Structural brain abnormalities in first-degree relatives of patients with bipolar disorder or schizophrenia

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Layman's summary

Bipolaire stoornis (BD) en schizofrenie (SCZ) zijn beide een ernstige psychiatrische stoornis. Patiënten van beide ziektes hebben overeenkomsten in cognitieve beperkingen, genetische factoren die meespelen in het risico op de ziekte en structurele brein afwijkingen. Het in kaart brengen van structurele brein afwijkingen (afwijkingen in het volume van bepaalde hersenstructuren) in eerstegraads familieleden van BD of SCZ patiënten kan helpen om oorzaken van overeenkomstige afwijkingen in de hersenen van patiënten zelf te achterhalen.

Het doel van deze scriptie is om een overzicht te verstrekken van structurele brein afwijkingen die gevonden zijn in eerstegraads familieleden van patiënten met BD of SCZ. Daarnaast zal er gekeken worden of er verschillen zijn tussen deze afwijkingen in broers en zussen, ouders, tweelingbroers en –zussen en de kinderen van BD of SCZ patiënten. Als laatste zal er onderzocht worden of er verschillen zijn in structurele hersenafwijkingen tussen de eerstegraads familieleden van BD patiënten en van SCZ patiënten.

Tweeëndertig studies die structurele hersenafwijkingen in eerstegraads familieleden van patiënten met BD onderzoeken zijn hier gebruikt. Hiernaast zijn er drie review artikelen en twee meta-analyses geraadpleegd om de structurele hersenafwijkingen in eerstegraads familieleden van SCZ patiënten vast te stellen. Uit het overzicht dat uit deze artikelen ontstond is een lijst gemaakt met hersenstructuren waarvan sprake was van een abnormaal volume in eerstegraads familieleden in vergelijking met gezonde controles.

Het bleek dat in eerstegraads familieleden van patiënten met BD weinig consistente resultaten worden gevonden. Een uitzondering hierop vormt de vrij consequent vastgestelde volumereductie in de prefrontale cortex. Verschillen in structurele hersenafwijkingen tussen broers en zussen, ouders, tweelingbroers en –zussen en de kinderen van BD patiënten werden niet gevonden. In eerstegraads familieleden van SCZ patiënten werden meer consistente resultaten gevonden. Een verkleind volume van de hippocampus en prefrontale cortex en een vergroot volume van de derde ventrikels werd vastgesteld in alle subgroepen van eerstegraads familieleden. De ouders van SCZ patiënten lijken ook een verkleind insula volume te hebben. Ondanks dat niet alle bevindingen consequent werden vastgesteld, kan er geconcludeerd worden dat eerstegraads familieleden van SCZ patiënten meer structurele hersenafwijkingen hebben dan de eerstegraads familieleden van BD patiënten.

Er is aanzienlijk meer onderzoek gedaan in de eerstegraads familieleden van patiënten met SCZ dan in de familie van patiënten met BD. Dit is waarschijnlijk de oorzaak van de meer consistente resultaten van de studies in deze groep proefpersonen. In de toekomst kan het daarom waardevol zijn om meer onderzoek te doen naar structurele hersenafwijkingen in eerstegraads familieleden van patiënten met BD, zodat in deze groep een duidelijker beeld kan ontstaan van welke afwijkingen consistent gevonden worden.

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Abstract

Patients suffering from either the severe mental disorder bipolar disorder (BD) or schizophrenia (SCZ) show resemblance in cognitive impairments, genetic etiology and structural brain abnormalities. Mapping the structural brain abnormalities in first-degree relatives of BD and SCZ patients can be valuable in order to elucidate the causes of brain abnormalities observed in the patients themselves.

The first aim of this thesis is to provide an overview of brain volume abnormalities found in first-degree relatives of BD and SCZ patients. It will also be studied whether there are differences in structural brain abnormalities between siblings, parents, co-twins and offspring of either BD or SCZ probands. Furthermore, the differences in brain volume abnormalities of first-degree relatives of BD patients and first-degree relatives of SCZ patients will be studied.

Thirty-two studies investigating structural brain abnormalities in first-degree relatives of BD patients, and three reviews and two meta-analyses investigating structural brain abnormalities in first-degree relatives of SCZ were examined here. From the overview that arose from these articles a list is made of brain regions that were in more than one study found to have an abnormal volume in first-degree relatives compared to healthy controls.

It appeared that in first-degree relatives of BD patients there is little consistency in the findings of these studies, with the exception of a rather consistent reported decrease in prefrontal cortex volume. Differences in structural brain abnormalities between siblings, parents, co-twins and offspring of BD probands could not be identified. Decreased hippocampus and prefrontal cortex volumes and increased third ventricle volumes have been consistently reported in all sub-groups of first-degree relatives of SCZ patients. Parents of SCZ patients are also likely to have decreased insula volumes. Although not all results are consistently found, it can be stated that there are more structural abnormalities in the first-degree relatives of SCZ patients than in those of BD patients.

Because of the large amount of research already conducted in first-degree relatives of SCZ patients resulting in rather consistent findings for these subjects, in the future it might be valuable to increase the amount of research conducted on structural brain abnormalities in first-degree relatives of BD patients in order to achieve more consistent results in these subjects.

Introduction

Bipolar disorder (BD) is a common and disabling mental disorder characterized by severe mood symptoms. According to the DSM-IV (the Diagnostic and Statistical manual of Mental disorders) there are three types of bipolar disorder: bipolar 1 disorder (BD1), bipolar 2 disorder (BD2) and cyclothymic disorder. In BD1 the primary presentation is manic, or rapid cycling episodes of mania and depression. Patients with BD2 suffer primary from recurrent depression accompanied by hypomanic episodes (a milder state of mania). Cyclothymic disorder is a chronic state of cycling between hypomanic and depressive episodes that do not reach the diagnostic standard for bipolar disorder. A manic episode is characterized by a period, at least one week, of abnormally and persistently elevated, expansive or irritable mood. The episodes can be recognized by inter alia an increased self-esteem, decreased need for sleep, pressure to keep talking or an increase in goal-directed activity. A depressive episode is inter alia accompanied by a depressed state most of the day, diminished interest or pleasure in all or most activities, insomnia or sleeping too much and feelings of worthlessness (American Psychiatric Association, 2000).

The second psychiatric disorder this thesis focuses on is schizophrenia (SCZ). SCZ patients suffer from social and/or occupational dysfunction, caused by at least two of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. These symptoms should at least last for one month and signs of disturbances should be notable for at least six months in order to meet the diagnosis of schizophrenia (American Psychiatric Association, 2000).

There is substantial evidence of clinical similarity between BD and SCZ (Stassen, Bridler, Hell, Weisbrod, & Scharfetter, 2004). First, cognitive performance is affected in both patient groups resulting in deficits in verbal memory, sustained attention, executive functions and visual memory. Although both BD and SCZ patients suffer from these cognitive impairments, BD patients show better cognitive performance than SCZ patients (Krabbendam, Arts, van Os, & Aleman, 2005). This difference between BD and SCZ patients however seems to disappear in older patients (Meesters et al., 2013). Second, also psychotic symptoms and the mood symptoms of mania and depression can be present in both BD and SCZ patients (Krabbendam et al., 2005). Third, in both patient groups neurological soft signs (NSS) occur. NSS are minor neurological abnormalities, including difficulties with simple motor coordination, complex motor sequencing and sensory integration (Zhao et al., 2013).

Beside the clinical overlap there are genetic studies suggesting that the same genes increase liability for both BD and SCZ. For example a genome-wide association study (GWAS) can be used in order to investigate this potentially shared genetic etiology of BD and SCZ(Lee et al., 2013). By comparing the genome of cases and controls, GWASs search for genetic variations, e.g. single-nucleotide polymorphisms (SNPs), associated with a trait. If one variant (one allele) is more common in patients than in healthy controls, this variation is likely to be associated with the disorder (Manolio, 2010). However, GWASs can also be used to estimate the total variance in liability to a disease and the genetic correlation of two diseases explained by SNPs (Lee et al., 2013).

From a recently conducted large GWAS by the Cross-Disorder Group of the Psychiatric Genomics Consortium it appeared that there is a high genetic correlation between BD and SCZ. That is to say, patients with BD showed higher genetic similarity to patients with SCZ than to healthy

controls, and vice versa. The SNP-based genetic correlation between BD and SCZ was found to be 0.68 (Lee et al., 2013).

Beside the phenotypic and genetic overlap there is also anatomical resemblance of brain abnormalities that have been found in BD and SCZ found. Structural and functional magnetic resonance imaging (MRI) studies gained popularity over the last decades and several abnormalities in the brain of BD and SCZ patients have been identified ever since. From a mega-analysis by Hallahan and colleagues (Hallahan et al., 2011), it appeared that bipolar patients have increased left temporal lobe, right putamen and right lateral ventricular volumes compared with healthy controls. In addition, some deviations have been found in several specific groups of bipolar patients. First-episode bipolar subjects had reduced cerebral and amygdala volumes. The global cerebral volume was also decreased in patients that did not take lithium in comparison with healthy controls and lithium treated bipolar patients. Subjects treated with lithium, which is a neuroprotective and neurogenerating substance, had larger hippocampal and amygdala volumes compared with healthy subjects or bipolar patients not treated with lithium.

A meta-analysis conducted by Haijma *et al.* (Haijma et al., 2012) demonstrated that schizophrenia patients, both medicated and antipsychotic-naïve, have significant reductions in intracranial, total brain, total gray matter and total white matter volumes in comparison with healthy controls. Antipsychotic-naïve patients were further only tested for the volumes of the thalamus, caudate nucleus and hippocampus, which were all significantly smaller in patients than in healthy controls. Medicated patients showed alterations in volumes of 33 of the 38 measured brain regions. Total cerebrospinal fluid and lateral ventricle volumes were increased in these patients, whereas all areas of the parenchymal brain tissue were decreased, except for the globus pallidus which appeared to be enlarged. White matter volumes of the frontal and temporal lobe and volumes of the total superior temporal gyrus, caudate nucleus and putamen were not significantly different in medicated patients compared to healthy subjects.

The structural brain changes found in SCZ and BD patients are thought to be associated with functional abnormalities in their brains. These functional deviations may cause the symptoms BD and SCZ patients suffer from (Ellison-Wright & Bullmore, 2010).

Although brain volume reductions thus appear in both disorders, the alterations seem to be more severe in schizophrenia than in bipolar disorder, which is similar to what has been reported on the cognitive aspects of the disorders. In the first place, this assumption is based on the fact that in patients with SCZ more brain structures are affected than in patients with BD. However, many subjects with BD that are included in the studies are treated with lithium. Lithium has neuroprotective effects and stimulates neurogenesis (Leeds et al., 2014), which potentially explains the larger volumes found in BD patients. Secondly, an increase in cerebral spinal fluid volume, and thus in lateral ventricle volume, has been related to a decrease in gray matter (Schneider-Axmann et al., 2006). A meta-analysis of Arnone and colleagues (Arnone et al., 2009), comparing schizophrenia with bipolar disorder, showed that lateral ventricle enlargement is more pronounced in SCZ patients. This again suggests that brain volume reductions are more prominent in SCZ than in BD.

As described earlier, genes play an important role in the risk to develop BD or SCZ. A prevalence study by Merikangas *et al.* showed that BD affects approximately 2.4% of the population worldwide (Merikangas et al., 2011). However, for first-degree relatives the risk for developing BD is higher; 9% (Barnett & Smoller, 2009) to 13% (Mesman, Nolen, Reichart, Wals, & Hillegers, 2013) of these family members develop BD. Monozygotic twins have an even higher chance (40-45%) of developing BD

when their co-twin suffers from the disease (Barnett & Smoller, 2009). Consequently, BD is considered to be highly heritable, as 60% to 80% of the risk for developing BD can be explained by genetic relationships among individuals (Kerner, 2014; Thompson et al., 2014).

SCZ affects approximately 1% of the population worldwide and, like BD, the disorder has a heritability of about 80%. The chance of developing SCZ thus rises when a family member is affected, which strongly suggests a genetic basis of the disease. 4.9% of the offspring of SCZ probands develops SCZ, dizygotic co-twins of SCZ patients have a chance of 17% to develop the disorder and monozygotic co-twins develop SCZ in 50% of the cases (S. Singh, Kumar, Agarwal, Phadke, & Jaiswal, 2014).

Mapping the structural brain abnormalities in first-degree relatives of BD and SCZ patients can be valuable in order to elucidate the causes of the brain abnormalities observed in the patients themselves. Brain volume differences in first-degree relatives can namely not be a consequence of medication, which is suggested to be a possible cause of measured brain abnormalities in probands. Furthermore, identifying brain abnormalities in first-degree relatives would clarify whether structural abnormalities found in probands are related to the illness state itself or to the familial (possibly genetic) risk of developing BD or SCZ, and may thus function as an endophenotype (Boos, Aleman, Cahn, Hulshoff Pol, & Kahn, 2007; Moran, Hulshoff Pol, & Gogtay, 2013).

Endophenotypes are traits with a clear genetic component that are related to a disease. They provide clues to the genetic foundation of a disorder. There have been five suggested criteria for the identification of a trait as an endophenotype: the endophenotype is associated with illness in the population, is primarily state-independent (manifests in an individual whether or not illness is active), is heritable, co-segregates with illness within families and the endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population (gottesman & gould 2003).

When structural MRI studies are conducted, the identified volume abnormalities in BD or SCZ patients thus have to satisfy these five criteria to be suited to function as an endophenotype for one of the disorders. The possibility that these structural abnormalities can be associated with the illness in the population and can be state-independent have already been discussed above. Volume abnormalities might also be related to the heritability of the disorders, as the influence of genetic factors on variation in volume of several brain structures have been established (Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007). This thesis will further focus on the question whether or not structural brain abnormalities co-segregate with an illness within families and whether brain volume abnormalities might be found at a higher rate in non-affected family members than in the general population. In the future the search for endophenotypes of BD and SCZ might result in a tool for predicting the development and progression of BD and SCZ in (new) patients (Karchemskiy et al., 2011).

In this thesis an overview will be given of recently conducted structural MRI studies on the neuroanatomical differences between BD probands, their first-degree relatives and healthy controls. From this data a summary will be made of the brain volume abnormalities found in siblings, twins, parents and offspring of BD patients, which may thus function as an endophenotype. I will try to make a distinction of structural brain anomalies between the different groups of first-degree relatives as well.

In order to provide an overview of structural brain anomalies in first-degree relatives of SCZ patients existing reviews and meta-analyses will be discussed which integrated such studies. I will try

to make a distinction of structural brain anomalies between offspring, siblings, co-twins and parents as well. These group-specific volume changes may thus function as sub-group specific endophenotypes.

Because of the clinical, genetic, and anatomical similarities between patients with BD and SCZ it might be possible that there is also an overlap of neuroanatomic markers or endophenotypes of these disorders. This is why also a comparison will be made between the structural brain abnormalities of first-degree relatives of BD probands and patients with SCZ.

Thus, in this thesis I first aim to provide an overview of brain volume abnormalities found in first-degree relatives of BD and SCZ patients, in order to identify potential endophenotypes. Next, I aim to study whether there are differences in structural brain abnormalities between siblings, parents, co-twins and offspring of either BD or SCZ probands. Third, I aim to study the differences in brain volume anomalies of the first-degree relatives of BD patients and the first-degree relatives of SCZ patients.

Assuming that there are structural differences in the brains of the different first-degree relative sub-groups, the hypotheses of this thesis are:

1. Offspring have more severe structural brain abnormalities than siblings or co-twins of BD or SCZ probands. This may be caused by the fact that, beside the genetic risk, offspring of a BD or SCZ proband grew up in a more seriously affected (i.e., stressful) environment compared with siblings and co-twins of BD or SCZ patients. Growing up with a BD or SCZ parent can potentially be more harmful to the young and developing brain than the less disturbing situation of growing up with a BD or SCZ sibling or co-twin.
2. First-degree relatives of SCZ patients have more prominent structural anomalies than first-degree relatives of BD patients. This is hypothesized because of the more severe structural abnormalities seen in SCZ probands than in BD probands.

Methods

Bipolar Disorder

The database PubMed was searched for structural MRI studies that looked at differences in brain volumes in first degree relatives of subjects with bipolar disorder compared with healthy controls. Search terms that were used were *bipolar, MRI* and *high-risk*. These terms were combined with one of the following keywords to specify the search for studies conducted in different first-degree relative groups: *offspring, sibling, twins* or *parent*. Titles and abstracts of the articles were read to determine whether or not the study could be included. Additional studies were obtained by using the option *related citations* in PubMed and by examining the reference lists of selected articles. The overview that arose in this way is supplemented with data from the recent review of Nery *et al.* (Nery, Monkul, & Lafer, 2013). From this overview a list is made with brain regions that were found to have an abnormal volume in more than one study.

Beside this list of brain volume abnormalities in all first-degree relatives of BD probands, offspring, siblings and twins of BD patients were also considered separately. Within each of these groups structures were sought that were found to be abnormal in more than one study.

I also divided all study cohorts into two groups based on age to study the differences in brain volume. This resulted in a group with younger and a group with older first-degree relatives. Also within these two groups brain regions were sought that were found to be abnormal in more than one study.

Schizophrenia

The database PubMed was searched for reviews on structural MRI studies that looked at differences in brain volumes in first degree relatives of subjects with schizophrenia compared with healthy controls. Search terms that were used were *(structural) MRI* and *schizophrenia*, combined with *high-risk* or *relatives*, and with the addition of *meta-analysis* or *review*. Titles and abstracts of the articles were read to determine whether or not the review could be used. The conclusions of in total five rather recent reviews and meta-analyses were used to create an overview of structural brain anomalies in first-degree relatives of SCZ patients. Study samples between the used reviews and meta-analyses were partially overlapping, but each of these articles also incorporated studies that were not used in the other four articles.

Two meta-analyses were used; Chan *et al*. (Chan, Di, McAlonan, & Gong, 2011) examined studies on structural brain anomalies in siblings, twins and offspring of patients with SCZ. In this analysis research articles were included that used a voxel-based morphometry (VBM) analysis on the MRI dataset, directly compared high-risk subjects with a healthy control group and normalized the results to a stereotactic standardized space. With this approach they tried to map hypothesized brain volume pathology in first-degree relatives. From the eight identified articles that satisfied the inclusion criteria, five studies defined the high-risk group as first- or second-degree relatives of SCZ patients. The meta-analysis by Boos and colleagues (Boos et al., 2007) included studies on brain volume anomalies in twins, siblings and parents of SCZ patients. Twenty-five articles were included that were MRI studies published in the English language before July 2005, comparing first-degree relatives of SCZ patients with a healthy control group and reporting sufficient data to obtain the effect size. With the analysis of these studies they aimed to determine the magnitude and extent of brain volume differences in first-degree relatives of SCZ patients. There is only one study overlapping between Chan *et al*. and Boos *et al.*.

Three reviews of the literature were used; Moran *et al*. (Moran et al., 2013) examined twenty-eight cross-sectional MRI studies in order to summarize structural brain imaging findings of abnormalities in siblings and twins of SCZ patients. Thirteen of the studies used in this review were also included in the meta-analysis of Boos *et al*. (Boos et al., 2007), one study was used by both Chan *et al*. (Chan et al., 2011) and Moran *et al*.. The review by Thermenos and colleagues (Thermenos et al., 2013) examined brain volume studies in offspring, twins and siblings of SCZ probands. In this extensive review neuroimaging studies of young (age <30) subjects at genetic high-risk for SCZ were discussed in order to provide an overview of the literature on the neural substrates of risk for SCZ. The review by Lawrie *et al*. (Lawrie, McIntosh, Hall, Owens, & Johnstone, 2008) included studies on structural brain anomalies in siblings, twins and offspring of patients with SCZ. The review aimed to identify premorbid changes in genetically high-risk subjects. In order to achieve this, several region of interest (ROI) studies were examined that investigated the volume of brain regions potentially affected in SCZ patients.

Because structural MRI studies on parents of SCZ probands were only included in the review of Boos *et al*., I made an overview of four additional parent studies. The database PubMed was used to identify studies that looked at differences in brain volumes in parents of SCZ patients compared with healthy controls. Search terms that were used were *MRI, schizophrenia* and *parent*. Titles and abstracts of the articles were read to determine whether or not the study could be included. Additional studies were searched by examining the reference lists of selected articles, but that did not yield extra publications.

Results

Structural abnormalities in first-degree relatives of patients with bipolar disorder

Thirty-two studies investigating structural brain abnormalities in first-degree relatives of BD patients were examined here. In tables 1, 2 and 3 (see appendix I) details of these studies are shown for offspring, siblings and twins of BD probands. Not all studies examined only one subgroup of first-degree relatives or specified the composition of the high-risk group. These studies are listed together in table 4 (see appendix I). No study was found which only analyzed parents of bipolar patients.

Some of the studies investigated the volume of a particular ROI. Most of these ROI studies investigated the involvement of limbic structures, basal ganglia and the thalamus in the genetic risk for BD. These structures are concerned with mood regulation, cognitive processes and behavior control and deficits in these areas may underlie the neurocognitive symptoms seen in BD patients (Matsuo et al., 2012). Other studies however looked for differences within all brain regions, or global and/or regional volume differences. This difference in methodology potentially results in a heterogeneity of findings. Although the imaging analysis methodology differs between the studies, in this thesis the findings will be discussed irrespective of methodology used.

Beside the analysis of brain volume abnormalities in all first-degree relatives of BD probands which is listed below, co-twins, siblings and offspring were also examined separately. It appeared that no abnormality of any brain structure is found more than once in neither group of first-degree relatives. Also in the subdivision of younger and older first-degree relatives there is no consistency in a group-specific volume abnormality of a particular brain structure.

It appeared that many contradicting results are found concerning structural brain abnormalities in first-degree relatives of BD probands. Volumes of brain regions that were found to be abnormal compared to healthy controls in more than one study will be discussed.

Hippocampus

Whereas two studies reported an increase in hippocampal volume, one in co-twins (van Erp et al., 2012) and one in offspring (Ladouceur et al., 2008), another study found a decreased hippocampal volume in first-degree relatives of BD patients (Boccardi et al., 2010). Five studies that looked specifically for hippocampal volume abnormalities in offspring (Hajek et al., 2009a; Karchemskiy et al., 2011), co-twins (Noga, Vladar, & Torrey, 2001) or a non-specified sample (Connor et al., 2004; McDonald et al., 2006) did not find any.

Parahippocampus

Two studies found abnormal parahippocampal volumes. However, the first found an association between a decreased parahippocampal volume and an increased risk for developing BD in co-twins (Hulshoff Pol et al., 2012), while the second found an increased gray matter volume in the parahippocampus in offspring of BD patients (Ladouceur et al., 2008).

Insula

Also, insula volume anomalies have been reported inconsistently. Two studies found a decrease in insular volume in first-degree relatives of BD probands, i.e. in a mixed sample (Matsuo et al., 2012) and in co-twins (van der Schot et al., 2010), and one study reported an increase in insular volume in siblings and offspring (Kempton et al., 2009).

Caudate nucleus

Caudate volume has been found to be abnormal as well. However, also for this structure findings are inconsistent, showing both a significant increased volume in co-twins (Noga et al., 2001) and a decrease of caudate volumes in young offspring (Ladouceur et al., 2008) and in a non-specified sample (McIntosh et al., 2004). Furthermore, Hajek *et al*. did not find a significant difference in caudate volume in offspring of BD patients (Hajek et al., 2009b).

Amygdala

A structure that has been examined rather extensively is the amygdala. Several studies that specifically looked for abnormalities in amygdala volume in offspring (Hajek et al., 2009a; M. K. Singh, Delbello, Adler, Stanford, & Strakowski, 2008), co-twins (Noga et al., 2001) and in a mixed sample (Matsuo et al., 2012) could not detect any abnormalities. However, a significant increase in a non-specified sample (Boccardi et al., 2010) and a trend towards an increased amygdala in young offspring (Ladouceur et al., 2008) have been reported.

Prefrontal structures

The most consistent findings are reported for prefrontal volume abnormalities. The right medial frontal gyrus was found to be smaller in first-degree relatives: gray matter reductions in this area were associated with an increased genetic risk for BD in a twin study (van der Schot et al., 2010), and also the white matter volume was found to be reduced in a mixed sample of first-degree relatives (Matsuo et al., 2012).

A smaller orbitofrontal cortex has also been associated with an increased genetic risk for BD in twins (Hulshoff Pol et al., 2012), and another study detected decreased orbitofrontal cortex volumes in siblings of BD patients (Eker et al., 2014). However, Van der Schot *et al.* found an increase in medial orbital gyrus volume in co-twins of BD patients (van der Schot et al., 2010).

Superior longitudinal fasciculus

Two diffusion tensor imaging (DTI) studies were included in the overview. One of these DTI studies suggests decreased fractional anisotropy in siblings and offspring of BD patients in the superior longitudinal fasciculus (Frazier et al., 2007). Also white matter volume in these bundles has been reported to be decreased in co-twins (van der Schot et al., 2010).

Structural abnormalities in first-degree relatives of patients with schizophrenia

Three reviews and two meta-analyses investigating structural brain abnormalities in first-degree relatives of SCZ were examined here (see table 5, see appendix II). Four additional studies were identified that examined the structural anomalies in the brains of parents with SCZ offspring. Details of these studies are listed in table 6 (see appendix II).

Beside the observation of brain volume abnormalities in all first-degree relatives of SCZ probands, I also considered structural brain abnormalities for offspring, siblings and twins of SCZ patients separately. Since Thermenos *et al*. (Thermenos et al., 2013), Lawrie *et al*. (Lawrie et al., 2008) and Chan *et al*. (Chan et al., 2011) did not make a distinction between siblings, co-twins and offspring, and Boos *et al*. (Boos et al., 2007) did not analyse siblings, parents and twins independently, it cannot be determined from these studies whether there are subgroup-specific brain volume abnormalities. Nevertheless, the review of Thermenos *et al*. (Thermenos et al., 2013) could be used to distinguish structure volume changes between younger and older first-degree

relatives when we compared the conclusions from this review with the findings from the four experimental parent studies. Also, the review by Moran and colleagues (Moran et al., 2013) could be used to identify brain volume abnormalities within subgroups, because there a separation could be made between the twin and sibling studies discussed.

From the meta-analyses, reviews and experimental structural MRI studies several abnormalities in brain volumes of first-degree relatives of SCZ patients can be identified. Volumes of brain regions that were found to be abnormal compared to healthy controls in more than one study will be discussed.

Hippocampus

These reviews show that siblings, parents, co-twins and offspring of SCZ probands have smaller hippocampi compared to healthy controls (Boos et al., 2007; Lawrie et al., 2008; Moran et al., 2013; Thermenos et al., 2013). The study performed by Harris *et al*. (Harris et al., 2002) however suggests that the hippocampus volume is larger in the parents of SCZ patients but this was not formally tested.

Insula

Lui *et al.* (Lui et al., 2009) established smaller right, and Tian *et al.* (Tian et al., 2011) established smaller left insula volumes in parents of SCZ probands. Only the (small) meta-analysis of Chan and colleagues (Chan et al., 2011) found a decreased (right) insula in the other subgroups of first-degree relatives.

In addition, Moran *et al*. (Moran et al., 2013) reported no study in which a significant altered insula volume was found in siblings or twins and also Thermenos *et al*. (Thermenos et al., 2013) did not report any volume alterations in this area in young siblings, offspring or co-twins of patients with SCZ. Thus, a smaller insula volume seems thus to be mainly reserved for parents of SCZ probands.

Amygdala

Thermenos *et al*. (Thermenos et al., 2013) reported inconsistent findings about the existence of amygdala volume abnormalities in young first-degree realtives. The meta-analysis of Boos *et al*. (Boos et al., 2007) did not establish amygdala volume abnormalities. Nevertheless, a smaller amygdala volume, possibly only in the left amygdala (Chan et al., 2011; Tian et al., 2011), has been determined in first-degree relatives (Lawrie et al., 2008; Moran et al., 2013; Thermenos et al., 2013).

When I separated the twin studies from the sibling studies analyzed by Moran *et al*. (Moran et al., 2013), it became clear that only the siblings, and not the twins showed reduced amygdala volumes. Tian and colleagues (Tian et al., 2011) reported reduced amygdala volume specifically in the parents of SCZ patients.

Prefrontal cortex

The prefrontal cortex (PFC) appears to be decreased in all groups of first-degree relatives. The meta-analysis of Chan and colleagues (Chan et al., 2011) identified a smaller left inferior frontal gyrus, but Thermenos *et al*. (Thermenos et al., 2013) reported that volume abnormalities in all areas of the PFC are among the most common and consistent findings in structural MRI studies within young siblings, co-twins and offspring of SCZ probands. Also Lawrie *et al*. (Lawrie et al., 2008) and Moran *et al*. (Moran et al., 2013) determined volume decreases in the whole PFC in siblings, co-twins and

offspring. In contrast to these regional volume abnormalities, Tian *et al.* (Tian et al., 2011) found a decreased volume of only the right orbitofrontal cortex in parents of SCZ patients.

Thalamus

Lawrie *et al*. (Lawrie et al., 2008), Moran *et al*. (Moran et al., 2013) and Tian *et al*. (Tian et al., 2011) showed a decreased thalamic volume in first-degree relatives of patients with SCZ. However, when consulting the various studies discussed by Thermenos *et al*. (Thermenos et al., 2013), it appeared that this is not a consistent finding, at least not in those first-degree relatives younger than 30 years of age. The inconsistency is also confirmed by the fact that no abnormal thalamic volume has been found in the meta-analyses of Boos *et al*. (Boos et al., 2007) and Chan *et al*. (Chan et al., 2011).

When we considered the twin studies and the sibling studies analyzed by Moran *et al*. (Moran et al., 2013) separately, it shows that only siblings, and not twins showed reduced thalamic volumes. Tian and colleagues (Tian et al., 2011) reported reduced thalamus volume in the parents of SCZ patients specifically.

Third ventricle

A well replicated finding is an enlarged third ventricle in all subgroups of first-degree relatives of SCZ probands. Larger third ventricles in offspring, parents, siblings and co-twins were reported by Thermenos *et al*. (Thermenos et al., 2013), Lawrie *et al*. (Lawrie et al., 2008), Boos *et al*. (Boos et al., 2007) and Moran *et al*. (Moran et al., 2013). Ohara and colleagues determined a larger ventricle-brain ratio in parents with SCZ offspring (Ohara, Sato, Tanabu, Yoshida, & Shibuya, 2006).

Bipolar disorder vs. schizophrenia

Differences between the first-degree relatives of BD and SCZ in the above mentioned structures with an abnormal volume will be discussed next.

Hippocampus

Whereas most ROI studies into first-degree relatives of patients with BD showed no abnormalities in hippocampal volume, a volume decrease in this structure is one of the best replicated findings in siblings, co-twins, parents and offspring of SCZ patients.

Parahippocampus

As mentioned above, the two studies that found an abnormal parahippocampal structure in first-degree relatives of BD patients had conflicting conclusions. From all the studies used in the reviews and meta-analyses of first-degree relatives of SCZ patients, there were only a few that mentioned cortical thinning in the parahippocampal gyrus (Thermenos et al., 2013). This indicates that this region is not very likely to have an abnormal volume in first-degree relatives of BD and SCZ patients.

Insula

There is some suggestive evidence that a decrease in insular volume is present in first-degree relatives of BD probands. In siblings, offspring and co-twins of SCZ patients no insular volume anomalies were reported. In parents of SCZ patients however, a decreased insula volume might be present. Although the meta-analysis of Boos *et al*. did not report insula volume anomalies, both studies that examined structural abnormalities in the whole brain in parents of SCZ patients found a decreased insular volume.

Caudate nucleus

Conflicting results have been reported about changes in caudate nucleus volumes in first-degree relatives of BD patients. Caudate volume has been found to be abnormal in first-degree relatives of BD, but it is not clear whether there is an increase or a decrease in volume. Although both meta-analyses and two of the three reviews do not mention caudate abnormalities in first-degree relatives of patients with SCZ, Thermenos *et al*. (Thermenos et al., 2013) states that in young first-degree relatives volume reductions in this nucleus have been found in several studies. It might be interesting to further investigate volume changes in this structure.

Amygdala

Although the majority of the ROI studies investigating the amygdala volume in first-degree relatives of BD patients could not detect volume anomalies in this nucleus, two studies found either a significant or a trend towards increased amygdalar volume. This is in contrast with the decrease in amygdala volume that has been reported in the siblings and parents of SCZ patients, although not entirely consistent.

Prefrontal cortex

A overlapping and consistent finding in both the first-degree relatives of BD and of SCZ patients seems a decrease in prefrontal cortex volume. In the first-degree relatives of BD probands it seems that there are mainly specific gyri or orbitofrontal cortex volume decreases. The orbitofrontal cortex decrease however is for first-degree relatives of SCZ patients only specifically reported in parents. In the other sub-groups volume decreases in all areas of the PFC or the prefrontal lobe as a whole are commonly and consistently mentioned.

Thalamus

Of interest are the results of the three ROI studies that specifically looked at volume anomalies in the thalamus in offspring (Karchemskiy et al., 2011; M. K. Singh et al., 2008) and in a mixed sample of first degree-relatives (Matsuo et al., 2012) of BD patients. None of these studies found significant differences in thalamic volume between first-degree relatives of BD patients and healthy controls. This appears to be contrasting with the findings in at least the siblings and parents of SCZ probands. Although it is not consistently reported, in these groups of first-degree relatives the thalamic volume seems to be decreased.

Third ventricle

None of the studies that investigated volumetric differences in the brains of first-degree relatives of BD patients reported abnormalities in third ventricle volume. This is highly contrasting with the first-degree relatives of SCZ patients, because in every sub-group of these relatives increased third ventricle volumes are among the most common and best replicated findings.

Discussion

In this thesis a literature overview was made of studies that researched brain volume abnormalities in first-degree relatives of BD and SCZ patients.

Thirty-two studies investigating structural brain anomalies in siblings, parents, twins and offspring of BD patients were listed. From this overview it became clear that there is little consistency in the findings of these studies. When replicated brain volume abnormalities were sought within the four different groups of first-degree relatives, it appeared that no brain structure is found to have an abnormal volume in more than one study in neither subgroup of first-degree relatives. When the structural MRI data of all first-degree relatives is however considered at once, several structures are found to have an abnormal volume in multiple studies, although there are also studies implicating no volume differences in some of these areas. Specifically, no consistency can be found on volumes of the hippocampus, parahippocampus, insula, caudate nucleus and amygdala, as both increases and decreases have been reported. Nevertheless, there is one relatively consistent finding in first-degree relatives of BD patients, namely a decrease in prefrontal cortex volume. Four studies found a decrease in the prefrontal cortex, with only one study identifying an enlarged prefrontal structure (Eker et al., 2014; Hulshoff Pol et al., 2012; Matsuo et al., 2012; van der Schot et al., 2010).

Two meta-analyses and three reviews were used to provide an overview of brain volume abnormalities in siblings, co-twins, parents and offspring of SCZ patients. Because structural MRI studies on parents of SCZ patients were only included in one review, four additional parent studies were included in the literature overview. From this overview several abnormalities in brain volumes of first-degree relatives of SCZ patients could be identified. It appeared that abnormal brain volumes in first-degree relatives have been more consistently reported for SCZ patients than for BD patients. A decreased hippocampus and prefrontal cortex volume and an increased third ventricle volume have been rather consistently established in all sub-groups of first-degree relatives of SCZ patients. Parents of SCZ patients are also likely to have decreased insula volumes. Insula abnormalities in siblings and offspring of SCZ patients were only identified by Chan *et al*. (Chan et al., 2011). Because of the different inclusion criteria for studies in this meta-analysis, which will be discussed later, it might be possible that this is a false positive finding. No consistency about volume abnormalities of the amygdala and the thalamus could be found. It appeared that reduced volumes of these structures could be found in siblings and parents, but not in co-twins of SCZ patients (Moran et al., 2013; Tian et al., 2011). Because of the fact that there is larger genetic similarity between SCZ patients and their co-twins then there is between probands and siblings or parents, it is hard to explain these findings.

Although not all results are consistently found, it can be stated that there are more structural abnormalities in the first-degree relatives of SCZ probands than in those of BD patients. A decreased hippocampus and an increased third ventricle volume have only been found in first-degree relatives of SCZ patients, and not in first-degree relatives of BD patients. Although inconsistently, a decrease in the volume of the amygdala and the thalamus have been reported in first-degree relatives of SCZ patients, but this is not likely to be an existing abnormality in first-degree relatives of BD patients. Parents of SCZ patients appear to have decreased insula volumes, whereas in first-degree relatives of BD patients insula volumes have been reported both increased and decreased. Both the first-degree relatives of BD and of SCZ patients are likely to have a decrease in prefrontal cortex volume. A structure that might be interesting for further investigation is the caudate nucleus. In first-degree

relatives of SCZ this nucleus has not been extensively studied, but there are some indications for an abnormal caudate volume. In first-degree relatives of BD patients caudate volume abnormalities have been inconsistently reported.

Because of the fact that an abnormal prefrontal cortex volume was found to be present in both the first-degree relatives of SCZ patients and of BD patients, it can be suggested that both disorders share a genetic basis (Hulshoff Pol et al., 2012).

A smaller brain structure volume is thought to be associated with less functional activity in that particular area (Ellison-Wright & Bullmore, 2010). Correlations have been found between anatomical or functional brain abnormalities and symptoms of BD and/or SCZ. Here the relation between psychiatric symptoms and brain abnormalities will be discussed for the structures that were in this thesis consistently found to be abnormal in first-degree relatives of BD and/or SCZ patients.

As mentioned above, in this thesis prefrontal cortex abnormalities are found to be present in first-degree relatives of both BD and SCZ patients. Smaller PFC volumes have shown to be related to problems with the effortful regulation of affective states (Phillips et al., 2003). It is also known that the more the activity of the PFC is reduced, the more severe psychotic symptoms in patients are (Ahmed et al., 2013). Reduced activity in the medial PFC has furthermore been associated with reduced performance in theory of mind tasks and, although less consistent reported, with reduced emotional perception (Brunet-Gouet & Decety, 2006). Also, the ability to distinguish imaginary circumstances from reality has been associated with PFC activity (Gallagher & Frith, 2003).

Furthermore, a reduced hippocampus volume was found in first-degree relatives of SCZ patients. It appeared, however, that a decreased hippocampus volume can neither predict symptoms, nor clinical status in SCZ patients (Ahmed et al., 2013).

A dysfunctional insula, which can be the result of the here reported decrease in volume in parents of SCZ patients, has been associated with a failure to identify internal speech. The insula is involved in the ability to integrate internally and externally generated perceptions. Problems with this ability can lead to auditory hallucinations, which are known to be common in SCZ patients (Cooper et al., 2014). A smaller insula volume in SCZ patients has also been linked to problems with the identification of emotional significance of a stimulus (Phillips et al., 2003).

From the literature overview of the structural MRI studies conducted in first-degree relatives of BD patients, it became clear that little consistency can be found in the results of these studies. It appeared that no brain structure is found to have an abnormal volume more than once in neither subgroup of first-degree relatives. This lack of consistency might be caused by the variety of inclusion criteria for the subjects of the high-risk group in the structural MRI studies.

For example, there are first-degree relatives included from both BD1 and BD2 patients. Some studies used only first-degree relatives of one type of BD patients, but most studies made no distinction between the first-degree relatives of BD1 and BD2 patients. There is a possibility that there are differences in the brain volumes of first-degree relatives between these two types of BD, so it might be preferable to study these high-risk subjects separate.

A second difference is the composition of the high-risk sample. In most studies the high-risk sample consists of healthy first-degree relatives, but in several studies (some of the) first-degree relatives suffer from a psychiatric disorder themselves. The high-risk offspring in the study of Karchemskiy *et al*. (Karchemskiy et al., 2011) suffers from ADHD or moderate mood symptoms, in the study of Singh *et al*. (M. K. Singh et al., 2008) 76% of the offspring meets the criteria for at least one psychiatric disorder, part of the offspring and sibling sample in the studies of Takahashi *et al*.

(Takahashi et al., 2010) and Kempton *et al*. (Kempton et al., 2009) suffers from a major depression. More consistency in the results, and a clearer view of the genetic base of brain volume abnormalities in BD might be found when all studies would use only unaffected high-risk subjects. On the contrary, first-degree relatives affected with psychiatric disorders are likely to share more genes that might cause psychiatric symptoms with probands than unaffected relatives do. The brains of these affected first-degree relatives might thus be valuable to identify structural abnormalities related to symptoms in the probands. Therefore, another possibility is to include both affected and unaffected first-degree relatives in structural MRI studies, with the exception of relatives affected with the disorder of interest in the study or with a more severe psychiatric disorder.

A clearer view on the structural differences between the different subgroups of first-degree relatives could possibly be obtained with better classification of the high-risk sample. As can be deduced from table 4, not every study reported the composition of the high-risk group and not every study made a distinction between data from siblings, offspring, twins and parents of BD patients. Nevertheless, it could certainly be possible that there are structural differences between these groups and that these differences are not detected when all data is considered at once.

More consistency in the findings of brain volume abnormalities and an increase in the detection of existing structural abnormalities in first-degree relatives of BD patients should be pursued. This could possibly be achieved with performing structural MRI experiments with more specifically composed high-risk groups, but also by increasing the power of the studies or by pooling the data of the studies. Most of the experimental structural MRI studies on the brain volume abnormalities contain very small samples of first-degree relatives of BD patients. By increasing these sample sizes, more power is created and the chance to detect subtle volume abnormalities in these subjects increases. Another way by which structural brain anomalies can be identified is through pooling the data of multiple studies. With such a large dataset meta-analyses could be performed and the chance to detect structural anomalies in first-degree relatives of BD patients rises.

Larger sample sizes, pooled data and a more extensive amount of research conducted in first-degree relatives of SCZ patients probably contributed to the less amount of inconsistency in the results of that section of this thesis. However, still some inconsistency was found in the results of the reviews and meta-analyses. A possible explanation for this could be the differences in inclusion criteria of studies in these articles. That is to say, the review of Lawrie *et al*. (Lawrie et al., 2008) only discussed ROI studies and the review of Thermenos *et al*. (Thermenos et al., 2013) only included studies performed in high-risk subjects younger than 30 years of age. The meta-analysis of Chan *et al*. (Chan et al., 2011) included only eight high-risk studies of which only five studies used first-degree relatives of SCZ patients as the high-risk sample. The meta-analysis of Boos *et al*. (Boos et al., 2007) was extensive but included only studies published before July 2005, while many studies followed that examined the volume of brain regions in first-degree relatives of SCZ patients. These differences in inclusion criteria and thus in used studies might be the reason for the somewhat inconsistent results reported in these articles.

Another potentially troubling issue is the fact that not all available data on brain volume abnormalities in first-degree relatives of SCZ patients is considered at once. Each of the five reviews and meta-analyses used in this theses discusses a section of all conducted studies. There is a possibility that information is missing within articles and that conclusions are thus not drawn appropriate, because not all studies are put side by side at once. Also the fact that Chan *et al*. (Chan et al., 2011) and Lawrie *et al*. (Lawrie et al., 2008) came to conclusions on basis of a small number of studies, while Thermenos *et al*. (Thermenos et al., 2013), Boos *et al*. (Boos et al., 2007) and Moran *et*

al. (Moran et al., 2013) each considered a large amount of literature can cause a difference in the conclusions that were drawn. For future reviews or meta-analyses it might be interesting to consider the available structural MRI data for siblings, co-twins, offspring and parents of SCZ patients separately. In this way a clearer picture can be drawn of specific brain volume abnormalities of each subgroup of first-degree relatives of SCZ patients.

As mentioned in the introduction, medicated SCZ patients have decreased volumes of all parenchymal brain tissue, except for the globus pallidus. Medication naïve SCZ patients have decreased thalamus, hippocampus and caudate nucleus volumes (Haijma et al., 2012). In first-degree relatives of SCZ patients decreased hippocampus and prefrontal cortex volumes and increased third ventricle volumes have been consistently reported. Parents of SCZ patients also show decreased insula volume. Decreased hippocampus, prefrontal cortex and insula volumes are thus present in both SCZ patients and first-degree relatives of SCZ patients and may therefore be expressions of genetic vulnerability predisposing to SCZ (Kieseppä et al., 2003).

BD patients have increased left temporal lobe, right putamen and lateral ventricle volumes. First-episode BD patients have decreased cerebrum and amygdala volumes; patients treated with lithium, a neuroprotective and neurogenerating substance, have increased hippocampus and amygdala volumes (Hallahan et al., 2011). As could be seen in tables 1, 2, 3 and 4, brain volume abnormalities have been reported inconsistently in first-degree relatives of BD patients. The volumes of the parahippocampus, insula and caudate nucleus have found to be decreased in some studies, but reported to be increased in others. This is also the case for the hippocampus volume, but this volume has five times been identified as normal. The amygdala volume has been reported to be normal four times, but has also once found to be increased. A decreased prefrontal cortex volume has been quite consistently reported. The increased left temporal lobe, right putamen and lateral ventricle volumes seen in BD patients, and the reduced cerebrum volume in first-episode BD patients have not been established in first-degree relatives of BD patients. These structural abnormalities could thus be disease related, instead of reflecting a genetic vulnerability to BD (Bearden et al., 2011). In other words, it is possible that these abnormalities occur as a result of the illness rather than as a preexisting risk factor (Karchemskiy et al., 2011). Interestingly, an increased amygdala is reported in lithium treated BD patients, and is possibly present in first-degree relatives, this increased volume might be protective against the illness (van Erp et al., 2012). More experimental structural MRI studies are needed to identify potential brain structural volume abnormalities in first-degree relatives of BD patients in order to categorize these abnormalities as either disease related, reflecting genetic vulnerability or protective against the illness.

Conclusion

In this thesis an overview is given of structural brain abnormalities in first-degree relatives of BD and SCZ patients. Brain volume abnormalities have been found inconsistently throughout the whole brain, but a decreased prefrontal cortex volume in first-degree relatives of both BD and SCZ patients, a reduced hippocampus volume and increased third ventricle volume in first-degree relatives of SCZ patients and a reduced insula volume in parents of SCZ patients appear to be the most consistent findings.

With information that can be extracted from the literature overview, the two hypotheses of this thesis can now be examined. The first hypothesis, which stated that offspring would have more severe structural brain abnormalities than siblings or co-twins of BD or SCZ probands can be partially rejected. No sub-group specific brain volume abnormality was found in relatives of BD patients. However, no clear distinction could be made between the brain volume abnormalities found in siblings, co-twins and offspring of SCZ patients, because these sub-groups were not considered separately in the reviews and meta-analyses here used. It might be of value for future research to consider the available structural MRI data for siblings, co-twins, offspring and parents of SCZ patients separately. The second hypothesis, which stated that first-degree relatives of SCZ patients would have more prominent structural anomalies than first-degree relatives of BD can be accepted as highly probable. It appeared that, although not all findings were consistently, more structural abnormalities could be identified in the first-degree relatives of SCZ probands than in those of BD patients. It might be valuable to conduct more research on structural brain abnormalities in first-degree relatives of BD patients in order to achieve more consistent results.

In conclusion, it can be stated that because of the fact that an abnormal prefrontal cortex volume was found to be present in both first-degree relatives of SCZ patients and of BD patients, whereas other structural abnormalities were specific for the genetic risk of either SCZ or BD, both overlapping and segregating effects on brain structures of genetic risks for SCZ and BD appear to exist.

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Appendix I.I Table 1: brain volume abnormalities in offspring of BD patients

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Hajek, …, Alda (Hajek et al., 2013) Brain structural signature of familial predisposition for bipolar disorder: replicable evidence for involvement of the right inferior frontal gyrus. Biol Psychiatry. 2013	Families were identified through adult probands with BD, who had participated in 1) previous genetic and high-risk studies for the Halifax sample and 2) the Czech Bipolar Disorder Case Registry for the Prague sample.	Unaffected high-risk offspring; n=50; 19 males Affected offspring; n=36; 10 males Healthy controls; n=49; 18 males Young BD patients; n=19; 7 males	MRI: 1.5 Tesla GE scanner	Investigating neuroanatomic markers of familial predisposition by comparing unaffected and affected relatives of BD probands as well as control subjects.	Unaffected and affected relatives of BD probands showed larger right inferior frontal gyrus (rIFG) volumes than control subjects.	Mean age +/- 22 years old	Reference of Nery, 2013 (Review)	The offspring and the BD patients participating in this study were not related.
Gunde, …, Hajek (Gunde et al., 2011) White matter hyperintensities in affected and unaffected late teenage and early adulthood offspring of bipolar parents: a two-center high-risk study. J Psychiatr Res. 2011	Participants were found in the same way as described in Hajek, 2009a.	Unaffected high-risk offspring; n=44; 16 males BD patients; n= 35; 9 males Healthy controls; n= 49; 18 males	MRI: 1.5 Tesla scanner FLAIR images	To test whether white matter hyperintensities represent an endophenotype for BD.	The proportion of WMH-positive subjects was comparable between the unaffected high-risk, affected familial and control groups.	Mean age +/- 20.5 years old	Reference of Mahon, 2013	The offspring in this study were the children of the patients in the study. In this study both BD1 and BD2 patients participated.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Karchemskiy, …, Chang (Karchemskiy et al., 2011) Amygdalar, hippocampal, and thalamic volumes in youth at high risk for development of bipolar disorder. Psychiatry Res 2011	Recruited from an ongoing study of BD offspring and from the community.	High-risk subjects with ADHD and moderate mood symptoms; n=22; 15 males Healthy controls; n=22; 15 males	MRI: 3 Tesla GE scanner ANCOVA	To examine amygdala volumes in high-risk offspring who have not yet developed a full manic episode.	High-risk offspring had similar amygdalar, hippocampal and thalamic volumes compared to the control group.	Mean age 12.3 years old.	Reference of Schneider, 2012 (review)	
Hajek, …, Höschl (Hajek et al., 2010) Subgenual cingulate volumes in offspring of bipolar parents and in sporadic bipolar patients. Eur Arch Psychiatry Clin Neurosci. 2010	High-risk offspring were identified through adult BD1 or BD2 probands who participated in Czech Bipolar Disorder Case Registry.	Unaffected high-risk offspring; n=20; 9 males Affected offspring (MD, BD1, BD2); n=15; 9 males Healthy controls; n=18; 7 males Sporadic BD patients; n= 19; 7 males	MRI: 1.5 Tesla scanner ANOVA ANCOVA for the sporadic patients	Subgenual cingulate volumes in young affected and unaffected offspring of bipolar patients (high-risk design) and in sporadic bipolar patients were measured to test whether SGC volumes represent an endophenotype for BD.	Comparable SGC volumes were found among unaffected and affected offspring of BD parents and controls.	15-30 years old	PubMed: Bipolar MRI offspring high-risk	The cohort included offspring of both BD1 and BD2 patients.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Hajek, …, Alda (Hajek et al., 2009a) Amygdala and hippocampal volumes in relatives of patients with bipolar disorder: a high-risk study. Can J Psychiatry. 2009a	Families were identified through adult probands with BD I or II, who had participated in genetic studies and had been recruited from outpatient clinics at the Queen Elizabeth II Health Centre in Halifax.	Unaffected high-risk offspring; n=26; 9 males Affected offspring (MDD, BD1 or BD2); n=20; 5 males Healthy controls; n=31; 11 males	MRI: 1.5 Tesla scanner ANOVA Analysis of covariance	Mesiotemporal volumes were measured in young affected and unaffected offspring of patients with BD, to test whether amygdala or hippocampus volumes represent an endophenotype for BD.	Comparable amygdala and hippocampal volumes among unaffected relatives, affected high-risk patients, and control subjects were found.	15 -30 years old	Reference of Karchemskiy, 2011	The cohort included offspring of parents with MDD (but with a second-degree relative with BD).
Hajek, …, Alda. (Hajek et al., 2009b) Striatal volumes in affected and unaffected relatives of bipolar patients--high-risk study. J Psychiatr Res. 2009b	Participants were found in the same way as described in Hajek, 2009a.	Same as Hajek, 2009a. Partially overlapping sample.	MRI: 1.5 Tesla scanner Repeated measures analysis of variance	To investigate whether striatal volume changes represent a primary biological risk factor for BD.	No significant differences in caudate volumes between affected, unaffected high-risk offspring, BD patients and healthy controls after controlling for non-independence of observations.	15-30 years old	Related citations in PubMed via Hajek, 2009	

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Hajek, …, Alda. (Hajek, et al., 2008a) Subgenual cingulate volumes in affected and unaffected offspring of bipolar parents J Affect Disord. 2008a	Participants were found in the same way as described in Hajek, 2009a.	Unaffected high-risk offspring; n=13; 4 males Affected offspring (MDD, BD1 or BD2); n=13; 4 males Healthy controls; n=31; 11 males	MRI: 1.5 Tesla scanner One-way ANOVA	To investigate whether subgenual cingulate volumes represent an endophenotype for BD.	Subgenual cingulate volume abnormalities were absent in unaffected or affected offspring of BD patients.	15 -30 years old	Related citations in PubMed via Hajek, 2009	The cohort consisted of offspring of BD1 patients only.
Hajek, …, Alda (Hajek, 2008b) Pituitary volumes in relatives of bipolar patients: high-risk study. Eur Arch Psychiatry Clin Neurosci. 2008b	Participants were found in the same way as described in Hajek, 2009a.	Unaffected high-risk offspring; n=24; 9 males Affected offspring; n=19; 5males Healthy controls; n=31; 11 males	MRI: 1.5 Tesla scanner ANOVA	To investigate whether abnormal pituitary volumes increase vulnerability for BD, or are secondary to burden of illness.	Comparable pituitary volumes among unaffected, affected relatives of bipolar patients and controls were found. There were no differences between subjects from families containing bipolar I versus families containing only bipolar II subjects.	15-30 years old	Reference of Nery, 2013 (Review)	Included subjects with family history of BD1 in second degree relatives or BD2 in first or second degree relatives.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Ladouceur, …, Phillips (Ladouceur et al., 2008) Subcortical gray matter volume abnormalities in healthy bipolar offspring: potential neuroanatomical risk marker for bipolar disorder? J Am Acad Child Adolesc Psychiatry 2008	Recruited from an ongoing longitudinal study on the psychopathology and functioning of bipolar offspring conducted at Western Psychiatry Institute and Clinic, University of Pittsburgh.	High-risk offspring; n=20; 9 males Healthy controls; n=22; 7 males	MRI: 3 Tesla scanner Between-groups comparisons	To study premorbid vulnerability neuroanatomical markers of BD and to identify potential structural neuroanatomical alterations that may contribute to the protection against subsequent development of BD.	High-risk offspring had significantly increased gray matter volume in left parahippocampal/ hippocampal gyrus. Effects that did not survive controlling for multiple comparisons: Increased GM volume in amygdala and orbitomedial prefrontal cortex and decreased GM volume in middle frontal and temporal gyrus and caudate nucleus in high-risk offspring.	8-17 years old	Reference of Schneider, 2012 (review)	Tested for brain regions known to be involved in affect regulation.
Singh, …, Strakowski (Singh, 2008) Neuroanatomical characterization of child offspring of bipolar parents. J Am Acad Child Adolesc Psychiatry 2008	Identified from ongoing studies at the University of Cincinnati and from local bipolar support groups.	High-risk offspring (76% met DSM-IV-TR criteria for at least one psychiatric disorder); n=21; 12 males Healthy controls; n=24; 11 males	MRI: 1.5 Tesla GE scanner MANCOVA ANCOVA	To examine structural differences in selected anterior limbic brain regions (prefrontal cortex, thalamus, striatum, and amygdala) between high-risk children of parents with BD and children with healthy parents.	No statistically significant differences were found in prefrontal, striatal, thalamic, and amygdalar volumes between high-risk children and healthy controls. Post-hoc analyses of prefrontal cortical volumes showed non-significant enlargement in high-risk offspring.	8-12 years old	Reference of Schneider, 2012 (review)	Tested for regions that modulate mood

Table 1: Details of structural MRI studies investigating brain volume abnormalities in offspring of BD patients.

Appendix I.II Table 2: brain volume abnormalities in siblings of BD patients

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Eker, …, Gonul (Eker et al., 2014) Brain regions associated with risk and resistance for bipolar I disorder: a voxel-based MRI study of patients with bipolar disorder and their healthy siblings. Bipolar Disord. 2014	All subjects were recruited from the Ege University School of Medicine's Department of Psychiatry.	High-risk siblings; n=28; 11 males BD1 probands; n=28; 16 males Healthy Controls; n=30; 10 males	MRI: 3 Tesla scanner Paired t-test	To identify brain structural endophenotypes associated with risk and resistance for BD.	Compared to healthy controls, siblings of BD patients had a smaller orbitofrontal cortex and a larger left dorsolateral prefrontal cortex. Additional ROI analyses also found volume deficits in the right cerebellum of healthy siblings of BD patients.	Mean age +/- 35 years old	PubMed: MRI bipolar sibling	Siblings had no mental illness.
Mahon, …, Szeszko (Mahon et al., 2013) Abnormal temporal lobe white matter as a biomarker for genetic risk of bipolar disorder Biol Psychiatry. 2013	No information provided	High-risk siblings; n=15; 6 males BD patients; n=26; 11 males Healthy Controls; n=27; 15 males	MRI: 3 Tesla scanner DTI Fractional anisotropy (FA) ANCOVA	Compare patients, adult unaffected siblings, and healthy controls using a voxelwise analysis of FA data to examine the possibility that FA abnormalities may serve as an endophenotype for BD.	FA differed significantly among the three groups within the right temporal white matter (healthy controls > unaffected siblings > bipolar disorder). The abnormal WM was found in the inferior frontal occipital fasciculus.	Mean age +/- 40 years old	PubMed: MRI bipolar sibling	BD1 and BD2

Table 2: Details of structural MRI studies investigating brain volume abnormalities in siblings of BD patients.

Appendix I.III Table 3: brain volume abnormalities in twins of BD patients

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Van Erp, …, Cannon (van Erp et al., 2012) Hippocampal morphology in lithium and non-lithium-treated bipolar I disorder patients, non-bipolar co-twins, and control twins. Hum Brain Mapp. 2012	The National Hospital Discharge Register of Finland was searched for patients. The National Population Register and the Finnish Twin Cohorts were queried to locate twins born between 1940 and 1969.	High-risk co-twins; n=14; 5 males Lithium-treated BD1 patients; n=10; 3 males BD1 patients no lithium; n=8; 5 males Control twins; n=32; 17 males	MRI: 1 Tesla scanner Mixed model regression analyses	To create detailed hippocampal surface maps comparing BD1 patients and non-bipolar co-twins with control twins.	High-risk co-twins showed significantly thicker hippocampi compared to control twins.	Mean age +/- 45 years old	PubMed: bipolar MRI twins	Monozygotic and dizygotic twins participated in this study.
Bearden, …, Cannon (Bearden et al., 2011) Mapping corpus callosum morphology in twin pairs discordant for bipolar disorder. Cereb Cortex 2011	Participants were found in the same way as described in Van Erp, 2012.	High-risk co-twins; n= 19; 8 males BD1 patients; n=21; 11 males Control twins; n=34; 17 males	MRI: 1 Tesla scanner Mixed model regression analyses	To assess genetic and/or disease-related contributions to altered midsagittal callosal morphometry in bipolar disorder.	No differences in callosal structure could be detected between co-twins and controls.	Mean age +/- 45 years old	PubMed: bipolar MRI twins	Monozygotic and dizygotic twins participated in this study.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Van der Schot, …, Kahn (van der Schot et al., 2010) Genetic and environmental influences on focal brain density in bipolar disorder. Brain 2010	Participants were found in the same way as described in Van der Schot, 2009.	BD twins (concordant and discordant); n=98; 30 males Healthy twins; n=134; 57 males As described in Van der Schot, 2009	MRI: 1.5 Tesla scanner Correlations	Investigating the genetic and environmental influences on gray and white matter density in bipolar disorder.	The brain abnormalities associated with the genetic risk for developing BD were bilaterally white matter decreases in the superior longitudinal fascicule, increased gray matter density in the right medial orbital gyrus and gray matter loss in the right medial frontal gyrus, precentral gyrus and insula.	Mean age +/- 40 years old 18-60 years of age	PubMed: MRI bipolar twins	Genetic liability study.
Van der Schot, …, Kahn (van der Schot et al., 2009) Influence of genes and environment on brain volumes in twin pairs concordant and discordant for bipolar disorder. Arch Gen Psychiatry 2009	Subjects were recruited from the population, the Netherlands Twin Register, and the twin pair cohort at the University Medical Center Utrecht, Utrecht, The Netherlands.	Bipolar twins; n=100; 32 males (9 MZ concordant; 15 MZ discordant; 4 DZ concordant; 22 DZ discordant) Control twins; n=134; 57 males (39 MZ, 28 DZ)	MRI: 1.5 Tesla scanner	To quantify the genetic and environmental effects on brain volume in bipolar disorder, by measuring global and regional (gray and white matter) brain volumes.	Decrease in white matter is related to the genetic risk of developing bipolar disorder (found in both bipolar patients and in their co-twins). Environmental factors, including the effects of illness, lead to decreased cortical gray matter volume.	Mean age +/- 40 years old 18-60 years of age	Reference of Bearden, 2011.	Genetic liability study.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Kieseppä, …, Lönngvist (Kieseppä et al., 2003) Reduced left hemispheric white matter volume in twins with bipolar I disorder. Biol Psychiatry. 2003	A twin sample partially overlapping with the one studied in Bearden, 2011. The National Hospital Dis-charge Register, National Popu-lation Register, and Finnish Twin Cohorts were used to identify bipolar twins.	High-risk co-twins; n=15; 6 males BD1 twins; n=24; 13 males Control twins; n=27; 14 males	MRI: 1 Tesla scanner Random-effects model for non-independent data.	To compare BD1 twins with their co-twins and a sample of control twin subjects, in order to detect structural alterations related to the disorder and to the increased genetic risk.	Patients and co-twins showed a significant decrease in left hemispheric white matter volume. No gray matter decrease or ventricular enlargement was seen in patients or co-twins.	Mean age +/- 45 years old	Reference of Ladouceur, 2008	Monozygotic and dizygotic twins participated in this study.
Noga, Vladar, Torrey (Noga et al., 2001) A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. Psychiatry Res 2001	Bipolar twins recruited with the assistance of the National Alliance for the Mentally Ill and the Schizophre-nia Society of Canada. Normal MZ twins were acquired by newspaper advertisement.	MZ twins discordant for BD; n=12, 2 males Normal MZ twins; n=22; 10 males	MRI: 1.5 Tesla GE scanner Two-way ANOVA One-way MANOVA	To compare twin pairs discordant for BD with normal twins on volumes of basal ganglia, amygdala-hippocampus, and cerebral hemisphere.	Caudate nuclei were larger in both affected and unaffected bipolar twins than in normal MZ twins.	Mean age 34 years old	Reference of Bearden, 2011.	

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Hulshoff Pol *et al.*, 2012 (Hulshoff Pol et al., 2012)		49 adult BD twin pairs (9 MZ and 4 DZ concordant; 14 MZ and 22 DZ discordant) 83 healthy twin pairs (44 MZ and 39 DZ)	Segmentation of GM volumes Cortical thickness measurements Estimate of genetic and environmental contribution to MRI outcomes		Genetic liability for BD was associated with higher intracranial volume, thinner right (and left) parahippocampi, thinner right orbitofrontal cortex, and thicker temporoparietal and left superior motor cortices.		Data from the review of Nery *et al*. (Nery, Monkul, & Lafer, 2013)	Sample included 44 BD type I and 18 BD type II. No control for the effects of antipsychotic medication. Few co-twins had Axis I psychiatric disorders.
Kieseppä *et al.*, 2002 (T Kieseppä et al., 2002)		28 BD spectrum cotwins 22 unaffected co-twins 34 HCs	Manual tracing of brain hemispheres, GM and WM volumes, ventricle volumes, and CSF volumes		No differences in hemispheric GM content between BD spectrum co-twins and HCs.		Data from the review of Nery *et al*. (Nery et al., 2013)	BD spectrum co-twin sample included 23 BD type I and five schizoaffective subtype manic individuals.

Table 3: Details of structural MRI studies investigating brain volume abnormalities in twins of BD patients.

Appendix I.IV Table 4: brain volume abnormalities in mixed or non-specified samples of first-degree relatives of BD patients

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Matsuo, …, Soares (Matsuo et al., 2012) New structural brain imaging endophenotype in bipolar disorder. Mol Psychiatry. 2012	The participants were recruited at hospitals and clinics and through advertisement broadcast in the community.	High-risk offspring (4), siblings (8), parents(9); n=20?; 15 males BD patients; n=35; 8 males Healthy Controls; n=40; 16 males	MRI: 3 Tesla scanner	To show anterior-limbic structural brain abnormalities in unaffected but genetically liable family members of BD1 patients.	BD1 patients and the high-risk subjects had smaller left anterior insular GM volumes compared with the healthy subjects. The high-risk subjects had smaller right medial frontal WM volumes compared with the healthy subjects.	Mean age +/- 42 years old.	From the review by Nery, 2013.	
Takahashi, …, Frangou (Takahashi et al., 2010) Pituitary volume in patients with bipolar disorder and their first-degree relatives. J Affect Disord. 2010	The entire sample was recruited at the Institute of Psychiatry, London, UK as part of the Vulnerability to Bipolar Disorders Study (VIBES). Cohort partially overlapped the one used in Walterfang, 2009.	High-risk siblings (23) and offspring (26); n=49; 23 males BD patients; n=29; 15 males Healthy Controls; n=52; 28 males	MRI: 1.5 Tesla GE scanner ANCOVA	To investigate the pituitary volume in BD patients, first degree relatives of BD patients and healthy controls.	Pituitary volume did not differ between healthy controls and healthy relatives or relatives diagnosed with major depression.	Mean age +/- 36 years old.	From the review by Nery, 2013.	15 of the high-risk relatives suffered from major depression.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Kempton, …, Frangou (Kempton et al., 2009) Dissociable Brain Structural Changes Associated with Predisposition, Resilience, and Disease Expression in Bipolar Disorder. J Neurosci. 2009	Patients were identified by clinicians' referrals.	High-risk siblings (23) and offspring (27); n=50; 24 males BD patients; n=30; 15 males Healthy Controls; n=52; 27 males	MRI: 1.5 Tesla GE scanner ANCOVA	To identify potential brain structural correlates for risk and resilience to BD1 in patients and their relatives.	Increased left insula volume was associated with genetic preposition to BD-I independent of clinical phenotype. Changes uniquely associated with the absence of a clinical diagnosis in BD relatives were observed in the left cerebellum.	Mean age +/- 36 years old.	From the review by Nery, 2013.	Genetic liability study. 14 of the high-risk relatives suffered from major depression.
Walterfang, …, Frangou (Walterfang et al., 2009) Corpus callosum size and shape alterations in individuals with bipolar disorder and their first-degree relatives. Prog Neuropsy-Chopharmacol Biol Psychiatry. 2009	The entire sample was recruited at the Institute of Psychiatry, London, UK.	High-risk siblings and offspring; n=45; 22 males BD patients; n=70; 33 males Healthy Controls; n=75; 39 males	MRI: 1.5 Tesla GE scanner ANCOVA	To compare the size and shape of the corpus callosum between high-risk relatives, BD patients and healthy controls.	First-degree relatives did not differ in callosal size or shape from healthy controls.	Mean age +/- 38 years old.	Reference of Bearden, 2011	

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Mondelli, …, Pariante (Mondelli et al., 2008) Pituitary volume in unaffected relatives of patients with schizophrenia and bipolar disorder. Psychoneuroen-docrinology. 2008	Families affected with BD were recruited through voluntary support groups or through referral from treating psychiatrists. Cohort partially overlapped the one used in the studies of McDonald.	High-risk relatives (mainly parents); n=38; 19 males BD patients; n=29; 11 males Healthy Controls; n=46; 22 males	MRI: 1.5 Tesla GE scanner ANCOVA	To investigate the pituitary volume in BD patients, first degree relatives of BD patients and HCs.	No significant difference in pituitary volume was found when comparing the relatives of bipolar patients with controls.	Mean age +/- 40 years old. Aged 17-68.	Related citations in PubMed at Takahashi, 2010.	
Frazier, …, Makris (Frazier et al., 2007) White matter abnormalities in children with and at risk for bipolar disorder. Bipolar Disord. 2007	The children with BD and the high-risk relatives were recruited through child outpatient and inpatient programs at McLean Hospital and Cambridge Health Alliance and through professional-patient advocacy groups.	High-risk relatives (53% had a sibling with BD, 43% a parent); n=7; 4 males Bipolar Children; n=10; 4 males Healthy Controls; n=8; 5 males	1.5 Tesla GE scanner DTI: Fractional anisotropy (FA)	Children with BD may have WM abnormalities that precede illness onset. To examine this possibility, children with BD were scanned and compared to healthy controls and high-risk relatives.	Both the BD patients and the high-risk relative groups showed reduced FA relative to healthy controls in bilateral superior longitudinal fasciculus I.	4-12 years	Reference of Schneider, 2012 (review)	

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Boccardi et al., 2010 (Boccardi et al., 2010)		10 healthy and nine affected first- or second-degree relatives of BD type I patients 19 HCs	Manual tracing of amygdala and hippocampus		Enlarged amygdala volumes and decreased right hippocampal volumes in healthy relatives compared with HCs.		Data from the review of Nery *et al*. (Nery, Monkul, & Lafer, 2013)	19 participants from only one family with one proband with BD type I.
McIntosh et al., 2004 (McIntosh et al., 2004)		26 BD type I adult patients 22 adult first-degree relatives 49 adult HCs	VBM Whole-brain and SVC analysis 2-group comparison of GM density		Reduced GM density in left anterior thalamus and caudate in relatives of BD patients compared with HC.		Data from the review of Nery *et al*. (Nery et al., 2013)	Families with at least two BD patients (up to second degree).
Connor et al., 2004 (Connor et al., 2004)		39 BD type I adult patients 54 adult unaffected first-degree relatives 219 adult HC	Hippocampal shape anomaly		5.1% of HSA in BD patients compared with 7.5% in first-degree relatives and 7.8% in HCs.		Data from the review of Nery *et al*. (Nery et al., 2013)	Families with at least two BD patients (up to second degree). Differences in HSA prevalence were not significant.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
McDonald et al., 2006 (McDonald et al., 2006)		38 BD type I adult patients 52 adult first-degree relatives 54 adult HCs	Stereological estimation of cerebral volume, lateral ventricles, third ventricle, and bilateral hippocampal volume		No statistical differences between BD patients and first-degree relatives compared with HCs regarding cerebral and ventricle volumes, and hippocampal volumes.		Data from the review of Nery *et al*. (Nery et al., 2013)	Families with at least two BD patients (up to second degree). Results did not change after excluding relatives with previous Axis I disorder.
McDonald et al., 2004 (McDonald et al., 2004)		37 BD type I adult patients 50 unaffected adult first-degree relatives	VBM Correlational analysis between genetic liability score and GM and WM volumes		Genetic liability score for BD inversely correlated with GM volumes in the right anterior cingulate and ventral striatum.		Data from the review of Nery *et al*. (Nery et al., 2013)	Families with at least 2 BD patients (up to second degree). Nine first-degree relatives had previous MDD. Results did not change after excluding relatives with previous Axis I disorders.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
McIntosh et al., 2006 (McIntosh et al., 2006)		26 BD type I adult patients 22 unaffected adult first-degree relatives	VBM Whole-brain and SVC Regression analysis of GM or WM volumes and genetic liability scores		No association found between genetic liability to BD and regional GM or WM volumes in Relatives.		Data from the review of Nery *et al*. (Nery et al., 2013)	Families with at least two BD patients (up to second degree).

Table 4: Details of structural MRI studies investigating brain volume abnormalities in first-degree relatives of BD patients; studies reported in this table used mixed samples or did not specify the composition of the high-risk sample.

Appendix II.I Table 5: brain volume abnormalities in first-degree relatives of SCZ patients

Study	High-risk sample	Aim	Inclusion criteria	Results
Thermenos, …, Seidman (Thermenos et al., 2013) A review of neuroimaging studies of young relatives of individuals with schizophrenia: a developmental perspective from schizotaxia to schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2013	Youth (<30 years old); siblings, twins and offspring of SCZ patients	To review the literature on the neural substrates of risk for SCZ, as reflected in neuroimaging studies of young (age <30) persons at genetic high-risk for SCZ.	1. Studies were MRI studies, e.g., structural (s)MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) 2. Studies used young, genetic high-risk samples (age<30 years old)	A broad overview of structural abnormalities in young first-degree relatives of SCZ patients. The most consistent findings were PFC alterations and hippocampal volume decreases, but many structures are being discussed.
Lawrie,…, Johnstone (Lawrie et al., 2008) Brain Structure and Function Changes During the Development of Schizophrenia: The Evidence From Studies of Subjects at Increased Genetic Risk. Schizophr Bull. Mar 2008	Mostly siblings and offspring of SCZ patients	To review the available evidence, from clinical, epidemiological, and imaging studies, for premorbid changes in subjects at genetic high-risk for SCZ.	Examined several ROI studies that investigated the volumes of brain regions that they suggested to be abnormal in SCZ patients, e.g. temporal and frontal lobes and ventricle- brain ratio.	Increased lateral ventricles, reductions of the volume in the amygdala-hippocampal complex, reduced gray matter density in the PFC, third ventricle enlargement and thalamus volume reductions.
Chan, …, Gong (Chan et al., 2011) Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression Schizophr Bull. Jan 2011	Meta-analysis with eight high-risk studies, five of which used a sample of first-degree relatives.	To map gray matter brain abnormalities in schizophrenia and high-risk individuals.	1. Only included research articles. 2. Studies used VBM analysis on MRI data. 3. Studies directly compared SCZ patients or high-risk subjects with a healthy control group. 4. Results of the studies were normalized to a stereotactic standardized space.	High-risk individuals appear to have significantly less gray matter in bilateral anterior cingulate gyrus, right insula, left amygdala, left subcallosal gyrus, and left inferior frontal gyrus

Study	High-risk sample	Aim	Inclusion criteria	Results
Boos, …, Kahn (Boos et al., 2007) Brain volumes in relatives of patients with schizophrenia: a meta-analysis. Arch Gen Psychiatry. 2007	Twenty-five studies reporting brain volumes of siblings, twins and parents of SCZ patients.	To determine the magnitude and extent of brain volume differences in first-degree relatives of SCZ patients.	1. MRI studies of brain structures published before July 2005 or a presented abstract at the International Congress on Schizophrenia Research in 2005. 2. Studies compared first-degree relatives of SCZ patients with a healthy control group. 3. Studies were published in the English language. 4. Studies reported sufficient data to obtain the effect size	First-degree relatives of SCZ patients have decreased volumes of the hippocampus and cerebral gray matter and increased third ventricle volumes.
Moran, Hulshoff Pol and Gogtay (Moran, Hulshoff Pol, & Gogtay, 2013) A family affair: brain abnormalities in siblings of patients with schizophrenia. Brain. 2013	Siblings and twins of SCZ patients. I made a distinction between these groups myself.	To assess and summarize the structural brain imaging findings of developmental changes in siblings and twin pairs discordant for SCZ.	No information provided.	The number of studies that identified the structure as abnormal (with a minimum of two) is mentioned between brackets. Siblings: decreased volume of the hippocampus (4), thalamus (2), frontal lobe (2), and amygdala (1xL+R, 1xR). Twins: decreased volume of the total brain (4), hippocampus (3), white matter (3), and frontal lobe (2). Siblings + twins: abnormalities mentioned above, decreased gray matter volume (2), enlarged third ventricles (2).

Table 5: Details of the here used reviews and meta-analyses comprising structural MRI studies investigating brain volume abnormalities in first-degree relatives of SCZ patients.

Appendix II.II Table 6: brain volume abnormalities in parents of SCZ patients

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Tian, …, Zhang (Tian et al., 2011) Convergent evidence from multimodal imaging reveals amygdala abnormalities in schizophrenic patients and their first-degree relatives. PLoS One, 2011	No details provided	Unaffected parents; n=55 SCZ patients; n=33 Healthy controls; n= 59	sMRI fMRI	To explore genetic influences on brain morphology of SCZ patients and their unaffected parents by looking for structural abnormalities of brain regions.	Parents showed gray matter reductions in the left amygdala, left insula, left thalamus and right orbitofrontal cortex compared to healthy controls.	No details provided	PubMed: MRI schizophrenia parent	
Lui, …, Gong (Lui et al., 2009) Neuroanatomical differences between familial and sporadic schizophrenia and their parents: an optimized voxel-based morphometry study. Psychiatry Res, 2009	All subjects participated in a large cohort family study of first episode schizophrenia in a Chinese population of Han Nationality in the Mental Health Centre of West China Hospital.	Unaffected parents; n=20; SCZ patients; n=20; 10 males Healthy controls; n=20; 9 males Half of the sample is studied for abnormalities in familial SCZ, the other half for abnormalities in sporadic SCZ.	MRI: 3 Tesla scanner Two sample t-tests	To examine neuroanatomical differences between patients with familial and sporadic schizophrenia and their parents.	Compared with healthy controls, familial parents showed lower gray matter density in the right insula extending to the right temporal lobe and the right parietal lobule.	Mean age +/- 43 years old.	PubMed: MRI schizophrenia parent	The parents in this study are the parents of the SCZ patients in this study.

Study	Cohort	Participants	Method	Aim	Results	Age	Found?	Comments
Ohara, …, Shibuya (Ohara, Sato, Tanabu, Yoshida, & Shibuya, 2006) Magnetic resonance imaging study of the ventricle-brain ratio in parents of schizophrenia subjects. Prog Neuropsycho-pharmacol Biol Psychiatry, 2006	Schizophrenics were in-/out-patients of the National Minami Hanamaki Hospital.	18 Unaffected Parents; n=18; 9 males SCZ patients; n=9; # of males not provided Healthy controls; n=18; 9 males (age-matched with the parents)	MRI Mann–Whitney U-test	To study the ventricle–brain ratio (VBR) of parents of schizophrenics.	The VBRs of the unaffected parents of the schizophrenic patients were significantly larger than those of the healthy controls.	Mean age males: 74.1; Mean age females: 64.0	PubMed: MRI schizophrenia parent	The parents in this study are the parents of the SCZ patients in this study.
Harris, …, Freedman (Harris et al., 2002) Increased hippocampal volume in schizophrenics' parents with ancestral history of schizophrenia. Schizophr Res, 2002	No details provided	Unaffected parents; n=12 SCZ patients; n=6 Healthy controls (matched to the patients); n=6	MRI: 1.5 Tesla scanner Linear modeling approach	To measure the hippocampal volume of the parents of schizophrenic probands, in relationship to the apparent transmission of genetic risk.	The total hippocampal volumes of the parents with ancestral family history of schizophrenia were significantly larger than those of their schizophrenic offspring and of healthy controls.	No details provided	PubMed: MRI schizophrenia parent	The parents in this study are the parents of the SCZ patients in this study. No direct comparison between parents and healthy controls.

Table 6: Details of structural MRI studies investigating brain volume abnormalities in parents of SCZ patients.