g. ROI, VBM, morphometric, DTI, cortical thickness)
4. Sample demographics were provided and standard deviations were available for each group
5. Mean age range of participants was 10.0-24.0 years
6. Full English texts

Furthermore, single case studies and studies focussing on patients with an established psychotic disorder at initial assessment were excluded. Studies that had overlap in groups of patients were allowed, and studies investigating both cross-sectional as longitudinal data were considered as two studies.

3. Results

3.1. Study inclusion

A total of 50 studies met inclusion criteria for this review (tables 1 – 3, appendix A). Nineteen studies used the clinical high risk approach (table 1), six studies were based on familial liability (table 2) and 25 studies focused on genetic disorders (table 3); four studies investigated Klinefelter syndrome, and 21 studies focused on patients with VCFS. Two major research centers provided the largest amount of studies; the Ultra-High Risk (UHR) studies from the Melbourne Group in Australia and the Edinburgh High-Risk Studies (EHRS) from Edinburgh, UK, using the familial high risk approach. The genetic studies are mainly originated from several sites within the USA and Geneva, Switzerland.

The majority of studies used a cross-sectional design, whereas longitudinal insights were provided by 11 studies. Five clinical high risk studies used a longitudinal design, and these were performed by Pantelis et al. (2003), Sun et al. (2009), Takahashi et al. (2009a,b) and Walterfang et al. (2008a). For the familial high risk studies, participants were followed over time by Lawrie et al. (2001, 2002), Johnstone et al. (2005) and Job et al. (2005). There were no longitudinal studies following patients with Klinefelter syndrome, and there were two longitudinal studies focussing on VCFS-patients, a study by Gothelf et al. (2007b), and a study by Schaer et al. (2009). Longitudinal imaging studies are necessary to track the development of prodromal symptoms within individuals at high risk and relate them to changes in the brain. By comparing longitudinal measures between subject groups, the researchers are provided with the possibility to study differential neurodevelopment. For the majority of the studies included in this review, there are typically two subject groups: On the one hand are individuals who are at increased risk for developing psychosis, regardless of the approach used to determine the increased risk, abbreviated as High Risk group (HR), and second there is a group of healthy control subjects which is termed the control group (HC).

In order to further disentangle neurobiological markers specific for transition to psychosis, the majority of studies divided their sample of at risk participants retrospectively, according to whether they developed a psychosis (HR-p) or not (HR-np).

It should be mentioned that cross-sectional studies often do perform a clinical follow-up in order to establish which individuals of their original at risk sample did develop a psychosis. Thereby, the researchers are able to retrospectively divide their baseline measurements into HR-p versus HR-np (e.g. Borgwardt et al., 2007; Karlsgodt et al., 2009), however, MRI scans were not made at follow-up. Therefore, for our review purposes, we considered a study as longitudinal if MRI data was also acquired during the follow-up assessment.

In the 2001 study by Lawrie et al., the HR-np was further divided in whether they experienced subthreshold psychotic symptoms (HR-nps) or not (HR-npns).

Although it was not always mentioned, the majority of studies did control for whole brain volume, and demonstrated further abnormalities for the HR groups, as described below.

3.2. Age of subject groups for each HR approach

The mean age in each subject group for all included studies was compared per HR approach. The mean age of the subject groups within clinical HR studies was 21.32±3.22 years (range: 15.75-34.90 years), the mean age for the familial high risk approach studies was 20.59±2.09 years (range: 15.40-23.10 years), and for the genetic disorder approach, the mean age was 12.82±2.65 years (range: 10.00-21.8 years) (figure 1). Using a General Linear Model (GLM) oneway ANOVA, a significant mean age difference was found between subject groups within all three approaches (F(2,147): 152,273, $p < .00$), with exclusion of the outliers. This finding is not confounded by unequal variances of mean ages per subject group, as measured with Levene's statistic (2,147): .407, $p = .67$. Post-hoc T-tests revealed no mean age differences between the studies using the clinical and familial approach studies ($p = .31$), however the mean age of the subject groups within the genetic disorder approach studies are significantly younger when compared to the clinical HR studies ($p < .01$) and familial HR studies ($p < .01$).

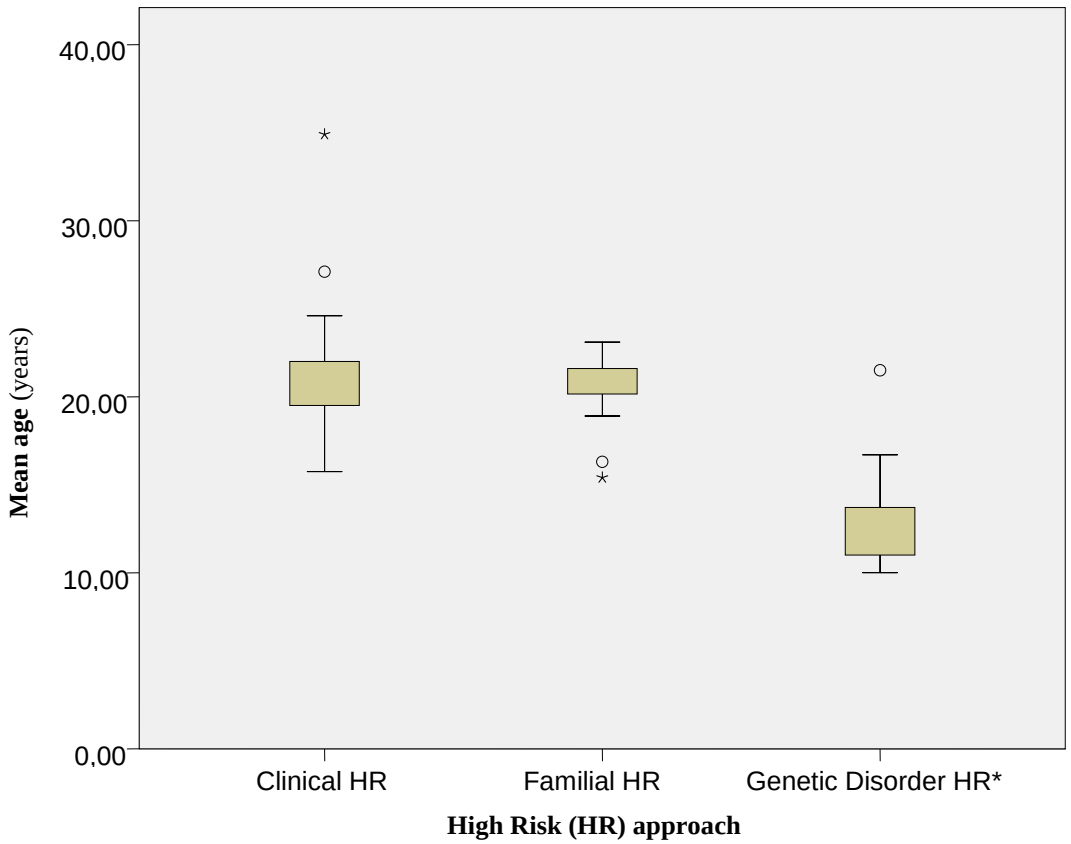

Fig. 1. Mean age (plotted in years of age) of the various subject groups used in the studies within each HR approach.

3.3. Whole brain

Structural MRI studies have observed various structural brain abnormalities in individuals with schizophrenia, when compared to HC. One of the more consistent findings is a reduced brain size for the schizophrenic subjects (Ward et al., 1996; Wright et al., 2000). In a meta-analysis by Vita et al. (2006), they observed a small, but significant, effect size for whole brain volume, in which 10 out of 11 studies reported a smaller total brain volume for schizophrenic patients (d = 0.242). This finding is in accordance with an earlier meta-analyses by Woods et al. (2005), who also demonstrated excessive whole brain volume loss in schizophrenia patients. Although the interpretation of a smaller whole brain volume is ambiguous, it has been suggested that a reduced whole brain volume indicates the occurrence of various anatomical changes, prodromal and probably in the perinatal period (Arango & Kahn, 2008; Woods et al., 1996).

3.3.1. Clinical High Risk

Velakoulis et al. (2006) reported smaller total brain volumes for UHR subjects as compared to HC. However, Voxel Based Morphometry (VBM) studies by Fornito (2008), Thompson (2007), and Ziermans (2009) did not replicate the finding of a smaller total brain between the UHR group and HC. Although Velakoulis et al. (2006) demonstrated decreased whole brain volumes, their intracranial volume (ICV) measurements yielded no differences between UHR groups. Moreover, in the same study by Velakoulis, when the HR-p was contrasted with the HR-np group, they demonstrated *enlarged* whole brain volumes for the HR-p (Velakoulis et al., 2006).

3.3.2. Familial High Risk

In a study by Lawrie et al. (2001), three HR groups were made based on familial liability (HR-high proximal familial risk, HR-proximal and distal familial risk and HR-distal familial risk). By dividing their HR group according to familial liability, they demonstrated a trend toward a negative association; higher familial liability equals smaller total brain volume (p = .07). Further dividing their HR-np group in subthreshold psychotic symptom experiences, Lawrie et al. (2001) also demonstrated smaller total brain volumes for HR-nps than HR-npns. This is in line with the UHR study by Velakoulis (2006) who also demonstrated smaller total brain volumes for the HR sample as compared to the HC. However, when further dividing the HR-np group into the experience of subthreshold psychotic symptoms, Lawrie et al. (2001) observed opposite findings of that of Velakoulis (2006); for the HR-nps, Lawrie (2001) reported enlarged total brain volumes as opposed to HR-npns.

At baseline cross-sectional comparisons (Lawrie et al., 2002) and also in their longitudinal set-up (follow-up approximately 2 years) (Job et al., 2005), using the conventional VBM method, Job et al. (2005) found no differences between groups. However, Job et al. (2005) also analysed their structural MRI data with an alternative method, in order to overcome some of the limitations of the traditional VBM method. In functional MRI data analysis, a frequently applied method is the within-group masking method (e.g. Critchley et al., 2000; Morcom et al., 2003). In their 2005 study, Job et al. applied this method of analysis on structural MRI data. In short, by using this alternative

method, groups are not directly compared, but any significant area of change in the second group, e.g. the control group, is excluded leaving only changes exclusive to the primary group, e.g. the at risk group, in the statistical assessment. In other words, the longitudinal changes found in the control group mask the longitudinal changes observed in the HR group, and the changes that are unique for the HR group will therefore not be masked and left in the statistical analysis (Job et al., 2005). By using the within-group masking method, Job et al. (2005) demonstrated that there was a differential spatial pattern of cortical development for the HR group, specifically resulting in a decrease of GM volume from baseline to two-year follow-up, which significantly differed from the HC group.

3.3.3. Genetic Disorders

Whereas whole brain findings are inconclusive from the clinical and familial high risk point of view, within the genetic disorder approach the finding of smaller total brain volumes for VCFS patients is replicated by several cross-sectional VBM studies (Bearden et al., 2004; Campbell et al., 2006; Eliez et al., 2001a,b, 2002; Kates et al., 2005, 2006b).

3.4. Frontal lobe

In previous studies, the morphology and functionality of the frontal cortex, and especially the prefrontal cortex, has been suggested as neurobiological correlate of the positive psychotic symptoms, such as the presence of auditory hallucinations (Gothelf et al., 2005). Therefore, this area might be implicated as a relevant neurobiological precursor of psychosis in the studies included in this review.

3.4.1. Clinical high risk approach

The differences in brain volumes between UHR-p and UHR-np were investigated by Pantelis et al. (2003). For the UHR-p, they demonstrated reductions in GM volume for right inferior frontal gyrus (IFG), and a trend in GM volume reduction in the left IFG. Furthermore, a trend in GM volume reduction was found for the dorsolateral prefrontal cortex (dlPFC) (Pantelis et al., 2003). Regarding the longitudinal findings from Pantelis

et al. (2003), they found a larger reduction in GM volume over 12 to 18 months for the UHR-p as compared to UHR-np for the left orbitofrontal cortex (OFC).

The dlPFC was studied in more detail by Sun et al. (2009), who used cortical pattern matching in order to compare brain surface contraction between UHR-p and UHR-np. They acquired baseline and one year follow-up MRI data, with which they demonstrated a greater contraction in bilateral dlPFC for the UHR-p, with a maximum magnitude of 0.4 mm per year. Overall, in the between-group comparisons, prefrontal regions showed the most prominent difference in reduced contraction.

However, no differences in GM volume between UHR and HC were found by Ziermans et al. (2009).

3.4.2. Familial high risk approach

In a study by Lawrie et al. (2001), already mentioned before for their whole brain findings, three HR groups were made based on familial liability. For the HR-high proximal familial risk group, bilateral prefrontal cortex (PFC) volume reductions were found as compared to HC. Furthermore, when only focussing on the HR subgroups, a tendency to negative association between genetic liability and bilateral PFC regions was found.

3.4.3. Genetic high risk approach

Several studies found reductions in GM volume within the frontal lobe for the HR group, as compared to HC (Eliez et al., 2000; Giedd et al., 2007; Schaer et al., 2006). However, Kates et al. (2004) found *increases* in GM volume for the frontal lobe, although, when manually based measures were used to assess frontal lobe volume, no differences were found.

In a later study by Kates et al. (2005), they observed a reduction in GM volume within the frontal lobe, but only in the male patient group. Furthermore, a trend toward reduced dlPFC volume for VCFS patients was found. Another year later, Kates et al. (2006b) confirmed the trend by demonstrating significant PFC reductions in VCFS patients as compared to healthy siblings and controls.

In another study published in 2006(a) by Kates et al., they investigated PFC volume in VCFS patients, focussing on COMT polymorphisms. They observed that female VCFS-patients hemizygous for the Val-allele and male VCFS-patients hemizygous for the Met-allele had reduced dorsal PFC volumes, compared to female VCFS-patients hemizygous for Met-allele and male VCFS-patients hemizygous for Val-allele. Concerning the orbital PFC, female VCFS-patients hemizygous for Met-allele and male VCFS-patients hemizygous for Val-allele had a reduced volume compared to female VCFS-patients hemizygous for Val-allele and male VCFS-patients hemizygous for Met-allele (Kates et al., 2006a).

Providing a longitudinal insight, Gothelf et al. (2005) demonstrated PFC reductions over a time-period of approximately 5.2 years within the VCFS group that were associated with COMT Met-allele and increased risk of developing psychosis. In a later study by Gothelf (2007a), they contrasted the patient group with idiopathic developmental disability control subjects, and found no difference between groups regarding PFC development over a follow-up period of 5 years.

3.5. Temporal lobe

GM decreases in temporal lobe regions, especially the middle temporal lobe regions such as the hippocampus and the amygdala, have been repeatedly associated with schizophrenia and bipolar disorder. However, this has not yet been established with structural MRI results, these studies are inconclusive or contradicting (Velakoulis et al., 2006). Furthermore, the superior temporal gyrus (STG) has been replicated in various structural MRI studies as reduced in the at risk groups (Takahashi et al., 2009b). Abnormalities in the STG and its subregions have been repeatedly described in schizophrenia research as to correlate with auditory hallucinations or thought disorder (Rajarethinam et al., 2000).

3.5.1. Clinical High Risk

Borgwardt et al. (2007), Jung et al. (in press) and Takahashi et al. (2009b) demonstrated significant decreases in GM volume in HR subjects in the STG, while compared to HC.

On the contrary, *increases* in the UHR-p group were found as opposed to the UHR-np for the fusiform gyri and posterior temporal region bilaterally (Borgwardt et al., 2007).

Concerning middle temporal lobe regions, the studies of Borgwardt et al. (2007) and Pantelis et al. (2003), comparing UHR-p with UHR-np and UHR with HC respectively, reported decreases in the medial temporal lobe regions. On the contrary, *increases* in the UHR-p group were found for the parahippocampus region bilaterally (Borgwardt et al., 2007).

Furthermore, decreases for UHR-p group in the lateral temporal region were also observed by Pantelis et al. (2003), while comparing UHR-p with UHR-np.

No differences in GM volume between HC, UHR, UHR-p and UHR-np were found by Velakoulis et al. (2006) and Ziermans et al. (2009).

Regarding the longitudinal research, Pantelis et al. (2003) and Takahashi et al. (2009b) measured GM volume over a period of 12 - 20 months in a UHR-p and UHR-np group. Both studies observed a greater reduction in GM volume over time for UHR-p within the left parahippocampal gyrus and left fusiform gyrus (Pantelis et al., 2003) and STG (Takahashi et al., 2009b).

3.5.2. Familial High Risk

Greater reductions for the HR group as compared to controls have been demonstrated over a time period of two years within the bilatereral fusiform gyrus, bilateral middle temporal gyrus, bilateral inferior temporal gyrus (ITG), right STG, bilateral parahippocampal gyrus, and lateral border of left amygdala (Job et al., 2005), and the right temporal lobe was observed as greater reduced in the HR-p group as compared to HR-np (Lawrie et al., 2002). Job et al. (2006) further concluded that the ITG had the best positive predictive value (60%) and best negative predicted value (92%) for the development of psychosis.

Johnstone et al. (2005) performed a follow-up of the participants whose baseline data were reported in the article by Lawrie et al. (2001). Contradicting the results by Job et al. (2005, 2006) and Lawrie et al. (2002), no correlations were found that could associate the

Amygdala-Hippocampus Complex volume difference and the presence of psychotic symptoms (Johnstone et al., 2005).

3.5.3. Genetic Disorders

The two studies by Eliez (2001a) and Giedd (2007) also found reductions in temporal lobe volume in the patient-group, as compared to HC. Moreover, although predominantly for the left hemisphere, reduced volumes were found for temporal gyri when contrasting the HR group with HC (Debbané et al., 2006; DeBoer et al., 2007; Eliez et al., 2001a; Gothelf et al., 2007b; Shen et al., 2004).

On the contrary, Glaser et al. (2007) demonstrated *increased* volumes within the right fusiform gyrus in the HR group compared to HC.

3.6. Parietal lobe

3.6.1. Clinical high risk approach

Increases in inferior parietal, postcentral cortex and a smaller region within the right supramarginal gyrus were found for the HR-p group compared to the HR-np group (Borgwardt et al., 2007). Additionally, Borgwardt et al. (2007) demonstrated a significant decrease of GM volume within the bilateral precuneus for the HR sample, compared to HC.

3.6.2. Familial high risk approach

A difference between groups over time was reported in the longitudinal study by Job et al. (2005), who demonstrated a significantly different spatial pattern of reduction of GM density within the right inferior parietal lobe and left uncus for the HR group, compared to the HC group.

3.6.3. Genetic high risk approach

This parietal cortex volume reduction in the patient group was also found by Antshel et al. (2008), Eliez et al. (2000) and Schaer et al.(2006).

3.7. Occipital lobe

Using the familial high risk approach, Borgwardt et al. (2007) observed increases in medial occipital gyrus, while comparing the HR-p group with the HR-np group (Borgwardt et al., 2007). This is in accordance with the study by Shen et al. (2004). They used a genetic high risk approach by focussing on males with Klinefelter syndrome, and it was observed that in the HR group, the occipital gyri were smaller (Shen et al., 2004).

3.8. Cingulate cortex

The cingulate cortex is a brain region which is studied frequently. It is investigated as one region or divided into subregions, e.g. its anterior part (ACC) and its posterior part (PCC). It is considered to be part of the limbic lobe, separately from the frontal lobe and parietal lobe. Especially a GM reduction in the ACC has frequently been demonstrated in both clinical and familial high risk approach studies, as well as in genetic high risk studies (Job et al., 2003; Fornito et al., 2008; Shen et al., 2004).

3.8.1. Clinical high risk approach

In a study by Pantelis et al. (2003), the cingulate cortex was investigated for the subgroups UHR-p and UHR-np, over a period of 12- to 18 months. They demonstrated a larger GM volume reduction over time for the UHR-p as compared to UHR-np for the bilateral cingulate gyri. Another study by Borgwardt et al. (2007) reported significantly smaller ACC volumes for the HR-p group, as compared to the HR-np. Significant decreases were also found for the PCC for the HR sample, compared to HC.

In order to investigate changes within the cingulate cortex, Fornito et al. (2008) investigated cortical thickness of 6 ACC subregions. A thinner bilateral rostal paralimbic ACC was found for the UHR-p group, as compared to the control group, and a thicker dorsal limbic ACC for the UHR-np group. When comparing the UHR-p with the UHR-np, the former group demonstrated significant thinner bilateral rostal limbic ACC. In order to assess the predictive value of the ACC thickness, Cox regression was used which revealed that 1mm thickness decrease in overall ACC equals 20% increase in risk for developing psychosis (Fornito et al., 2008).

3.8.2. Familial high risk approach

McIntosh et al. (2007) focused on a COMT polymorphism and its consequences for the risk of developing psychotic symptoms. They demonstrated that individuals hemizygous for the Val-allele had significantly less GM within the ACC, although it was not possible to determine whether this effect of the Val-allele on the ACC is developmentally mediated or is part of an ongoing pathological process.

The reduction within the left cingulate gyrus, as demonstrated in the clinical HR studies, has also been observed in the study by Job et al. (2005), using the within group masking method. This reduction was observed for the HR group only (Job et al., 2005), using the HC group differences over time as a mask.

3.8.3. Genetic high risk approach

Further evidence for smaller ACC volumes for the HR group were demonstrated by Shen et al. (2004), who compared male patients with Klinefelter syndrome with HC.

3.9. Insular cortex

The insular cortex has been suggested to play a crucial role in emotion and various cognitive functions. It is considered to be a part of the limbic integration cortex (Augustine, 1996) and has been repeatedly described in schizophrenia (Takahashi et al., 2004, 2005). GM reduction in the insular region has been associated with the manifestation of psychotic symptoms (Shapleske et al., 2002) and cognitive impairments (Crespo-Facorro et al., 2001,a,b,c). Therefore, the insular cortex could be a potential marker of later transition to psychosis (Takahashi et al., 2009).

3.9.1. Clinical high risk approach

In the studies by Borgwardt et al. (2007) and Pantelis et al. (2003), and in the ROI study by Takahashi et al. (2009a), they investigated the volume of the insular cortex. Using a cross-sectional design, they observed a smaller bilateral insula when the HR-p was compared to HR-np, and a smaller right insula for the UHR-p compared to HC. Furthermore, Takahashi et al. (2009a) divided the insular region into a long and a short

insular cortex. When the two regions were analysed separately, they found a reduction in volume in the right hemisphere short insula in UHR-p, compared to the long insula.

In the 2009(a) study by Takahashi et al., besides the cross-sectional results mentioned before, they also followed an UHR and HC group for a period of 1- to 4 years. After this follow-up period, they measured the volume of the insular region and demonstrated an increased reduction of GM volume of the insular cortex for the UHR-p as compared to either HC and UHR-np.

3.9.2. Familial high risk approach

The study by Shen et al. (2004) demonstrated a more reduced volume of the left insular region for the HR group, which is in accordance with the results of Pantelis et al. (2003).

3.10. Cerebellum

3.10.1. Clinical high risk approach

In the 2003 longitudinal study by Pantelis et al., they observed a greater GM volume reduction of the left cerebellar cortex over time for the UHR-p as compared to UHR-np. They also found a significant *increase* in GM volume of the left cerebellar cortex for the UHR-np group over time (Pantelis et al., 2003).

3.10.2. Genetic high risk approach

The cerebellum was a focus of investigation in the cross-sectional studies by Campbell et al. (2006) and Gothelf et al. (2007b). They observed a reduction in cerebellar regions in subjects with VCFS, as compared to healthy control subjects and healthy siblings.

3.11. Thalamic nuclei, ventricular system and adhesio interthalamica

In a review by Shenton et al. (2001), ventricular enlargement and reductions in the thalamus have been described among the most commonly observed deviant findings in studies which investigate the neural substrates of schizophrenia (Campbell et al., 2002). Since this review, a decade of new research has also focused on these subcortical regions, and these recent findings are mentioned below.

3.11.1. Clinical high risk approach

The adhesio interthalamica (AI), a narrow bridge of glial cells connecting the medial surfaces of the thalami, was studied by Takahashi et al. (2008), especially its presence, length and correlation with ventricular enlargement. Takahashi et al. (2008) demonstrated that the length of the AI was smaller for both the UHR-np and UHR-p groups as compared to the control group. The presence or absence of the AI was not different between groups. AI length is negatively correlated with ventricular enlargement in all groups, while Pantelis et al. (2008) found signifcant group enlargement of the ventricular system in UHR subjects compared to HC in the same sample.

Furthermore, increases in a smaller region comprising the red nucleus and thalamus, was found for the HR-p group compared to the HR-np group (Borgwardt et al., 2007).

3.11.2. Familial high risk approach

In the study by Lawrie et al. (2001), already mentioned before, three HR groups were made based on first and second degree affected relatives. They observed that the bilateral thalamic region was significantly smaller for the distal familial risk-group as compared to HC, and the right thalamic region was reduced in volume for the proximal and distal HR contrasted with HC. They concluded that there was a tendency towards a negative association between genetic liability and right thalamus volume (p = .13) (Lawrie et al., 2001).

Based on the findings of a study by Lawrie et al. (2002), Johnstone et al. (2005) performed a follow-up of the same population for the same ROIs which were found to be significantly different in their first study. Johnstone et al. (2005) found a significant reduction of the left thalamic nucleus volume in the HR-p group compared to controls over time.

3.11.3. Genetic high risk approach

Eliez et al. (2000) observed an increased ventricle-to-brain ratio in VCFS-patients, and several studies investigating differences between Klinefelter syndrome patients and HC have found an increase in ventricle size in the patient group (Bearden et al., 2004; Campbell et al., 2006; Giedd et al., 2007; Shen et al., 2004; Warwick et al., 1999).

3.12. Other findings

3.12.1. Pituitary

Another region of interest is the pituitary, a gland which, among others, secretes adrenocorticotrophic hormone (ACTH), due to the secretion of ACTH-releasing factor (CRF) from the hypothalamus. ACTH subsequently stimulates the secretion of glucocorticoids from the adrenal cortex, which, in turn interacts with receptors in multiple target tissues, also forming a feedback loop back. This cascade is known as the hypothalamic-pituitary-adrenal (HPA) axis, and is involved in psychiatric disorders. However, the mechanisms underlying its abnormalities are still unclear.

Hyperactivity of the HPA axis has been demonstrated by increased levels of cortisol and ACTH in patients who are in the acute phase of a psychotic disorder, at their first-episode, but also in patients with recent onset psychosis and in HR subjects (Pariante, 2009).

Consistent with these findings, Garner et al. (2005) who investigated the pituitary volume using the clinical high risk approach, found an increased pituitary volume for the UHR-p group who were close to transition, as compared to the UHR-np and HC groups. With a Cox regression it was furthermore demonstrated that $10mm^3$ increase in pituitary volume equals a 6% increase in risk for developing psychosis, i.e. 10% increase in pituitary volume equals 20% increase in risk for developing psychosis (Garner et al., 2005).

In order to further investigate the role of the pituitary within the HPA-axis, Thompson et al. (2007) investigated HPA-axis dysfunction as a potential candidate marker for the development of psychotic symptoms. They correlated GM volumes of the pituitary with plasma cortisol levels and glucocorticoid receptor numbers. However, no significant correlations were found.

3.12.2. Basal Ganglia

3.12.2.1. Clinical high risk approach

The basal ganglia are a group of subcortical nuclei which have been studied both as one region and as individual nuclei. In a study by Pantelis et al. (2003), they investigated the

GM volume of the basal ganglia, and demonstrated decreased volumes for the UHR-p group as compared to the UHR-np group for bilateral basal ganglia (Pantelis et al., 2003).

3.12.2.2. Familial high risk approach

In the study by Lawrie et al. (2001), it was observed that the lentiform nuclei (comprising the putamen and the globus pallidus) were bilaterally smaller in volume for the proximal and distal familial risk-group as compared to HC, and the left lentiform nuclei was significant smaller for the distal familial risk as compared to HC.

Another region of interest was found by Rajarethinam et al. (2007), who focused on the caudate nucleus. They compared subjects who had at least one parent with schizophrenia and thus are at familial HR for developing a psychotic disorder, with healthy control subjects. The familial HR subjects demonstrated a significantly smaller right caudate GM volume and a trend toward a significantly smaller left caudate.

3.12.2.3. Genetic high risk approach

In the studies by Campbell et al. (2006) and Eliez et al. (2002), an enlarged right caudate volume for the VCFS group was demonstrated, as compared with healthy siblings and control subjects. Furthermore, Kates et al. (2004) found a trend towards significant reversed asymmetry with the right caudate being larger than the left caudate for the VCFS group.

3.12.3. Corpus callosum

The corpus callosum was studied by Walterfang et al. (2008b), using the clinical high risk approach. No group differences were found for total area, length and curvature of the corpus callosum. However, after the corpus callosum was divided into 40 segments, a significant decrease in callosal thickness was demonstrated for the UHR-p group as compared to the control group for the anterior and posterior genu. Furthermore, the UHR-p had a significant smaller anterior genu and a trend was found for a smaller posterior genu as compared to the UHR-np. When analysed using Cox regression, it was observed that one millimetre reduction in mean thickness anterior genu equals a 52% risk increase of transition to psychosis (Walterfang et al., 2008b).

Antshel et al. (2005) also focused on the corpus callosum, using a genetic high risk approach, and found an increase in callosal volume for the VCFS group, as compared to controls.

3.12.4. Cavum Septum Pellucidum

In their 2008 study, using the clinical high risk approach, Choi et al. investigated prevalence and length of the cavum septum pellucidum (CSP) in subjects at UHR for psychosis. No differences between groups were found. However, when categorizing the CSP in 4 grades ranging from normal to abnormal (Degreef et al., 1992), they found that the UHR sample showed a significant higher incidence of abnormal CSP than in the HC group.

3.13. Cortical thickness

3.13.1. Clinical high risk approach

In a recent cross-sectional study by Jung et al. (in press), measurements of mean cortical thickness did not yield any significant differences between UHR and HC. However, there were some regional reductions in cortical thickness for the UHR while compared to HC subjects. This thinning of the cortex was observed in the right inferior frontal cortex and medial frontal cortex, the right middle temporal cortex and the parahippocampal cortex, bilateral ACC, the right lingual and parietal cortices (Jung et al., in press).

3.13.2. Genetic high risk approach

Schaer et al. (2009) used a longitudinal design to measure cortical thickness over a time period of approximately three years. They observed deviant trajectories of cortical thickness changes with age in VCFS subjects, as compared to healthy controls, in which the VCFS had thinner cortices. However, they found no effect for COMT polymorphism on cortical maturation (Schaer et al., 2009).

3.14. White matter, voxel based morphometry studies

VBM is a conventional neuroimaging analysis technique that allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping (Ashburner and Friston, 2000).

3.14.1. Clinical high risk approach

Walterfang et al. (2008a) focused on differences between UHR-p and UHR-np, investigating if white matter (WM) volume is a possible predictor of transition to psychosis. They observed that UHR-p had a significantly larger WM volume than UHR-np for the left premotor cortex. A trend toward increased WM volume in the homologous region in the right hemisphere was also found. Furthermore, they demonstrated a significantly increased WM volume in a region adjacent to left frontal operculum and SLF, and a trend in homologue in right hemisphere.

Walterfang et al. (2008a) did not report any decreases in WM volume for the UHR-p group in their baseline measurements. In the longitudinal part of their study, Walterfang et al. (2008a) observed WM volume decreases over a period of 12 – 18 months follow-up, within the UHR-p group as compared to UHR-np. These WM volume decreases were found in two regions, one within the left parietal lobe, near the fronto-occipital fasciculus, and a second region subjacent to calcarine cortex. Furthermore, Walterfang et al. (2008a) reported increases in WM volume for the UHR-p within the bilateral posterior cerebellum. The UHR-np demonstrated significant decreases over time for the left posterior cerebellum and an area subjacent to right inferior parietal lobule, which was not seen in the UHR-p group.

In contrast, no differences in WM density were found for UHR as compared to HC by Ziermans et al. (2009).

3.14.2. Genetic high risk approach

A reduction in total brain WM volumes was found by the VBM studies performed by Eliez et al. (2001a, 2000), Gothelf et al. (2007b), and Shen et al. (2004), focusing on the comparison of genetic syndrome patients and HC.

This reduction was also found for the right parietal lobe after correction for total brain volume (Barnea-Goraly et al., 2005, 2003; Eliez et al., 2001a, 2000; Gothelf et al., 2007b; Shen et al., 2004). In addition, Barnea-Goraly et al. (2005, 2003) observed that a VCFS specific WM decrease in posterior parietal regions (not seen in controls) is positively correlated with the arithmetic performance in VCFS.

Frontal lobe regions have also been demonstrated to have reduced WM volumes for the HR group as compared to a healthy sibling group (Bearden et al., 2004; Campbell et al., 2006; Giedd et al., 2007).

Further reductions in WM volumes for the HR group as compared with a healthy sibling group were found for the cerebellum and internal capsule (Bearden et al., 2004; Campbell et al., 2006).

On the contrary, increases in WM were also demonstrated. Antshel et al. (2008) found an increase in WM in the frontal lobe and Giedd et al. (2007) found an increase in WM for the patient group within parietal regions, results which were in agreement with the clinical high risk study by Walterfang et al. (2008a) mentioned above.

3.15. White matter, diffusion tensor imaging studies

In addition to WM volumetric measurements, conventionally performed with VBM studies, new MR-based imaging techniques can detect changes in white matter microstructure based on properties of diffusion (Pierpaoli et al., 1996). Diffusion of water in white matter tracts is affected by myelin and the orientation and regularity of fibers and provides an index of brain connectivity. Diffusion tensor imaging (DTI) is the neuroimaging technique in which this brain white matter (WM) structure can be assessed. The degree of fractional anisotropy (FA) in a voxel indexes white matter integrity, potentially reflecting both myelination and tract organization (Ciccarelli et al., 2003).

3.15.1. Clinical high risk approach

Karlsgodt et al. (2009) investigated whether FA values differ at baseline measurements between an UHR sample and HC. They demonstrated a significant reduction in FA values within the superior longitudinal fasciculus (SLF) for the UHR group. When age

was included as covariate, they found that older HC had increased FA values in the medial temporal lobe, but this positive correlation was not found in the UHR group (Karlsgodt et al., 2009). Furthermore, over a period of 6 months after the baseline measurements, Karlsgodt et al. (2009) observed a marginally significant association between lower FA values in left and right inferior longitudinal fasciculus (ILF) and a decline in social functioning on the Global Functioning: Social scale (GFS). After 15 months, the association became even more pronounced, demonstrated by a significant association between lower FA values in right ILF and deterioration in Global Functioning: Role scale and GFS.

Peters et al. (2008) also investigated WM integrity using DTI and compared UHR and HC groups. After controlling for medication, they did not observe differences in FA values or trace between the groups in any of the fibertracts, contradictory to the study of Karlsgodt et al. (2009). When analyzing the data of medication naive subjects only, the sample size became too small to examine possible significant differences (Peters et al., 2008). However, a year later, Peters et al. (2009) presented preliminary evidence for reduced white matter integrity as a biomarker for UHR at psychosis. They found reduced FA values within the UHR sample, as compared to the HC sample, predominantly in the frontal lobe (Peters et al., 2009).

In the 2009 study by Bloemen et al., reduced FA values were observed in the left and right superior frontal lobes within the UHR sample. This was in agreement with the findings reported by Peters et al (2009). Post hoc, Bloemen et al. (2009) found a reduction of FA values in the UHR-p group compared to the UHR-np group in a region lateral to the right putamen and STG. Furthermore, a positive correlation was found in the UHR group relating the severity of positive psychotic symptoms to a reduction of FA values in the right STG. Moreover, Bloemen et al., (2009) also demonstrated *increased* FA values for the left medial temporal lobe, for the UHR-p group while compared to the UHR-np group.

3.15.2. Genetic high risk approach

In agreement with the clinical HR studies of Bloemen et al. (2009) and Peters et al. (2009), Barnea-Goraly et al. (2005, 2003) also demonstrated a reduction in FA values in

bilateral PFC tracts, the external capsule and the splenium for the VCFS cohort as compared to HC.

4. Discussion

The purpose of this review was to investigate potential neurobiological markers that predict the onset of psychosis. We investigated neuroanatomical abnormalities of various groups at increased risk for developing psychosis. These studies have been reviewed before (see for example: Owens and Johnstone, 2006; Pantelis et al., 2007; Smieskova et al., 2010). However, they focused on clinical high risk and familial high risk cohorts, as well as first episode patients and chronic schizophrenia patients of all ages. In this review, we additionally included results from various genetic disorder studies. In some genetic disorders, it has been proven that the incidence of psychotic disorders is high, thereby providing a unique situation to associate behaviour to genetic makeup and derive macroscopic neurobiological abnormalities. To our knowledge, this has been the first attempt to combine the clinical and familial high risk studies with genetic disorder studies. Furtermore, this review focuses on adolescence. Prodromal signs are present approximately 5 years prior to the onset (Häfner and Maurer, 2006), and onset of psychosis occurs generally at young adulthood. This indicates that prodromal research should aim at adolescence. Therefore, we focused on reviewing studies that used a sample within the mean age range of 10 – 24 years old.

By comparing the developmental neurobiological changes within, and between the studies from the three different approaches (i.e. clinical, familial and genetic HR approaches), results might elucidate the neurobiological changes which constitute to the eventual onset of psychosis, thereby creating a more coherent scope of potential neuroanatomical precursors of psychosis research.

Reviewing the findings from the clinical and familial high risk studies, the results regarding whole brain volumes and thickness remain inconclusive. However, when also taking into account the findings from the genetic disorders, a reduced total brain volume is frequently reported for the at risk sample. Although this finding is difficult to interpret, it has been suggested that a reduced whole brain volume indicates the occurrence of various anatomical changes, prodromal and probably in the perinatal period (Arango & Kahn, 2008; Woods et al., 1996). Furthermore, it might suggest that multiple neuropathological processes occur at the same time, indicating the need for a multiple

pathway model to predict the onset of psychosis, in which various factors and predictors interplay to enhance the chance of accurately predicting the onset of psychosis (Pantelis et al., 2005).

In the frontal lobe regions, three areas are repeatedly observed to be reduced in volume, the inferior frontal gyrus (IFG), the prefrontal cortex (PFC) and the orbitofrontal cortex (OFC). These reductions are found in studies from all three approaches. The frontal cortex, and especially the PFC, has been suggested to play a more crucial role in the actual transition to psychosis (Sun et al., 2009). Furthermore, it is important to note that regardless of a risk for developing a psychosis, it has been demonstrated that the maturation of the brain of healthy controls is a dynamic process in itself. This maturation starts during childhood in posterior regions and progresses toward anterior brain regions, ending at late adolescence and young adulthood with maturation of the prefrontal cortex (Pantelis et al., 2007; Paus et al., 1999; Paus, 2005). This maturation includes increased myelination, synaptic proliferation and pruning, as well as subtle loss of gray matter volume (Pantelis et al., 2007; Paus et al., 1999; Paus, 2005; Sun et al., 2009).

Reductions in the temporal lobe, and predominantly the superior temporal gyrus (STG), are consistent findings in structural neuroimaging studies of schizophrenia. The STG is the site of the primary and secondary auditory cortex, and abnormalities in this region have been associated with the presence of auditory hallucinations (Eliez et al., 2001b; Lawrie and Abukmeil, 1998; Pandya, 1995; Takahashi et al., 2009b). Morphological and functional abnormalities within the STG and its subregions have been repeatedly described in schizophrenia (e.g. Borgwardt et al, 2007; Garner et al., 2005; Velakoulis et al., 2006), and especially volumetric decreases predominantly in the left hemisphere have been found to correlate with auditory hallucinations and thought disorder (Rajarethinam et al., 2000; Takahashi et al., 2009b). Also in this review, there are various studies which replicate the finding of smaller STG or STG subregions for the HR-p group (Borgwardt et al., 2007; Job et al., 2005; Jung et al., in press; Takahashi et al., 2009b). These findings suggest that a regional progressive pathological process in the STG precedes the onset of psychosis, and the extend of the neuropathology within the STG may reflect the severity of positive symptomatology during the early course of psychosis.

Two studies demonstrated increased volumes for the fusiform gyrus (Borgwardt et al., 2007; Glaser et al., 2007), whereas other studies reported decreased volumes regarding the left fusiform gyrus (Job et al., 2005; Pantelis et al., 2003). The fusiform gyrus has been found in fMRI studies to activate in tasks regarding facial identity and expression, suggesting a central role for the fusiform gyrus within the development of social cognition (Haxby et al., 2000; Grossmann and Johnson, 2007). As a consequence, fusiform gyrus dysfunction has been suggested as a key to understanding socio-emotional deregulation in individuals with schizophrenia (Glaser et al., 2007; Gur et al., 2002). Further studies are necessary to investigate the exact role of the fusiform gyrus in the development of the prodromal phase.

The anterior part of the cingulate cortex (ACC) has frequently been demonstrated to be smaller in GM volume for the at risk subjects in all three approaches (Job et al., 2003; Fornito et al., 2008; Shen et al., 2004). The ACC has been implicated in conflict detection and error monitoring, and it has been postulated that to a certain extent, a deviant contribution of the ACC might lead to disturbances in the ability to detect conflict or errors in ongoing processing. This in turn may lead to deficits in the ability to regulate and control a range of other executive functions which are frequently seen in schizophrenia (Barch, 2005). The findings from this review are in line with this theory, as the ACC is frequently observed to be reduced within the at-risk populations who later develop psychosis, both in cross-sectional and longitudinal design studies from all three approaches (Borgwardt et al., 2007; Fornito et al., 2008; Job et al., 2005; Jung et al., in press; Pantelis et al., 2003; Shen et al., 2004; Yücel et al., 2003). In order to assess the predictive value of the ACC thickness, Fornito et al. (2008) used a Cox regression which revealed that 1mm thickness decrease in overall ACC equals 20% increase in risk for developing psychosis (Fornito et al., 2008).

The suggestion of a possible pituitary enlargement in the upcoming onset of psychosis, has been postulated by several authors, also mentioned in this review (Garner et al., 2005; Pariante, 2009; Thompson et al., 2007). Garner et al. (2003) did report the presence of enlarged pituitary volumes in their HR-p sample, and further elaborated on this finding by suggesting that distress and arousal of the (incipient) psychotic experience could activate the stress response in HR-p subjects, or alternatively, that a larger volume could

represent an activation of the stress response by the environment in the phase preceding the onset of psychosis. However, in the study by Thompson et al. (2007), there was no association with levels of plasma cortisol levels or number of glucocorticoid receptors with prodromal signs. This contradicts with the theory postulated before. However, Thompson et al. (2007) argue that in their sample, the HPA axis hyperactivity-absence could be explained because of their low transition rate (i.e. 5 of 23 subjects had developed an acute psychotic episode within two-years from recruitment).

Another perspective on precursors of psychosis is research concerning possible genetic loci for schizophrenia. The *COMT* gene is an example of a locus which has received considerable attention in schizophrenia research and has been independently replicated in various studies (Egan et al., 2001; Eisenberg et al., 2010; Lewis et al., 2003; Männistö & Kaakkola, 1999). The catechol-O-methyltransferase (COMT) protein is encoded by the *COMT* gene, located on chromosome 22q11.2, a region frequently implicated in genome scans of schizophrenia and VCFS (Grossman et al., 1992; Lewis et al., 2003). The COMT protein is involved in the metabolism of catecholamines such as dopamine (Caspi et al., 2005). In turn, dopamine transmission has been observed to be increased in patients with schizophrenia, including medication naive patients and patients experiencing their first psychotic episode (Seeman and Kapur, 2000). Furthermore, antipsychotic medications have a high affinity for dopamine receptors (D2 receptor form), and because of the antagonistic effect, the medication blocks the dopamine receptors, in turn increasing levels of dopamine (Seeman, 1987). These findings suggests that elevated dopamine transmission could be an important part of the aetiology of schizophrenia (Kandel et al., 2000, chap. 60).

A functional polymorphism of the *COMT* gene results in the substitution of the amino acid valine (Val) for methionine (Met) at codon 158 in the COMT enzyme (Caspi et al., 2005; Lotta et al., 1995). It has been demonstrated that the Val variant breaks down dopamine approximately 4 times faster than the Met variant, thus the substitution leads to less enzymatic activity and slower break down of dopamine (Lotta et al., 1995). Since there are relatively low numbers of dopamine transporters in the PFC in the typically developing brain (Morón et al., 2002), the effect of the *COMT* gene polymorphism is particular large this brain region (Caspi et al., 2005; Seamans and Yang, 2004). It has

been suggested that the high activity Val allele is associated with inefficient prefrontal functioning and poor working memory performance in both healthy subjects and schizophrenia patients (Egan et al., 2001; Ho et al., 2005). Although it remains predominantly inconclusive, there is a small number of studies that provide evidence to establish the Val allele as a susceptibility factor for schizophrenia (Allen et al., 2008; Eisenberg et al., 2010; Fan et al., 2005). In contrast, in the longitudinal VCFS study by Gothelf et al. (2005), they suggested the low activity Met allele as a risk factor for decline in prefrontal cortical volume and cognition, and for the development of psychotic symptoms during adolescence. Further complicating these results is a PFC subregion * gender * allele interaction, demonstrated in the 2006(a) VCFS study by Kates et al. They observed a reduced dorsal PFC volume for female the Val-allele patients and male Met-allele patients, and the opposite for a reduced orbital PFC: female Met-allele patients and male Val-allele patients. Concerning the orbital PFC, female VCFS-patients hemizygous for Met-allele and male VCFS-patients hemizygous for Val-allele had a reduced volume compared to female VCFS-patients hemizygous for Val-allele and male VCFS-patients hemizygous for Met-allele (Kates et al., 2006a).

Nevertheless, the PFC has been repeatedly observed in this review to be smaller in subjects at risk for psychosis, regardless of the approach was based on clinical, familial or genetic disorder high risk (Eliez et al., 2000; Giedd et al., 2007; Jung et al., in press; Kates et al., 2004, 2005, 2006a,b; Lawrie et al., 2001; Pantelis et al., 2003; Schaer et al., 2006; Sun et al., 2009). The exact role of the PFC within the development of psychosis is difficult to establish, as maturation of the PFC develops in parallel to the gradual onset of psychosis, thereby confounding the cross-sectional results. Longitudinal results might therefore provide better insights in the role of the PFC in the prodromal phase. However, the consistent finding of reduced PFC volumes is in line with the research on COMT genotype and further establishes a neurobiological consequence of genetic malfunctioning (McIntosh et al., 2007). Future research might aim at hypothesising and studying possible associations between VCFS and Klinefelter syndrome with the COMT genotype, and linking these pathways to the development of psychosis. In line with this future direction, Coman et al. (in press) studied the effects of the COMT genotype on PFC activation in patients with VCFS, and they suggested that in VCFS, the effect of the

Val allele is moderated by gender during the processing of emotional stimuli; girls activated the cingulate gyrus more than boys did. This result could be contributable to the understanding of the way in which the Val allele affects vulnerability to neuropsychiatric disorders (Coman et al., in press; Kates et al., 2006a; McIntosh et al., 2007). Furthermore, the study by Coman et al. (in press) suggests that the Val allele affects the activity of the cingulate gyrus, another frequently observed brain region reported to be smaller in various HR samples (Borgwardt et al., 2007; Job et al., 2005; Fornito et al., 2008; Jung et al., in press; McIntosh et al., 2007; Pantelis et al., 2003; Yücel et al., 2003). The anterior part of the cingulate cortex (ACC) has at least 3 major functional subdivisions of the ACC, i.e., affective, cognitive and motor components, and plays a crucial role in monitoring and detecting conflict in ongoing information processing (Botvinick et al., 2001; Yücel, 2003). Because of its diversity, it is often related to cognitive functions such as decision making, which is frequently affected in schizophrenia. Decreased volume, neuronal density, and activation of the ACC are consistently observed in schizophrenia (Yucel et al., 2002). The cingulate cortex and PFC have been implicated to work together in one network (Barch, 2005). However, this connectivity between the PFC and cingulate cortex has not been found using a DTI-study by Hao et al. (2009).

Concluding, there is accumulating evidence for structural brain abnormalities, especially within the prefrontal regions and ACC, which could implicate that a malfunctioning interactive network of prefrontal regions and anterior cingulate (sub)regions might be associated with the gradual onset towards psychosis. This is further established by the genetic disorder studies which explain the (chemical) degradation of various parts of the network. Future research should aim at further investigating this network with more subtle new imaging techniques such as DTI and magnetization transfer imaging.

4.1. Methodological issues and limitations

The current review acknowledges that various limitations must be noted when comparing results of the three different approaches that were used in this review.

First, there is a conceptual problem with studying the prodromal phase, as it is difficult to exactly define the prodromal phase. The boundary between healthy and pre-illness is vague, and since there is also a lack in what exact event constitutes the shift towards illness, the borders between healthy, prodrome and illness are difficult to define (Owens and Johnstone, 2006). Elaboration on this conceptual issue reveals that there is a substantial difference between research centres regarding the definition of transition to psychosis. For example, the Edinburgh High Risk Studies (EHRS) defined transition as when patients met criteria for the diagnosis of schizophrenia. Therefore, the conversion rate was based on the number of high risk individuals who were diagnosed with a schizophrenia spectrum disorder. This contradicts with the Melbourne Ultra High Risk (UHR) studies, which practised a different, more broad focus and therefore used a lower threshold as definition for transition, leading to higher conversion rates and more heterogeneous samples than in the EHRS. (Pantelis et al., 2007, Owens and Johnstone, 2006).

Another issue is the difference of inclusion of at risk participants between the three HR approaches. Moreover, this difference even exists between research centers that use the same HR approach strategy for inclusion. For example, the study by Jung et al. (in press) illustrates this point. Jung et al. (in press), from a research center in Seoul, Korea specifically searched for subjects at Ultra High-Risk, thereby using the clinical HR approach as postulated by the Melbourne group. However, they excluded individuals who had a first, second or third degree relative with a psychotic disorder. This is not in line with the inclusion criteria used in the UHR studies, which do not specifically include or excluded their HR subjects based on affected family members. In the Melbourne group, the existence of an affected family member is one of the five inclusion criteria for UHR subjects. Comparing the inclusion criteria of Jung et al. (in press) with the familial HR approach, it is the exact opposite as the EHRS only include HR subjects based on familial

liability. Thus, although the centers in Seoul and Melbourne use the same abbreviation (i.e., UHR), there is an important difference between these two research centers.

There are other important methodological differences between the various research centres, leading to a complicated comparison of studies. One methodological issue is (antipsychotic) medication, which is frequently mentioned as confounder as its use has been proven to cause structural brain changes, potentially confounding the results from high risk research (Barch, 2005; Owen and Johnstone, 2006; Peters et al., 2008). In order to solve this issue, some studies focused on antipsychotic-naive participants, thereby reducing the chance of confounding results (Job et al., 2005, Pantelis et al., 2003). For instance, Velakoulis et al. (2006) looked at medication status of their sample and divided them accordingly. However, when they examined whether medication status possibly confounded their results, they found no structural differences between groups for bilateral hippocampus, bilateral amygdala or whole brain. A downside of using medication naive participants only is that sample sizes might reduce drastically, making it difficult to retrieve any significant differences between groups (Johnstone et al., 2005). Somewhat related confounding factors are gender and cannabis usage, which can be possible confounders (Walterfang et al., 2008a). However, results of studies that controlled for gender and cannabis use, do not seem to be affected (Garner et al, 2005; Takahashi et al., 2009a).

Another methodological issue is the use of cross-sectional research in children, which has been stated not to be valid at this young age, as brain maturation during childhood and adolescence is already very variable amongst healthy, typically developing children. Drawing conclusions from differences between a group of typically developing children and atypically developing children thereby needs very careful consideration (Pantelis et al., 2009). In line with this, Fornito et al. (2008) mentioned that in studies in which the overall group differences were not significant, authors tend to shift their focus to the at risk group itself, and on the differences found between baseline and follow-up. The healthy control group is thereby omitted from further statistical analysis. Furthermore, age has been a methodological issue in this review, since there was a significant age difference between the three High Risk approaches: The genetic HR approach focused on approximately 8 year younger children than the clinical and familial HR approaches. The

mean age of the subject groups within clinical HR studies was 21.32±3.22 years (range: 15.75-34.90 years), the mean age for the familial high risk approach studies was 20.59±2.09 years (range: 15.40-23.10 years), and for the genetic disorder approach, the mean age was 12.82±2.65 years (range: 10.00-21.8 years). As a consequence, comparing the results of the genetic HR studies with the other two approaches could potentially be confounded with brain maturation differences. In order to overcome this age difference, a more narrow age-range should be used to compare the three approaches, or shift the focus more towards longitudinal research, thereby surpassing cross-sectional shortcomings.

Besides the methodological issues regarding the concept of transition, inclusion criteria, and medication, the method of analysis of MRI data is important. VBM is a frequently used research method to analyse brain volumes as assessed with structural MRI. This method of analysis has received a critical note in the studies by Fornito et al. (2008) and Wood et al. (2008). Fornito concluded that VBM is restricted in its capacity to detect relatively subtle changes, and that it fails to account for the considerable inter-individual anatomic variability of small structures. Furthermore, in a review by Wood et al. (2008), it was mentioned that the VBM is inadequate to deal with problems of brain registration (Crum et al., 2003). Other methods of data analyses have been applied, such as a Region of Interest-approach and the within-group masking method (Job et al., 2005). To further explain the latter approach, Job et al. (2005) used a completely different imaging analysis, usually applied in functional imaging. In short, the significant longitudinal changes observed in the second group, i.e. the control group, are excluded leaving only changes exclusive to the primary group, i.e. the HR group, in the statistical assessment (Job et al., 2005). By applying this technique, Job et al. (2005) were able to discovered clusters of regional brain changes that were different for the HR groups as compared to HC. Moreover, regarding the previous point of differential brain maturation, this alternative method of analysis could potentially handle longitudinal MRI data more elegant. By our knowledge, Job et al. (2005) is the only study using this alternative method of analysis, therefore the potential benefits and limitations need to be further assessed by other researchers in the field of child and adolescent research.

An additional methodological limitation is a difference between the studies across the various research centers concerning scanning parameters, image analysis and packages

(Smieskova et al., 2010). By creating multi-site studies, this problem, and the limitation of small sample sizes may be overcome.

A final methodological limitation, which is frequently mentioned, is the sample size of the groups. Especially given relative small transition rates, as mentioned by Yung et al. (2008), the number of subjects in the HR-p group in various studies is small.

5. Conclusions

The aim of this review was to investigate potential neurobiological markers that precede the onset of psychosis. By focussing on adolescence and by combining results from studies using clinical, familial and genetic HR approaches, we were able to search for neurobiological precursors of psychosis in the age range where first psychosis usually occurs from a multi-perspective view. In this review, despite methodological limitations and inconclusive results, we tentatively postulate that structural GM reductions in prefrontal cortex, superior temporal gyrus and anterior cingulate cortex could be regarded as precursors for the onset of psychosis. Regarding the WM studies, the results from both VBM and DTI studies were inconsistent. Furthermore, the number of studies that used cortical thickness was inadequate to draw conclusions.

There are many caveats to overcome when comparing MRI results from different high risk groups and research centers. However, an important consistent factor among the various research centers is the aim to elucidate neurobiological predictors of psychosis onset. By attempting to reach this goal, the possibility increases to provide better multi-domain detection approaches and eventually on an individual basis predict whether a psychotic disorder will develop. This shared aim of improving intervention techniques is demonstrated by the believe that prodromal intervention will improve illness outcome, i.e. delay the onset of the psychosis, attenuate the symptoms or ideally prevent the psychotic symptoms from developing into a full-blown psychosis. Genetic disorder research can be of substantial additive value to prodromal research in trying to disentangle the specific genetic makeup that increases the risk of developing psychosis. Certainly, with the high incidence of psychosis, VCFS and XXY could yield potential valuable insights from the genetic point of view. A research field not specifically incorporated in this review but potentially important to the model is that of environmental influences and its sibling, twin and adoption studies. These data could provide fine-tuning of the genetic disorder results, thereby adding subtle conditional variables to the model of clinical high risk, resulting in a balance between nature and nurture.

These goals are difficult to accomplish, although the ongoing improvement of imaging methods and analyses will provide the current research fields with modern technologies. With these gradual developments in the neuroimaging field, it becomes possible to understand pathophysiological mechanisms and their specificity, thereby also unravelling the evolution of these mechanisms and investigating how brain changes relate to clinical phenomenology in the shift from premorbid to prodromal and ultimately psychosis. Nevertheless, it is important to urge caution in determination of the prodromal model, with various neurobiological predictors and pathways having to be replicated in studies across all research centers. With all mentioned developments in the near future, the three high risk research fields tend to come together and all can provide a substantial piece of the puzzle in a model of predicting the onset of psychosis.

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Appendix A

Table 1: Clinical High Risk Studies

It should be noted that studies from the same centers did not necessarily use independent samples across studies. Furthermore, only the relevant group differences are mentioned, i.e. the high risk groups and healthy control groups, thereby omitting the results reported for, e.g. first episode patient groups and chronic schizophrenic patient groups.

Melbourne, Australia: Ultra high risk studies CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Pantelis *et al.* (2003)	UHR-p: 23 UHR-np: 52	13:10 30:22	19.3 (3.7) 21.6 (3.3)	VBM: GM volume	TB: no group differences GM: UHR-p < UHR-np (medial temporal cortex (R), lateral temporal cortex (R), inferior frontal cortex (R), cingulate gyri (L+R))
Garner *et al.* (2005)	UHR-p: 31 UHR-np: 63 HC: 49	20:11 38:25 32:17	19.1 (3.6) 20.1 (3.1) 20.2 (2.7)	ROI: pituitary volume	UHR-p + HC > UHR-np, UHR-p > HC (trend) Cox: 10% pituitary vol increase = 20% risk increase of developing psychosis
Velakoulis *et al.* (2006)	UHR-p: 39 UHR-np: 96 FEP: 162 CS: 89 HC: 87	24:15 54:42 108:54 76:13 55:32	19.0 (3.5) 20.6 (3.6) 21.5 (3.4) 34.9 (9.6) 26.9 (10)	ROI: ICV, TB, hippocampus, amygdala	ICV, hippocampus, amygdala: no group differences between UHR-p, UHR-np, HC. TB: HC > UHR TB: UHR-p + HC > UHR-np
Thompson *et al.* (2007)	UHR: 23	14:9	18.9 (3.3)	ROI: pituitary, hippocampus, TB and ICV	No correlations volumes with plasma cortisol level or glucocorticoid receptor numbers

Takahashi *et al.* (2008)	UHR-p: 39 UHR-np: 96 FEP: 162 CS: 89 HC: 87	24:15 54:42 108:54 76:13 55:32	19.0 (3.5) 20.6 (3.6) 21.5 (3.4) 34.9 (9.6) 26.9 (10.1)	ROI: adhesio interthalamica prevalence and length	AI prevalence: no group differences between UHR-p, UHR-np, HC. AI length: UHR-np + UHR-p < HC
Fornito *et al.* (2008)	UHR-p: 35 UHR-np: 35 HC: 33	21:14 20:15 21:12	19.30 (3.49) 19.91 (3.40) 20.97 (6.18)	ROI: ACC GM volume, CTh, cortical surface	GM volume: No group differences Surface area: No group differences CTh: UHR-p < HC (rostal paralimbic ACC (L+R)) CTh: UHR-np > HC (dorsal limbic ACC) CTh: UHR-np > HC (rostal limbic ACC – trend) CTh: UHR-p < UHR-np (rostal limbic ACC (L+R)) CTh: UHR-p < UHR-np (subcallosal paralimbic ACC – trend) Cox: 1 mm ↓ CTh = 20% ↑ risk of developing psychosis
Walterfang *et al.* (2008a)	UHR-p: 23 UHR-np: 52	13:10 30:22	19.3 (3.7) 21.6 (3.3)	VBM: WM DWI	WM volume: UHR-p > UHR-np (frontal lobe regions + SFO(L), SLF (L))
Walterfang *et al.* (2008b)	UHR-p: 27 UHR-np: 73 HC: 33	18:9 41:32 23:15	18.72 (2.60) 20.72 (3.37) 21.02 (3.40)	ROI: CC	CC area, length, bending angle, thickness: No group differences Regional CC thickness: UHR-p < HC (anterior + posterior genu) Regional CC thickness: UHR-p < UHR-np (anterior genu) Regional CC thickness: UHR-p (restricted to UHR-p who developed schizophrenia) < HC + UHR-np (slice 1 of anterior genu) Cox: 1 mm ↓ mean thickness anterior genu = 52% ↑ risk of transition
Takahashi *et al.* (2009a)	UHR-p: 31 UHR-np: 66 HC: 55	20:11 39:27 36:19	19.1 (3.6) 20.2 (3.3) 20.8 (3.6)	ROI: GM insula	insula (L+R): UHR-p < UHR-np insula (R): UHR-p < HC UHR-p: short insula < long insula (R)

Takahashi *et al.* (2009b)	UHR-p: 12 UHR-np: 23 FEP: 23 HC: 22	7:5 12:11 16:7 12:10	19.5 (5.1) 20.2 (4.0) 21.6 (3.5) 22.0 (4.7)	Cortical pattern matching: STG	caudal STG: No group differences planum temporal: No group differences
LONGITUDINAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Pantelis *et al.* (2003)	UHR-p: 10 UHR-np: 11	3:7 4:7	18.9 (4.5) 20.5 (3.7)	VBM: GM volume	UHR-p: t2 < t1 (cingulate gyri (L+R), parahippocampal gyrus (L), fusiform gyrus (L), OFC (L), cerebellum (L)) UHR-p: t2 > t1 (cuneus (R)) UHR-np: t2 < t1 (cerebellum (L))
Walterfang et al. (2008a)	UHR-p: 10 UHR-np: 11	3:7 4:7	18.9 (4.5) 20.5 (3.7)	VBM: WM DWI	WM volume: UHR-p t2 < t1 (fronto-occipital fasciculus (L), calcarine cortex (L)) WM volume: UHR-p t2 > t1 (posterior cerebellum (L+R)) WM volume: UHR-np t2 > t1 (posterior cerebellum (L) + inferior parietal lobule (R))
Sun *et al.* (2009)	UHR-p: 12 UHR-np: 23	7:5 12:11	19.5 (5.1) 20.2 (4.0)	Cortical pattern matching: brain surface contraction	dlPFC (L+R): UHR-p > UHR-np
Takahashi et al. (2009a)	UHR-p: 11 UHR-np: 20 HC: 20	6:5 11:9 12:8	19.5 (5.3) 20.3 (4.3) 21.6 (4.7)	ROI: % GM change insula	% reduction GM insula: UHR-p > HC + UHR-np

Takahashi et al. (2009b)	UHR-p: 12 UHR-np: 23 FEP: 23 HC: 22	7:5 12:11 16:7 12:10	19.5 (5.1) 20.2 (4.0) 21.6 (3.5) 22.0 (4.7)	Cortical pattern matching: % GM change STG	% reduction: UHR-p > HC (planum polare (L), planum temporal (L+R), caudal STG (L)) % reduction UHR-p > UHR-np (planum polare (R), planum temporal (L))
Amsterdam AMC, the Netherlands CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Peters *et al.* (2008)	UHR: 10 FE: 10 HC: 10	10:0 10:0 10:0	21.6(2.8) 21.2(3.0) 21.1(2.8)	WM Integrity (DTI)	FA + trace: no group differences
Peters *et al.* (2009)	UHR: 10 HC: 10 Schiz: 10	10:0 10:0 10:0	21.6(2.8) 21.1(2.8) 21.2(3.0)	WM Integrity (DTI)	FA: UHR < HC (superior frontal lobe (R), middle frontal lobe (L)) FA: FEP < HC (parietal lobe (L+R), superior temporal lobe (L), insula (R), frontal lobe (L))
Bloemen *et al.* (2009)	UHR-p: 10 UHR-np: 27 HC: 10	8:2 18:9 8:2	20.7(4.3) 18.9(4.0) 22.7(3.9)	WM Integrity (DTI)	FA: UHR-p < HC (superior frontal lobes (L+R)) FA: UHR-p < UHR-np (putamen (R) + superior temporal lobe (L)) FA: UHR-p > UHR-np (medial temporal lobe (L))

Seoul, South Korea CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Choi *et al.* (2008)	UHR: 30 GHR: 23 HC: 34	18:12 11:12 14:20	22.13 (3.75) 23.39 (5.36) 23.32 (4.01)	Cavum Septum Pellucidum (CSP) grading system based on overall CSP size (4 categories)	CSP length, prevalence and size: No group differences Incidence of abnormal CSP: UHR > HC
Jung *et al.* (in press)	UHR: 29 CS: 31 HC: 29	15:14 17:14 15:14	22.24(4.33) 24.26(4.24) 23.24(2.71)	CTh	Mean CTh: UHR < HC (ACC (L+R), parahippocampal cortex (L+R), medial frontal cortex (L+R), STG (L), lingual cortex (R), inferior frontal + parietal cortex (R), middle temporal cortex (R)) Gradual thinning: UHR < HC: in all regions Mean CTh: CS < UHR (inferior parietal cortex (L+R), medial frontal (L+R), STG (L), superior frontal cortex (L), parahippocampal cortex (L), inferior temporal cortex (L), insula (R), uncus (R), PCC (R), precentral (R), middle temporal cortex (R))
Utrecht, UMC Utrecht, the Netherlands: Dutch prediction of psychosis studies (DUPS) CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Ziermans *et al.* (2009)	UHR: 54 HC: 54	33:21 27:27	15.76 (2.05) 15.75 (1.49)	ROI: TB, IC, ventricles, cerebellum, lobes VBM: GM & WM density	no group differences

Los Angeles, University of California, USA CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Karlsgodt *et al.* (2009)	UHR: 36 HC: 25	27:9 12:13	17.02(3.37) 17.96(3.40)	WM Integrity (DTI)	FA: UHR < HC (SLF)
Basel, Switserland CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Borgwardt *et al.* (2007)	ARMS-all: 35 ARMS-T: 12 ARMS-NT: 23 FE: 25 HC: 22	22:13 9:3 23:0 18:7 13:9	23.7(5.6) 24.6(5.3) 23.3(5.8) 27.1(6.3) 23.0(4.3)	VBM GM	GM: ARMS < HC (STG (L+R), insula (L+R), PCC (L+R), precuneus (L+R), posterior cerebellar hemispheres (L+R), parahippocampal gyrus (L), hippocampus (L), amygdala (L)) GM: ARMS-T < ARMS-NT (insula (R), anterior STG (R), ACC) GM: ARMS-T > ARMS-NT (parahippocampus (L+R), fusiform (L+R), medial occipital gyri (L+R), posterior temporal(L+R), inferior parietal(L+R) and postcentral cortex(L+R), red nucleus, thalamus, supramarginal gyrus (R))

% = percentage; ACC = anterior cingulate cortex; AI = adhesio interthalamica; ARMS-all = at risk mental state complete group; ARMS-NT = at risk mental state not transitioned to psychosis; ARMS-T = at risk mental state transitioned to psychosis; CC = corpus callosum; Cox = Cox regression; CS = chronic schizophrenia; CSP = cavum septum pellucidum; CTh = cortical thickness; dlPFC = dorsolateral prefrontal cortex; DTI = diffusion tensor imaging; ICV = intracranium volume; f = female; FA = fractional anisotropy; FEP = first episode patients; GHR = genetic high risk; GM = grey matter; HC = healthy control; L = left; m = male; MRI = magnetic resonance imaging; m:f = male:female ratio; n = number; N.A. = not available; OFC = orbitofrontal cortex; PCC = posterior cingulate gyrus; R = right; *r* = Pearson's correlation coefficient; ROI = region of interest; sd = standard deviation; SFO = superior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; STG = superior temporal gyrus; t1 = time of first assessment; t2 = time of second assessment; TB = total brain volume; UHR-np = ultra high risk not transitioned to psychosis; UHR-p = ultra high risk transitioned to psychosis; VBM = voxel based morphometry; WM = white matter.

Table 2: Familial High Risk Studies

It should be noted that studies from the same centers did not necessarily use independent samples across studies. Furthermore, only the relevant group differences are mentioned, i.e. the high risk groups and healthy control groups, thereby omitting the results reported for, e.g. first episode patient groups and chronic schizophrenic patient groups.

Edinburgh, United Kingdom: High risk studies (EHRS) CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Lawrie *et al.* (2001)	HR: 147 FEP: 34 HC: 36 *- High proximal familial risk: 19* *- Proximal and distal familial risk: 76* *- Distal familial risk: 52*	74:73 22:12 17:19	21.2 (2.9) 21.6 (3.6) 21.2 (2.4)	ROI: AHC, TB, prefrontal lobe, lentiform nuclei	AHC (L+R): HC > HR thalamus (L): HC > HR Differences after controlling for familial clustering: AHC (R): HC > HR thalamus (R): HR < HC third ventricle : No group differences AHC length / volume: no group differences TB: HR-nps ↓ prefrontal lobe (L+R): High proximal familial risk < HC lentiform nuclei (L+R), thalamus (R): Proximal and distal familial risk < HC lentiform nuclei (L), thalamus (L+R): Distal familial risk < HC

McIntosh et al. (2007)	HC MM 4 HC MV 8 HC VV 3 HR-np MM12 HR-np MV 17 HR-np VV 6 HR-p MM 13 HR-p MV 14 HR-p VV 5 HR-sc MM 1 HR-sc MV 3 HR-sc VV 7	4:0 4:4 1:2 3:9 10:7 3:3 5:8 5:9 0:5 1:0 1:2 3:4	21.9 (2.2) 21.3 (3.0) 22.0 (1.6) 22.7 (3.1) 21.6 (2.9) 20.9 (2.8) 21.6 (2.8) 21.5 (2.9) 18.9 (2.9) 16.3 18.9 (3.7) 19.4 (2.1)	VBM: GM, WM, CSF	COMT Val-allele: ↑ risk of CS within HR ↑ levels Val-allele: ↓ ACC GM density
LONGITUDINAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Lawrie *et al.* (2002)	HR: 66 HC: 20	34:32 13:7	23.1(2.7) 22.9(2.2)	VBM: % GM change temporal lobe	No group differences over time Clinical symptom observations: GM reduction: HR-nps > HR-npns (temporal lobe (R))
Johnstone *et al.* (2005)	HR: 147 HC: 7	N.A.	21.19 (2.97) 21.17 (2.37)	VBM: AHC (L+R), thalamus (L)	thalamus (L): HR-p groups < HC

Job *et al.* (2005)	HR: 65 HC: 19 *- HR-npns: 47* *- HR-nps: 10* *- HR-p: 8*	34:31 12:7	21.4(2.7) 21.0(2.0)	VBM, within group masking method	No group differences over time HC group mask overlay: HR t2 < t1(fusiform gyrus (L+R), middle temporal gyrus (L+R), inferior temporal gyrus (L+R), parahippocampal gyrus(L+R), cingulate gyrus (L), uncus (L), amygdala (L), inferior parietal lobe (R), STG (R)) HC group mask overlay without exclusion of significant control group changes: HR t2 < t1 (cerebellum (L+R), STG (L), cingulate gyrus (R), occipital lobe (R), uncus (R)) HR-nps + HR-p t2 < t1: cerebellum (R), fusiform gyrus (L), parahippocampal gyrus (L+R), amygdala (R) HR-npns mask overlay: HR-nps + HR-p t2 < t1 (fusiform gyrus (L), uncus (L), superior + inferior temporal gyri (L), superior lateral surface of hippocampus (L) HR-nps mask overlay: HR-p t2 < t1 (inferior temporal gyrus (L), uncus (L), cerebellum (R)) HC t2 < t1: gyrus rectus (R)

Detroit, Mitchigan, USA

CROSS-SECTIONAL

Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Rajarethinam *et al.* (2007)	GHR: 50 HC: 53	22:28 27:28	15.4 (3.6) 16.5 (4.4)	ROI: TB, caudate	TB: GHR < HC caudate (R): GHR < HC

% = percentage; ACC = anterior cingulate cortex; AHC = amygdalo-hippocampal complex; COMT = catechol-O-methyltransferase; CS = chronic schizophrenia; CSF = cerebrospinal fluid; f = female; FEP = first episode patients; GHR = genetic high risk; GM = grey matter; HC = healthy control; HR = high risk; High proximal familial risk = the HR subject had at least two first degree relatives with a psychotic disorder; Proximal and distal familial risk = the HR subject had both a first and a second degree relative affected with a psychotic disorder; Distal familial risk = the HR subject had only second degree affected relatives with a psychotic disorder; L = left; m = male; MM = Met-Met; MRI = magnetic resonance imaging; MV = Met-Val; m:f = male:female ratio; n = number; N.A. = not available; R = right; *r* = Pearson's correlation coefficient; ROI = region of interest; sd = standard deviation; STG = superior temporal gyrus; t1 = time of first assessment; t2 = time of second assessment; TB = total brain volume; val = val allele; VBM = voxel based morphometry; VV = Val-Val; WM = white matter.

Table 3: Genetic Disorders

It should be noted that studies from the same centers did not necessarily use independent samples across studies. Furthermore, only the relevant group differences are mentioned, i.e. the high risk groups and healthy control groups, thereby omitting the results reported for, e.g. first episode patient groups and chronic schizophrenic patient groups.

3.1 Klinefelter Syndrome (karyotype 47,XXY)					
National Institute of Mental Health, Bethesda, Maryland, USA CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Rose *et al.* (2004)	16 CAH 20 KS 40 HC	m m m	10.5 (2.9) 15.1 (4.6)	ROI: hippocampus, amygdala	Hippocampus: KS < HC (total+L+R) Amygdala: KS < HC (total+L) Amygdala: CAH < HC (total+L)
Shen *et al.* (2004)	34 KS 62 HC	m m	12.6 (4.3) 12.9 (4.3)	VBM	GM: KS < HC (total GM volume, temporal gyri, cingulate gyri, occipital gyri, hippocampus, insula, amydala, (predominantly L)) WM: KS < HC (total WM volume, parietal lobe (R)) Ventricular CSF: KS > HC

Giedd *et al.* (2007)	42 KS 87 HC	m m	12.8 (5.0) 12.7 (5.0)	ROI: TB, total + frontal + temporal + parietal GM, total + frontal + temporal + parietal WM, lateral ventricles, caudate, CC (mm^2), cerebellum CTh	TB: KS < HC GM : KS < HC (total+frontal+temporal) WM : KS < HC (frontal) WM : KS > HC (parietal) Caudate: KS < HC Lateral ventricles: KS >HC CTh: KS < HC: temporal (L+R), inferior parietal (L), inferior frontal (L), motor strip (L)
Royal Edinburgh Hospital, Edinburgh, UK CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Warwick *et al.* (1999)	10 XYY 10 KS 26 HC	m m m	21.8 (3.2) 21.8 (4.2) 21.5 (1.3)	ROI: TB, pre-frontal lobe, temporal lobe, ventricles, amygdala-hippocampus, caudate nuclei, lentiform nuclei, thalamic nuclei,	TB : XXY < HC Lateral ventricles: KS > HC (L+R) Lateral ventricles: KS > XYY (R)

3.2 Velo-cardio-facial syndrome (VCFS)					
Stanford University School of Medicine, Stanford, USA CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Eliez *et al.* (2000)	15 VCFS 15 HC	10:5 10:5	10.5 (3.1) 10.8 (2.7)	ROI: TB, hemispheres, lobes, subcortical region, cerebellum, ventricle-to-brain ratio	TB: VCFS < HC (mainly through ↓ WM) Hemispheres: VCFS < HC (mainly ↓ WM) Frontal lobe: VCFS > HC (L+R) Parietal lobe: VCFS < HC (L+R, mainly ↓ GM) Ventricle-to-brain ratio: VCFS > HC
Eliez *et al.* (2001a)	9 VCFS+M all 9 VCFS+P all 18 HC	6:3 5:4 11:7	12.1 (2.9) 11.8 (3.9) 12.5 (3.8)	ROI: TB, GM, WM	TB: VCFS < HC GM: VCFS + M all < VCFS+ P all
Eliez *et al.* (2001b)	23 VCFS 23 HC	15:8 15:8	12.7 (3.9) 12.9 (4.1)	ROI: TB, temporal lobe, STG, hippocampus, amygdala	TB: VCFS < HC GM: VCFS < HC WM: VCFS < HC
Eliez *et al.* (2002)	30 VCFS 30 HC	NA	12.1 (3.8) 12.2 (4.4)	ROI: GM, caudate	GM: VCFS < HC Caudate (head): VCFS > HC (L+R)

Barnea-Goraly *et al.* (2003)	19 VCFS 19 HC	13:6 13:6	12.2 (3.9) 14.4 (4.2)	DTI	FA: VCFS < HC in L+R prefrontal tracts FA: VCFS < HC in parietal tracts (mainly L) FA: VCFS < HC in L+R external capsule/temporal horn FA: VCFS < HC in pre- + postcentral gyri FA: VCFS > HC in splenium
Barnea-Goraly *et al.* (2005)	19 VCFS 19 HC	13:6 13:6	12.2 (3.9) 14.4 (4.2)	DTI	VCFS arithmetic subtest scores correlated with FA values (covariates IQ + age) FA: VCFS WM left intraparietal sulcus, left angular gyrus, left supramarginal gyrus
LONGITUDINAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Gothelf *et al.* (2007b)	29 VCFS 29 HC	20:9 20:9	12.3 12.7	GM and WM: TB, lobes, hippocampus, cerebellum	TB- GM + WM: VCFS < HC Hippocampus: VCFS < HC Cerebellum: VCFS < HC
State University of New York Upstate Medical University, Syracuse, USA CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Kates *et al.* (2004)	10 VCFS 10 HC	7:3 7:3	10.1 (1.8) 10.0 (1.9)	ROI: TB, subcortical WM, frontal lobe, prefrontal GM/sulcal WM, motor cortex, caudate, cingulate	TB: VCFS < HC Frontal lobe: VCFS > HC

Kates *et al.* (2005)	19 VCFS 18 HC	8:11 8:10	11.8 (2.1) 12.0 (2.1)	ROI : TB, frontal lobe, PFC	TB: VCFS < HC (m only) Frontal lobe: VCFS < HC (m only)
Antshel *et al.* (2005)	60 VCFS 52 HC	31:29 25:27	11.1 (2.7) 10.8 (2.3)	ROI: CC	CC: VCFS > HC (except for genu)
Kates *et al.* (2006a)	47 VCFS 15 sibs 18 HC	22:25 5:10 12:6	11.7 (2.1) 11.5 (1.8) 11.5 (2.0)	ROI: TB, PFC, hippocampus, amygdala	TB: VCFS < sibs + HC PFC: VCFS < sibs + HC Hippocampus: VCFS < sibs + HC (L+R, disappear after correction for TB volume) Amygdala: VCFS > sibs + HC (L+R)
Kates *et al.* (2006b)	11 VCFS Met 15 VCFS Met 15 VCFS Val 17 VCFS Val	f m f m	10.7 (3.3) 10.8 (2.2) 11.0 (1.8) 11.2 (3.3)	ROI: TB, PFC	PFC: f VCFS Met + m VCFS Val > f VCFS Val + m VCFS Met PFC: - f VCFS Met + m VCFS Val < f VCFS Val + m VCFS Met
Antshel *et al.* (2008)	92 VCFS 59 HC	51:41 34:25	11.0 (2.6) 10.4 (2.6)	ROI: TB, lobes	TB: VCFS < HC parietal lobe: VCFS < HC (L+R, GM + WM) frontal lobe: VCFS > HC (WM)
University of Geneva School of Medicine, Geneva, Switzerland CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Schaer *et al.*(2006)	37 VCFS 36 HC	11:26 15:21	16.6 (9.1) 14.4 (8.2)	Gyrification index	Frontal lobe: VCFS < HC (L+R) Parietal lobe: VCFS < HC (L+R)

Debbané *et al.* (2006)	43 VCFS 40 HC	16:27 17:23	16.7 (8.7) 15.1 (7.9)	ROI: TB, hippocampus, amygdala	TB: VCFS < HC Hippocampus (body): VCFS < HC (L+R)
Glaser *et al.* (2007)	42 VCFS 54 HC	18:24 23:31	13.98 13.44	ROI: fusiform gyrus, TB	TB: VCFS < HC Fusiform gyrus: VCFS < HC
Schaer *et al.* (2009)	59 VCFS: *6-9yr: 15* *9-12yr: 11* *12-15yr: 10* *15-18yr: 4* *18+yr: 19* 80 HC: *6-9yr: 16* *9-12yr: 22* *12-15yr: 8* *15-18yr: 7* *18+yr: 27*	24:35 36:44	15.9 (8.9) 15.9 (8.4)	CTh, COMT polymophism	Mean thickness values: VCFS > HC (predominantly frontal regions in young patients) CTh with increasing age: VCFS > HC (thinning): 6-9yr: VCFS > HC (L hemisphere, widely distributed) 9-12yr: VCFS > HC (L+R hemisphere, predominantly frontal) 12-15yr: VCFS > HC (L+R hemisphere, predominantly dorsal frontal regions) 15+yr: no group differences COMT polymorphism: no group differences
LONGITUDINAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Schaer *et al.* (2009)	32 VCFS 31 HC	13:19 11:20	T1: 11.4 (3.5) T2: 14.5 (3.6) T1: 11.1 (3.6) T2: 14.2 (3.6)	CTh, COMT polymophism	% thinning over time: VCFS > HC COMT polymorphism: no group differences

Institute, Psychiatry and Behavioral Sciences; Laboratory of Neuro Imaging, University of California, Davis, USA CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
De Boer *et al.* (2007)	36 VCFS 36 HC	17:19 23:13	10.75 10.5	ROI: hippocampus, TB GM + WM	TB- GM + WM: VCFS < HC Hippocampus: VCFS < HC
Bearden *et al.* (2007)	21 VCFS 13 HC	10:11 7:6	11.7 10.9	CTh WM integrity ROI: TB + lobes	TB thickness: VCFS < HC
Children's Hospital of Philadelphia, Philadelphia, USA CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Bearden *et al.* (2004)	13 VCFS 9 sibs	6:7 5:4	12.3 (3.2) 12.2 (2.7)	ROI: TB, GM, WM, ventricular CSF	TB: VCFS < sibs WM: VCFS < sibs Ventricular CSF: VCFS > sibs

King's College London, Institute of Psychiatry, London, UK CROSS-SECTIONAL					
Authors	**Sample characteristics**			**Measure(s) of interest**	**Results**
	size (n)	**m:f (n)**	**mean age (sd)**		
Campbell *et al.* (2006)	39 VCFS 26 sibs	20:19 16:10	11 (3) 11 (3)	ROI: hemispheres, lobes, ventricles, caudate, putamen, hippocampus, cerebellum VBM	VBM: VCFS < sibs (hemisphere (L),occipital-parietal lobe (L+R), cerebellum) VBM: VCFS > sibs (caudate (R), lateral ventricle (L+R)) WM: VCFS < sibs in frontal lobe, cerebellum, internal capsule

% = percentage; CAH = congenital adrenal hypoplasia; CC = corpus callosum; CSF = cerebrospinal fluid; COMT = catechol-O-methyltransferase; CTh = cortical thickness; DTI = diffusion tensor imaging; f = female; FA = fractional anisotropy; GM = grey matter; HC = healthy control; IQ = intelligence quotient; KS = Klinefelter syndrome; L = left; m = male; M all = maternal allele; met = met allele; mm^2 = square millimetre;MRI = magnetic resonance imaging; m:f = male:female ratio; n = number; N.A. = not available; OFC = orbitofrontal cortex; P all = paternal allele; PCC = posterior cingulate gyrus; PFC = prefrontal cortex; R = right; ROI = region of interest; sd = standard deviation; sibs = siblings; STG = superior temporal gyrus; t1 = time of first assessment; t2 = time of second assessment; TB = total brain volume; val = val allele; VBM = voxel based morphometry; VCFS = velocardiofacial syndrom; WM = white matter; XYY = subjects with trisomy XYY.