Biomarqueurs neuroanatomiques chez les individus à haut risque pour le trouble bipolaire

Thèse

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Résumé

Le trouble bipolaire est une maladie psychiatrique grave qui affecte de façon significative la population générale, et dont la physiopathologie nous est encore largement inconnue.

Il a été rapporté que les enfants de patients souffrant de troubles bipolaires ont un risque plus élevé de développer différents types de troubles de l'humeur. L''évaluation de ces personnes alors qu'ils sont à un âge précédant celui d'apparition de la maladie est une stratégie pertinente pour élucider le développement probable du trouble bipolaire ou d'autres troubles affectifs tel la dépression majeure, ainsi que leurs facteurs de risque concomitants.

Les études qui utilisent l'imagerie par résonance magnétique pour examiner ces jeunes à haut risque (HR) nous donnent la possibilité d'identifier des vulnérabilités génétiques et/ou des marqueurs potentiels de risque d'apparition précoce, en mesurant la nature et l'ampleur des changements du cerveau qui se produisent au cours du développement de cette maladie et / ou de maladies associées au trouble bipolaire.

Cette thèse contribue à la recherche dans ce domaine en explorant la morphologie du cerveau chez des adolescents et jeunes adultes asymptomatiques qui ont un risque élevé de développer le trouble bipolaire.

Dans la première étude (*cf*. Chapitre II), nous avons effectué une méta-analyse d'études publiées utilisant la morphométrie cérébrale basée voxel (« voxel-based morphometry ») comparant la matière grise et blanche de patients avec un diagnostic de trouble bipolaire à des sujets sains, dans le but de mieux expliquer et comprendre les changements neuroanatomiques reliés à la maladie. Cette méta-analyse a démontré l'implication de régions spécifiques de matière grise et blanche, particulièrement les cortex frontaux, cingulaire, et parahippocampiques, le striatum, et les connections de matière blanche situées dans le lobe temporal, le cingulum et dans le cortex insulaire.

À la lumière de ces résultats, nous avons voulu investiguer ces mêmes régions chez des individus asymptomatiques mais à risque de développer une maladie bipolaire, afin d'y déceler, si possible, des indices du développement précoce de la maladie. Ainsi, notre deuxième étude (*cf*. Chapitre III) explore à l'aide de différentes techniques la matière grise et blanche de huit enfants de patients bipolaires recrutés au Québec, comparés à des sujets témoins, sans antécédents familiaux de troubles psychiatriques, et appariés pour l'âge et pour le sexe**.** Les résultats chez les enfants à haut risque révèlent des altérations principalement situées dans les volumes et les épaisseurs corticales des régions parahippocampiques, pariétales et frontales, ainsi qu'une intégrité réduite de la matière blanche dans les connexions fronto-thalamique.

Avec cette étude nous avons confirmé l'implication des cortex frontaux et parahippocampique non seulement dans la maladie bipolaire mais aussi comme possible endophenotype relié à un risque génétique de développer ce trouble.

Enfin, nous avons étudié l'intégrité de la matière blanche dans un plus grand échantillon de jeunes à HR pour les troubles de l'humeur recrutés en Écosse,

à l'entrée dans l'étude ainsi qu'aux suivis longitudinaux, alors que certains HR ont développé un trouble affectif (dépression majeure). Les différences d'intégrité de matière blanche entre les membres de la famille des patients et les contrôles ont été analysées via l'imagerie par résonance magnétique de diffusion.

De façon générale, nous avons remarqué une intégrité réduite dans les connections de la matière blanche chez tous les sujets à haut risque par rapport aux témoins (*cf*. Chapitre IV) à l'entrée dans l'étude. De plus, nous avons démontré une association entre l'intégrité de la matière blanche dans différentes régions cérébrales et les symptômes dépressifs sous-cliniques dès l'entrée dans l'étude chez les sujets HR qui ont développé une dépression lors du suivi. Finalement, nous avons détecté une perte progressive de l'intégrité de la matière blanche dans le temps dans tous les sujets (HR comme témoins) lors du suivi longitudinal, mais aucune différence entre les sous-types de HR et les témoins (*cf*. Chapitre V).

Cette thèse fournit donc des preuves convaincantes que les individus à HR présentent des caractéristiques neuroanatomiques distinctes dans la matière grise et blanche comparativement à des individus de même âge et sexe. Ces résultats ont des implications théoriques et cliniques importantes qui contribuent à clarifier les caractéristiques morphologiques de ce groupe et d'augmenter notre connaissance de la physiopathologie du trouble bipolaire, dans le but d'améliorer le processus de diagnostic.

Abstract

Bipolar disorder (BD) is a severe psychiatric disorder that affects a considerable proportion of humankind, and whose pathophysiology is still mostly unknown.

Because relatives of patients with bipolar disorders are known to be at heightened risk for developing different types of mood disorders, the assessment of these individuals at an age that typically precedes disease onset is a relevant strategy for elucidating developmental and risk factors associated with an increased risk for BD and other affective disorders such as major depression.

Magnetic resonance imaging (MRI) investigations in youths at high risk (HR) can help identify genetic vulnerabilities and potential risk markers of the earliest presence, nature, and extent of brain changes that occur during development of this illness and/or diseases associated with BD.

This dissertation contributes to the body of research in this field by exploring brain morphology in asymptomatic adolescents and young adults at high risk of developing BD.

In the first study (*cf*. Chapter II), we performed a meta-analysis of voxel-based morphometry (VBM) studies comparing grey and white matter in patients diagnosed with BD to healthy subjects, in order to better explain and understand the neuroanatomical changes related to the disease. This meta-analysis demonstrated the involvement of some gray and white matter regions, especially the frontal, cingulate, and parahippocampal cortices, the striatum, and connections located in the temporal lobe, the cingulate and insular cortices.

In light of this study, we wished to explore the same regions in a group of asymptomatic subjects at high risk of developing the disease. Thus, in our second study (*cf.* Chapter III), we explored gray and white matter morphology using different techniques in eight children of BD patients from Québec compared with age- and sex-matched control individuals without family history of psychiatric disorders. Results reveal alterations in BD offsprings mainly located in cortical volumes and thicknesses in limbic, parietal, and frontal areas, as well as reduced white matter integrity in fronto-thalamic connections.

With this study we confirmed the involvement of the frontal and parahippocampal cortices not only in bipolar disorder, but also as a possible endophenotype associated with a genetic risk of developing this illness.

Finally, we investigated white matter (WM) integrity using diffusion tensor images (DTI) in a bigger sample of young subjects at HR of mood disorders recruited in Scotland. WM integrity differences between relatives of BD patients and controls were analyzed both at baseline and after longitudinal follow-up, at which point some high-risk subjects developed major depressive disorder. A reduced WM integrity in genetic high-risk subjects compared with controls was confirmed in this largest Scottish sample (*cf*. Chapter IV). Moreover, we demonstrated an association between WM integrity in different regions and sub-clinic symptoms of depression at baseline in HR subjects. Finally, we detected a progressive loss of WM integrity with time in both HR subjects and controls (*cf*. Chapter V).

This dissertation provides compelling evidence that HR individuals present distinct neuroanatomical characteristics in both gray and white matter. The results have important theoretical and clinical implications, in that they contribute to clarifying the morphological features of this group and increasing our knowledge of the pathophysiology of BD in order to ameliorate the diagnostic process.

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Liste des abréviations

BD = bipolar disorder
BFS = Bipolar Familial Study
DSM = Diagnostic and Statistical Manual of Mental Disorders
DTI = diffusion tensor imaging
FA = fractional anisotropy
GM = gray matter
HR = high genetic risk
MDD = major depressive disorder
MRI = magnetic resonance imaging
ROI = region of interest
TB = trouble bipolaire
TBSS = tract-based spatial statistics
VBA = Voxel-based analysis
VBM = Voxel-based morphometry
WM = white matter
y.o = years old

Alla mia nonna

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Avant-propos

Rossana Ganzola is the lead author of the Introduction and the Conclusion of this dissertation, as well as of the reports on the exploratory results of the QUEBEC study and the three scientific papers presented.

She was instrumental in the data collection of participants for the QUEBEC study (*cf*. Chapter II), and selected the subjects for the Scottish studies (*cf*. Chapters IV, V). In addition, she performed all neuroimaging and statistical analyses throughout the thesis, and interpreted all results.

Simon Duchesne, Associate Professor in the Department of radiology at Université Laval, acted as the Ph.D. supervisor, providing an overview of the entire scientific process and assisting in the drafting of manuscripts and the final thesis.

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The first paper of this dissertation entitled “Voxel-based morphometry meta-analysis of gray and white matter finds significant areas of differences in bipolar patients from healthy controls” was written by Rossana Ganzola. Simon Duchesne is the co-author and he contributed to the drafting and revision of the manuscript.

The second paper of this thesis entitled “Diffusion tensor imaging correlates of early markers of depression in youth at high familial risk for bipolar disorder” was written by Rossana Ganzola. Co-authors are Andrew M. McIntosh, M.D., Ph.D, Thomas Nickson, Ph.D, Emma Sprooten, Ph.D, Mark E. Bastin, Ph.D, Stephen Giles, Alix Macdonald, MA, Jessika Sussmann, MRCPsych, Simon Duchesne, Ph.D, and Heather C. Whalley, Ph.D.

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The third paper entitled “Longitudinal differences in white matter integrity in youth at high familial risk for bipolar disorder” was written by Rossana Ganzola. Co-authors are Andrew M. McIntosh, M.D., Ph.D, Thomas Nickson, Ph.D, Mark E. Bastin, Ph.D, Stephen Giles, Alix Macdonald, MA, Jessika Sussmann, MRCPsych, Simon Duchesne, Ph.D, and Heather C. Whalley, Ph.D.

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At the time of submission of the thesis, all three papers were under revision to the journal *Bipolar Disorders.*

CHAPTER I: GENERAL INTRODUCTION

Bipolar Disorder

Bipolar disorder (BD) is one of the most common psychiatric illnesses affecting humankind. Prevalence estimates suggest that 1.5-3.0% of the general population will develop BD (Angst, 1998; Narrow et al., 2002), which places it as the sixth leading cause of disability worldwide (Murray et al., 1996). With a mean age of onset at 30 years old (Weissman et al., 1996), BD affects young adults entering their prime productive years for society and themselves.

The disease is characterized by a fluctuating course that includes manic, depressive, and mixed episodes, with intervals of varying levels of euthymic remission. According to the current classification system put forward by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Battle, 2013), BD presentation has been categorized as two main types:

1. Bipolar Disorder Type I, in which at least one manic episode is necessary to make the diagnosis. Depressive episodes are common in the vast majority of cases with bipolar disorder I, but unnecessary for its diagnosis; and

2. Bipolar Disorder Type II, in which the primary symptom presentation is recurrent depression accompanied by hypomanic episodes - a milder state of mania in which the symptoms are not severe enough to cause marked impairment in social or occupational functioning or need for hospitalization, but are sufficient to be observable by others.

Manic episodes are characterized by:

A. Distinct periods of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary);

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) increased self-esteem or grandiosity;

(2) decreased need for sleep (e.g., feels rested after only three hours of sleep);

(3) more talkative than usual or pressure to keep talking;

(4) flight of ideas or subjective experience that thoughts are racing;

(5) distractibility (i.e., attention too easily drawn to unimportant or

irrelevant external stimuli);

(6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation; and/or

(7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

Depressive episodes are characterized by depressed mood and/or loss of interest or pleasure in life activities for at least two weeks and at least five of the following symptoms that cause clinically significant impairment in social, work, or other important areas of functioning almost every day:

(1) Depressed mood most of the day;

(2) Diminished interest or pleasure in all or most activities;

(3) Significant unintentional weight loss or gain;

(4) Insomnia or sleeping too much;

(5) Agitation or psychomotor retardation noticed by others;

(6) Fatigue or loss of energy;

(7) Feelings of worthlessness or excessive guilt;

(8) Diminished ability to think or concentrate, or indecisiveness; and/or

(9) Recurrent thoughts of death.

These psychiatric symptoms are furthermore associated with cognitive problems, such as deficits in executive functions, memory, and attention that persist in the euthymic state (Robinson et al., 2006).

It is likely that BD is caused by neuronal disruptions, brought about by the cumulative impact of genetic predispositions, neurodevelopmental hazards, and environmental factors, all contributing to its development and progression. This accretion model is probably common to the pathophysiology of several psychiatric disorders (Maziade et al., 2005; Paccalet et al., 2016). Thus, the study of biological factors, including brain structure and function, holds promise to shed some light on the causes and effects related to its aetiology.

Neuroimaging findings in bipolar disorder

Since the late 90s, this growing interest in the neurobiological underpinnings of BD has led to the design and reporting of several magnetic resonance imaging

(MRI) studies, in which different techniques have been used to clarify its neuronal substrates.

Here, we will focus on anatomical MRI studies, i.e. those that investigated morphological brain differences in gray and white matter when comparing BD patients and healthy subjects.

Gray Matter

Studies using T1-weighted acquisitions on MRI can reveal differences in individual brain structures such as volumes, cortical thicknesses, or gray matter (GM) concentrations. In BD, these have revealed alterations in volume of prefrontal and limbic regions such as the amygdala, parahippocampal and cingulate cortices (Houenou et al., 2012). In a recent systematic review, the majority of studies reported decreased cortical thickness in the anterior cingulate/paracingulate and the superior temporal gyrus, as well as several prefrontal regions bilaterally in patients with BD when compared to controls (Hanford et al., 2016). Meta-analyses on voxel-based morphometry studies have also identified reduced GM concentrations mainly located in the prefrontal and anterior cingulate cortex, and insula (Bora et al., 2010, 2012; De Peri et al., 2012; Ellison-Wright and Bullmore, 2010; Goodkind et al., 2015; Houenou et al., 2011; Kempton et al., 2008; McDonald et al., 2004; Selvaraj et al., 2012).

White Matter

Studying white matter (WM) on MRI can be done via several anatomical acquisition techniques. T1-weighted images can reveal macroscopic structural alterations related to the general concentration of WM; T2-weighted MRI can be used to study signal hyperintensities within the WM; and finally, diffusion tensor imaging provides a signal related to the fibrous nature of WM, and is therefore useful to assess its integrity as well as its role in connectivity.

Voxel-based morphometry studies investigating differences in WM volumes and/or density in BD patients compared with controls revealed WM reductions in prefrontal and orbitofrontal areas (Bruno et al., 2004; Stanfield et al., 2009), corpus callosum (McDonald et al., 2005), temporal and fronto-thalamic connections (McIntosh et al., 2008; Watson et al., 2012).

Several MRI studies have repeatedly reported diffuse WM hyperintensities in T2-weighted sequences, spread out over subcortical, periventricular and callosal WM areas (Beyer et al., 2009). Pieces of evidence suggested an

association between more severe WM hyperintensities and poorer outcome measures, such as increased clinical severity (Tighe et al., 2012), greater number of hospitalizations, poorer response to treatments (Breeze et al., 2003) and higher suicide risk (Pompili et al., 2008). Nevertheless, similar patterns of WM alterations did not seem to be specific to BD, as they have been found in neuropathological processes, such as cerebrovascular damage, astrocytic gliosis and demyelination processes (Agarwal et al., 2010).

Diffusion tensor imaging (DTI), the most prevalent form of diffusion MRI, provides a more sensitive tool to investigate WM integrity and microstructure (Beaulieu, 2002; Le Bihan, 2003). Basically, DTI produces multiple indices for the study of WM physical integrity. We will limit our interest to the study of fractional anisotropy (FA), which is the most widely used measure of fiber integrity, as well as the most consistently applied across DTI studies.

FA measures the diffusion of water molecules throughout the brain. When the movement of water molecules is constrained to a single direction, for example when restricted along the longitudinal axes of neural fibers due to thick myelin sheaths, the diffusion is said to be anisotropic; whereas when the movement of water molecules is unbound and happens freely in random directions following Brownian motion, for example for free water within the ventricles, the diffusion is said to be isotropic. FA expresses this global motion on a scale of 0 (isotropic) to 1 (anisotropic). To higher values of FA therefore corresponds a strong (myelin) integrity of the underlying WM axonal tracts.

DTI studies have reported FA findings following three major analysis techniques. The first is a region-of-interest (ROI) approach, in which diffusion measures are obtained from a specific brain region defined by manual delineation or by automated segmentation or parcellation. The second is a voxel-based analysis (VBA) approach that allows DTI data analysis over the whole brain volume without a priori hypotheses on specific regions of interest, thus overcoming possible selection bias from the ROI approach – it is akin to voxel-based morphometry as mentioned earlier, but rather than performing tests on GM or WM concentrations, one uses FA or another DTI-derived metric. Finally, the third DTI analysis technique under consideration is referred to as tract-based spatial statistics (TBSS), which extracts and expresses regional FA values on the centers of fiber bundles, improving the probability that the given space

voxels contain uniform data from the same WM tract (the most compact WM skeleton). TBSS approach overcomes the misinterpretation of crossing fibers areas hindering the reliability of traditional voxel-wise analysis (Smith et al., 2006).

Most DTI studies based on a region of interest (ROI) approach have shown lower FA among BD patients compared with healthy controls, mainly in WM tracts of the prefrontal, anterior cingulum, callosal, and limbic-striatal areas (Arnone et al., 2008; Beyer et al., 2005; Wang et al., 2008). These abnormalities, particularly in deep prefrontal WM, are reported to be present at the first episode of mania (Adler et al., 2006). Though consistent and replicated, these results might be limited by a selection bias, as the ROI-based approach is hypothesis-driven and provides information only about selected brain regions.

A recent meta-analysis (Nortje et al., 2013) of voxel-based analysis studies has shown decreased FA in all major WM tracts classes (i.e., commissural, association and projection), with more robust findings in Type 1 vs. Type 2 BD. These findings suggest a wider alteration of the WM in BD than uncovered with ROI-based approaches, involving not only an anterior fronto-limbic pathway but also fibers connecting temporal and parietal cortices. Moreover, the meta-analysis of Marlinge et al. (Marlinge et al., 2014) found two consistent clusters of FA and mean diffusivity alterations located in areas relevant for emotional processing in the right hemisphere. The first cluster was close to the right parahippocampal gyrus in a WM area crossed by the superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and posterior thalamic radiations, while the second one was close to the right anterior cingulate cortex and the right subgenual cingulate cortex These findings prompted the authors to speculate that a pattern of disrupted WM connectivity may underlie abnormal emotional processing in BD patients when compared with healthy controls (Figure 1).

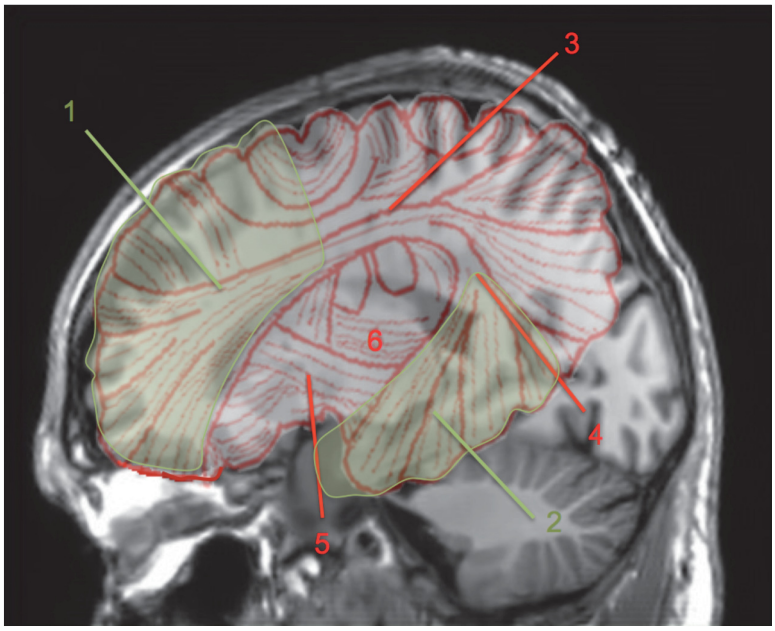
Significant widespread decreases in FA for BD patients have been predominantly reported so far by TBSS DTI studies in all major WM tracts (commissural, association, projection, and limbic). Indeed, in a recent published meta-analysis of such TBSS studies, Nortje and colleagues (Nortje et al., 2013) showed a decreased FA in all main classes of WM tracts, though the pattern of bundles was different between studies. These widespread WM diffusion

abnormalities, including fronto-temporal and ventral striatal regions, were marked by significant differences in diffusivity measures other than FA, leading the authors to conclude that dysmyelination and demyelination - rather than axonal loss - were implicated in BD (Harsan et al., 2006; Travers et al., 2012). Providing further support to this line of inquiry, a TBSS study considering inpatients with BD to healthy controls showed a reduced FA in the following WM areas: corpus callosum, cingulum, corona radiata and superior longitudinal fasciculus (Benedetti et al., 2011b). The authors considered these WM alterations in interhemispheric as well as in frontal, parietal and fronto-occipital connections as the biological underpinning of cognitive and emotional deficits of bipolar depression.

Thus, DTI studies have consistently shown an alteration in prefrontal–limbic anatomical connectivity, leading to the hypothesis of BD as a connectivity disorder. According to this hypothesis, prefrontal regions would fail to regulate limbic regions, triggering emotional hyper reactivity and emotional instability. Besides this core feature, consistently displayed, other lines of inquiry are considering evidences of temporo-parietal WM abnormalities in long association tracts as the structural background of cognitive rather than affective symptoms in BD.

In conclusion, when put together, structural neuroimaging studies considering both white and gray matter alterations in BD patients support a model of dysfunction within subcortical-prefrontal networks and associated limbic modulating regions.

Figure 1. Brain regions showing gray and white matter alterations in patients with bipolar disorder.



GM abnormalities (in green) were mainly located in frontal/anterior cingulate (1) and cortical/subcortical temporal (2) regions. WM alterations occurred in superior (3) and inferior fasciculi (4), in fronto-limbic pathway (5), and thalamic radiations (6).

BD as a neurodevelopmental disorder

Despite these promising results, several caveats remain with this proposition. In particular, a central question is related to the aetiology of the identified abnormalities: is it neurodevelopmental or neurodegenerative?

Neurodevelopmental disruptions may be implicated in the pathophysiology of several psychiatric disorders that begin in childhood or adolescence, notably schizophrenia, where the classic hypothesis of progressive degeneration has been increasingly supplanted by neurodevelopmental models (Murray and Lewis, 1987; Vita et al., 1997; Weinberger, 1987). The symptomatic and neurobiological overlap between schizophrenia and bipolar disorders, as well as the presence of premorbid alterations in many bipolar patients, have led to the speculation that similar neurodevelopmental alterations may underlie bipolar

disorder as well.

Several models have been evoked to explain the role of neurodevelopmental events in the establishment of mental disorders of child or adolescent onset (Vita et al., 1997; Weinberger, 1987). The “early neurodevelopmental models” suggest that intrauterine factors (genetic or environmental) can lead to a relative dysplasia or hypoplasia of some key cerebral structures, such as the limbic system and the prefrontal cortex. These models suggest that normal brain maturational processes around adolescence would interact with early developmental alterations leading to the emergence of psychiatric symptoms. Alternative models suggest that, even in the absence of congenital brain abnormalities, the disorders could result from dysfunctions in later maturational processes during adolescence and early adulthood. The period of life when most of the psychiatric disorders have their onset (adolescence and early adulthood) coincides with major brain maturational events, such as reductions in the cortical gray matter content and increase in the white matter content, which may reflect neuronal and/or synaptic elimination and axonal growth/myelination, respectively (Feinberg, 1982; Keshavan et al., 1994; Woods, 1998). An understanding of such processes is critical for determining the course and timing of disease onset in bipolar disorder, and thus for early identification and intervention efforts.

Recent research has expanded our understanding of the neural circuitry underlying mood regulation as well as their developmental underpinnings. The nature of developmental deviations predisposing to BD may be better elucidated in the light of such knowledge. The availability of noninvasive techniques for investigating *in vivo* brain structures makes this area of research promising, especially if we were to focus our investigation on subjects at high-risk, before the onset of BD.

Individuals at high genetic risk for BD

In recent years, ‘high-risk’ strategies have been helpful in assessing brain structural and functional changes surrounding the onset of bipolar disorder and schizophrenia. These have largely been undertaken in two ways, one based

around genetic risk, and a second based on the identification of prodrome from clinical symptoms (Correll et al., 2007; Olsen and Rosenbaum, 2006b).

In a review which we conducted on MRI studies measuring hippocampal and amygdala volumes in subjects at high risk for schizophrenia (cf. Annex I), we considered both high-risk criteria (genetic and symptomatic) and reclassified subjects in three new high-risk categories: presence of only risk symptoms (psychotic moderate symptoms), presence of only risk factors (genetic, developmental or environmental), and presence of combined risk symptoms/factors (Ganzola et al., 2014).

After we had deeply understood the different nuances that the concept of high-risk implies in both bipolar disorder and schizophrenia, we decided to focus our attention on genetic risk factors occurring in bipolar disorder neurodevelopment in order to selectively explore one aspect of a model otherwise too complex and rich in potentially confounding variables. The best way to investigate the genetic components involved in the neurodevelopmental model in BD is to study individuals at high risk (HR) for the disorder, such as first-degree relatives of bipolar parents.

These children have been well established to be at higher risk than the general population or control samples for development of psychosis and mood disorders. BD is known to have one of the highest heritability rates among psychiatric disorders (0.79–0.90) (Bienvenu et al., 2011; Craddock et al., 2005; Dean et al., 2010; Kieseppa et al., 2004; McGuffin et al., 2003; Nurnberger et al., 2011; Wray and Gottesman, 2012). A meta-analysis of studies conducted before 1997 found bipolar offspring to be at 2.7 times higher risk for development of any psychiatric disorder and four times higher risk for developing a mood disorder than children of parents without psychiatric illness (Lapalme et al., 1997). Since 1997, cross-sectional studies have continued to report that approximately 50% of bipolar offspring meet criteria for at least one DSM-IV psychiatric disorder (Chang et al., 2000; Duffy et al., 1998). In these studies, the incidence of bipolar spectrum disorders (including bipolar I, II, and cyclothymia) has mostly ranged from 14% to 50%. In this perspective, children of parents with bipolar disorder and relatives of BD patients do represent a rich cohort to study its neurodevelopmental aspects.

Neuroimaging findings in high genetic risk individuals

As stated previously, brain imaging provided much information regarding the neurobiological condition of adults with BD, most with fairly long disease duration. Thus, it is difficult to establish whether the findings were present before the onset of BD or if they occurred afterwards. Furthermore, many patients with BD have been exposed to years of psychotropic medications and/or illicit substances. To identify markers of risk for BD and investigate neurodevelopmental factors, an adequate strategy is therefore to study a high-risk sample of bipolar offsprings and perform serial longitudinal assessments covering the time needed to fully develop BD. The identification of anatomical brain abnormalities in this population may help define structural brain endophenotypes for the disorder, which in turn may help understand the mechanisms of vulnerability for or protection against the disease. Ultimately, this knowledge can help develop primary and secondary prevention mechanisms for BD.

Salient information reported in anatomical neuroimaging studies of GM and WM in populations at high genetic risk for BD is summarized below.

Gray matter

A recent review (Nery et al., 2013) of 24 studies focused on cortical or subcortical GM abnormalities. In this article, studies were grouped according to the methodology used to investigate GM differences between BD relatives and controls. The most frequently used technique was ROI manual tracing, in which the investigation focused on one hypothesis-driven brain region, followed by voxel-based morphometry studies, which allows a survey of the whole brain.

ROI approaches showed that first-degree relatives of BD patients do not differ from controls in terms of volumes for cortical GM regions, such as the hemispheres, frontal and temporal lobes, or subcortical structures, such as the subgenual anterior cingulate cortex, amygdala-hippocampus complex, amygdala, hippocampus, thalamus, striatum, and putamen (Hajek et al., 2008a; Hajek et al., 2008b; Hajek et al., 2009a; Hajek et al., 2010; Kieseppa et al., 2002; Kieseppa et al., 2003; Noga et al., 2001; Singh et al., 2008; Takahashi et al., 2010).

Studies using VBM, on the other hand, yielded different results. McIntosh et al.

(McIntosh et al., 2004) reported abnormal GM density in the left caudate nucleus of adult first-degree relatives of BD patients, although in a different direction (decreased volume) than Noga et al. (Noga et al., 2001) (increased volume). Two studies reported increased volume of the insular cortex in adult first-degree relatives of BD patients (Kempton et al., 2009; Matsuo et al., 2012), which is among the few replicated findings in the literature. Another interesting replicated finding was reported within the same study, in which the investigators performed the same experiment in two unrelated samples and found larger GM volumes in the right inferior frontal gyrus of the healthy offspring of BD parents compared with controls (Hajek et al., 2013). Finally, there was an isolated finding of decreased GM density in the left anterior thalamus (McIntosh et al., 2004), and reduced GM volumes in the left parahippocampal gyrus and left hippocampus of healthy offsprings of BD patients compared with healthy offsprings of healthy parents (Ladouceur et al., 2008).

Thus, according to this review, despite the substantial literature very few structural brain abnormalities were consistently found in relatives of patients with BD, with the exception of larger insular cortex volumes in adult first-degree relatives and larger right inferior frontal gyrus in offspring of probands with bipolar disorder, both when compared with healthy controls. Isolated findings included decreased gray matter density in the left thalamus, decreased gray matter volumes in the left hippocampus and parahippocampal gyrus, and thicker right hippocampus in unaffected first-degree relatives. Moreover, genetic liability for bipolar disorder was associated with gray matter volumes in regions of the anterior cingulate cortex, ventral striatum, medial frontal gyrus, right precentral gyrus, right insular cortex, and medial orbital gyrus.

Multisite, prospective, larger studies with more homogeneous samples would likely advance the field. For example, the recent Bipolar Familial Study (BFS) in Scotland involved a relatively large cohort of subjects at HR for bipolar disorders that were examined longitudinally on different occasions, two years apart. Longitudinal GM voxel-based morphometry in this cohort detected significant decreases in the right amygdala of HR subjects who developed a major depressive disorder (MDD) at follow-up when compared to controls, and when compared to HR individuals who remained healthy during the same time period (Nickson et al., 2016b). However, volume measurements of subcortical

structures automatically segmented did not detect significant differences between groups over time (Papmeyer et al., 2016). Rather, longitudinal analysis showed reduced cortical thickness in the right parahippocampal and fusiform gyrus in both high-risk groups (ill and healthy). High-risk subjects who met MDD criteria at the follow-up also had thinner parahippocampi and thicker left inferior frontal and precentral gyri than high-risk individuals without psychiatric symptoms and controls (Papmeyer et al., 2015).

Thus, in this cohort, reduced right parahippocampal and fusiform gyrus thickness could be conceived as familial trait markers for vulnerability to mood disorders. In other words, there was an increase in risk for onset of depression in offsprings with thicker left inferior frontal and precentral gyri.

White matter

To date, few studies have examined WM integrity in unaffected youths with familial risk for BD.

Unaffected siblings, of patients with BD, showed subtle FA reduction when compared to controls, which are most apparent in the corpus callosum (Sprooten et al., 2016; Sprooten et al., 2013) once they are adults and mostly past the typical age onset of BD.

FA reductions were therefore observed using TBSS in siblings, mainly restricted to the corpus callosum, posterior thalamic radiations, and left superior longitudinal fasciculus (Sprooten et al., 2013). Using tractography analysis, reduced FA was not detected in the siblings compared to the controls, except for a trend in the corpus callosum (Sprooten et al., 2016).

Frazier et al. (Frazier et al., 2007) have compared seven unaffected children at genetic risk for BD (mean age = 9 y.o.) to eight control subjects and found reduced FA in two clusters in the superior longitudinal fasciculi however, that study was obviously underpowered. In a different but marginally larger group, Versace et al. observed a linear decrease of FA with age in the left corpus callosum of twenty asymptomatic adolecents (mean age = 13 y.o.) with familial risk for BD, whereas healthy controls showed an increase in the same regions (Versace et al., 2010b).

In the Scottish cohort mentioned previously, adolescent and young adult relatives of BD patients without psychiatric disorders showed widespread FA

reductions when compared to controls. Moreover, these reductions were inversely correlated in the high-risk subjects with temperamental mood fluctuations in the internal capsules bilaterally connected via deep subthalamic WM; and in the left hemisphere, contained several fronto-temporal and fronto-thalamic connections, including the external capsule, inferior longitudinal fasciculus, anterior parts of the left arcuate fasciculus, dorsal left uncinate fasciculus, as well as left occipital white matter (Sprooten et al., 2011). These findings suggest that WM integrity is an endophenotype for mood disorder with important behavioural associations linked to the aetiology of the condition.

Thesis objectives and structure

The overall objective of this thesis is to fill gaps in knowledge related to the neuroanatomical architecture of BD, specifically with respect to GM and WM alterations before disease onset. Achieving this objective would allow us to shed more light on disease aetiology, and possibly find image-based biomarkers that can be used for early detection or even prediction of BD onset.

The approach we took was to analyze brain morphology in individuals at high-genetic risk of developing BD at an age that typically precedes disease onset, in order to find a possible image phenotype related to future psychiatric status, and/or linked to a genetic weakness.

We first performed a meta-analysis of all gray and white matter VBM studies comparing patients diagnosed with BD to healthy subjects. This allowed us to investigate which structures are primarily affected by this disease (*cf.* Chapter II).

We then performed exploratory analyses of gray and white matter morphology using different techniques in a small sample of healthy adolescents/young adults offsprings of BD patients from Québec and individuals without family history of psychiatric disorders (*cf.* Chapter III).

Next, we focused our attention on the white matter connections and investigated the fractional anisotropy in a bigger sample of young subjects at HR of mood disorders recruited in the context of the Scottish Bipolar Familial Study mentioned previously. FA differences between adolescent / young adult relatives of BD patients and controls were analyzed both at baseline (cf.

Chapter IV) and after longitudinal follow-up, at which point some high-risk subjects developed major depressive disorder (*cf.* Chapter V).

Finally, results from all studies were analyzed and interpreted in an integrative perspective in a general discussion presented in Chapter VI.

CHAPTER II: VOXEL-BASED MORPHOMETRY OF GRAY AND WHITE MATTER FINDS SIGNIFICANT AREAS OF DIFFERENCES IN BIPOLAR PATIENTS FROM HEALTHY CONTROLS

Résumé
Nous présentons ici une méta-analyse rétrospective des différences dans la concentration de matière grise et matière blanche entre les patients atteints de troubles bipolaires et les sujets témoins sains. Nous avons inclus vingt-six articles dans l'analyse. Nous avons observé que les sujets malades avaient une concentration de matière grise plus faible bilatéralement dans le gyrus frontal inférieur, à droit dans les gyri précentral et médial, ainsi que dans le gyrus temporal moyen gauche. Des concentrations plus élevées ont été trouvées dans les gyri parahippocampique et postcentral gauche, dans le putamen gauche et dans le cortex cingulaire antérieur droit. Enfin de plus faibles concentrations de matière blanche ont été détectées dans l'hémisphère gauche, en particulier dans le faisceau longitudinal inférieur, dans la corona radiata supérieure et dans le cingulum postérieur. Cette méta-analyse confirme un modèle pour le trouble bipolaire qui implique des anomalies dans des régions cérébrales modulant les émotions et liées à des fonctions plus fondamentales.

Voxel-based morphometry meta-analysis of gray and white matter finds significant areas of differences in bipolar patients from healthy controls

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Abstract

Objective

We present a retrospective meta-analysis of voxel-based morphometry (VBM) of gray (GM) and white matter (WM) differences between patients with bipolar disorder and behaviorally-healthy controls.

Methods

We used the activation likelihood estimation (ALE) and Sleuth software for our meta-analysis, considering P value maps at the cluster level inference of 0.05 with uncorrected $P < 0.001$ and with a minimum size of 200 mm^3. Results were visualized with the software MANGO.

Results

We included twenty-six articles in the analysis, and separated the comparisons where BD patients had *lesser* GM or WM concentrations than controls (1304 subjects, 29 experiments, and 139 locations/455 subjects, six experiments, 16 locations, respectively); and comparisons where BD patients had *greater* GM concentrations than controls (598 subjects, 14 experiments, 59 locations). Greater WM concentrations in BD patients were not detected.

We observed for BD smaller GM concentrations in the inferior frontal gyrus bilaterally, in the right precentral and medial frontal gyri, in the left middle-temporal gyrus, and greater GM concentrations in the left parahippocampal and postcentral gyri, left putamen, and right anterior cingulate cortex. Further, smaller WM concentrations were detected in the left inferior longitudinal fasciculus, left superior corona radiata, and left posterior cingulum.

Conclusions

This meta-analysis confirms a model for BD that involves abnormalities in cerebral areas belonging to the limbic system, which modulates emotions. We also found GM alterations in parietal and temporal regions that have been linked to more basic functions, which could point to sensory and specific cognitive deficits as amongst the first signs of the disease.

Context of study

Bipolar disorder (BD) is one of the most common psychiatric illnesses affecting humankind, with prevalence estimates suggesting that between 1.5 to 3.0% of the population develop BD in their lifetime (Angst, 1998; Narrow et al., 2002), making it the sixth leading cause of disability (both physical and mental) worldwide (Murray et al., 1996). This high prevalence is frequently under-recognized (Hirschfeld et al., 2003) which results in delayed diagnosis, leading to inadequate treatment, huge medical costs and high rates of comorbidity (Keck et al., 2008). As a consequence, besides increasing awareness, there is a clear need to improve the diagnostic tools available to clinicians, and to identify objective biomarkers of the disease. Our research addresses the latter issue.

BD is characterized by a fluctuating course that includes manic, depressive, and mixed episodes, with intervals of varying levels of euthymic remission. These psychiatric symptoms are associated with cognitive problems, such as deficits in executive functions, memory, and attention that persist in the euthymic state. Many studies have attempted to clarify the neuronal substrates of BD using neuroimaging techniques. Reports have associated BD with an enlargement of the ventricular system, with changes in white matter structure and volume, and with limbic system abnormalities (Kempton et al., 2008). A recent review (Savitz and Drevets, 2009) and meta-analysis (Arnone et al., 2009) have suggested that the prefrontal lobe, in general, and cortical-cognitive network components such as the dorsolateral prefrontal cortex, in particular, are smaller in BD patients. Diverse findings have been reported for ventral-limbic structures such as increased amygdala volume, normal hippocampal sizes and smaller than normal gray matter concentrations in the orbitofrontal cortex (Hajek et al., 2009b; Savitz et al., 2010).

To arrive at a convergent picture, meta-analytic tools are now available for functional and structural neuroimaging studies (e.g., Anatomical Likelihood Estimation (ALE)) (Eickhoff et al., 2009; Laird et al., 2005a; Laird et al., 2005b; Turkeltaub et al., 2002) and as the meta-analytic approach explores the generalizability of findings (Rosenthal and DiMatteo, 2001), meta-analyses of neuroimaging data now allow the identification of findings common to several

magnetic resonance imaging (MRI) studies without subjective bias. Additionally, meta-analytic tools for neuroimaging data make brain localizations in different studies comparable by transforming them into a single common stereotactic space (Talairach) and using a single terminology.

Most meta-analyses addressing structural changes in BD have focused on particular regions of interest (ROI), such as the amygdala (Arnone et al., 2009; Kempton et al., 2008; McDonald et al., 2004). Otherwise, the ALE approach has recently been used to analyze whole-brain voxel-wise differences in gray matter concentrations only (voxel-based morphometry (VBM)) in adult and pediatric bipolar disorder (Ellison-Wright and Bullmore, 2010).

We describe here a meta-analytic approach using ALE to uncover reliable, structural cerebral biomarkers of BD in whole-brain studies of both gray and white matter (GM/WM) in adult patients with BD.

Methods and Materials

Data sources and study selection

Systematic and comprehensive searches were conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), and Brainmap (www.brainmap.org) databases from January 1991 to December 2015 using the keywords 'voxel-based morphometry', and 'bipolar disorder'. The investigators were not blinded to the names of the study's authors, journals, and results.

Inclusion/Exclusion criteria

Two investigators attentively reviewed all emerging studies independently to determine whether it was qualified for inclusion in this meta-analysis, based on the following criteria: a) studies had to be published in English; b) studies had to report original results of whole-brain group analyses (as opposed to ROI) as coordinates in a standard reference space (Talairach and Tournoux (Talairach and Tournoux, 1988) or Montreal Neurological Institute (MNI) (Collins et al., 1994)); c) comparisons had to be between BD type I or BD type II patients with or without psychotic symptoms to healthy subjects; and d) all participants had to be adults (mean age above 18), as neurodevelopment during adolescence influences neural modifications in BD (Blumberg et al., 2004).

Data extraction

The raw data (GM/WM peaks) provided in each publication were extracted, alongside the publication date, name of first author, location, sample size, diagnosis, age of participants, and gender ratio.

Studies not yet included in BrainMap were coded along with the corresponding design data via BrainMap Scribe (Version 3.0) and submitted for quality control and insertion into the BrainMap database.

ALE algorithm

Ginger ALE (Version 2.3) (Eickhoff et al., 2009; Laird et al., 2005a; Turkeltaub et al., 2012) was used in combination with Sleuth (Version 2.3) (Laird et al., 2005b) for the ALE meta-analysis. The ALE technique treated the reported foci as spatial probability distributions centered on the given coordinates instead of points (Laird et al., 2005a). The ALE technique uses maximum Gaussian sphere model distribution. The ALE statistic describes the voxel-wise likelihood of activation, and is a measure of agglomeration among included coordinates in the reported area. Hereby, a random-effects inference is invoked, focusing on inference on the above-chance convergence between studies, not clustering of foci within a particular study.

Foci in MNI space were converted to Talairach space (Lancaster et al., 2007). Some of the papers used Brett's formulation to convert from MNI to Talairach, so the results were first converted back to MNI coordinates, and then transformed into the Talairach space using Lancaster's transform.

To address the comparison problem, we used the cluster level-inference thresholding algorithm. With the cluster-level inference, the simulated data is thresholded through a ‘cluster-forming threshold’ using an uncorrected P value. We considered $P < 0.001$ as a cluster-forming threshold and 0.05 for cluster-level inference as the GingerAle authors suggested (https://www.brainmap.org/ale/manual.pdf).

For visualization, whole-brain maps of thresholded ALE results were imported into the Multi-image analysis software MANGO (Research Imaging Center, UTHSCSA) (http://ric.uthscsa.edu/mango); and overlaid onto a standardized anatomical template in Talairach space (colin1.1.nii) [18]. Anatomical labels were drawn from the Talairach Daemon (Lancaster et al., 2000).

Results

Review of the Related Literature

Firstly, we found 32 papers in the original Brainmap dataset using keywords "voxel based morphometry" in the field "Study", and "bipolar disorder" in the field "Diagnosis".

From these, 18 (Adler et al., 2005; Almeida et al., 2009; Brown et al., 2011; Bruno et al., 2004; Chaddock et al., 2009; Chen et al., 2007; de Azevedo-Marques Perico et al., 2011; Doris et al., 2004; Ha et al., 2009; Haldane et al., 2008; Lochhead et al., 2004; McDonald et al., 2005; McIntosh et al., 2004; McIntosh et al., 2005; Molina et al., 2011; Stanfield et al., 2009; Watson et al., 2012; Yatham et al., 2007) were papers that met our inclusion criteria.

Secondly, we found 100 articles performing a PubMed research using the same keywords. Eight papers detecting significant concentrations differences that were not available in the Brainmap dataset were considered eligible for our study. We added these eight papers to the Brainmap dataset through BrainMap Scribe (Ambrosi et al., 2013; Cai et al., 2015; Haller et al., 2011; Kim et al., 2013; Narita et al., 2011; Redlich et al., 2014; Saricicek et al., 2015; Tang et al., 2014). Five additional papers were considered eligible but there were no significant results in their VBM comparisons between BD patients and controls (cf. Limitations).

In fine, we incorporated 26 articles in our meta-analysis according to our inclusion/exclusion criteria (Table 1).

In the following sections, we report on the comparisons where BD patients had lesser GM concentrations than controls (1304 subjects, 29 experiments, and 139 locations), the comparisons where BD patients had greater GM concentrations than controls (598 subjects, 14 experiments, 59 locations), and the comparisons where BD patients had lesser WM concentrations compared to healthy subjects (455 subjects, six experiments, 16 locations). Greater WM concentrations in BD patients compared to controls were not detected.

Significant ALE values for lesser GM concentrations *in BD patients compared to controls*

The ALE analysis detecting smaller GM concentrations in subjects with BD revealed five significant clusters ($P < 0.001$ for cluster-forming threshold, and $P < 0.05$ for cluster-level inference, voxels > 200 mm^3) (Table 2, Figure 1).

We found significant ALE scores in the left inferior frontal and middle temporal gyri. ALE analysis further revealed significant clusters in the right inferior, medial, and precentral frontal gyri.

Significant ALE values for greater GM concentrations *in BD patients compared to controls*

For bigger GM concentrations in BD patients, ALE analysis obtained four statistically significant clusters ($P < 0.001$ for cluster-forming threshold, and $P < 0.05$ for cluster-level inference, voxels > 200 mm^3) (Table 2, Figure 1).

Three larger significant clusters were found in the left postcentral and parahippocampal gyri and in the left putamen. Furthermore, ALE analysis revealed an additional significant cluster in the right anterior cingulate gyrus.

Significant ALE values for lesser WM concentrations *in BD patients compared to controls*

Three clusters showed significant ALE scores for smaller WM concentrations in BD patients compared to healthy subjects ($P < 0.001$ for cluster-forming threshold, and $P < 0.05$ for cluster-level inference, voxels > 200 mm^3) (Table 2, Figure 1).

These three clusters were located in the left hemisphere, more precisely in the inferior longitudinal fasciculus, superior corona radiata, and posterior cingulum.

Summary of Findings and Conclusions

Meta-analysis is an increasingly popular and valuable tool for summarizing results across many neuroimaging studies. It can be used to establish consensus on the locations of brain abnormalities, test hypotheses of the relationship between symptoms and neuropathology, and find potential biomarkers to detect the disease early.

GM differences

There has been an increasing interest in using meta-analysis method in neuroimaging studies to identify structural brain changes in patients with BD. Previous meta-analyses mainly focused on GM volumes differences of BD patients compared to healthy subjects and showed GM volumes abnormalities in the paralimbic regions, such as the frontoinsular cortex and amygdala, and in the anterior cingular, prefrontal, and middle-temporal cortex (Bora et al., 2010,

2012; Ellison-Wright and Bullmore, 2010; Goodkind et al., 2015; Houenou et al., 2011; Selvaraj et al., 2012). Findings from our whole brain voxel-based meta-analysis of BD confirm these GM regions changes already found in previous studies.

Reduced GM in prefrontal cortex is a consistent finding in brain changes occurring in BD and supports neurobiological models of bipolar disorder that attribute mood dysregulation to frontolimbic abnormalities, with the likely modulatory role exercised by the prefrontal cortex over the limbic system (Lyoo et al., 2004; Strakowski et al., 2005). Prefrontal regions have been shown to be crucial in behavioral and emotional control (Kringelbach, 2005; Passingham et al., 2000). Further, the inferior frontal gyrus plays an important role in executive functions, such as cognitive inhibition (Aron et al., 2004).

In our study, we found a morphometric reduction in the precentral frontal gyrus, which is part of the ventrolateral prefrontal cortex, together with the inferior frontal gyrus, and we detected a GM concentration increase in the left putamen. The ventro-lateral prefrontal cortex is anatomically connected to both the striatum and thalamus in the cortico-striatal-thalamic functional network involved in decision making (Tekin and Cummings, 2002), and with the limbic system involved in emotional regulation (Aron et al., 2004). The presence of abnormalities in this network in bipolar disorder is consistent with the post-mortem, lesion, and functional neuroimaging literature (Bakchine et al., 1989; Blumberg et al., 2003b; Cotter et al., 2005; Lawrence et al., 2004; Rajkowska, 2000; Robinson et al., 2008; Starkstein et al., 1991).

We also found reduced concentrations in the left middle temporal cortex. The temporal cortex is involved in the processing of auditory information, language comprehension, semantic memory, visual perception, and sensory integration (Nolte and Sundsten, 2002). In particular, the left middle temporal gyrus has long been observed to be important for sentence comprehension, especially the acquisition and retrieval of lexical syntactic information from memory (Snijders et al., 2009). Functional abnormalities in the left and middle temporal gyri have been recently associated with BD (Lv et al., 2016; Wang et al., 2014). Moreover, a functional MRI study reported that healthy subjects, but not depressed BD patients, showed neural responses in the middle temporal gyrus when presented with captioned emotional pictures (Malhi et al., 2004).

Conversely, we report greater GM concentrations in BD patients in the parahippocampal gyrus and the anterior cingulate cortex, both belonging to the limbic system, when compared to healthy subjects. This can probably be explained by the fact that most of the BD patients included in this meta-analysis were medicated (Table 1); lithium is the mood stabilizer most used for the treatment of BD. Lithium use was associated with increased anterior cingulate cortex and hippocampal gray matter in BD (Hajek and Weiner, 2016). Consistent with this finding are recent longitudinal studies that suggest lithium use is associated with GM increases in some regions, including the frontal lobes and subgenual cingulate (Monkul et al., 2007; Moore et al., 2009). Like Sassi et al. (Sassi et al., 2004), lithium use was associated with increased left anterior cingulate cortical volume, suggesting that lithium use might explain some contradictory findings about these volumes in BD, possibly via a neuroprotective effect.

We finally observed increased concentrations also in the left postcentral gyrus in BD patients. The postcentral gyrus is a prominent structure in the parietal lobe including the primary somatosensory cortex that is the main sensory receptive area for the sense of touch, well known as the sensory homunculus, the space where the brain represents the body (Penfield, 1950). Visual stimuli that imply touch have also been observed to activate the primary somatosensory cortex (Meyer et al., 2011). In the context of BD, it is possible that abnormalities in parietal regions could be related to a misinterpretation of sensations. For example, patients with BD during episodes of mania (euphoria) show an extra vigilance accompanied by attention sub-tenacity (Young et al., 1994). However, during the euphoria periods, the patients manifest superficial and dispersed attention, where they pause on environmental stimuli and have great difficulty to focus their attention on a specific object (Lagopoulos et al., 2007). These comments were observed in a study, which also states that the parietal cortex is involved in manic and mixed episodes (Berrios and Chen, 1993).

WM differences

Regarding WM, we did not find significant increases in BD patients compared to healthy subjects. We instead observed regions with smaller WM concentrations in BD patients located in the left hemisphere.

A cluster of white matter density reduction was found in the left corona radiata, a structure that contains axonal fibres in their transition between the internal capsule and subcortical WM. The anterior internal capsule carries frontothalamic projections that form a portion of the cortico–thalamo–striato–cortical circuits which have an important role in cognition and psychiatric illnesses (Cummings, 1998). Anterior internal capsule deficits were found in BD, which were related to genetic liability (McIntosh et al., 2005), and disruptions of the coronal radiata may implicate the distal continuation of this pathway.

WM reductions were also noted in the left temporal portion of the inferior longitudinal fasciculus, and posterior cingulum. The inferior longitudinal fasciculus connects the temporal lobe and the occipital lobe; the posterior cingulate receives input from the temporal, occipital, and parietal regions, and plays functional roles in visual processing, orientation of the body in space, auditory processing, and monitoring the emotional relevance of sensory stimuli (Vogt et al., 2006).

Functional imaging findings have established alterations of these brain regions in BD, including abnormal activation of inferior parietal, temporal, and frontal cortices on visuospatial working memory tasks (Townsend et al., 2010). Abnormal activation of temporal and parietal regions in BD has been observed when processing emotional faces (Vizueta et al., 2012), and parietal activation during rest has been associated with mania severity (Madden et al., 2004). WM abnormalities in pathways that connect bilateral posterior cortical regions with each other, as well as with the posterior cingulate cortex, further associated with our finding of abnormal GM concentrations in the parietal post-central gyrus, may explain some of the difficulties of BD patients in integrating complex sensory input and integrating affective contributions to perceptual processes. Integration of these inputs during perceptual processing provides important drive to frontal-limbic systems via cingular and inferior fronto-occipital fasciculae, and alterations in this circuitry may contribute to emotional dysregulation in BD.

Limitations

Two important limitations of the ALE method are that it does not take into account non-significant findings (i.e. articles reporting no findings above statistical significance) and that foci from one or a few studies may drive singlehandedly a significant finding, giving the wrong impression of consistency

across most studies. Thus, results must be interpreted under this limitation. However, we only found five studies with negative or not-significant findings in the literature, as opposed to 26 included in this study. While there might be a second, publication bias underneath these numbers (i.e. only reports with positive findings tend to be published), we believe that we adequately surveyed the literature and therefore our report is an accurate meta-analysis of the current state of knowledge on the topic.

Another limitation of a meta-analysis, given that we do not control the inclusion criteria in each study, is the fact that the analysis is performed on a heterogeneous set of bipolar patients, despite excluding children and adolescent subjects. Further analyses should attempt to select bipolar adults patients with similar characteristics to better understand relationships between symptomatology, medication, genetics and brain morphology.

Conclusions

In summary, we found both GM and WM alterations in subjects with bipolar disorder performing a meta-analysis on extensive VBM significant results.

Frontal regions and regions belonging to the limbic system showed abnormal GM concentrations when compared to healthy subjects. Moreover, smaller concentrations were detected in WM tracts connecting these areas. These findings confirm a model for BD that involves morphological abnormalities in cerebral areas belonging to the fronto-limbic system, which primarily modulates emotions.

Interestingly, we also found GM alterations in parietal and temporal regions that have been linked to more basic functions as sensory perception and lexical retrieval. It would be interesting to understand if sensory and specific cognitive deficits could be the first signs of the disease. Deficits in verbal and visual memory were already found in unaffected young subjects with a high genetic risk to develop bipolar and schizophrenia disorders (Maziade et al., 2011b).

A well-timed cognitive therapy could be a valid help to enhance the treatment and prognosis in these types of patients.

Further studies should better investigate the different aspects of the symptomatology in relation to the brain morphology, the duration of the disease, and the drugs assumption.

Acknowledgements

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Disclosures

R.G. declare no competing financial interests. S.D. is officer and shareholder of True Positive Medical Devices inc.

Table 1. Demographic information of included articles in the meta-analysis

Study	Sample size		Mean age		Gender ratio (M/F)		Handedness ratio (R/L)		Treatment status (med/unmed)	Age matched	Sex matched	Siginificant results
	ctrl	BD	ctrl	BD	ctrl	BD	ctrl	BD	BD			
Bruno 2004	35	39	35	39	10/25	13/26	not reported	not reported	36/3	Yes	Yes	BD < ctrl, WM
Doris 2004	16	11	39	41	7/9	6/5	not reported	not reported	11/0	Yes	Yes	BD < ctrl, GM
Lochhead 2004	31	11	36	38	16/15	6/5	31/0	11/0	11/0	Yes	Yes	BD < ctrl, GM BD > ctrl, GM
McIntosh 2004	49	19	35	40	23/26	7/12	46/3	19/0	not reported	No	No	BD < ctrl, GM
Adler 2005	27	32	31	31	12/15	19/13	26/1	31/1	23/9	No	No	BD < ctrl, GM BD > ctrl, GM
McDonald 2005	52	41	39	41	24/28	15/22	50/2	34/3	36/5	Yes	Yes	BD < ctrl, WM
McIntosh 2005	49	26	35	41	23/26	14/10	46/3	14/10	not reported	not reported	not reported	BD < ctrl, WM
Chen 2007	25	24	38	38	7/18	6/18	25/0	24/0	20/4	Yes	Yes	BD < ctrl, GM BD > ctrl, GM
Yatham 2007	15	15	36	36	6/9	6/9	14/1	14/1	7/8			BD < ctrl, GM
Haldane 2008	44	44	43	43	20/24	20/24	40/4	42/2	44/0	Yes	Yes	BD < ctrl, GM
Almeida 2009	28	27	31	32	13/15	10/17	28/0	27/0	24/3	Yes	Yes	BD < ctrl, GM
Chaddock 2009	18	19	42	43	10/8	9/10	15/3	18/1	15/4	Yes	Yes	BD < ctrl, WM
Stanfield 2009	66	66	39	36	31/35	30/36	not reported	not reported	mixed, not specified	Yes	Yes	BD < ctrl GM/ WM
Ha 2010	23	46	36	35	8/15	16/30	23/0	46/0	29/17	Yes	Yes	BD < ctrl, GM
Haller	47	19	70	69	25/22	5/14	47/0	19/0	17/2	Yes	Yes	BD < ctrl, GM

2011												
Narita 2011	84	31	41	41	48/36	17/14	84/0	31/0	28/3	Yes	Yes	BD < ctrl, GM
Molina 2011	24	19	35	38	16/8	12/7	not reported	not reported	mixed, not specified	Yes	Yes	BD < ctrl, GM
Perico 2011	94	26	30	27	53/41	10/16	91/3	26/0	19/7	Yes	Yes	BD > ctrl, GM
Brown 2011	21	15	45	46	10/11	7/8	not reported	not reported	15/0	Yes	Yes	BD > ctrl, GM
Watson 2012	24	24	36	36	8/16	8/16	not reported	not reported	24/0	Yes	Yes	BD < ctrl, GM BD > ctrl, GM
Ambrosi 2013	21	20	35	42	6/15	5/15	21/0	20/0	19/1	Yes	Yes	BD < ctrl, GM
Kim 2013	50	49	34	34	21/19	19/20	not reported	not reported	25/24	Yes	Yes	BD < ctrl, GM
Redlich 2014	58	58	38	38	21/37	21/37	not reported	not reported	54/4	Yes	Yes	BD < ctrl, GM
Tang 2014	27	27	33	32	11/16	10/17	27/0	27/0	27/0	Yes	Yes	BD < ctrl, GM BD > ctrl, GM
Cai 2015	23	23	28	26	13/10	167	23/0	23/0	12/11	Yes	Yes	BD < ctrl, GM
Saricicek 2015	29	28	34	36	13/16	10/18	29/0	28/0	28/0	Yes	Yes	BD < ctrl, GM BD > ctrl, GM

BD = bipolar disorder patients
ctrl = controls
M = male
F = female
R = right
L = left
med = patients taking medications
unmed = patients not taking medications
GM = gray matter

WM = white matter

Table 2. Significant ALE values in bipolar patients and controls comparisons.

Cluster Volume (mm^3)	ALE Value ($x\ 10^{-3}$)	X	Y	Z	Location			
					Hemisphere	Lobe/Sub-Lobe	Gyrus/Nucleus/ fasciculus	Brodmann Area
BD < ctrl, GM								
1696	41.033	-45	-75	13	L	Temporal	Middle Temporal	39
936	18.461	41	23	-2	R	Frontal	Inferior Frontal	47
560	15.226	-43	29	-9	L	Frontal	Inferior Frontal	47
504	19.898	55	7	6	R	Frontal	Precentral	44
456	15.276	-2	48	25	R	Frontal	Medial Frontal	9
BD > ctrl, GM								
696	12.974	-46	-21	30	L	Parietal	Postcentral	2
488	14.850	-29	-7	-1	L	Lentiform nucleus	Putamen	-
464	15.335	-17	-20	-20	L	Limbic	Parahippocampal	28
384	12.771	0	47	6	R	Limbic	Anterior Cingulate	32
BD < ctrl, WM								
408	10.216	-26	-12	28	L	Temporal	Inferior Longitudinal	-
160	9.805	-40	-15	-8	L	Insula	Superior Corona Radiata	13
160	9.177	-4	-38	33	L	Limbic	Posterior Cingulum	31

BD = bipolar disorder patients
Ctrl = controls
R = right
L = left
GM = gray matter
WM = white matter

Figure 1. Gray and white matter significant differences in bipolar pateints compared to controls.

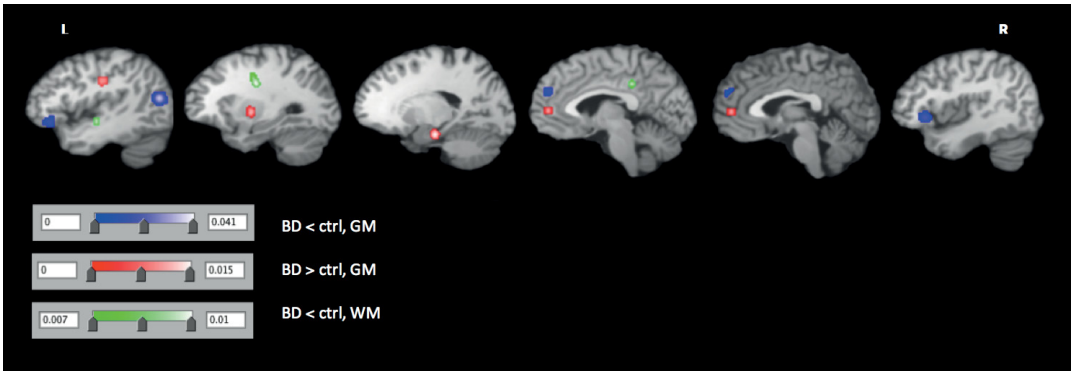

Figure shows significant GM and WM differences in BD patients compared to healthy controls with a cluster-forming threshold of $P < 0.001$ and $P < 0.05$ for cluster-level inference.

In blue/light-blue, regions where BD patients had significant smaller GM concentrations compared to controls. In red/light-red, regions where BD patients had significant greater GM concentrations compared to controls. In green/light-green, regions where BD patients had smaller WM concentrations compared to controls.

Chapter III: ANATOMICAL NEUROIMAGING BIOMARKERS IN SUBJECTS AT HIGH-GENETIC RISK FOR BIPOLAR DISORDER: EXPLORATORY RESULTS

Resumé
Cette étude visait à examiner les différences neuroanatomiques chez huit descendants à haut risque génétique (HR) de TB, et huit sujets témoins appariés pour le sexe et l'âge. Dans l'hémisphère gauche, les sujets HR avaient une épaisseur et un volume plus grand dans le cortex parahippocampique que chez les témoins, ainsi qu'une plus grande épaisseur corticale dans le cortex cingulaire postérieur; et des volumes et des épaisseurs réduites dans le cortex frontal médial et de plus petits volumes dans le cortex péricalcarin. Dans l'hémisphère droit, nous avons trouvé de plus grands volumes du cortex pariétal inférieur dans les descendants; des volumes anormaux et épaisseurs corticales dans les régions impliquées dans la régulation des émotions et généralement affectés dans le TB (cingulaire postérieur et frontal médial); et finalement des changements volumétriques dans les structures impliquées dans le traitement de l'information visuelle (péricalcarine et inférieure du cortex pariétal). Combiné avec la différence dans le cortex parahippocampal gauche, la participation de ces zones peut expliquer les déficits de mémoire visuelle observés chez les sujets HR.

Anatomical neuroimaging biomarkers in subjects at high genetic risk for bipolar disorder: exploratory results

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Abstract accepted as poster presentation at the *Human Brain Mapping Conference*, held in Hamburg, June 8-12, 2014.

Abstract

Objective

Brain changes in patients with Bipolar Disorder (BD) are well documented, and include abnormal volumes in prefrontal cortical areas, striatum, hippocampus and amygdala, which are all components of the limbic networks that modulate behaviors affected in BD. Other abnormalities were found in the midline cerebellum, lateral ventricles and other prefrontal regions (e.g., subgenual prefrontal cortex). Little is know about possible morphological changes occurring prior to disease onset. Studies on offsprings at high genetic risk (HR) of BD provide the opportunity to describe early changes and putative prognostic markers.

Methods

We recruited eight offsprings (3 males – 5 females, age range: 15 to 25 y.o.) with at least one parent diagnosed with BD, and eight age- and sex-matched control subjects. Clinical and cognitive evaluations were performed on all participants. We collected 3T T1-weighted structural MRIs and used an automated procedure (*FreeSurfer*) to analyze differences in cortical thickness and cortical/subcortical volumes. We used a non-parametric Mann-Whitney test to compare demographics and cerebral structures between offsprings and controls.

Results

Offsprings and controls had similar sociodemographic characteristics. In the left hemisphere, offsprings of BD patients had significantly *greater* cortical thickness and volumes in the parahippocampal cortex (p=0.05 and p=0.02, respectively) than controls, as well as *greater* cortical thickness in the posterior cingulate cortex (p=0.05). We also observed *reduced* cortical volumes and thicknesses in the medial frontal cortex (p=0.05 and p=0.04, respectively) and smaller cortical volumes in the pericalcarine cortex (p=0.04). In the right hemisphere, we found larger inferior parietal cortex volumes in the offsprings when compared to controls (p=0.05). No difference was found in subcortical structures in both sides.

Conclusions

In our sample, offsprings of patients with BD exhibited abnormalities in cortical

volumes and thickness when compared to controls in limbic, parietal, and frontal areas. Abnormal volumes and cortical thicknesses were found in regions involved in the regulation of emotions and typically affected in BP (posterior cingulate and medial frontal cortices) Moreover, volumetric changes were detected in sectors implicated in the processing of visual information (pericalcarine and inferior parietal cortex). Combined with the observation of left parahippocampal cortex differences (results observed elsewhere (Ladouceur 2008)), the involvement of these areas may explain visual memory deficits previously found in this type of high-risk individuals (Maziade 2011). Together, these patterns of reduction/increases in volume/thickness could be a potential marker of increased susceptibility for the disease.

Context of study

The Eastern Québec High Risk study

The Eastern Québec High Risk study is a longitudinal study of over 1,500 subjects from a large multigenerational family (kindred) sample from Eastern Québec. This sample has been followed up longitudinally for 20 years since 1989 (Maziade et al., 1992), and includes both schizophrenia and bipolar disorder kindred assessed with the same methods. It has generated consistent linkage findings (Maziade et al., 2009a; Maziade et al., 2005; Maziade et al., 2001; Merette et al., 2008).

This research population is the only one to our knowledge where HR offsprings, i.e. potential carriers of susceptibility genes without clinical manifestations, belong to densely[1] affected multigenerational families. In these kindred the presence of cognitive dysfunctions, specifically verbal (VEM) and visual episodic memory (VISEM) impairment in the high-risk subjects were demonstrated (Maziade et al., 2009b; Maziade et al., 2011b). Yet, the underlying neurobiology and its influence on clinical and cognitive development has not been investigated.

Objective

Our initial objective was to investigate the underlying neurobiology and its influence on clinical and cognitive development in a large sample of HR subjects from the Eastern Quebec study. Our first line of investigation was to understand the relationship between cognitive impairment and putative brain abnormalities in HR subjects. In particular, our plan included:

- to obtain specific morphological measures related to gray matter in specific structures (hippocampus, amygdala) as well as cortices (cortical thicknesses); and
- to perform statistical analyses of white matter using TBSS.

[1] At least one first-degree relative affected with the same disorder as the proband and at least four affected individuals with the same disorder

Methods and Materials

Out of the complete sample of the Eastern Quebec study, we recruited offsprings that met our inclusion criteria (age range: 15 to 25 y.o.; at least one parent diagnosed with BD) as well as unrelated age- and sex-matched control subjects.

For each individual we collected anatomical MRIs at 3 Tesla at the IRM Québec imaging clinic using a standard, NIHPD-like anatomical imaging protocol(http://pediatricmri.nih.gov/nihpd/info/Documents/Protocol_Nov06.pdf), which includes an isotropic 3D T1-weighted acquisition for volumetric and cortical analyses, as well as a 60-direction diffusion acquisition, from which we can extract the diffusion tensor.

We manually traced the amygdala and hippocampus using MultiTracer (http://www.loni.usc.edu/Software/MultiTracer) following the Harmonized Protocol for hippocampal segmentation of Frisoni and colleagues (Frisoni et al., 2015)[2]. We further extracted cortical thickness across the whole brain using the well-known and validated *FreeSurfer* automated algorithm (version 5.3; http://freesurfer.net/). We used the FSL toolkit (version 5.0.6; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) to perform TBSS analyses (*cf*. section IV for further details on the TBSS procedure).

With the data collected, we performed the following analyses:

a) differences in demographic characteristics between HR and controls using a non-parametric Mann-Whitney test;

b) differences in medial temporal lobe volumes between HR and controls with a non-parametric Mann-Whitney test;

c) differences in cortical thicknesses and cortical/subcortical volumes using automatically-segmented measures and a non-parametric Mann-Whitney test; and

d) voxel-wise between-group comparisons of fractional anisotropy using TBSS.

[2] Protocol in which the current investigators (R. Ganzola, S. Duchesne) played a major part in its design, development, and dissemination – cf. www.hippocampal-protocol.net

Results

a) Sociodemographic features

Out of a complete sample of 81 individuals, we could only recruit eight offsprings that matched our inclusion criteria, and were available for the study (3 males – 5 females, age range: 15 to 25 y.o.). We further recruited eight unrelated age- and sex-matched control subjects without personal or familial history of psychiatric disease. Offsprings and controls had similar sociodemographic characteristics (Table 1).

b) Manual tracing of medial temporal structures

Comparisons of medial temporal volumes obtained by manual tracings showed that HR subjects and controls had similar hippocampal and amygdala volumes in both hemispheres (Table 2).

c) Cortical thicknesses and cortical/subcortical volumes

In the left hemisphere, offsprings of BD patients had significantly greater cortical thickness and volumes in the parahippocampal cortex ($p=0.05$ and $p=0.02$, respectively) than controls, as well as greater cortical thickness in the posterior cingulate cortex ($p=0.05$). We also observed reduced cortical volumes and thicknesses in the medial frontal cortex ($p=0.05$ and $p=0.04$, respectively) and smaller cortical volumes in the pericalcarine cortex ($p=0.04$). In the right hemisphere, we found larger inferior parietal cortex volumes in the offsprings when compared to controls ($p=0.05$). No difference was found in subcortical structures. Significant results are summarized in Table 3.

d) TBSS analysis

TBSS analysis showed a considerable reduction of WM integrity in the eight high-risk subjects compared to controls. This reduction was mainly located in the anterior thalamic radiation and in the WM of the brainstem bilaterally, as well as in the internal capsule, and superior and inferior longitudinal fasciculus on the right side (in red, Figure 1). Few areas indicating smaller value of FA were detected in the control groups compared to HR subject, precisely in the left inferior longitudinal and fronto-occipital fasciculi (in green, Figure 1). These results did not survive the permutation test.

Summary of Findings and Conclusions

In the first study of this thesis, we performed an exhaustive analysis of the brain morphology of a small sample including subjects with a genetic high-risk to develop bipolar disorder compared with their age- and sex-matched controls.

Gray matter findings

Since cognitive dysfunctions, specifically verbal (VEM) and visual episodic memory (VISEM) impairment were already detected in this population, we firstly investigated the hippocampus and amygdala as they are known to be implicated in memory processes and affected in BD. We used a manual tracing technique, considered the gold standard, to obtain the most precise measurements of these brain structures.

Despite our initial hypothesis, we surprisingly did not find a difference in volumes between HR individuals and controls. These manual results were confirmed with automated segmentation measurements, as we did not detect any abnormal volume between groups in subcortical structures.

However, we found significant differences between the two groups in various cortical regions. Offsprings of BD patients had significantly greater cortical thicknesses/volumes in the parahippocampal, posterior cingulate, and inferior parietal cortex. Reduced cortical thicknesses/volumes were observed in the medial frontal and pericalcarine cortex. Furthermore, cortical abnormalities were more concentrated in the left hemisphere.

We can conclude from these exploratory findings in GM morphology that children of BD patients exhibited abnormalities in cortical volumes and thicknesses in limbic, parietal, and frontal areas. These regions are involved in the regulation of emotions and are typically affected in BD (posterior cingulate and medial frontal cortices). Moreover, volumetric changes were detected in regions implicated in the processing of visual information (pericalcarine and inferior parietal cortex). Combined with the observation of left parahippocampal cortex differences, the involvement of these areas may explain visual memory deficits previously found in this type of high-risk individuals.

Memory impairments found in this high-risk population may therefore be associated to cortical abnormalities rather than alterations in subcortical

structures that were found similar to controls.

White matter findings

Regarding WM integrity, we found considerable reduction in FA in the eight high-risk subjects compared to controls. This reduction was mainly located bilaterally in the anterior thalamic radiation, in the portion of inferior longitudinal fasciclus located in the temporal lobe and in the WM of the brainstem, as well as in the right hemisphere in the internal capsule, anterior cingulum, and the superior longitudinal fasciculus of the frontal lobe (in red, Figure 1).

We can conclude from these exploratory findings in WM morphology that WM integrity may represent an early endophenotype of BD, given the fact that widespread reduced WM integrity mainly concentrated in similar regions, i.e. temporal and fronto-thalamic connections, is a finding well confirmed in bipolar patients (Sprooten et al., 2011). It suggests that impaired WM integrity might be one of the underlying mechanisms of genetic predisposition to BD, preceding onset.

Strengths and limitations

These exploratory conclusions must be carefully weighted, however, against the major limitation of this study, that is the very small size of the cohort. There are two immediate corollaries to this fact: the first, that studies of BD offsprings pose significant difficulties in terms of recruitment; and the second, that these findings must be replicated in a larger cohort. The small size of the cohort also did not allow us to perform regression analyses with sufficient power between biomarkers and VEM/VISEM variables in order to understand the underlying biology of these deficits.

Conclusion

In conclusion, we found alterations in the cortical regions and white matter integrity when we compared our eight healthy children having a parent affected by bipolar disorders with children without a history of psychiatric disorder in their family. Moreover, our findings seem to be consistent with the current available literature.

To address the major limitation of this exploratory study (small cohort), we therefore struck a collaborative agreement with the University of Edinburgh to access and collaborate on the larger Bipolar Familial Study. These investigations are detailed in the following Chapters.

Table 1. Sociodemographic features of the high-risk subjects recruited in Québec and their controls.

	HR (n=8)	**Controls** (n=8)	**P**
Age, years	20.8±3.8 [15-26]	21.1±4.0 [15-26]	NS
Sex, male	3 (37.5%)	3 (37.5%)	NS
Parent's diagnosis			
BD I	7	/	/
BD II	1	/	/

Figures denote means ± SD [range] or n (%). P denotes significance on Mann-Whitney- or χ-test.

HR = high genetic risk subjects

BD = bipolar disorder patients

NS = not significant

Table 2. Means ± Standard Deviation [range] of hippocampal and amygdala volumes in each group obtained by manual tracing.

	HR (n=8)	**Controls** (n=8)	P
Hippocampal volumes (mm^3)			
Right	4392±623 [3682 - 5387]	4605±305 [4160 - 5092]	NS
Left	4395±650 [3832 - 5861]	4462±274 [4026 - 4880]	NS
Amygdala volumes (mm^3)			
Right	1496±196 [1243 - 1792]	1463±157 [1223 - 1825]	NS
Left	1480±114 [1223 - 1825]	1476±186 [1260 - 1920]	NS

P denotes significance on Mann-Whitney test.

HR = high genetic risk subjects

NS = not significant

Table 3. Significant differences in cortical volumes and thickness found in high-risk subjects compared to controls.

	HR (n=8)	Controls (n=8)	P	HR *vs* Controls
LEFT SIDE				
Cortical volumes (mm^3)				
Caudalmiddlefrontal	6285.6 ± 463.0	6969.8 ± 816.7	0.05	-
Pericalcarine	2176.2 ± 375.5	2537.4 ± 255.0	0.04	-
Parahippocampal	2912.2 ± 228.7	2476.6 ± 297.7	0.02	+
Cortical thickness (mm)				
Caudalmiddlefrontal	2.3 ± 0.1	2.4 ± 0.1	0.04	-
Posteriorcingulate	2.8 ± 0.2	2.6 ± 0.2	0.05	+
Parahippocampal	3.2 ± 0.2	2.8 ± 0.2	0.05	+
RIGHT SIDE				
Cortical volumes (mm^3)				
Inferiorparietal	15639.6 ± 1422.0	14064.4 ± 1443.5	0.05	+

Figures denote means ± SD. P denotes significance on the Mann-Whitney U test.

Cortical volumes were normalized to intracranial volumes.

HR = high genetic risk subjects

Figure 1. Significant differences of fractional anisotropy values between unaffected bipolar patient's relatives recruited in Québec and controls.

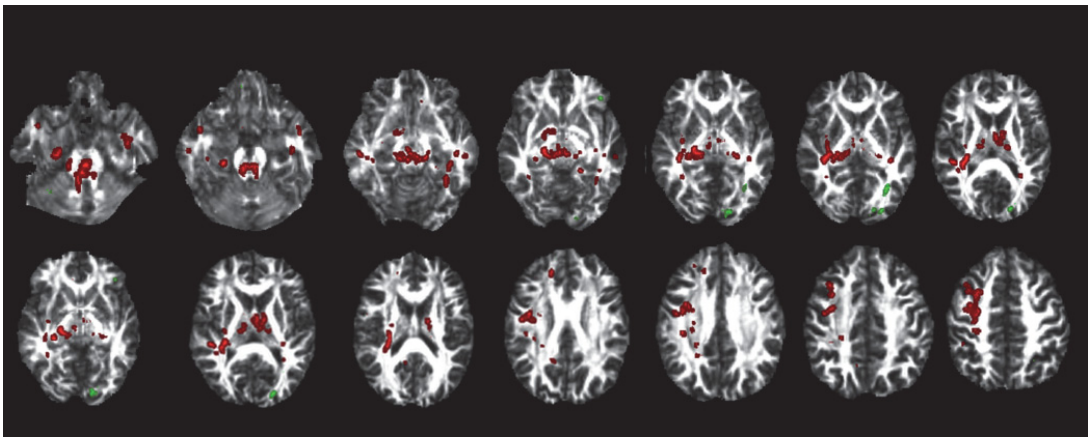

Figure show reduced fractional anisotropy in unaffected BD patients' relatives compared with control subjects (in red), and in controls compared HR subjects (in green). Uncorrected P value < 0.05. For better visibility the results are thickened with the "tbss-fill" command. The images are in radiological convention.

CHAPTER IV: DIFFUSION TENSOR IMAGING CORRELATES OF EARLY MARKERS OF DEPRESSION IN YOUTH AT HIGH FAMILIAL RISK FOR BIPOLAR DISORDER

Résumé
Le but de cette étude était d'analyser l'intégrité de la matière blanche sur les données d'imagerie de la première évaluation des sujets à haut risque génétique du « Bipolar Family Study » (Écosse). Les images de résonance magnétique de diffusion ont été acquises pour 61 sujets témoins et 106 sujets à haut risque. Le groupe de sujets à haut risque a été divisé selon le suivi de deux ans en 78 individus qui sont demeurés sans symptômes psychiatriques et 28 qui ont rencontré les critères diagnostic de trouble dépressif majeur. Par rapport aux témoins, les deux groupes à haut risque ont montré une diminution significative de l'anisotropie fractionnelle à la première évaluation, mais sans différences significatives entre les deux groupes à haut risque. Ces résultats suggèrent que la diminution de l'anisotropie fractionnelle pourrait être reliée à la présence d'un risque familial de troubles de l'humeur et aux symptômes dépressifs légers, plutôt qu'être associée à un prognostic de trouble dépressif majeur.

Diffusion tensor imaging correlates of early markers of depression in youth at high familial risk for bipolar disorder

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Abstract

Objective

Mood disorders are familial psychiatric diseases, in which patients show reduced white matter (WM) integrity. We sought to determine whether WM integrity was affected in young offspring at high familial risk of mood disorder before they go on to develop major depressive disorder (MDD).

Methods

The Bipolar Family Study is a prospective longitudinal study examining individuals at familial risk of mood disorder on three occasions two years apart. This study used baseline imaging data, categorizing groups according to clinical outcome at follow-up. Diffusion tensor MRI data were acquired for 61 controls and 106 high-risk individuals, the latter divided into 78 high-risk subjects who remained well throughout the study ("high-risk well"), and 28 individuals who subsequently developed MDD ("high-risk MDD"). Voxel-wise between-group comparison of fractional anisotropy (FA) based on diagnostic status was performed using Tract-based Spatial Statistics (TBSS).

Results

Compared to controls, both high-risk groups showed widespread decreases of FA ($P_{corr}<0.05$) at baseline. Although FA in the high-risk MDD group negatively correlated with sub-threshold depressive symptoms at the time of scanning ($P_{corr}<0.05$), there were no statistically significant differences at p-corrected levels between the two high-risk groups.

Conclusions

These results suggest that decreased FA is related to presence of familial risk for mood disorder along with sub-diagnostic symptoms at the time of scanning, rather than predictive of subsequent diagnosis. Due to the difficulties performing such longitudinal prospective studies we note, however, that this latter analysis may be underpowered due to sample size within the high-risk MDD group. Further clinical follow-up may clarify these findings.

Context of study

Bipolar disorder (BD) is a mood disorder characterized by manic or hypomanic episodes during which the mood becomes euphoric and labile (Nussbaum and American Psychiatric Association., 2013). Depressive episodes are also common in BD during which pleasure-seeking is reduced and experiences are rated as less rewarding. Many studies have sought for the structural and functional brain mechanisms of BD in which altered connectivity has been proposed to play a key role (Sexton et al., 2009; Strakowski et al., 2005).

Fractional anisotropy (FA) is a sensitive diffusion tensor MRI (DTI) metric of white matter (WM) integrity, which estimates the degree of restriction of water molecule diffusion due to tissue organization. A recent meta-analysis of DTI studies in BD found three large clusters showing decreased FA compared with controls (Nortje et al., 2013), with the main tracts being the inferior longitudinal and fronto-occipital fasciculi located in the temporal lobe, the cingulum, and the anterior thalamic radiations. Some studies have, however, found increases in FA in BD patients compared with healthy individuals (Versace et al., 2008; Wessa et al., 2009), while others report no detectable difference (Houenou et al., 2007; Scherk et al., 2008).

Previous reviews and meta-analyses of DTI studies on patients with major depressive disorder (MDD) have found reduced FA in the left superior longitudinal fasciculus (Murphy and Frodl, 2011), the genu of the corpus callosum (Wise et al., 2016), bilateral frontal lobe, right fusiform and right occipital lobe (Liao et al., 2013), and frontal and temporal lobes (Sexton et al., 2009). The majority of studies of brain abnormalities in mood disorder have mostly been conducted on adult patients with longstanding illness *vs.* controls. It is unclear therefore whether brain structure may be altered before the development of the disorder, and whether abnormalities are confounded by secondary effects of long-term illness or treatment, or predictive of subsequent illness.

White matter integrity as indexed by FA is heritable (Chiang et al., 2011; Kochunov et al., 2010), and DTI studies have revealed suggestive evidence of WM integrity reductions in unaffected relatives of BD patients (Chaddock et al., 2009; Frazier et al., 2007). Versace et al. (Versace et al., 2010b) demonstrated

age-by-group interactions in the unaffected teenage offspings of bipolar probands. Moreover, the largest studies to date are consistent with the notion of subtle but widespread effects in relatives (Sprooten et al., 2016; Sprooten et al., 2013).

The Scottish Bipolar Family study (BFS) is a prospective cohort imaging study precisely examining young individuals (16-25 years) at high familial risk of mood disorder, along with a group of healthy controls with no family history, which aimed to investigate whether brain alterations precede and predict the later development of mood disorders (Whalley et al., 2011).

In a previous DTI study on this sample at baseline, we reported widespread FA reductions in unaffected young relatives of BD compared to subjects without family history of psychiatric disorders. Although the effects of genetic risk were diffuse, the associations with cyclothymia were more localized to fronto-temporal and prefrontal-thalamic connections (Sprooten et al., 2011). These findings therefore suggest that WM integrity is a marker of genetic risk for mood disorder with additional behavioral association linked to the etiology of the condition.

The Young Mania Rating Scale (Young et al., 1978) (YMRS) and the Hamilton Rating Scale for Depression (Hamilton, 1960) (HAM-D) are the most frequently utilized rating scales to assess manic and depressive symptoms that are the core features of BD. In the previous study (Sprooten et al., 2011), high-risk healthy subjects for mood disorders showed significantly higher scores in both these clinical scales compared to controls, suggesting that manic and depressive subclinical symptoms could also be a potential endophenotype for BD.

Individuals in the study, by virtue of the shared genetic architect of MDD/BD, are at risk for both mood disorders. Over the course of the BFS, a number of individuals have developed one or the other, with MDD being the predominant outcome (defined as meeting formal diagnostic criteria, Diagnostic and Statistical Manual of Mental Disorder, 4th edition, DSM-IV) and in sufficient numbers as to make a prospective comparison of well *vs*. affected individuals.

The current study presents findings for the same individuals, as acquired in the BFS, categorised into those at high familial risk who remained asymptomatic over the course of the study (“high-risk well”), compared to those who

developed a mood disorder at either of the follow-up assessments ("high-risk MDD"). We hypothesized, based on our previous study and the wider literature, that abnormalities in WM integrity assessed using DTI, in particular fronto-limbic and fronto-thalamic connections would precede subsequent illness in initially unaffected familial high-risk individuals.

Methods and Materials

Participants

Participants were recruited as part of the BFS (BFS; (Principal investigator A. McIntosh, U. of Edinburgh) (Sprooten et al., 2011; Whalley et al., 2011). Participants, including controls, have been followed up on three occasions two years apart (Whalley et al., 2015). Only the first two occasions contained imaging assessments, the third assessment being primarily a follow-up clinical evaluation. At the first assessment, patients with a clinical diagnosis of BD I were identified from the case loads of psychiatrists across Scotland. Each patient was asked to identify members of their close family between 16 and 25 years of age and to consent to either a review of their case notes or to a structured clinical interview. The diagnosis of all affected subjects was then confirmed with the Structured Clinical Interview for DSM-IV (SCID) or the OPCRIT symptom checklist (McGuffin et al., 1991). After informed consent, unaffected relatives of the proband with at least one first-degree or two-second degree relatives with BD I were then invited to participate in the study.

Wherever possible, to optimize matching on key confounds, control subjects were recruited from the social networks of the high-risk subjects themselves.

All participants, controls and high-risk subjects, were interviewed by one of two experienced psychiatrists (A.M.M., J.E.S.) using the SCID (First, 2002) to confirm the lifetime absence of any Axis I disorders at the baseline (T1), and at the fist follow-up (T2) to determine the presence of any mood disorder meeting diagnostic criteria over the intervening period. At the second follow-up (T3) diagnostic status was determined either by face-to-face assessment, or through accessing clinical records at the National Health Service (NHS) as to whether a clinical diagnosis had been made or not (Whalley et al., 2015).

For a number of individuals (controls, n = 22; high-risk, n = 21), it was not possible to determine the clinical status at T3; either the general practitioner (GP) did not provide details or the GP address was unknown. In the absence of further clinical information indicating that they had become unwell, and since they had remained well over the previous two assessments, these individuals were presumed to have remained well. This, however, necessitated an additional confirmatory analysis excluding these individuals, reported below (*cf*. Results section – TBSS Comparisons).

Manic and depressive symptoms were rated using the Young Mania Rating Scale and the Hamilton Rating Scale for Depression. Estimates of trait-liability to mood disorder (cyclothymia, neuroticism and extraversion) were measured using the TEMPS-A and NEO-FFI (Akiskal et al., 2005; McCrae and John, 1992).

The final sample consisted of 167 individuals categorized into three groups: (i) healthy controls who remained well (n = 61; note that four control individuals developed MDD or BD at the follow-up; however, due to small group size these individuals were not included in the current analysis); (ii) familial high-risk participants who remained well throughout the study (*high-risk well*, n = 78); and (iii) familial high-risk participants who developed a mood disorder (*high-risk MDD*) at any time throughout the period of study (20 by T2, a further eight by T3; high-risk MDD, n = 28; also of note is that three high-risk individuals had developed BD over the course of the study, similar to above these individuals were not included in the current analyses).

Written informed consent was provided by all participants, and the study was approved by the Multicentre Regional Ethics Committee for Scotland.

Scan Acquisition and Preprocessing

The current study reports findings from imaging data collected at entry in the study (‘baseline’). The MRI data were collected on a 1.5-T GE Signa Horizon HDX (General Electric, Milwaukee, Wisconsin) clinical scanner equipped with a self-shielding gradient set (22 mT/m maximum gradient strength) and manufacturer-supplied “birdcage” quadrature head coil. Whole brain DTI data were acquired for each subject with a single-shot pulsed gradient spin-echo echo-planar imaging sequence with diffusion gradients (b = 1000 sec/mm2) applied in 64 non-collinear directions and seven non-diffusion weighted (b=0)

echo-planar baseline volumes. Fifty-three 2.5-mm contiguous axial slices were acquired with a field-of-view of 240 x 240 mm, acquisition matrix of 96 x 96 (zero-filled to 128 x 128), giving an isotropic acquisition voxel dimension of 2.5 mm. In addition, a T1-weighted volume was acquired with time of inversion = 500 msec, echo time = 4 msec, flip angle = 8°, and voxel-size = 1.25 x 1.25 x 1.20mm (192 x 192voxels, 180 slices).

The DTI data were converted to 4D NIfTI volumes and preprocessed with standard tools available from the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). This included the following processes: correction for eddy current induced distortions and bulk subject motion in the scanner by registering the diffusion weighed volumes to the first T2-weighted volume within each subject; brain extraction; and calculation of diffusion tensor characteristics, including principal eigenvectors and FA values with DTIFIT.

Tract-Based Spatial Statistics

Tract-based Spatial Statistics (TBSS) was carried out according to standard FSL procedures (Smith et al., 2006) (http://www.fmrib.ox.ac.uk/fsl). First, FA volumes of all subjects were nonlinearly registered to a standard template. Secondly, a mean of all registered FA volumes was calculated, and a white matter “skeleton” created. This was achieved by searching for the maximum FA values in directions perpendicular to the local tract direction in the mean FA map. A threshold of FA > 0.25 was applied to the FA skeleton to exclude predominantly non-white matter voxels. Thirdly, the maximum voxel FA value perpendicular to the local direction was projected onto the skeleton at each point in all subjects. This resulted in one FA skeleton map per subject, assumed to contain the anatomically corresponding centroids of the WM structure, which we used to test for between-group differences and correlations with clinical scores.

With the obtained TBSS skeletons we performed two statistical tests. Firstly, to test for between-group differences in FA, nonparametric voxel-wise T tests were applied to the skeletons using the FSL “randomize” function, with three regressors in the design matrix, one for each group. Secondly, we examined the relationship between FA and measures of depressive symptoms at the time of the scan (from HAM-D scores), and measures of trait-liability (cyclothymia, neuroticism and extraversion). This was performed in ‘FSL’ testing separately

for association in each group and interactions between groups by adding three regressors to the design matrix, each containing the scores of one group.

Threshold-free cluster enhancement (TFCE) was applied to obtain cluster-wise statistics corrected for multiple comparisons. This method transforms local T-statistics into TFCE statistics that reflect both the size of the local effect (or "height") and the cluster extent (Smith and Nichols, 2009). The major advantages are that no predefined T-threshold is required, and that TFCE is sensitive to detect both large clusters of modest effects and single voxels of large effects, at the same time.

With the obtained TFCE maps, "randomize" then calculates a *p*-value (*p*-corrected) for each voxel, corrected for whole-brain family wise error (FWE) rate via permutation testing (5,000 permutations). These TFCE corrected p-maps were thresholded at $pFWE < 0.05$. We report the sizes of contiguous clusters of suprathreshold voxels. Significant results were localized to white matter tracts/structures with the Johns Hopkins University DTI-based white matter atlas and the Johns Hopkins University white matter tractography atlas (van Zijl, 2005) digitally available in FSL.

Statistical analysis of demographic and clinical data was conducted using SPSS software, version 23.0 (http://www-01.ibm.com/software/analytics/spss/). Differences between groups were tested using one-way ANOVA, Kruskal-Wallis or chi-squared tests as appropriate.

Results

Demographic and clinical features

There were no significant differences between groups with respect to gender, age, handedness, IQ, or substance use. Scores for the YMRS, HAM-D, cyclothmic, depressive, irritability, and anxious traits as measured by the TEMPS-A scale, as well as for neuroticism and agreeableness factors as measured using the NEO-FFI differed significantly between groups (Table 1). Post-hoc analysis revealed that high-risk MDD individuals had greater scores for the YMRS and HAM-D scales versus the controls; and for cyclothymic, depressive, and irritability traits, as well as neuroticism, they differed from both the controls and high-risk well groups. Moreover, the two high-risk groups were

significantly different on anxious traits and agreeableness (Table 2).

TBSS comparisons groups (controls, high-risk well, and high-risk MDD)

WM integrity differences between groups surviving the permutation testing are shown in Figure 1, and Table 3 ($p_{corr} < 0.05$). Compared to controls, at baseline neither high-risk group showed significantly *higher* FA values

Both high-risk groups however demonstrated significant decreased FA in comparison with the control group. The largest WM *reduction* in high-risk well *vs* controls was in a cluster that included the posterior thalamic radiation, extending to the posterior corona radiata and the superior longitudinal fasciculus in the right hemisphere (K=7,340, $p_{corr} = 0.02$). Other significant differences at p-corrected levels included smaller clusters in the right superior longitudinal fasciculus (K=53, $p_{corr} = 0.05$), and right anterior corona radiata (K=15, $p_{corr} = 0.05$), the left posterior thalamic radiation, and left posterior cingulum until the body of the corpus callosum (K= 839, $p_{corr} = 0.03$; and K=234, $p_{corr} = 0.05$, respectively).

High-risk MDD subjects compared with controls showed reduction of WM integrity mainly located in four large clusters in the right hemisphere. The largest cluster included the uncinate fasciculus and extended to the anterior corona radiata and inferior fronto-occipital fasciculus (K=4,092, $p_{corr} = 0.03$). Other clusters involved the inferior longitudinal fasciculus (K=2,849, $p_{corr} = 0.04$), posterior limb of internal capsule, extending to the anterior limb of internal capsule, anterior corona radiata and thalamic radiation (K=2,190, $p_{corr} = 0.04$), and the last one comprised posterior cingulum (k=2,014, p = 0.04). Smaller clusters were also found in the splenium and the body of corpus callosum, and bilaterally in the superior cortical spinal tract, in the brainstem corticospinal tract extending to the cerebellar peduncle, in the inferior and superior longitudinal fasciculi, and in fronto-occipital fasciculi.

Figure 2 demonstrates these two contrasts (high-risk well versus controls and high-risk MDD versus controls) overlaid onto a single image; however no differences were observed that survived permutation testing comparing directly the two high-risk groups.

Removing the 22 controls and 21 high-risk well individuals who were presumed well due to unavailable follow-up clinical data at T3, we detected significant

decreased FA in both high-risk groups (ill and well) compared with controls and no differences between the high-risk groups when directly compared. We therefore confirmed the main results found including all the subjects. Figure showing significant reduced FA in the high-risk that we know were well at T3 (n=57) and in the high-risk MDD both compared to control subjects well at T3 (n=39) is available in Figure 3.

TBSS correlation with clinical measures

A widespread negative association of HAM-D scores and FA values within the TBSS skeleton was found in the MDD high-risk group (Figure 4, Table 4). The three larger significant clusters were located in (i) the body of the corpus callosum comprising the genu and the splenium (K=6,860 voxels, $p_{corr} = 0.01$), (ii) in the right posterior thalamic radiation extending over the external capsule and the uncinate fasciculus (K=6441, $p_{corr} = 0.02$), and (iii) in the left inferior longitudinal and fronto-occipital fasciculi (K=2958, $p_{corr} = 0.03$).

Smaller significant clusters contained the superior longitudinal fasciculus bilaterally, and the forceps major, the inferior fronto-occipital fasciculus, and the anterior thalamic radiation in the right side, and the left cingulum, and left posterior thalamic radiation were also detected (Table 4). We did not find any association between FA and cyclothymia, neuroticism or extraversion.

Summary of Findings and Conclusions

This study investigates WM integrity in a relatively large sample of young subjects at high genetic risk of mood disorder with and without a subsequent diagnosis of MDD. The main aim of the project was to determine whether there was any distinguishing white matter microstructure features associated with the onset of subsequent mood disorder.

High-risk versus control differences

The comparison between high-risk subjects who remained well and controls, and high-risk individuals who subsequently develop MDD and controls revealed FA reductions in both high-risk groups. These results confirmed our previous baseline findings where we examined the high-risk subjects as an entire group, rather than sub-dividing based on outcome of clinical follow-up. In that study we reported significantly reduced integrity in the major WM association pathways,

extending from frontal to occipital lobes in unaffected youth with familial risk for BD when compared to healthy controls without a family history of psychiatric disorders (Sprooten et al., 2011).

In particular, smaller FA values in posterior WM tracts such as the posterior portion of the thalamic radiation, superior longitudinal fasciculus, cingulum, and in fibers belonging the body of the corpus callosum were detected in both high-risk groups compared with controls. High-risk individuals who developed MDD compared with controls however showed further reduced integrity in WM tracts located in the brainstem and anterior brain regions, such as the uncinate fasciculus, the anterior limb of the internal capsule, the anterior corona radiata and thalamic radiation, and sections of the inferior fronto-occipital and superior longitudinal fasciculi located in the middle and orbital frontal lobe.

To date, few other studies have examined WM integrity in unaffected youth individuals with familial risk of BD (Frazier et al., 2007; Versace et al., 2010b). Frazier et al. (Frazier et al., 2007) compared seven unaffected relatives with eight control subjects and found reduced FA in two clusters in the superior longitudinal fasciculi. Versace et al. observed that asymptomatic youth with familial risk for BD had a linear decrease between age and FA in the left corpus callosum, whereas healthy controls showed a linear increase in the same regions (Versace et al., 2010b). Another study detected increased FA in youth having both a parent with BD and mood dysregulation compared to controls (Roybal et al., 2015). Unaffected siblings, of patients with BD, once they are adults and mostly past the typical age onset of BD (mean age of 30 years old), also showed subtle FA reduction when compared to controls, which are most apparent in the corpus callosum (Sprooten et al., 2016; Sprooten et al., 2013). FA reductions were therefore observed using TBSS in siblings, mainly restricted to the corpus callosum, posterior thalamic radiations, and left superior longitudinal fasciculus (Sprooten et al., 2013). Using tractography analysis, reduced FA were not detected in the siblings compared to the controls, except for a trend in the corpus callosum (Sprooten et al., 2016).

Our findings support the suggestion that alterations in WM integrity may be an endophenotype for BD and encourage future studies assessing its relationship with the onset of mood disorders.

Despite not finding formally statistically significant differences in FA comparing

directly the two high-risk groups (high-risk well *vs* high-risk MDD), when comparing the high-risk MDD group to controls we found reduced FA values in the anterior fronto-thalamic connections, especially in the right side. We did not find WM disintegration in these tracts in the high-risk well compared to controls.

In vivo structural and functional imaging studies, as well as postmortem investigations of adults suggest that cortical–subcortical neural circuits play an important role in the pathogenesis of depression, especially limbic–thalamic–frontal networks (Mayberg, 2003; Price and Drevets, 2010). Structural and functional imaging data in pediatric populations, although limited, also support these models (Pine, 2002; Rosenberg, 2006). WM abnormalities constitute one element of these dysfunctional networks (Fields, 2008; Maller et al., 2010; Sexton et al., 2009).

A more widespread disconnection involving selectively fronto-thalamic tracts would be consistent with a temporally close MDD onset and mild sub threshold depressive symptoms; however, in our samples these emerging differences in high-risk MDD vs. controls comparison are too subtle to be detected between the two high-risk groups directly. It is important to note, nevertheless, that this analysis may be underpowered due to the relatively small sample size within the high-risk MDD group. The difficulties in conducting prospective longitudinal high-risk studies on young individuals with a family history of mental illness particularly relating to cumulative attrition over the course of the study should not be underestimated. Clinical longitudinal follow-up of these high-risk cohort and larger samples could clarify this point and relationships between WM integrity and the onset of mood symptoms.

Associations with symptoms

Although the 28 subjects who later developed MDD did not meet diagnostic criteria at baseline, these individuals had significantly increased levels of symptoms as measured by the clinical scales (HAM-D and YMRS) as well as greater scores for the cyclothymic, depressive traits, and neuroticism. These subclinical symptoms may indicate predictors of subsequent illness, or they could reflect the prodromal phase of a mood disorder.

In the current study, we detected in the high-risk MDD subjects a significant negative association between severity of depressive symptoms measured by the HAM-D scale and WM integrity, mainly located in the corpus callosum and

in the cortical and thalamic pathways. This finding could suggest that FA levels are sensitive to behavioural changes associated with clinical measures. The largest cluster of negative association in our group was found in the corpus callosum comprising the genu, the body, and the splenium.

The relationship between severity of depressive symptoms and WM integrity has previously been reported in the corpus callosum of patients with recurrent MDD (Cole et al., 2012; Lamar et al., 2010). Interestingly, Lamar et al. (Lamar et al., 2010) studied a sample consisting solely of euthymic patients with major depressive disorder, indicating that the relationship persists into remission.

In our sample, high-risk MDD subjects showed reduced FA levels in the body and the splenium of corpus callosum when compared to controls. As stated previously, Versace et al. found that asymptomatic youth with familial risk for BD had a linear decrease between age and FA in the corpus callosum (Versace et al., 2010b), and other studies using TBSS have also reported WM integrity reduction in the corpus callosum in siblings of BD patients (Sprooten et al., 2016; Sprooten et al., 2013), adolescents with a parental history of depression (Huang et al., 2011), and in adolescent patients with MDD (Bessette et al., 2014). Reduced volume and deformations in the corpus callosum have been observed also in MDD (Walterfang et al., 2009b), suicidal behaviour (Cyprien et al., 2011), bipolar depression (Benedetti et al., 2011b), and dysthymia (Lyoo et al., 2002). Together, these findings suggest that impairments in corpus callosum tracts may be involved early in the aetiology of depressive symptoms.

Other findings of increased severity of depressive symptoms with decreased WM integrity in the same regions that we found in the current study has been previously reported, such as the posterior thalamic radiation (Cole et al., 2012), inferior frontal regions (Nobuhara et al., 2006), cingulum (Keedwell et al., 2012), superior longitudinal fasciculus, and uncinate (Dalby et al., 2010; Sprooten et al., 2016). The varied pattern of WM tracts implicated in the literature indicates that further research is necessary to clarify the specificity of the relationship between depressive symptoms severity and brain changes and their association to functional impairments in people with depressive symptoms.

Limitations

Firstly, the early diagnosis of MDD in a young group of individuals at risk of BD may herald the onset of BD (Hillegers et al., 2005), where often the first episode

is depressive (Duffy, 2010a; Hillegers et al., 2005). Moreover, the high-risk subjects who subsequently became ill had higher clinical scores than controls at baseline. It is difficult therefore to dissociate neural markers underlying genetic risk for the disease trait from those co-occurring with the development of MDD symptoms, and indeed the two may be inherently related. Continued clinical longitudinal follow-up of the sample will ultimately contribute to a better understanding of prodromal phases of illness and associated disease pathways. Furthermore, genetic liability is not the only viable explanation of the findings. Shared environmental risk factors could also contribute to neural differences in high-risk population. For example, poverty, exposure to violence or chronic stress could also contribute to shared neural changes.

We did not find significant different changes between high-risk groups, but it is important to note that this analysis may be underpowered due to the relatively small sample size within the high-risk MDD group. Considering the mean FA of each subjects and a p value = 0.05, we obtained a statistical power = 0.69 when comparing the 28 high-risk MDD subjects with the 78 high-risk well individuals. The reduced sample size is unfortunately a reality in research in relatives of population with mood disorders because of the difficulties in conducting prospective longitudinal high-risk studies on young individuals with a family history of mental illness. Larger samples are therefore always sought after to confirm findings and better understand subtle WM changes.

Finally, although DTI is currently our best tool for estimating WM integrity, DTI results should be interpreted with caution because of the limitations of this in vivo technique: crossing fibers may occur within the region measured, and the resolution does not allow for a physiological interpretation at the cellular level. Thus a lower FA measurement is not necessarily always synonymous for “lower connectivity”.

In conclusion, using DTI we report altered microstructure within specific WM tracts in youth with high-risk for mood disorders that will or will not develop MDD. Although we did not find a different pattern of FA reduction in high-risk individuals who subsequently met MDD criteria compared to those who remained well, these findings provide evidence for an association between sub-threshold depressive symptoms and WM integrity. These FA reductions therefore may reflect subtle differences in current mood state (at baseline)

rather than predictors of future state.

Further follow-up studies will allow us to identify other individuals in the high-risk group who develop mood disorders and who remain healthy in order to clarify the early phases of mood disorder pathways.

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Table 1. Demographic and Historical Characteristic.

Variable	**Controls** (n=61)	**High-risk well** (n=78)	**High-risk MDD** (n=28)	**P value**
age[a]	20.8 (2.3)	21.4 (2.7)	21.1 (2.9)	0.50
Gender[b]				
Male	27 (44.35)	41 (52.6%)	12 (42.9%)	0.52
Female	34 (55.7%)	37 (47.4%)	16 (57,1%)	
Handedness[b]				
Left	4 (6.6%)	7 (9%)	1 (3.6%)	0.50
Right	57 (93.4%)	69 (88.5%)	27 (96.4%)	
Mixed	0	2 (2.5%)	0	
NART IQ[c]	110 (8)	110 (10)	107 (12)	0.58
Clinical measures				
YMRS[c]	0 (0)	0 (0)	0 (1)	0.02
HAM-D[c]	0 (1)	0 (2)	1.5 (6)	0.01
Temperament and personality measures				
Cyclothymia[c]	1 (4)	2 (3)	2 (7)	< 0.001
Depressive[c]	0 (2)	0 (1)	2 (3)	< 0.001
Irritability[c]	1 (2)	1 (2)	2 (2)	< 0.001
Hyperthymia[c]	2.5 (3)	2 (2)	2 (2)	0.29
Anxious[c]	1 (2)	0 (1)	1 (3)	0.04
NEO - Five Factor Inventory				
Neuroticism[a]	20.4 (9.3)	21.04 (9.2)	30.5 (10.5)	< 0.001
Extraversion[c]	31 (7)	30 (7)	27.5 (12)	0.21
Agreeableness[c]	33 (6)	34 (8)	30.5 (7)	0.03
Coscientiousness[c]	28 (9)	29.5 (12)	23 (12)	0.19
Openness[c]	29 (10)	28 (7)	29.5 (3)	0.07
Substance Use				
Alcohol[b]	55 (91.7%)	69 (88.2%)	21 (75%)	0.08
if yes: units/week[c]	15 (13)	12 (16.5)	15 (15.5)	0.68
Cigarettes[b]	20 (33.3%)	21 (26.9%)	11 (39.3%)	0.51
If yes:cig/day[c]	10 (6)	10 (11)	10 (18)	0.80
Cannabis[b]				
past	40 (66.7%)	53 (67.9%)	17 (60.7%)	0.78
current	5 (8.3%)	13 (16.7%)	6 (21.4%)	0.20
Stimulants[b]				
past	17 (28.3%)	23 (29.5%)	10 (35.7%)	0.77
current	6 (10%)	5 (6.4%)	1 (3.6%)	0.71
Hallucinogenic[b]				

past	10 (16%)	12 (15.4%)	6 (21.4%)	0.76
current	0	2 (2.6%)	2 (7.1%)	0.13
Opiates[b]				
past	1 (1,7%)	4 (5.1%)	1 (3.6%)	0.56
current	1 (1,7%)	0	1 (3.6%)	0.31
Sedatives[b]				
past	1 (1,7%)	5 (6.4%)	2 (7.1%)	0.91
current	0	1 (1.3%)	1 (3.6%)	0.36

Table shows statistical comparisons of demographic, clinical, behavioral measures and substance use in the three comparison groups at baseline.

[a]Group means and standard deviation for variables normally distributed (ANOVA).

[b]Frequency and percentages for categorical variables (chi-squared).

[c]Medians and interquartiles for variables not normally distributed (Kruskal-Wallis test).

MDD, Major Depressive Disorder; IQ, intelligent Quotient; YMRS, Young mania rating scale; HAM-D, Hamilton Scale for Depression.

Table 2. Post-hoc comparisons of clinical and temperamental measures.

Variable	Comparison group	Post-hoc p value
Clinical measures, and childhood trauma measures		
YMRS	Controls *vs* High-risk well	0.228
	Controls *vs* High-risk MDD	0.021*
	High-risk well *vs* High-risk MDD	0.474
HAM-D	Controls *vs* High-risk well	0.458
	Controls *vs* High-risk MDD	0.009*
	High-risk well *vs* High-risk MDD	0.149
Temperament and personality measures		
Cyclothymia	Controls *vs* High-risk well	1.000
	Controls *vs* High-risk MDD	0.002*
	High-risk well *vs* High-risk MDD	0.008*
Depressive	Controls *vs* High-risk well	1.000
	Controls *vs* High-risk MDD	0.003*
	High-risk well *vs* High-risk MDD	0.000*
Irritability	Controls *vs* High-risk well	1.000
	Controls *vs* High-risk MDD	0.021*
	High-risk well *vs* High-risk MDD	0.003*
Anxious	Controls *vs* High-risk well	0.517
	Controls *vs* High-risk MDD	0.451
	High-risk well *vs* High-risk MDD	0.037*
NEO - Five Factor Inventory		
Neuroticism	Controls *vs* High-risk well	1.000
	Controls *vs* High-risk MDD	0.000*
	High-risk well *vs* High-risk MDD	0.000*
Agreableness	Controls *vs* High-risk well	0.357
	Controls *vs* High-risk MDD	0.646
	High-risk well *vs* High-risk MDD	0.031*

Table shows results from post-hoc comparisons on variables found significantly different among the three groups (*cf.* Table 1).

The Bonferroni and the Dunn-Bonferroni corrections were respectively used for variables normally distributed and not normally distributed.

*indicates a significant statistical difference with $p \leq 0.05$,

MDD, Major Depressive Disorder; YMRS, Young mania rating scale; HAM-D, Hamilton Scale for Depression.

Table 3. Regions showing significant reductions in fractional anisotropy in high-risk subjects (well and MDD) compared to controls.

Cluster size (voxels)	WM region	Side	X	Y	Z	P value
Reduced FA in high-risk well vs controls						
7340	Posterior thalamic radiation	R	30	-71	9	0.02
53	Superior longitudinal fasciculus		40	-51	13	0.05
15	Anterior corona radiata		25	31	13	0.05
839	Posterior thalamic radiation	L	-33	-67	-2	0.03
234	Posterior cingulum		-21	-59	30	0.05
Reduced FA in high-risk MDD vs controls						
4092	Uncinate fasciculus	R	13	35	-14	0.03
2849	Inferior longitudinal fasciculus		45	-23	4	0.04
2190	Posterior limb of internal capsule		21	-16	-2	0.04
2014	Posterior cingulum		16	-41	40	0.04
713	Splenium of corpus callosum		22	-47	8	0.04
630	Superior longitudinal fasciculus		36	-62	28	0.04
596	Inferior fronto-occipital fasciculus		27	-67	26	0.04
105	Superior longitudinal fasciculus		47	-39	19	0.05
13	Corticospinal tract		6	-28	-34	0.05
3	Inferior longitudinal fasciculus		40	-53	1	0.05
2	Body of corpus callosum		3	1	25	0.05
767	Corticospinal tract	L	-22	-30	44	0.04
518	Inferior fronto-occipital fasciculus/ Inferior longitudinal fasciculus		-41	-31	-6	0.04
497	Posterior thalamic radiation		-34	-63	-3	0.04
29	Inferior fronto-occipital fasciculus/ Inferior longitudinal fasciculus		-19	-84	15	0.05
18	Superior longitudinal fasciculus		-32	-13	52	0.05
7	Inferior longitudinal fasciculus		-52	-13	-1	0.05
2	Superior longitudinal fasciculus		-35	-10	55	0.05
1	Superior longitudinal fasciculus		-39	-7	51	0.05

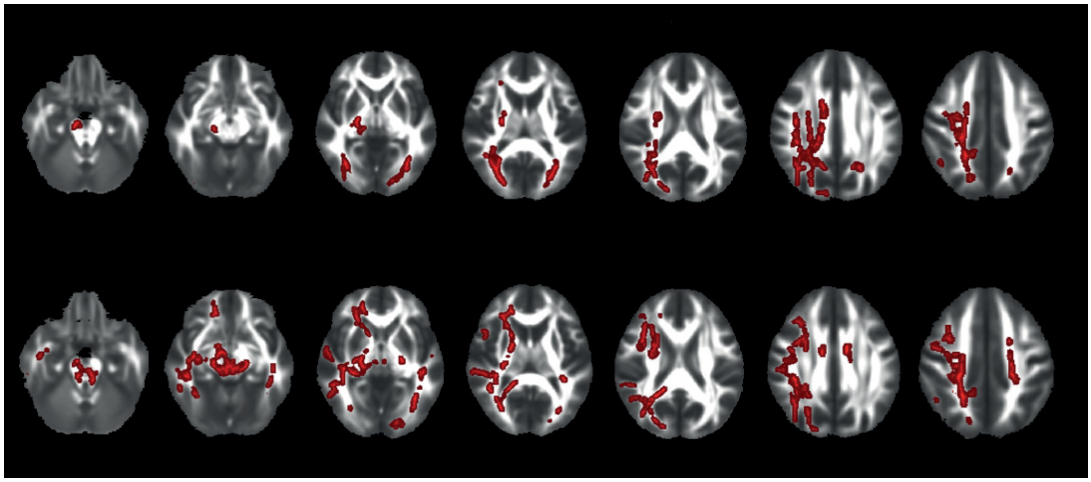
WM, White Matter; FA, Fractional Anisotropy; R, Right; L, Left; MDD, Major Depressive Disorder.

Table 4. Regions showing significant negative correlation between fractional anisotropy and symptoms of depression in high-risk subjects who developed a major depressive disorder.

Cluster size (voxels)	WM region	Side	X	Y	Z	P max-value
6860	body of corpus callosum	R	7	-21	25	0.01
6441	Posterior thalamic radiation		35	-59	8	0.02
546	Forceps major		10	-88	19	0.05
201	Inferior fronto-occipital fasciculus		35	24	19	0.05
68	Inferior fronto-occipital fasciculus		33	33	11	0.05
33	Superior longitudinal fasciculus		50	-6	22	0.05
10	Anterior thalamic radiation		11	-3	-6	0.05
2958	Inferior longitudinal fasciculus/inferior fronto-occipital fasciculus	L	-43	-24	14	0.03
700	Superior longitudinal fasciculus		-38	-24	-14	0.04
698	Posterior thalamic radiation		-32	-64	9	0.04
218	Cingulum		-6	-8	35	0.05
112	Superior longitudinal fasciculus		-46	-53	1	0.05
105	Superior longitudinal fasciculus		-40	-52	11	0.05
83	Cingulum		-14	-54	22	0.05
51	Posterior thalamic radiation		-36	-49	5	0.05

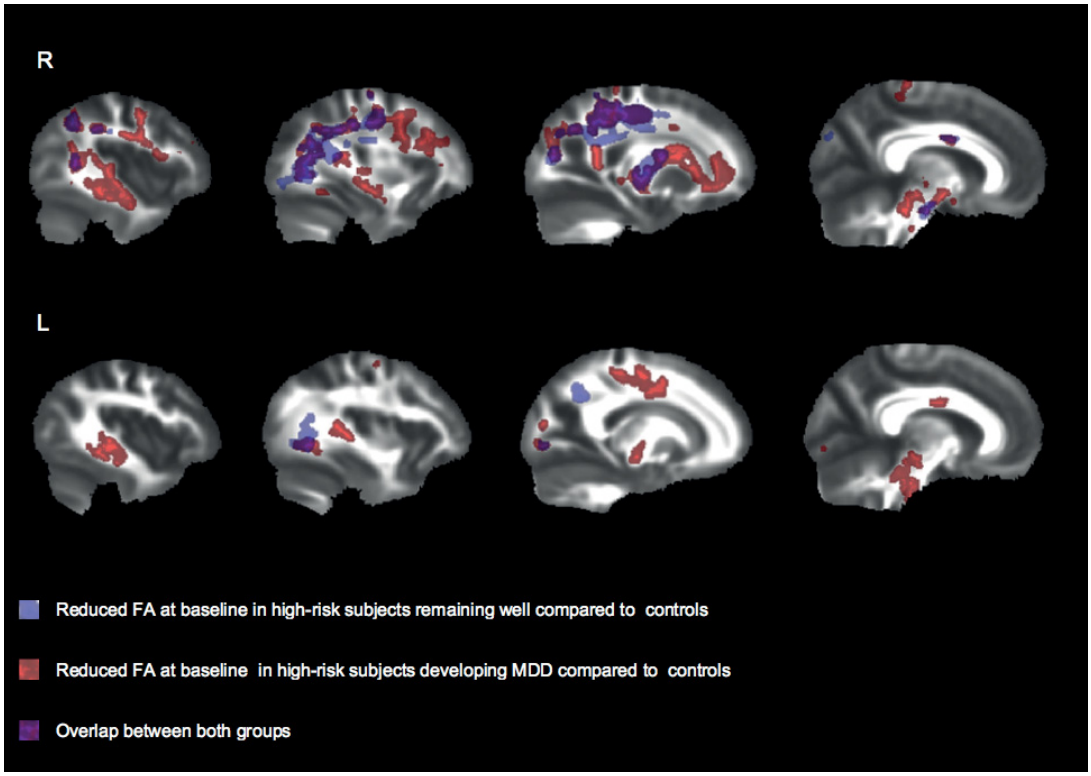
WM, White Matter; R, Right; L, Left.

Figure 1. Reduced fractional anisotropy at baseline in unaffected bipolar patients' relatives compared to controls.



Reduced fractional anisotropy at baseline in unaffected bipolar patients' relatives who did not develop psychiatric symptoms at follow-up ('High-risk well') compared to control subjects (Top row; High-risk Well < Controls); and in BD patients' relatives who met the criteria for MDD ('High-risk MDD') at follow-up compared with controls (Bottom row; High-risk MDD < controls). Corrected P value < 0.05. For better visibility the results are thickened with the "tbss-fill" command. The images are display in radiological convention.

Figure 2. Sagittal view of reduced fractional anisotropy at baseline in unaffected bipolar disorder patients' relatives compared with control subjects.



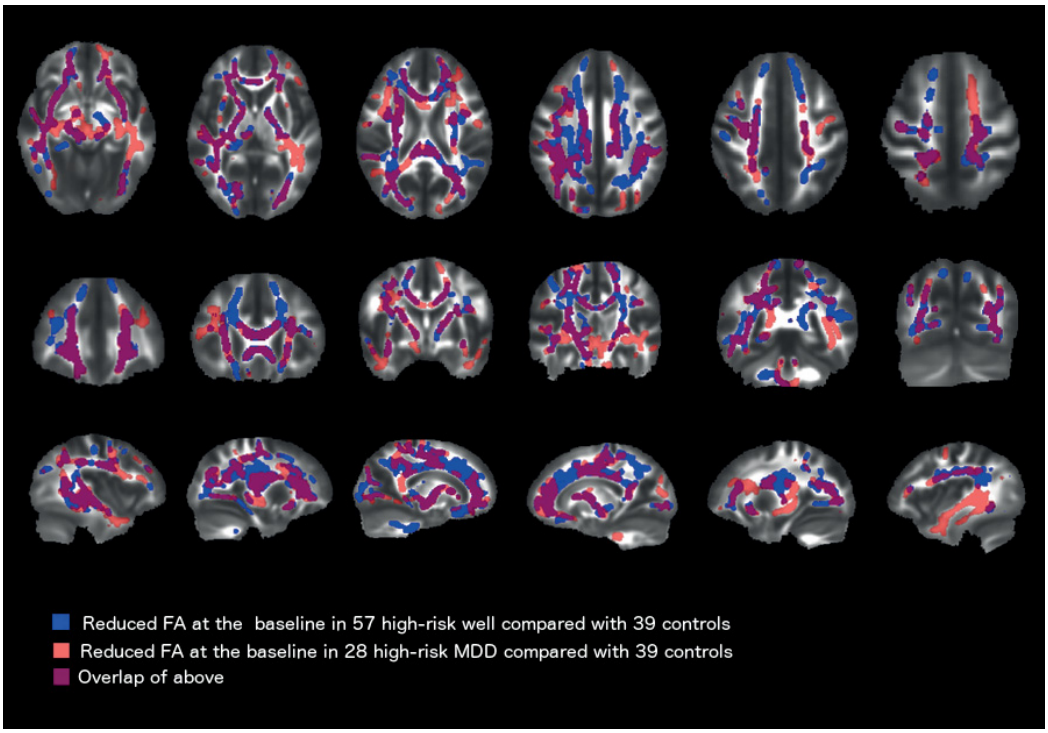
Sagittal view of reduced fractional anisotropy (FA) at baseline in unaffected bipolar disorder (BD) patients' relatives who did not develop psychiatric symptoms at follow-up compared with control subjects (in blue); reduced FA in BD patients' relatives who met the criteria for MDD at follow-up compared to controls (in red); and the overlap between the previous comparisons (in purple). Note that WM integrity is reduced in high-risk subjects, and more so for the deep connections and frontal regions in high-risk subjects who became depressed.

Corrected P value < 0.05. For better visibility the results are thickened with the "tbss-fill" command.

The images are in radiological convention.

R= right side, L=left side, MDD = Major Depressive Disorder

Figure 3. Reduced fractional anisotropy at baseline considering high-risk well subjects and controls with clinical outcomes at T3.



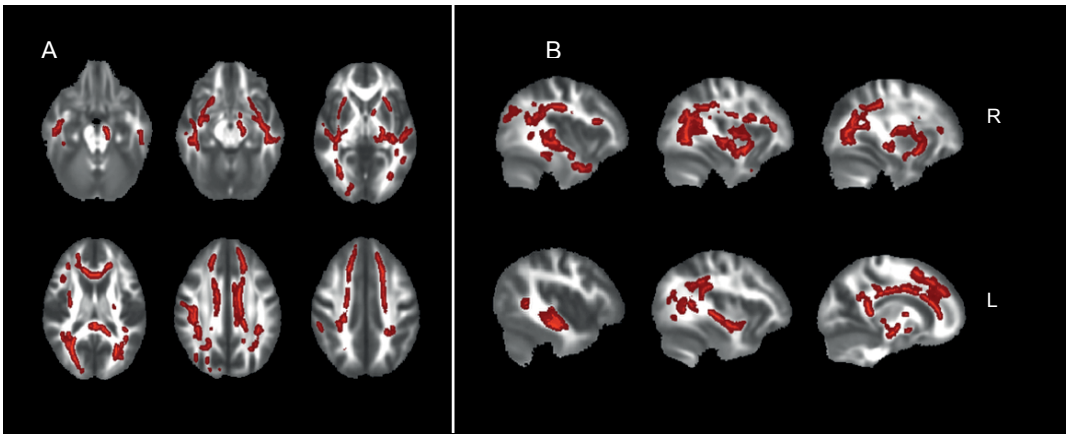
Axial, coronal, and sagittal views of reduced fractional anisotropy (FA) at baseline in unaffected BD patients' relatives who did not develop psychiatric symptoms at follow-up compared to control subjects (in blue); reduced FA in BD patients' relatives who met the criteria for Major Depressive Disorder (MDD) at follow-up compared to controls (in red); and the overlap between the previous comparisons (in purple). We included in the analysis only the high-risk subjects and controls with the available clinical data at T3.

One can notice that white matter integrity is reduced in both high-risk subjects compared with controls. The FA reduction patterns detected in both high-risk groups compared to controls appear to be different than those detected in the previous analysis (cf. Figure 2) however, no difference survived permutation testing and therefore, none were statistically significant.

Corrected P value < 0.05. For better visibility the results are thickened with the "tbss-fill" command.

The images are in radiological convention.

Figure 4. Negative correlation between fractional anisotropy values and symptoms of depression in high-risk subjects who deloped a major depression disorder.



Axial (A) and sagittal (B) view of negative correlation between fractional anisotropy values and scores obtained by the Hamilton scale of depression in high-risk subjects who developed a major depression disorder.

Corrected P value < 0.05. For better visibility the results are thickened with the "tbss-fill" command. The images are in radiological convention.

R= right side, L=left side

CHAPTER V: LONGITUDINAL DIFFERENCES IN WHITE MATTER INTEGRITY IN YOUTH AT HIGH FAMILIAL RISK FOR BIPOLAR DISORDER

Résumé
Dans cette étude, nous examinons la trajectoire des anomalies de la substance blanche avec les données d'imagerie collectées à la première et deuxième évaluation du Bipolar Familial Study chez 43 contrôles et 69 personnes à haut risque génétique, sous-divisés en deux sous-groupes de 53 sujets étant restés sains et 16 individus avec un diagnostic de trouble dépressif majeur lors du suivi. Nous avons détecté une réduction significative de l'anisotropie fractionnelle dans l'intervalle de deux ans pour chaque groupe, répandue dans plusieurs régions du cerveau. La trajectoire de l'anisotropie fractionnelle ne différait pas significativement entre les groupes. Ces résultats suggèrent qu'il y aurait des trajectoires similaires de réduction d'anisotropie fractionnelle pour les sujets témoins comme pour les jeunes adultes à risque, malgré le fait que les ces derniers étaient au point de départ désavantagés par rapport aux témoins. Une différence cliniquement parlante dans l'intégrité de la matière blanche chez les sujets à haut risque pourrait donc se produire plus tôt dans l'enfance et être une condition nécessaire mais non suffisante pour développer de futurs troubles de l'humeur.

Longitudinal differences in white matter integrity in youth at high familial risk for bipolar disorder

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Abstract

Objectives

Previous neuroimaging studies have reported abnormalities in white matter (WM) pathways in subjects at high familial risk of mood disorders. In the current study, we examine the trajectory of these abnormalities during the early stages of illness development using longitudinal diffusion tensor imaging (DTI) data.

Methods

Subjects (16-28 years) were recruited in the Scottish Bipolar Family Study, a prospective longitudinal study that has examined individuals at familial risk of mood disorder on three occasions, 2 years apart. The current study concerns imaging data from the first and the second assessment. We analyzed DTI data from 43 controls and 69 high-risk individuals that were further sub-divided into a group of 53 high-risk subjects who remained well (high-risk well), and 16 who met diagnostic criteria for major depressive disorder (high-risk MDD) at follow-up.

Longitudinal differences in fractional anisotropy (FA) between groups based on diagnostic status were investigated using tract-based spatial statistics technique (TBSS).

Results

We found a significant reduction in FA ($P_{corr} < 0.05$) across widespread brain regions over two years in all three groups. The trajectory of FA reduction did not differ significantly between groups.

Conclusions

These results suggest that there are similar trajectories of FA reductions for controls and high-risk young adults, despite high-risk individuals were at a disadvantaged starting point considering their reduced WM integrity detected at the baseline in previous studies.

Difference in WM integrity between high-risk and controls could therefore occur in earlier childhood and be a necessary but not sufficient condition to develop future mood disorders.

Context of study

Bipolar disorder (BD) and major depressive disorder (MDD) are highly heritable mood disorders sharing overlapping symptomatology, neural basis, and genetic architecture. Whereas sporadic elevation of mood is only present in BD, episodic depression is observed in both. The disorders seemingly share common neurobiological traits; notably, it has been reported that a disconnection in cortical-limbic pathways are significantly associated with both disorders (McMahon et al., 2010).

To explain these findings and propose an aetiological model, the importance of development in MDD and BD has been recently recognized and neurodevelopmental models have supplanted the classic hypothesis of progressive degeneration (Ansorge et al., 2007; Hagan et al., 2015). In this perspective, offspring and relatives of BD patients are a population rich in potential for revealing important aspects in the development of mood disorders before the onset of the disease, considering that familial studies showed an increased frequency of both BD and MDD in first-degree relatives of bipolar patients (McGuffin et al., 2003).

Diffusion tensor imaging (DTI) - a magnetic resonance technique able to quantify microstructural integrity using indices of preferential diffusion such as fractional anisotropy (FA) - has been used in studies comparing white matter (WM) microstructure in relatives of BD patients with those of subjects without a family history of psychiatric disorders (controls). Recent evidence indicates that early WM abnormalities may have a significant part in the pathophysiology of both BD and MDD, and could therefore represent an early marker of mood disorders (Adler et al., 2006; Barnea-Goraly et al., 2009; Bessette et al., 2014; Chen et al., 2004).

In a previous DTI study on this sample at baseline, we reported widespread FA reductions in unaffected young relatives of BD compared to subjects without family history of psychiatric disorders. Although the effects of genetic risk were diffuse, the associations with cyclothymia were more localized to fronto-temporal and prefrontal-thalamic connections (Sprooten et al., 2011). These findings confirm that WM integrity is an endophenotype for mood disorder with important behavioural association linked to the etiology of the condition.

Moreover, it could be stated that abnormal connectivity between regions may contribute to developmental alterations of key neural structures in BD.

However, there is a paucity of studies in the literature studying the longitudinal development of WM in young adults at high-risk for mood disorders, and hence whether these initial differences remain or if their trajectory changes through time. Only Versace and colleagues (Versace et al., 2010b) have reported group by age interactions in FA values in a cross-sectional design comparing healthy offspring of BD patients with individuals without familiar history of psychiatric disorders. The results showed a linear increase in FA in controls in the left corpus callosum and right inferior longitudinal fasciculus, whereas in BD offspring there was a linear decrease in FA with age in the left corpus callosum, and no relationship between FA and age in the right inferior longitudinal fasciculus.

To our knowledge, there have been no other longitudinal studies investigating changes in WM during the young adulthood development of individuals at high-risk for mood disorders, and none with sufficient follow-up to include subjects that went on to develop MDD. To fill this gap in knowledge, we propose in the current study an analysis of findings from scans acquired at baseline and at two-year follow-up of individuals recruited in the Scottish Bipolar Family Study (BFS).

Individuals in the study, by virtue of the shared genetic architect of MDD/BD, are at risk for both mood disorders. Over the course of the BFS, a number of individuals have developed one or the other, with MDD being the predominant outcome (defined as meeting formal diagnostic criteria, Diagnostic and Statistical Manual of Mental Disorder, 4th edition, DSM-IV) and in sufficient numbers as to make a longitudinal comparison of well v. affected individuals (Nickson et al., 2016a). Our analysis focused on individuals at high family risk who remained well at the time of the second assessment (the high-risk well) compared those who met the diagnostic criteria for a MDD between baseline and follow-up.

We hypothesized, based on our previous results, that WM integrity changes according to different trajectories in controls than high-risk individuals that become subsequently ill and in those that remain unaffected.

Methods and Materials

Initial baseline recruitment

Baseline recruitment has been described in full previously (Sprooten et al., 2011; Whalley et al., 2011). Briefly, at the beginning of the study (time 1, T1), individuals with a diagnosis of bipolar I disorder were identified by psychiatrists across Scotland. Diagnosis was confirmed with the OPCRIT symptom checklist (McGuffin et al., 1991) using data from clinical notes and the Structured Clinical Interview for DSM-IV (SCID; (First, 2002). Each affected subject was asked to identify members of close family aged 16–28 years. Following informed consent, unaffected individuals with at least one first-degree or two second-degree relatives with BD I were invited to participate. Unaffected, unrelated comparison subjects with no personal or family history of BD were identified from the social groups of the high-risk subjects and matched for age, gender and intelligence quotient (IQ) to the high-risk group. Comparison subjects were also screened using the SCID (First, 2002). Exclusion criteria for both groups at initial recruitment included a personal history of major depression, mania or hypomania, psychosis, or any major neurological or psychiatric disorder, a history of substance dependence, learning disability, or any history of head injury that included loss of consciousness and any contraindications to magnetic resonance imaging (MRI). No group differences in lifetime substance misuse were observed previously in this sample (Whalley et al., 2011). Written informed consent was obtained. The study was approved by the Multi-Centre Research Ethics Committee for Scotland.

Current study population

Participants were recruited for the current study as part of the BFS as described above (Sprooten et al., 2011; Whalley et al., 2011).

Only the first two occasions [T1, time 2 (T2)] contained imaging assessments, the third assessment (T3) being primarily a follow-up clinical assessment. All participants, controls and high risk, were interviewed by one of two experienced psychiatrists (A.M.M., J.E.S.) using the SCID (First and Pincus, 2002) to confirm the lifetime absence of any Axis I disorders at T1, and at to determine the presence of any mood disorder meeting diagnostic criteria over the intervening period. At T3 diagnostic status was determined either by face-to-face assessment, or through accessing clinical records at the National Health

Service (NHS) as to whether a clinical diagnosis had been made or not (Whalley et al., 2015). For a number of individuals (n = 19), it was not possible to determine the clinical status at T3, either the general practitioner (GP) did not provide details or the GP address was unknown. In the absence of further clinical information indicating that they had become unwell, and since they had remained well over the previous two assessments, these individuals were presumed to have remained well.

If other disorders were present along with depressive features these individuals were excluded from the current analysis. Moreover, we excluded MR images of subjects that did not pass quality control during the different analysis steps.

Manic and depressive symptoms were rated using the Young Mania Rating Scale (YMRS; (Young et al., 1978)) and the Hamilton Rating Scale for Depression (HAM-D; (Hamilton, 1960)).

Estimates of trait-liability to mood disorder (cyclothymia, neuroticism and extraversion) were measured using the TEMPS-A and NEO-FFI (Akiskal et al., 2005; McCrae and John, 1992).

The current study concerns structural brain changes between T1 and T2 in relation to the development of MDD at the second assessment (T2) throughout the study.

Groups

The final sample consisted of individuals categorized firstly into two groups: (i) healthy controls who remained well (n=43); and (ii) familial high-risk participants (n=69). Controls meeting criteria for psychiatric disorders at the follow-up and high-risk patients developing conditions other than MDD were removed from the study because numbers did not allow robust statistical testing. Moreover, controls and high-risk subjects whose images did not pass quality check during the registration to the standard space were also excluded. Figure 1 details the subjects' selection process.

The high-risk group was then split in two sub-groups, based on diagnosis at the time of the second MRI scan: subjects who remained well between the baseline (T1) and the second assessment (T2) (high-risk well, n = 53); and familial high-risk participants who had developed MDD by the second assessment (high-risk MDD, n =16).

Scan Acquisition and Preprocessing

The current study reports findings from imaging data collected at T1 and T2. MRI data were collected on a 1.5-T GE Signa Horizon HDX (General Electric, Milwaukee, Wisconsin) clinical scanner equipped with a self-shielding gradient set (22 mT/m maximum gradient strength) and manufacturer-supplied "birdcage" quadrature head coil. Whole brain DTI data were acquired for each subject with a single-shot pulsed gradient spin-echo echo-planar imaging sequence with diffusion gradients (b = 1000 sec/mm2) applied in 64 non-collinear directions and seven T_2-weighted echo-planar imaging baseline scans. Fifty-three 2.5-mm contiguous axial slices were acquired with a field-of-view of 240 x 240 mm, acquisition matrix of 96 x 96 (zero-filled to 128 x 128), giving an isotropic acquisition voxel dimension of 2.5 mm. In addition, a T1-weighted volume was acquired with time of inversion = 500 msec, echo time = 4 msec, flip angle = 8°, and voxel-size = 1.25 x 1.25 x 1.20mm (192 x 192voxels, 180 slices).

The DTI data were converted to 4D NIfTI volumes and preprocessed with standard tools available from the Fmrib Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). This included the following processes: correction for eddy current induced distortions and bulk subject motion in the scanner by registering the diffusion weighed volumes to the first T2-weighted volume within each subject; brain extraction; and calculation of diffusion tensor characteristics, including principal eigenvectors and FA values with DTIFIT.

Tract-Based Spatial Statistics

We used tract-based spatial statistics (TBSS) to study longitudinal WM changes across time and between groups. TBSS was carried out according to standard FSL procedures (Smith et al., 2006) (http://www.fmrib.ox.ac.uk/fsl). First, FA volumes of all subjects were nonlinearly registered to a standard template. Secondly, a mean of all registered FA volumes was calculated, and a white matter "skeleton" created. This was achieved by searching for the maximum FA values in directions perpendicular to the local tract direction in the mean FA map. A threshold of FA > 0.25 was applied to the FA skeleton to exclude predominantly non-white matter voxels. Thirdly, the maximum voxel FA value perpendicular to the local direction was projected onto the skeleton at each point in all subjects. This resulted in one FA skeleton map per subject, assumed to contain the anatomically corresponding centroids of the WM structure.

With the obtained TBSS skeletons we performed three statistical analyses.

Firstly, to test for between-group difference in FA changes over time, repeated meausures ANOVA were applied to the skeletons by using the “randomize” function in FSL, with four regressors in the design matrix, one for each group and one for each time of acquisition.

Secondly, we used TBSS to study the difference over time between High-risk Well and high-risk MDD groups. In this case, we used six regressors in the design matrix, one for each group (controls/high-risk well/high-risk MDD) and one for each time of acquisition (T1 andT2)

Thirdly, we substracted the FA volume obtained for each subject at the second scan to the FA volume obtained at baseline. We used this FA difference to perform a correlation with age using age as covariate in the GLM model to investigate the relationship between FA changes and development in each group.

Threshold-free cluster enhancement (TFCE) was applied to obtain cluster-wise statistics corrected for multiple comparisons. Briefly, this method transforms local T-statistics into TFCE statistics that reflect both the size of the local effect (or “height”) and the cluster extent (Smith and Nichols, 2009). The major advantages are that no predefined T-threshold is required, and that TFCE is sensitive to detect both large clusters of modest effects and single voxels of large effects, at the same time.

With the obtained TFCE maps, “randomize” then calculates a *p*-value (*p*-corrected) for each voxel, corrected for whole-brain family wise error (FWE) rate via permutation testing (5,000 permutations). These TFCE corrected p-maps were thresholded at $pFWE < .05$. We report the sizes of contiguous clusters of suprathreshold voxels. Significant results were localized to white matter tracts/structures with the Johns Hopkins University DTI-based white matter atlas and the Johns Hopkins University white matter tractography atlas (van Zijl, 2005) digitally available in FSL.

Statistical analysis of demographic and clinical data was conducted using SPSS software, version 23.0 (http://www-01.ibm.com/software/analytics/spss/). Differences between groups were tested using one-way ANOVA, t- chi-squared tests or using non-parametric tests as appropriate.

Results

Demographic and clinical features

We did not find any significant differences between groups with respect to gender, age, IQ, or scan interval (Table 1, Table 2). Scores for the HAM-D, cyclothmic, depressive, and irritability traits as measured by the TEMPS-A scale, as well as for neuroticism and extraversion factors as measured using the Five Factor Inventory differed significantly between groups at baseline (Table 3). Post-hoc analysis revealed that High-risk MDD individuals differed significantly for the HAM-D, cyclothymia, and extraversion scores from Controls, and for depressive trait and neuroticism from both Controls and High-risk Well. These effects were in the directions predicted in accordance with other studies, namely High-risk MDD > High-risk Well > Controls for neuroticism, cyclothymia, depressive and HAM-D scores, and High-risk MDD < High-risk Well < Controls for extraversion.

TBSS analysis

Results (a) were obtained by analysis of FA longitudinal changes in each group and comparisons of FA changes over time between Controls and all High-risk subjects.

Results (b) were obtained by analysis of FA longitudinal changes in the two sub-high-risk groups and comparisons of FA changes over time between the 53 High-risk Well and 16 High-risk MDD.

Results (c) describe TBSS results from the correlation between FA changes and age in each of the three groups (Controls/High-risk Well /High-risk MDD).

a) Controls vs High-risk

a.1. FA changes over time in Control group

There was no significant increase in FA in the control group along the two-year time interval between assessments, whereas a widespread decrease of FA was detected. TBSS followed by permutation testing resulted in a large diffuse cluster (K=35,921, $p_{corr} < 0.05$) extending over most of the white matter skeleton, indicating decreases over time in the body and the splenium of the corpus callosum, internal and external capsule (including thalamic radiation), inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculi, corona radiata, parts of the cortical spinal tract and the right uncinate fasciculus (Figure 2).

a.2. FA changes over time in High-risk group

Like Controls, increase in FA over time in the high-risk group was not detected. An FA decrease surviving the permutation test was observed in a larger cluster (K=57,451, $p_{corr} < 0.05$), comprising the same regions as the Controls, . However, there were further WM areas with FA loss for High-risk subjects includingthe left uncinate fasciculum, genu of the corpus callosum, and the anterior portion of the thalamic radiation, corona radiata, cingulum, and inferior fronto-occipital fasciculus (Figure 2).

a.*3.* Group x Time interactions

Despite the different pattern of FA loss found separately in the Control and High-risk group, there was no significant differences surviving permutation test when FA changes between groups where directly compared.

b) Controls, High-risk Well, and High-risk MDD

b.1. FA changes over time in High-risk MDD and High-risk Well individuals

There was a significant widespread decrease in FA along the two-year time course in both high-risk groups. Hovewer, High-risk Well individuals had relatively spared bilateral posterior thalamic radiation, body of the corpus callosum, left inferior and fronto-occipital fasciculi, and left anterior cingulum and corona radiata in the medial frontal lobe. Moreover, in that same group an increase of FA was detected in a small cluster (K= 133, $p < 0.05$) located in the right posterior superior longitudinal and fronto-occipital fasciculi (Figure 3).

b.2. Groups (Controls/High-risk Well/High-risk MDD) x Time interactions

There were no significant differences surviving the permutation test in any comparison of FA between groups over time.

c) Correlation with age

Results of the TBSS correlation with age show a negative correlation between FA and age surviving the permutation tests in the right inferior longitudinal and fronto-occipital fasciculi, and anterior thalamic radiation in the Control group (Figure 4).

Summary of Findings and Conclusions

We investigated longitudinal WM changes in youth at high genetic risk for mood disorders compared to unrelated controls. We further stratified the analysis by

looking at two sub-groups, the first composed of those high-risk subjects that met the criteria for MDD at two-year follow-up, compared to the second group of subjects that remained healthy.

We found a significant decrease of FA over two years in all three groups, albeit diffuse over the whole brain. No significant increase in FA over time was detected, except for a small cluster including posterior connections in the High-risk Well group.

a) Lifetime trajectory of FA

A diffuse increase in FA from newborn to adolescence and a rapid widespread decrease from old age onwards is a consistent finding in studies tracking WM changes across the lifespan. However, WM changes during adulthood are not as well defined. Indeed, studies on WM variations in young and mid-adults have reported conflicting results (Yap et al., 2013). An explanation for this discrepancy could be that the peak of FA for different WM areas may be reached at varying ages during adulthood. Indeed, there is evidence for myelination occurring into fronto-temporal cortical areas well into the late-adulthood (Bartzokis, 2011), which will inevitably impact FA. More specifically, FA of the corpus callosum and long association fibers such as the inferior longitudinal and inferior fronto-occipital fasciculus peak in the early to mid-20s, while it has been shown that projection fibers such as those in the anterior limb of the internal capsule as well as corticospinal tracts peak in the early to mid-30s. Of note, the long association tracts connected with the limbic system have differing developmental trajectories; the fornix and cingulum bundles reach their FA peak before 20 and after 40 years of age, respectively (Lebel et al., 2012). Overall, it can be said that the details of the WM maturation process for different brain structures as well as within each structure over time are still not entirely understood. This is further supported by the fact that our understanding of lifespan brain WM integrity is based on mostly cross-sectional studies of different age periods, as demonstrated in a recent review on this subject (Yap et al., 2013). Cross-sectional results must be considered as models of longitudinal outcome with caution. Longitudinal designs will provide better evidence to elucidate the normal developmental course of WM changes with age, and path to illness.

Given this background, we can assess our results in Controls, where we found a negative correlation between age and FA values in these subjects, aged between 16 and 28, therefore late adolescents to young adults. After permutation testing, clusters of voxels were still significant in the WM fibers of the right medial temporal lobe for the Control group. This result suggests that the decrease in FA over time found in Controls could be partially explained by maturation processes related to normal development of these early adult individuals.

b) FA trajectory in high-risk population

To the best of our knowledge, the present study is the first longitudinal analysis on WM integrity changes over time in subjects with high familial risk of mood disorders.

We found FA reductions in adolescents and young adults with and without familial risk for mood disorders over a time course of two years, and we did not find significant differences in the amount of FA decrease between the groups surviving the permutation test. Our results suggest that WM abnormalities found previously between high-risk individuals and controls in this cohort (Sprooten et al., 2011) are stable by the late teens/early twenties.

Most of studies of WM in relatives of BD patients have focused on adult individuals. Studies assessing macrostructural WM alterations revealed reduced WM volumes (Bearden et al., 2011; van der Schot et al., 2009; Walterfang et al., 2009a), and more WM hyperintensities (Gulseren et al., 2006). DTI analysis comparing first-degree relatives of BD patients with controls detected significantly reduced FA in the right anterior limb of the internal capsule and right uncinate fasciculus (Linke et al., 2013). FA reductions were also observed using TBSS in unaffected siblings of BD probands, mainly restricted to the corpus callosum, posterior thalamic radiations, and left superior longitudinal fasciculus (Sprooten et al., 2013). Using tractography analysis, reduced FA were not detected in the siblings compared to the controls, except for a trend in the corpus callosum (Sprooten et al., 2016). Presence of WM abnormalities in adult relatives of patients with BD was therefore a consistent finding in MRI investigations.

Only two studies analyzed FA in younger subjects with familial risk for BD. Frazier et al. (Frazier et al., 2007) found that children aged between four and 12

years having a first-degree relative with the disorder showed reduced FA relative to controls in bilateral superior longitudinal fasciculi. Versace et al. (Versace et al., 2008) observed that asymptomatic youth with familial risk for BD aged between eight and 17 years had a linear decrease between age and FA in the left corpus callosum, whereas healthy controls showed a linear increase in the same regions. WM alterations were therefore already present in children and in adolescents with familial risk for BD.

In the current study, we did not detect differences in FA changes comparing both high-risk young adults who developed and who did not develop MDD with controls, despite previously finding reduced FA in all high-risk subjects when compared with controls at the baseline.

Together these findings could suggest that differences between cases and controls probably don't emerge proximal to the onset of illness but may therefore have existed from birth or emerged earlier in childhood and adolescence.

Longitudinal studies are needed to determine the nature of the developmental changes in WM during childhood and adolescence that may precede the onset of BD or other psychiatric disorder in youth at risk for BD.

Despite not finding significant differences surviving the permutation test comparing longitudinal FA changes between groups, considering the progressive changes of WM integrity in each group, we detected a decrease of FA in both controls and high-risk subjects with further FA loss in the High-risk group mainly located in anterior regions, such as the uncinate fasciculum, and the anterior portion of corpus callosum, thalamic radiation, corona radiata, cingulum, and inferior fronto-occipital fasciculus.

Convergent evidence supports a central role for altered development of frontotemporal neural systems in BD. Frontotemporal WM abnormalities have been reported in many adult DTI studies related to BD (Benedetti et al., 2011a; Beyer et al., 2005; Lin et al., 2011; Linke et al., 2013; McIntosh et al., 2008; Sui et al., 2011; Sussmann et al., 2009; Versace et al., 2008; Versace et al., 2010a; Versace et al., 2014; Wang et al., 2009). Studies of children and adolescents with BD have also shown findings of reduced structural integrity in frontal WM regions, compared to healthy children and adolescents (Adler et al., 2006; Barnea-Goraly et al., 2009; Frazier et al., 2007; Gao et al., 2013; Gonenc et al.,

2010; Kafantaris et al., 2009; Lagopoulos et al., 2013; Pavuluri et al., 2009). Moreover, frontotemporal structural integrity abnormalities have been reported in DTI studies of adults with BD and their high-risk BD adult relatives, both showing decreased FA values in the right uncinate fasciculus (Linke et al., 2013).

Taken together, these reports indicate that intra- and inter-hemispheric frontotemporal WM abnormalities are already present in childhood, continue in adolescence and remain throughout adulthood, and therefore could represent some of the earliest markers of the disorder.

In the current study, the sample size of the groups could be too modest in order to detect what could be biologically meaningful small effects. Further samples are therefore needed to understand if a loss of WM integrity is present during development in familial high-risk subjects for mood disorders when compared to individuals without family history of psychiatric disorders.

c) Conclusion

In conclusion, we found FA progressive reductions in our sample of adolescents and young adults with and without familial risk for mood disorders.

We did not find significant different changes between the groups, but it is important to note that this analysis may be underpowered due to the relatively small sample size within the high-risk MDD group. The difficulties in conducting prospective longitudinal high-risk studies on young individuals with a family history of mental illness particularly relating to cumulative attrition over the course of the study should not be underestimated. Clinical longitudinal follow-up of these high-risk cohort and larger samples could clarify relationships between WM integrity and the onset of mood symptoms.

In summary, research on WM in BD supports an important role for frontotemporal WM. Neurodevelopmental abnormalities that affect trajectories of WM development during childhood and adolescence could be implicated before the onset of mood disorder symptoms in subjects with genetic risk. Longitudinal studies of high-risk children and adolescents and increased sample sizes might clarify these abnormalities in brain changes to target for early identification, intervention and prevention strategies.

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Table 1. Demographic measures comparing controls with all high-risk subjects group.

	Controls (n=43)		**High-risk** (n=69)		**Significance**
	Mean	St dev	Mean	St dev	P value
age baseline (yrs)	20.8	2.6	21.6	2.9	0.17
age FU (yrs)	22.9	2.7	23.8	2.9	0.12
Gender (M/F)	16/27	-	32/37	-	0.4
NART IQ	110	7.6	109*	9	0.49
Scan interval (yrs)	2.1	0.3	2.2	0.3	0.16

P denotes significance on t- or Chi-squared-test

Table 2. Demographic measures comparing controls with high-risk subjects split in high-risk well and high-risk MDD.

	Controls (n=43)		**High-risk well** (n=53)		**High-risk MDD** (n=16)		**Significance**
	Median	IQR	Median	IQR	Median	IQR	P value
age baseline (yrs)	21.1	4.6	21.8	5.4	20.4	4.5	0.2
age FU (yrs)	23.0	4.6	24.0	5.4	22.5	4.5	0.19
Gender (M/F)	16/27	-	27/26	-	5 /11	-	0.2
NART IQ	110.0	8.0	110.0	11.0	107.0	8.0	0.27
Scan interval (yrs)	2.1	0.1	2.0	0.4	2.2	0.5	0.1

P denotes significance on Kruskal-wallis. IQR = Interquartile range

Table 3. Clinical and temperamental features at baseline.

Variable	Controls (n=36)	High-risk well (n=49)	High-risk MDD (n=14)	P value
Clinical Measures				
YMRS	0 (0)	0 (0)	0 (1)	0.38
HAM-D	0 (1)	0 (2)	2 (6)	0.01[a]
Temperament and personality measures				
Cyclothymia	1 (6)	2 (3)	6.5 (8)	0.02[a]
Depressive	0 (1)	0 (1)	2.5 (4)	0.01[b]
Irritability	1 (2)	1 (2)	2 (4)	0.05
Hyperthymia	2 (3)	2 (2)	2 (3)	0.59
Anxious	1 (2)	0 (1)	1.5 (3)	0.09
NEO - Five Factor Inventory				
Neuroticism	19.5 (14)	20.5 (13)	32.5 (20)	0.01[b]
Extraversion	32 (7)	30 (8)	24.5 (13)	0.04[a]
Agreeableness	32.5 (6)	32 (11)	29.5 (14)	0.50
Conscientiousness	29.5 (10)	30 (12)	23.5 (14)	0.39

P denotes significance on Kruskal-wallis test.

Median (interquartile range) reported in the table

a: high-risk MDD ≠ controls at post-hoc analysis

b: high-risk MDD ≠ both controls and high-risk well at post-hoc analysis

Figure 1. Flowchart for inclusion of subjects.

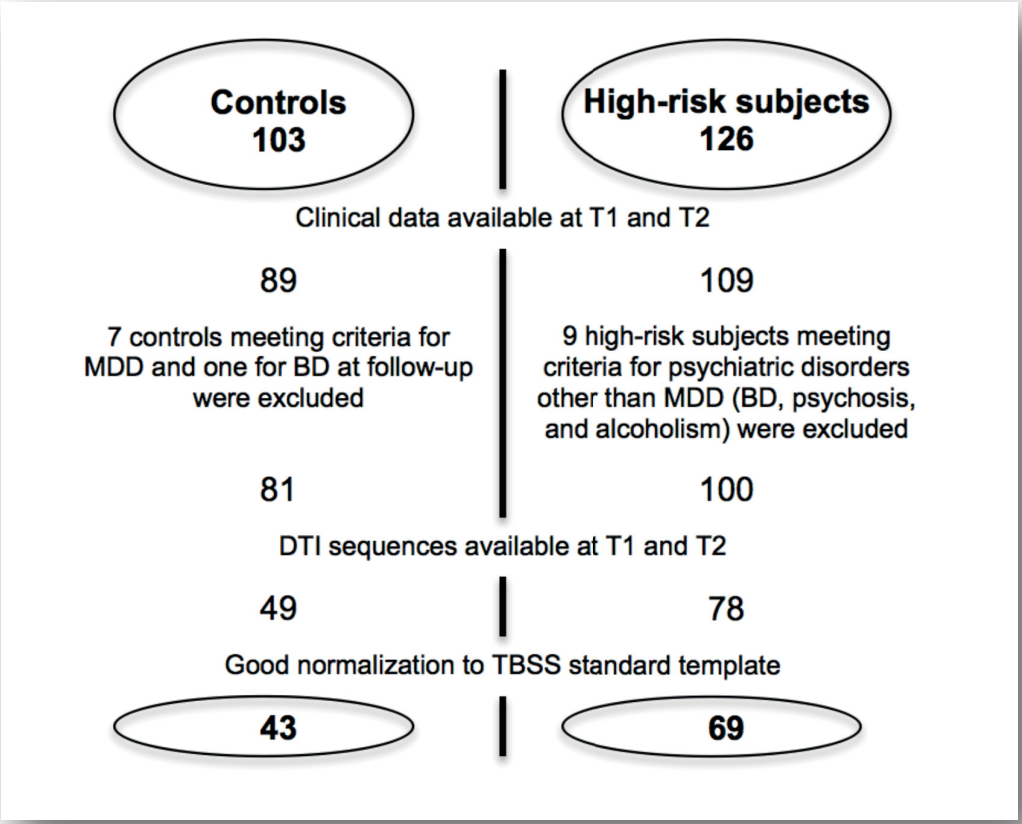
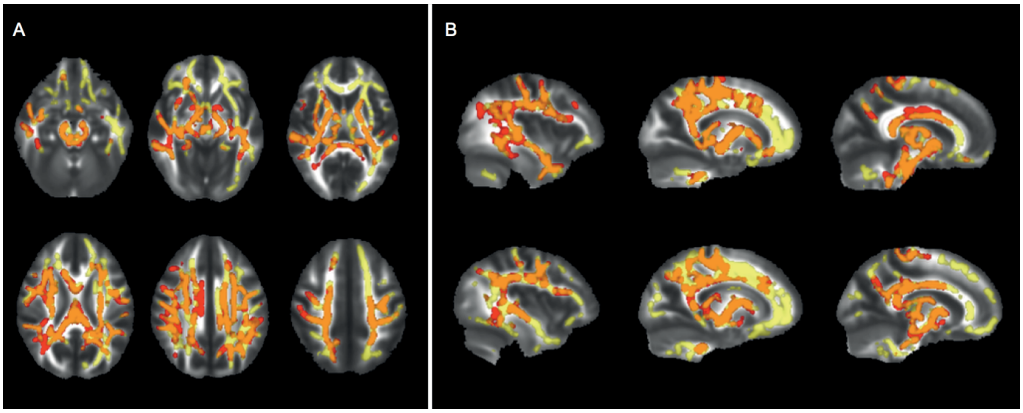


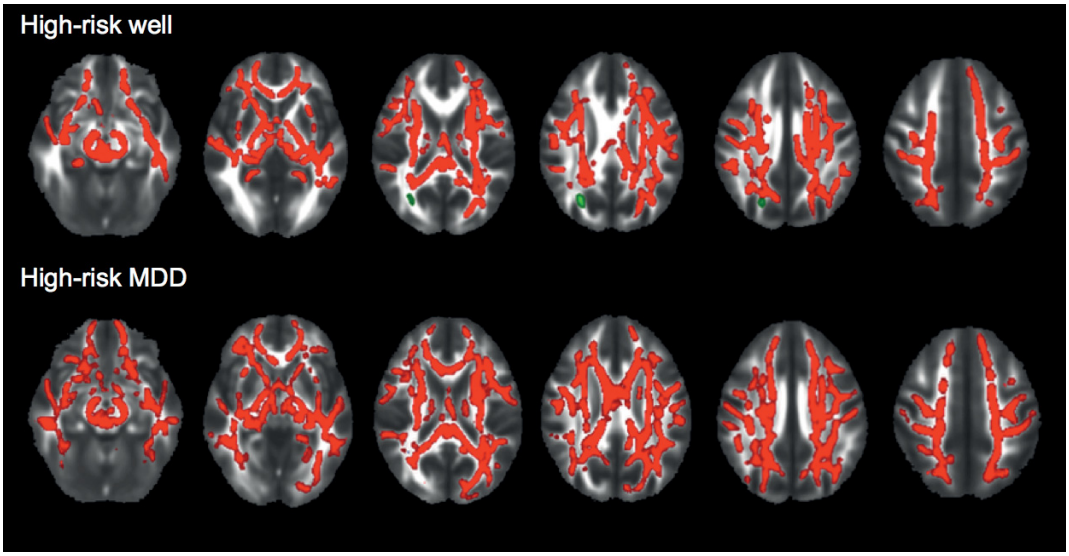
Figure 2. Significant decrease of fractional anisotropy along the two years time course in the control group, in the high-risk group and in both groups.



Axial (A) and sagittal (B) view showing significant decrease of FA along the two-year time course in the control group (in red), in the high-risk group (in yellow) and in both groups (in orange). There was no significant increase in FA detected.

For better visibility the results are thickened with the “tbss-fill” command. The images are in radiological convention. Corrected *p*-value < 0.05.

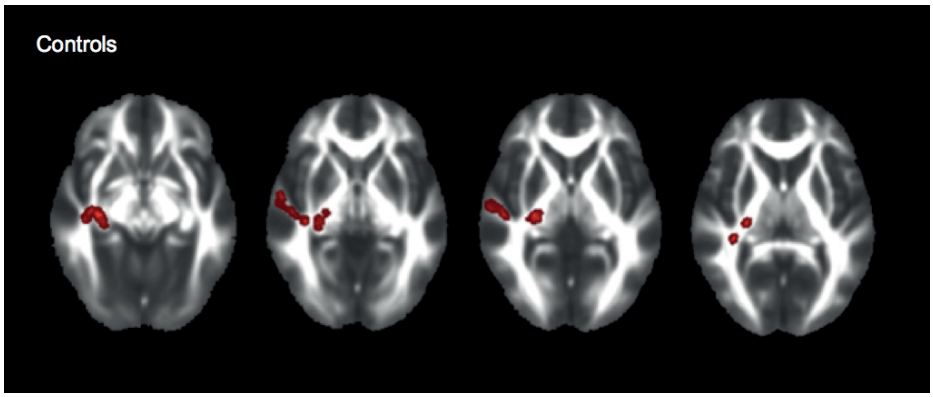
Figure 3. Significant fractional anisotropy changes in the high-risk well subjects as well as high-risk MDD individuals.



Axial rendering showing significant decrease (in red) and increase (in green) of FA along the two-year time course in the high-risk well subjects as well as high-risk MDD individuals.

For better visibility the results are thickened with the “tbss-fill” command. The images are in radiological convention. Corrected *p*-value < 0.05.

Figure 4. Significant negative correlation between age and fractional anisotropy in the control group.



No significant positive correlation was found. No significant results were detected in the high-risk MDD and high-risk well groups.

For better visibility the results are thickened with the “tbss-fill” command. The images are in radiological convention. Corrected *p*-value < 0.05.

CHAPTER VI: GENERAL DISCUSSION AND CONCLUSION

Contextual summary

BD is a serious public health issue, being one of the leading causes of disability worldwide (Angst, 2004; Wittchen et al., 2011). The higher rate of comorbidity with other psychiatric diseases especially with anxiety disorders and substance/alcohol abuse, risk of unemployment, and suicide increase its burden for the individual, her or his immediate family, and society as a whole (Fajutrao et al., 2009). This is especially worrisome given that it affects individuals at the prime of their life, with an age of onset in early adulthood (mean age 30 years); although the illness can start in early childhood or as late as the 40's and 50's (Weissman et al., 1996).

Yet BD manifests itself early, in adolescence and early adulthood. In a recent survey of a large, representative sample of individuals aged 14–24 in the United States (US National Comorbidity Survey; n=10,123), the incidence of MDD was 7.6%; BD 2.5%; unipolar mania 1.7%; and unipolar hypomania 3.6% (Merikangas et al., 2012).

As late diagnosis of the disorder heightens its impact (Leopold et al., 2012), early detection, if not prediction of future decline during adolescence or young adulthood would allow for immediate interventions to curb the disease trajectory. Preventative approaches in at-risk individuals could even limit severity if not delay or thwart occurrence altogether. Biomarkers related to early diagnostic or prognostic would therefore be extremely useful to achieve this goal.

As stated in Chapter I, it has been well established that relatives of patients with BD are at higher genetic risk than the general population for development of BD. Adolescents and young adult relatives of patients represent therefore an enriched cohort where to study the neurodevelopmental aspects of BD, and uncover biomarkers sensitive and specific to the early phases of this disease.

In this thesis, we have firstly tried to define neuroanatomical changes occurring in bipolar disorder through a meta-analysis on VBM studies that compared BD patients with healthy controls; we then analyzed a cohort of children of patients with BD recruited in Québec, and a cohort of relatives of bipolar patients recruited in Scotland. These relatives were adolescents or young adults free of psychiatric symptoms at the time of recruitment in both studies. In these HR individuals, we observed different neuroanatomical abnormalities when

compared to subjects without a family history of psychiatric disorders.

The next sections will recall the main findings of our four studies, followed by a general interpretation.

Study 1: VBM meta-analysis

In the first study, we carried out a retrospective meta-analysis of voxel-based morphometry of gray and white matter differences between patients with bipolar disorder and controls.

We included twenty-six articles in the analysis, and observed smaller GM volumes in the inferior frontal gyrus bilaterally, in the right precentral and medial frontal gyri, and in the left middle-temporal gyrus of BD patients compared with healthy subjects.

Greater GM volumes were detected in the left parahippocampal and postcentral gyri, left putamen, and right anterior cingulate cortex. Further, smaller WM volumes were detected in the left inferior longitudinal fasciculus, left superior corona radiata, and left posterior cingulum.

Study 2: Exploratory study

In the second study, we performed an explorative analysis of brain morphology of eight adolescents with a parent affected by BD (type I or II) recruited in the QUEBEC project (HR group). We compared their anatomical MRI scans with those obtained from eight adolescents without a family history of psychiatric diseases (controls).

We investigated GM subcortical structures using both manual and automatic techniques and did not find any difference in specific mesial temporal (hippocampi, amygdalae), as well as subcortical volumes between both groups.

However, using an automated software, we detected abnormalities in cortical volumes and thicknesses of children with a BD parent when compared with controls. These alterations were found in regions involved in the regulation of emotions, typically affected in full onset BD (posterior cingulate and medial frontal cortices), as found in our first study. Moreover, volumetric changes were detected in sectors implicated in the processing of visual information (pericalcarine and inferior parietal cortex), which matched cognitive impairment

in visual memory in the larger cohort from which those subjects were recruited (Maziade et al., 2011b).

We also analyzed WM integrity and found considerable reduction in FA, with few areas of FA increase, in the eight high-risk subjects when compared with controls. Reductions of WM integrity were mainly located in temporal and fronto-thalamic connections as anterior thalamic radiation bilaterally, and internal capsule and the superior longitudinal fasciculus of the frontal lobe and anterior cingulum in the right hemisphere.

Discussion of GM/WM findings

Overall, the results of studies 1 and 2 are consistent with other studies of brain structural alterations in BD. Firstly, GM reduction in frontal cortex detected in both studies is a consistent finding in cortical abnormalities occurring in BD and supports neurobiological models of bipolar disorder that confers mood dysregulation to frontolimbic alterations, with the modulatory role of the frontal cortex on the limbic system (Lyoo et al., 2004; Strakowski et al., 2005).

In particular, we found a consistent GM decrease in the middle frontal gyrus. The middle frontal gyrus has been proposed to be a gateway between top-down and bottom-up control of attention (Andersson et al., 2009; Japee et al., 2015), and is proposed to be critical in the reorientation of attention. Attention abnormalities have been noted in symptomatic adult BD patients, persisting after remission (Quraishi and Frangou, 2002). Moreover, chronic attention deficits could explain impairments in memory and executive functions found in young offspring (mean age of 17.3 years) born to a parent having schizophrenia or BD in the large multigenerational family Eastern Québec study, from which our Study 1 cohort was recruited (Maziade et al., 2009b).

Furthermore, offsprings of BD probands, much like the BD patients from the meta-analysis, displayed significantly greater GM volumes in the left parahippocampal cortex. Although some studies have found hippocampal/parahippocampal differences between adult BD patients relative to healthy controls (Houenou et al., 2012), most studies typically have not found any significant difference in hippocampal/parahippocampal GM volume (Hauser et al., 2000). Alterations in hippocampal morphology could be explained by

medication assumption as discussed in our meta-analysis (*cf*. Chapter III). Yet, decreases in hippocampal GM volume have been reported in adolescent BD (Blumberg et al., 2003a; Frazier et al., 2005), suggesting the involvement of the hippocampus in the pathophysiology of adolescent BD that may represent a particular characteristic of early-onset BD. Moreover, our findings are congruent with previous data reporting significantly increased GM volume in left hippocampal/parahippocampal gyri of 20 youths (8–17 years old) with at least one parent diagnosed with BD compared to controls (Ladouceur et al., 2008). This finding is particularly interesting because of the potential role of these regions in the regulation of stress and emotional responses. Indeed, as part of the limbic system, the parahippocampal gyrus has multiple direct connections with the hippocampus and amygdala (Stefanacci et al., 1996), and it has been suggested that a dynamic relationship between the amygdala and parahippocampal gyrus may confer a protective effect against potentially harmful experiences (McNaughton and Corr, 2004). Another study reported significant decreases in parahippocampal gyral activity to emotional words in adults with BD relative to age-matched healthy controls (Malhi et al., 2007). These findings therefore support a protective role for the parahippocampal gyrus in the normal appraisal of emotional information, which may become dysfunctional in adult BD.

Hence, it is possible that the pattern of increased GM volume in the left hippocampus/parahippocampus gyri of BD offspring represents a potential neuroanatomical risk marker for BD. However, another interpretation of the observed GM increase calls for a potential protective role to delay, if not prevent the subsequent development of BD, given that high-risk subjects in our explorative study were completely free of any Axis I disorder. Pediatric or adult BD onset is often preceded and/or accompanied by other psychiatric disorders such as disruptive behavior disorders or anxiety disorders (Birmaher et al., 2006; Henin et al., 2005). It is therefore possible that our sample represents a potentially emotionally resilient group, despite being at risk for BD. The pattern of increased rather than decreased GM volume observed in our high-risk group may be interpreted as being associated with successful affect regulation that acts as a compensatory mechanism against the development of mood or anxiety disorders, or because of the repeated exposition to situations requiring

these bipolar offsprings to regulate their affect (e.g., family conflicts). The latter interpretation would be consistent with a possible neuroprotective effect of lithium that could justify GM increase detected of bipolar patients included in our meta-analysis.

Regarding white matter, we found WM volume reductions in the meta-analysis on bipolar patients compared to healthy subjects, and we also detected a FA decrease in many brain regions of HR individuals when compared with controls, despite this difference not surviving the permutation test.

In the meta-analysis, we detected reduced WM concentrations in the left hemisphere, in particular in the WM connections located in temporal lobe, insula, and posterior cingulum. In our exploratory study, HR subjects showed a reduced WM integrity in other different areas as the right anterior cingulum, right frontal lobe, and bilaterally in anterior thalamic radiation.

We need to consider that there are few studies using VBM analysis on WM (we found only five papers for our meta-analysis), and the study performed in Québec was exploratory due to the limited sample size.

In general, WM disintegration have been repeatedly demonstrated in BD, which is also considered by some as a disconnection syndrome, much like schizophrenia (McIntosh et al., 2008). Moreover, a previous study on a larger sample of individuals at HR for BD has shown widespread WM integrity decreases surviving permutation test, suggesting that impaired WM integrity might be an endophenotype of BD and one of the underlying mechanisms of genetic predisposition to BD (Sprooten et al., 2011). These findings on this cohort were further studied in the second part of my thesis.

Study 3: Cross-sectional TBSS study

In the third study, we selected diffusion tensor MRI data from 61 controls and 106 HR individuals recruited in the Scottish Bipolar Family Study, a prospective longitudinal study examining individuals at familial risk of mood disorder on three occasions, two years apart. HR individuals were further divided into 78 subjects who remained well throughout the study (“high-risk well”), and 28 individuals who subsequently developed MDD (“high-risk MDD”). Voxel-wise

between-group comparison of FA based on diagnostic status was performed using TBSS.

Compared to controls, both HR groups showed widespread decreases of FA at baseline but there were no statistically significant difference at p-corrected levels between the two high-risk groups. Despite this, we found a negative correlation between FA values and sub-threshold depressive symptoms at the time of scanning in the high-risk MDD group.

Study 4: Longitudinal TBSS study

The fourth study concerned imaging data from the first and the second assessment of the Scottish Bipolar Family Study. We analyzed DTI data from 43 controls and 69 high-risk individuals that were further sub-divided into a group of 53 high-risk subjects who remained well (high-risk well), and 16 who met diagnostic criteria for major depressive disorder (high-risk MDD) at follow-up. Like the previous study, longitudinal differences in FA between groups based on diagnostic status were investigated using TBSS.

We found a significant reduction in FA across widespread brain regions over two years in all three groups. The trajectory of FA reduction did not differ significantly between groups.

Discussion of diffusion findings

Despite not finding significant differences between the two high-risk groups, reduced FA levels were detected when we compared both high-risk groups with controls. Moreover, high-risk individuals who later developed MDD compared to controls showed further reduced integrity in WM tracts located in anterior brain regions, such as the uncinate fasciculus, the anterior limb of the internal capsule, the anterior corona radiata and thalamic radiation, and sections of the inferior fronto-occipital and superior longitudinal fasciculi located in the middle and orbital frontal lobe.

Considering longitudinal WM integrity changes investigated in Study 4, itself a subsample selected from Study 3, there were significant FA reductions over time in all three groups (controls/high-risk well/high-risk MDD) but no

differences comparing the amount of FA changes among the groups. However, considering the progressive changes of WM integrity in our controls and high-risk subjects with age, we observed a further FA loss in the high-risk group mainly located in anterior regions, such as the uncinate fasciculum, and the anterior portion of the corpus callosum, thalamic radiation, corona radiata, cingulum, and inferior fronto-occipital fasciculus. Moreover, uncorrected p-maps showed a greater WM integrity loss in the high-risk group bilaterally for WM anterior tracts, and elsewhere in the left hemisphere. Namely, at an uncorrected p value ($p < 0.05$), all high-risk subjects (well and ill) showed a greater reduction of FA when compared to controls (Figure 1).

Greater progressive loss of WM integrity in the high-risk group was detected bilaterally in the inferior longitudinal fasciculi, uncinate fasciculi, and anterior corona radiata. On the left side, a widespread bigger FA decrease was found in the high-risk subjects compared to controls. Regions involved in the left hemisphere were the internal and external capsule (including anterior thalamic radiation), superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and parts of corticospinal tract.

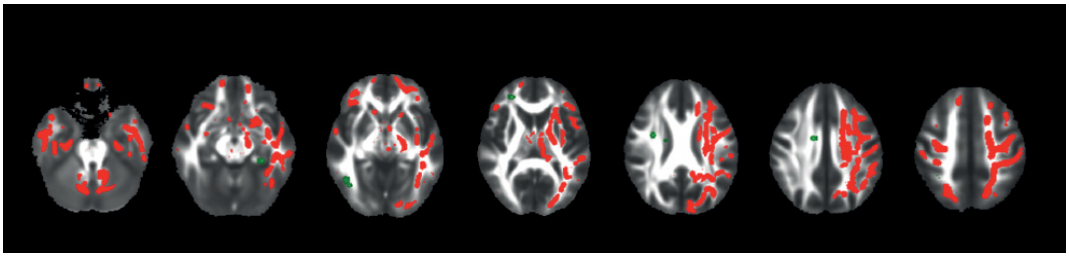
These findings are consistent with other morphological studies in high-risk BD adults, that have shown reduced WM volumes in the left hemisphere (Kieseppa et al., 2003) and abnormalities in WM integrity changes (Frazier et al., 2007), suggesting that WM disconnectivity might also be occurring in the neurodevelopment of high-risk BD individuals. Interestingly, uncorrected p-maps also showed greater progressive loss of WM integrity in high-risk individuals who developed MDD when compared to both controls and high-risk well relatives (Figure 2). However, all these finding did not survive permutation testing and should be, therefore, considered preliminary and in need of replication in a large cohort.

In summary, we did not detect significant differences in WM integrity at baseline between high-risk subjects who later develop MDD and high-risk individuals who remained well. Furthermore, we did not find significant differences in WM integrity loss over time (2 years) among high-risk subjects and controls. Despite this, we found a negative correlation between FA values and sub-threshold depressive symptoms at the time of scanning in the high-risk MDD group.

These data, therefore, show that progressive WM integrity loss in individuals aged between 16 and 28 years is apparently independent of their risk of later mood disorder, and that WM integrity reductions found previously in individuals with high genetic risk manifests before early adulthood and does not emerge immediately before or after the illness. However, considering uncorrected p values, our results suggest a greater rate of loss in high-risk subjects, even more pronounced in subjects who developed depressive symptoms. Therefore, we claim that more research is critically needed. We would propose that the changes happen earlier in the development process of the brain, even as early as birth, as a function of genetic predispositions. Thus, neurodevelopmental abnormalities that affect the trajectory of WM development during adolescence and early adulthood could be implicated before the onset of mood disorder symptoms in subjects with genetic risk. They could predispose a long-acting and chronic incapacity at processing information, in particular, dysregulation of emotion, and more specific cognitive impairments as memory and attention deficit. Moreover, when present at the same time as other factors (e.g. history of familial conflicts, other genetic risks), they could be instrumental in the triggering of a spiral of decline, resulting in BD. At the very least, lacking a proper aetiological model, they could be used as an additional factor that increases the risk profile for individuals.

Thus, longitudinal studies of adolescents with BD are needed to help identify the processes involved in its neurodevelopment, contributing to our understanding of abnormality progression, as well as in finding protective factors. Increased sample sizes, as well as proper representation of various heterogeneous demographic and clinic features, are needed. Future studies might clarify these abnormalities in brain changes to target for early identification, intervention and prevention strategies.

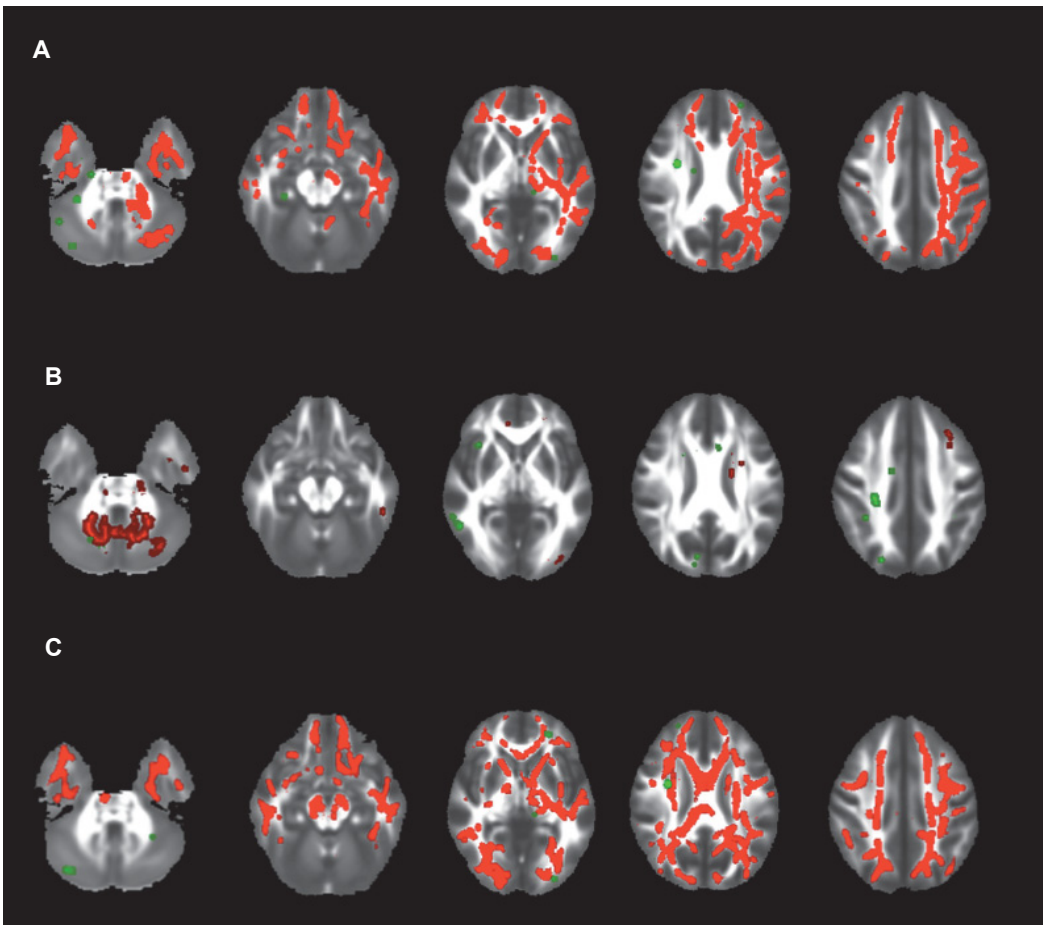
Figure 1. Axial rendering showing WM regions where high-risk group had a progressive FA decrease and increase over time compared to controls.



Progressive FA decrease and increase are shown in red and green, respectively.

For better visibility the results are thickened with the “tbss-fill” command. The images are in radiological convention. *Uncorrected* P value < 0.05.

Figure 2. Comparisons between groups of progressive fractional anisotopy changes.



Progressive reduction (in red) and increase (in green) of FA in: a) high risk subjects who became depressed compared to controls (high-risk MDD *vs* controls), b) high risk subjects who remained well compared to controls (high-risk well vs controls), c) high risk subjects who became depressed compared to high risk individuals who remained well (high-risk MDD *vs* high-risk well). For better visibility, the results are thickened with the "tbss-fill" command. The images are in radiological convention. *Uncorrected* p-value < 0.05

Strengths and limitations

The strengths of this thesis are firstly, our use of different techniques to investigate GM and WM in our samples of subjects, from voxel-based morphometry (Study 1) to manual and automated segmentation techniques (Study 2), and TBSS of FA (studies 3, 4). These techniques allowed us to explore differences between high-risk individuals and controls in the best way possible.

Secondly, the studies performed in Scotland analyzed one of the largest sample of subjects at high-risk of BD worldwide. It effectively solved the difficulties in recruitment for this field exemplified in Study 2.

Moreover, this study recruited subjects in a prospective longitudinal design, including MRI, which is nearly unique. To date, few studies have investigated brain abnormalities of high-risk subjects for mood disorders and, to our knowledge, our WM analysis in the Scottish sample represent the first work on longitudinal FA changes in high-risk individuals before the onset of mood disorders.

The thesis, much like any other work, is also hampered by some limitations. Regarding the meta-analysis, two important limitations of the ALE method are that it does not take into account non-significant findings (i.e. articles reporting no findings above statistical significance) and that foci from one or a few studies may drive singlehandedly a significant finding, giving the wrong impression of consistency across most studies. Thus, results must be interpreted under this limitation. Another limitation of the meta-analysis, given that we do not control the inclusion criteria in each study, is the fact that the analysis is performed on a heterogeneous set of bipolar patients, despite excluding children and adolescent subjects. Further analyses should attempt to select bipolar adult patients with similar characteristics to better understand relationships between symptomatology, medication, genetics and brain morphology.

Another important limitation is the small sample size of Study 2, a limitation offset by the larger samples of studies 3 and 4.

It remains that considering studies 3 and 4, the sample of individuals that became ill after the first imaging assessment is relatively small (28 subjects for the cross-sectional study and 16 subjects for the longitudinal study). The difficulties in conducting prospective longitudinal high-risk studies on young individuals with a family history of mental illness should not, however, be underestimated.

It is equally important to note that the early diagnosis of MDD in a young group of individuals at risk of bipolar disorder may herald the onset of BD (Hillegers et al., 2005), where often first episode is depression (Duffy, 2010b; Hillegers et al., 2005). Similarly, in such a young cohort there may be individuals within the high-risk well group who may still develop illness, MDD or BD.

It is also notable that at the baseline, the high-risk who subsequently became ill had higher scores at the Hamilton scale for depression symptoms than those that remained well. It is difficult, therefore, to dissociate neural markers underlying the disease trait from those underlying subsequent MDD diagnosis and, indeed, the two may be inherently related. Continued clinical longitudinal follow-up of the sample will ultimately contribute to a better understanding of prodromal phases of illness and associated disease pathways.

Finally, only FA may not be sufficient for investigating specific axonal or myelin abnormalities. For example, identical FA values may be induced by different combinations of changes in axial and radial diffusivities. Axial diffusivity refers to diffusivity along the principal axis, and reflects axonal integrity, whereas radial diffusivity is measured along the two minor axes of the diffusion tensor, and is more sensitive to myelination. Thus, they detect subtly different aspects of white matter abnormalities. Further work should add radial diffusion measurements, and possibly tractography, that would prove useful to visualize and deeply explore specific WM tracts that we found were involved.

Further investigation should be therefore performed to provide additional information of WM differences between subjects with genetic liability for mood disorders and controls.

Overall conclusions and future perspectives

This thesis achieved its main goal, that is of adding knowledge to the current corpus of neurodevelopment, and thus enhance our understanding of the pathophysiology of BD in order to improve the efficiency and specificity of the diagnostic process.

Morphological differences between bipolar patients and healthy subjects is a consistent finding, demonstrated by our meta-analysis. However, to clarify when these abnormalities began, as well as their relationship with genetics and symptoms, we performed three studies.

In our exploratory study, we found differences in both the GM and WM of eight adolescents/ young adults with a parent with BD compared to individuals without psychiatric disorders in their family. A reduction of WM integrity in genetic high-risk subjects was further confirmed in the largest Scottish sample. These findings support the notion of WM integrity as an endophenotype of BD and suggest that impaired WM integrity might be one of the underlying mechanisms of genetic predisposition to BD.

In addition, we demonstrated an association between symptoms of depression and WM integrity in different regions, further supporting the view that WM abnormalities have behavioral associations that are related to the symptomatology of the clinical disorder. However, there were no differences that survived permutation testing comparing FA changes in HR subjects and controls along a time course of 2 years. Despite this, uncorrected p-maps showed a trend of a further decrease of FA along the time in the high-risk group compared to controls. Moreover, when we split the high-risk group into individuals who became depressed (“high-risk MDD”) and subjects who remained well (“high-risk well”), uncorrected p-maps exhibited a reduction of FA in the high-risk MDD compared to both controls and hish-risk well.

Acknowledging these limitations, we call for a greater generalization to a larger sample with longer follow-up, in order to determine actual WM changes related to genetic vulnerability to BD and the onset of mood disorders. Continued clinical follow-up will ultimately contribute to a better understanding of prodromal phases of illness and associated disease pathways. In addition to better understand these findings, other diffusion parameters should be investigated.

Thus the research may lead to clarify pathological mechanism underlying BD and improve the diagnosis by adding biomarkers to clinical measures.

Overall, this thesis has contributed to the advancement of knowledge on brain anatomical alterations in subjects with a high genetic risk for mood disorders. Results and conclusions of the studies conducted here were aimed at elucidating the pathophysiologic substrates that could lead to mood disorders. These findings will be important to guide future studies in order to find biomarkers able to early detect mood disorders in subjects with genetic vulnerabilities for this kind of psychiatric diseases.

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ANNEX: HIPPOCAMPUS AND AMYGDALA VOLUMES IN CHILDREN AND YOUNG ADULTS AT HIGH-RISK OF SCHIZOPHRENIA: RESEARCH SYNTHESIS

Hippocampus and amygdala volumes in children and young adults at high-risk of schizophrenia: research synthesis

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Abstract

Objectives

Studies have reported hippocampal and amygdala volume abnormalities in schizophrenic patients. It is necessary to explore the potential for these structures as early disease markers in subjects at High Risk (HR) of schizophrenia.

Methods

We performed a review of 29 Magnetic Resonance Imaging (MRI) studies measuring hippocampal and amygdala volumes in subjects at HR for schizophrenia. We reclassified subjects in 3 new HR categories: presence of only risk symptoms (psychotic moderate symptoms), presence of only risk factors (genetic, developmental or environmental), and presence of combined risk symptoms/factors.

Results

Hippocampal volume reductions were detected in subjects with First Episode (FE) of psychosis, in all HR young adults and in adolescents with risk factors for schizophrenia. The loss of tissue was mainly located in the posterior part of hippocampus and the right side seems more vulnerable in HR young adults.
Instead, the anterior sector seems more involved in HR subjects with genetic risks. Abnormal amygdala volumes were found in FE subjects, in children with combined risk symptoms/factors and in older subjects using different inclusion criteria, but not in young adults.

Conclusion

Hippocampal and amygdala abnormalities may be present before schizophrenia onset. Further studies should be conducted to clarify whether these abnormalities are causally or effectually related to neurodevelopment. Shape analysis could clarify the impact of environmental, genetic, and developmental factors on the medial temporal structures during the evolution of this disease.

Context of study

Several studies in the literature focus on finding early disease markers of schizophrenia, with the goal to detect subjects in a preclinical phase in order to plan pre-onset interventions. One such putative marker is structural neuroimaging, as, for example, measurements obtained from magnetic resonance imaging (MRI). Authors have reported reduced total brain and gray matter and increased ventricular volumes in schizophrenic patients compared to controls (Shenton et al., 2001; Steen et al., 2006). Reductions have also been observed in the hippocampus (**HC**), amygdala (**AG**), and superior temporal gyri (Lawrie and Abukmeil, 1998; Nelson et al., 1998), in the prefrontal cortex and thalamus (Konick and Friedman, 2001), in the anterior cingulate gyrus (Baiano et al., 2007), and the corpus callosum (Woodruff et al., 1995) between these two groups. Total brain volume reductions are subtle and close to the detection thresholds of current MRI methods however (~ 3%) (Wright et al., 2000), while changes are larger in the hippocampus (~ 8%) (Wright et al., 2000) and in the amygdala (6-10%) (Lawrie and Abukmeil, 1998; Nelson et al., 1998; Wright et al., 2000).

It has been shown that medial temporal lobe reductions correlate with memory impairment (Antonova et al., 2004) and that structural, functional, and neurochemical abnormalities in the hippocampus have been related to impairment in declarative memory function in schizophrenic patients (Weiss and Heckers, 2001), as well as an important vulnerability indicator for this disorder (McCarley et al., 1993; Seidman et al., 2002; Seidman et al., 2003; Tamminga et al., 2010). Further, smaller amygdala volumes seem to be related to reduced emotional expression and emotion recognition in schizophrenic subjects (Aleman and Kahn, 2005). Hippocampal and amygdala volume reductions are also seen in the unaffected relatives of schizophrenic probands (Boos et al., 2007; O'Driscoll et al., 2001; Seidman et al., 1999; Van Erp et al., 2002) and in first-episode (**FE**) of schizophrenia (Adriano et al., 2011; Joyal et al., 2003; Vita, 2007).

<u>High risk subjects</u>

Many recent studies have analyzed HC and AG volumes in young subjects at high risk for schizophrenia, based on the dual hypotheses that within this group of subjects, many are, in fact, in a prodromal period, and that later changes in MRI measures would be apparent in that prodromal period.

Thus, in recent years, **'**high-risk**'** strategies have been helpful in assessing brain structural and functional changes surrounding the onset of psychosis and schizophrenia. These have largely been undertaken in two ways, one based around genetic risk, and a second based on the identification of prodrome from clinical symptoms (Olsen and Rosenbaum, 2006a).

Within the genetic risk paradigm, Boos et al. conducted a meta-analysis of family studies in schizophrenia and showed that first-degree relatives had lower hippocampal, total grey matter, and ventricular volumes, compared with healthy volunteers (Boos et al., 2007). Other studies considering only genetic risk provide an overview of brain changes in subjects with high risk for schizophrenia (Keshavan et al., 2002; Keshavan et al., 1997; Lawrie et al., 2008; Moran et al., 2013; Whalley et al., 2005) reporting abnormalities mainly in the frontal and temporal regions.

To our knowledge, only Jung et al. have proceeded with systematically reviewing the literature for MRI studies considering all type of HR subjects (Jung et al., 2010). The authors concluded that abnormalities in prefrontal, temporal and anterior cingulate cortices occur before illness onset, but they did not report their findings from a neurodevelopmental perspective, but rather simply as differences between controls, HR and patients.

Objectives

We aim to review published evidence regarding HC and AG volumetric differences in HR subjects for schizophrenia.

The objective was to determine if hippocampal and amygdala volumes differ in HR individuals in order to understand whether these volumes can help in the early detection and clinical intervention of schizophrenia.

As is the case with many major neuropsychiatric illnesses, the typical age of onset for schizophrenia is late adolescence or early twenties, with a slightly later onset in females (Hafner et al., 1994). Neuroimaging studies that focus on this age range may provide unique insights into the onset and course of psychosis. Based on this finding, we examined evidence from studies spanning ages from early childhood to young adulthood.

We chose to focus our review solely on the hippocampus and amygdala because: (i) they are both part of the limbic circuit involved in schizophrenia pathology; and (ii) there is evidence that they are both affected in schizophrenia. Our intent was to address issues of heterogeneity in the HR concept, including age, and to analyze results taking into account different risk factors and neurodevelopmental stages.

Methods and materials

Studies were included in our research synthesis if they met the following criteria:

(1) Papers had to be drafted in English;

(2) Papers were original works (i.e. no review);

(3) Subjects were defined as “high risk”, “ultra-high risk” or “at-risk mental state” to develop schizophrenia;

(4) High risk subjects were between 8 and 30 years of age (group mean age). As we stated earlier, the aim of the present review is to provide an overview of hippocampal and amygdala changes between childhood and young adult period;

(5) Structural magnetic resonance imaging techniques analyzing cerebral gray matter were used to obtain information specifically on the HC, AG or both (HC/AG complex).

We conducted an extensive PUBMED search for online listings from 1990 until January 2014 using the following keyword combinations: “schizo* [ti] AND risk [ti] AND MRI’’ ; “schizo* [ti] AND offspring* [ti] AND MRI’’ ; “psychosis [ti] AND risk [ti] AND MRI”; and “psychosis [ti] AND offspring* [ti] AND MRI”, as well as cited references in articles and review papers.

One of the first hurdle to proceed with a synthesis relates to the fact that “high-risk for psychosis” is a very heterogeneous concept in the literature, alternatively related to risk **symptoms or** risk **factors,** with some studies combining both. In light of this, we reclassified all articles as per the following HR categories, defined below:

1. Studies of HR subjects with only psychotic symptoms;
2. Studies of HR subjects with only risk factors; and
3. Studies of HR subjects with both psychotic symptoms and risk factors.

Due to the large age range, and the necessity to identify patterns of volumetric changes possibly related to maturation and neurodevelopment, we further synthesized results according to age groups. We considered the subject's age range or what authors declared about the stage of age of subjects included in their study.

We found the following age groups: children (8-12 y.o.); children/adolescents (8-18 y.o) adolescents (13–19 y.o); adolescents/young adults (13 y.o and above), and young adults (20 y.o. and above). Two studies considered all age phases (children/adolescents/young adults).

Risk symptoms considered in the studies reviewed were: symptoms of early onset schizophrenia or schizotypal personality disorder (Hendren et al., 1995) attenuated psychotic symptoms (Witthaus et al., 2009; Witthaus et al., 2010; Wood et al., 2005), and brief limited intermittent psychotic symptoms (Wood et al., 2005) (*cf*. FIGURE 1 – A). Such risk symptoms are thus related to the definition of a 'prodromal phase' of a disease, where this phase is generally described as a subsyndromal stage preceding disease onset (Keith and Matthews, 1991).

Risk factors mainly considered in the studies were genetic risks associated with (i) having a first-degree relative with diagnosis of schizophrenia or schizoaffective disorder (Keshavan et al., 2002; Keshavan et al., 1997; Schreiber et al., 1999); (ii) having first or second degree relatives with schizophrenia (Lawrie and Abukmeil, 1998; Lawrie et al., 1999; Lawrie et al., 2001) or psychotic disorder (Wood et al., 2005); (iii) having at least one first-degree relative with a diagnosis of schizophrenia or schizoaffective disorder, and one second- or third-degree relative with a history of psychosis, suicide, or psychiatric hospitalization (*cf*. FIGURE 1 – B).

Extensive findings support the view that genetic factors are the single most powerful predictor of schizophrenia (Moldin and Gottesman, 1997; Prescott and Gottesman, 1993).

Of the other risk factors confirmed by the literature (Byrne et al., 1999; Geddes and Lawrie, 1995; Goldstein et al., 2000; Zornberg et al., 2000), were low Intelligence Quotient (**IQ**) studied in association with other factors in some studies (Walter et al., 2012; Welch et al., 2010) and the presence of obstetric complications considered only in association with the presence of attenuated psychotic symptoms and/or genetic risk (Hurlemann et al., 2008).

In some studies, HR subjects were selected to exhibit both risk factors and symptoms concurrently, e.g. genes, obstetric complications or low IQ accompanied by moderate psychotic symptoms (*cf*. FIGURE 1 –C). Whether or not these subjects have a higher conversion to psychosis remains to be determined.

We included in this category studies where:

- HR subjects had attenuated psychotic symptoms and/or brief limited intermittent psychotic symptoms, and/or first degree relative with psychotic disorder or schizotypal personality disorder (Buehlmann et al., 2010; Moorhead et al., 2013; Phillips et al., 2002; Velakoulis et al., 1999); and/or presence of schizotypal personality disorder in the last 12 months (Mittal et al., 2013);

- Early prodromal state subjects, i.e. subjects with basic symptoms with a positive predictive value for the transition to first-episode psychosis, and/or reduction of the global assessment of functioning and a first degree relative with psychotic disorder or obstetric complications (Hurlemann et al., 2008);
- HR subjects with low IQ, and high scores in either the structured interview for schizotypy and child behavior checklist (Welch et al., 2010).

Results

Upon applying our search criteria, we obtained 267 articles via PUBMED, of which only 24 papers matched all inclusion criteria.

Using references included in these 24 papers, we were able to add a further five references that were both relevant and within the inclusion criteria.

A total of 29 papers were analyzed (see figure 2 for more information about the reviewing process).

The age range between studies was 8 (Hendren et al., 1995) to 45 years old (Ho and Magnotta, 2010). MRI techniques used to measure hippocampus and amygdala volumes were voxel based morphometry, semiautomated segmentation algorithm and manual tracing.

Results are summarized in Table 1. In Tables 2, 3 and 4 (*cf.* Supplemental information), the column 'Inclusion criteria' allows the reader to return to the operational criteria used by the original authors.

Hippocampus

We found 21 papers analyzing hippocampus in subjects with high risk for schizophrenia. In the majority of these papers, subjects were adolescents/young adults or only young adults. The inclusion criteria most used were symptoms and/or risk factors, following by genetic risk factors. The hippocampus of HR subjects was smaller compared to controls in most studies (Buehlmann et al., 2010; Hurlemann et al., 2008; Keshavan et al., 1997; Phillips et al., 2002; Witthaus et al., 2009; Witthaus et al., 2010; Wood et al., 2005).

Considering the age, children had the same hippocampal volumes when compared to controls (Hendren et al., 1995) Smaller hippocampi were found in adolescents and young adults HR subjects (Keshavan et al., 1997; Moorhead et al., 2013; Tepest et al., 2003; Witthaus et al., 2009; Witthaus et al., 2010), but these results were not confirmed in some studies analyzing different age groups in the same sample. Indeed, reduced hippocampal volumes were found in a study on children/adolescents (Sismanlar et al., 2010) and in studies on adolescents/young adults HR subjects (Ho and Magnotta, 2010; Moorhead et al., 2013; Phillips et al., 2002; Wood et al., 2010), but these results were not replicated in others (Buehlmann et al., 2010; Dougherty et al., 2012; Mattai et al., 2011; Velakoulis et al., 2006; Wood et al., 2005).

Considering inclusion criteria, smaller hippocampi were found in HR subjects with psychotic symptoms (Witthaus et al., 2009; Witthaus et al., 2010).

In the categories "risk factors" and "symptoms and/or risk factors", results are inconsistent. The majority of studies (Francis et al., 2013; Ho and Magnotta, 2010; Hurlemann et al., 2008; Keshavan et al., 1997; Mittal et al., 2013; Moorhead et al., 2013; Phillips et al., 2002; Sismanlar et al., 2010; Tepest et al., 2003; Wood et al., 2010) but not all (Bhojraj et al., 2011; Buehlmann et al., 2010; Dougherty et al., 2012; Hendren et al., 1995; Mattai et al., 2011;

Velakoulis et al., 2006; Wood et al., 2005) found reduced hippocampal volumes in HR subjects compared to controls.

Moreover, results obtained by cross-sectional and longitudinal studies on HR subjects who later converted to psychosis (**HRp**) and those who did not (**HRnp**) are even more conflicting. Most of the studies did not find differences in the hippocampal volumes of HRp and NRnp (Buehlmann et al., 2010; Velakoulis et al., 2006; Walter et al., 2012; Wood et al., 2005). Other studies detected smaller volumes bilaterally in HRp when compared to controls (Moorhead et al., 2013) and in the right side when compared to HRnp (Whittaus 2010), but in another one HRnp had lesser volumes bilaterally than controls as well as in the left side when compared to HRp (Phillips et al., 2002).

All the FE subjects were young adults (16 y.o. and above) and showed smaller hippocampi, mainly in the left side.

HR subjects with risk symptoms

We found 5 studies using “psychotic symptoms” as inclusion criteria for HR subjects for schizophrenia (Hendren et al., 1995; Hurlemann et al., 2008; Witthaus et al., 2009; Witthaus et al., 2010; Wood et al., 2005) (see Table 2 in the supplementary material, for more information about the scales used in the inclusion criteria).

Family history of HR subjects was collected in one study (Hendren et al., 1995) and 4 subjects on 12 had history of schizophrenia in first- and second- degree relatives.

For this, we include this paper in the category "combined symptoms and risk factors". Information about family history was not provided in the other three papers. In one study (Witthaus et al., 2010), approximately half of the HR subjects had other psychiatric disorders as well as attenuated psychotic symptoms and in two papers, approximately 40% of the HR subjects (Witthaus et al., 2009; Witthaus et al., 2010) were taking psychotropic drugs.

All three papers studying young adults HR subjects showed reduced hippocampal volumes bilaterally when compared to controls (Hurlemann et al., 2008; Witthaus et al., 2009; Witthaus et al., 2010). In particular, body and tail were found smaller in HR subjects (Witthaus et al., 2009; Witthaus et al., 2010).

Right hippocampus was smaller in HR subjects diagnosed psychotic at follow up compared to HR subjects not psychotic at the follow-up (Witthaus et al., 2010) and reduced right hippocampal volumes correlated significantly with lower RAVTL delayed recall in HR subjects in another study (Hurlemann et al., 2008).

In another study (Wood et al., 2005), adolescents and young adults HR subjects with psychotic symptoms did not show differences in their hippocampal volumes when compared to controls, but they had smaller left hippocampus when compared with HR subjects with a family history of psychosis.

HR subjects with risk factors

We found 11 articles (Bhojraj et al., 2011; Dougherty et al., 2012; Francis et al., 2013; Ho and Magnotta, 2010; Johnson et al., 2013; Keshavan et al., 1997; Mattai et al., 2011; Moorhead et al., 2013; Sismanlar et al., 2010; Tepest et al., 2003; Wood et al., 2005) using the presence of risk factor as inclusion criteria for HR subjects (see Table 2 for more information about inclusion criteria). Almost all studies use the presence of genetic risk factors such as inclusion criterion except one that uses low IQ (Moorhead et al., 2013). In all studies, individuals who had diagnosis of psychotic disorder or an acute psychotic

episode in their lifetime were excluded. Nevertheless, in almost all studies in the HR group there were at least 34% of subjects with diagnosis of psychiatric disorder other than psychotic disorder or schizophrenia (Bhojraj et al., 2011; Francis et al., 2013; Ho and Magnotta, 2010; Johnson et al., 2013; Keshavan et al., 1997; Sismanlar et al., 2010; Tepest et al., 2003). The psychiatric disorders most reported were: major depression, anxiety disorder and Attention Deficit Hyperactivity Disorder (ADHD).

The majority of studies (Francis et al., 2013; Ho and Magnotta, 2010; Keshavan et al., 1997; Moorhead et al., 2013; Sismanlar et al., 2010; Tepest et al., 2003), but not all (Bhojraj et al., 2011; Dougherty et al., 2012; Mattai et al., 2011; Wood et al., 2005) found smaller hippocampi in HR subjects at different stages of age (childhood to early adulthood) when compared to controls. Furthermore, studies comparing hippocampal shapes in HR subjects and controls found differences between the two groups in specific regions.

Francis et al. (Francis et al., 2013) found that the right and left subicula were significantly reduced in HR individuals and the smaller volumes of these regions correlated with immediate verbal recall of stories impaired in HR sample.

Mittal et al. (Mittal et al., 2013) reported that siblings of schizophrenia patients (17.4 y.o. age average) showed areas of deformation in the anterior hippocampus compared to controls. These areas overlapped with that seen for schizophrenia patients but did not survive FDR correction.

Hippocampal shape inward in the anterior sub-regions of genetic HR subjects was also observed in other studies (Ho and Magnotta, 2010; Tepest et al., 2003).

Moreover, in the HR group, a greater number of obstetric complications were significantly associated with smaller hippocampi and hippocampal volumes were not inversely correlated with age (as detected in the control group) (Ho and Magnotta, 2010).

Abnormal development of the hippocampus of HR subjects was also observed in another study where familial risk subjects demonstrated greater positive volume-age relationship in hippocampus than controls (Dougherty et al., 2012).

Hippocampal reductions found in this group of HR subjects compared to controls were initially significant but this difference did not survive FDR correction.

No significant differences in hippocampal volumes of subjects with family history of schizophrenia and controls were found in two other studies (Bhojraj et al., 2011; Wood et al., 2005).

Only three studies provided follow-up of HR subjects. No subject was psychotic at follow-up (1 year) in one study (Bhojraj et al., 2011) and half of the study subjects were psychotic at follow-up in another one (Wood et al., 2005). In the latter, HR individuals with a family history of psychosis had similar volumes to controls but they had bigger left hippocampal volumes when compared to HR individuals with attenuated psychotic symptoms and without a family history of psychosis. Finally, a longitudinal study on adolescents with a low IQ showed a reduced right hippocampal volume at the baseline and bilaterally at the follow-up in adolescents who later converted to psychosis (Moorhead et al., 2013).

Combined symptoms/factors

We found 9 studies (Buehlmann et al., 2010; Hendren et al., 1995; Hurlemann et al., 2008; Mittal et al., 2013; Phillips et al., 2002; Thompson et al., 2007; Velakoulis et al., 2006; Walter et al., 2012; Wood et al., 2010) that used the

presence of psychotic symptoms and/or risk factors as inclusion criteria for HR subjects to develop schizophrenia disorder (see Table 2 for more information about inclusion criteria).

In most studies, the presence of other psychiatric disorder in HR subjects was not reported. In one study (Thompson et al., 2007), more than half of HR individuals had a diagnosis of psychiatric disorder different than schizophrenia or acute psychotic disorder. In another one (Hurlemann et al., 2008), no subjects had a diagnosis of psychiatric disorder and were not taking psychiatric medications (presence of psychiatric disorder was an exclusion criterion).

Studies investigating if HR subjects took psychiatric medication (Buehlmann et al., 2010; Hurlemann et al., 2008; Thompson et al., 2007; Velakoulis et al., 1999); reported at least 11% of psychotropic drugs users in HR group (except the Hulermann's study).

Eight studies compared hippocampal volumes in HR subjects and controls (Buehlmann et al., 2010; Hendren et al., 1995; Hurlemann et al., 2008; Mittal et al., 2013; Phillips et al., 2002; Velakoulis et al., 1999; Wood et al., 2010). In most, but not all, of those studies (Buehlmann et al., 2010; Hendren et al., 1995; Velakoulis et al., 2006), the authors reported smaller hippocampi in adolescents/young adults (Phillips et al., 2002; Wood et al., 2010), and young adults (Hurlemann et al., 2008) HR individuals. Two studies analyzed the hippocampus only in the HR group (Thompson 2007; Walter 2012), and found no correlation between stress and hippocampal volumes (Thompson et al., 2007) and no difference between hippocampal volumes of HR individuals psychotic at the follow-up and those not psychotic (Walter et al., 2012).

One study recruiting children with HR did not detect differences in their hippocampal volumes (Hendren et al., 1995), nor were differences found in two other articles studying adolescents/young adults HR individuals (Buehlmann et al., 2010; Velakoulis et al., 1999).

Differences in hippocampal volumes between HRp (progressing) and HRnp (non-progressing) subjects 'symptoms and/or risk factor' have been investigated in two age-groups, namely "adolescents" and "adolescents/young adults", using either cross sectional comparison or longitudinal studies, although the findings have shown contradictory results.

Cross-sectional comparisons in the "adolescent/young adults" phase revealed that HRnp subjects had smaller hippocampal volumes at baseline bilaterally compared to controls, and more specifically on the left side (Phillips et al., 2002). Wood et al. (Wood et al., 2010) reported reduced bilateral hippocampal volumes in HRnp and only in the left side in HRp compared to controls. However, two studies found no significant differences between HRp (Velakoulis et al., 2006) (Buehlmann et al., 2010) and HRnp individuals

Similar volume differences between HRp and HRnp were observed in a longitudinal study on young adults HR subjects (Walter et al., 2012). Furthermore, a decrease in hippocampal volumes was detected over time in all HR individuals, independently of clinical outcome. Despite this absence of difference, antipsychotic medication at the follow-up was associated with an increased hippocampal volume in HRp when compared to the HRnp group.

FE subjects

All studies found smaller hippocampus in First Episode (FE) subjects (> 20 years old) compared to controls.

Three studies found decreased hippocampal volumes bilaterally or only in the left side when FE were compared to controls and HR subjects (Buehlmann et al., 2010; Velakoulis et al., 2006), while only the left side resulted atrophic compared to HR subjects psychotic at follow up (Phillips et al., 2002)
In a following study using the manual tracing technique, hippocampal body and tail of FE subjects were smaller compared to healthy subjects (Witthaus et al., 2010).

Amygdala

Abnormal amygdala volumes were found in children and adolescent HR subjects (Bhojraj et al., 2011; Hendren et al., 1995; Keshavan et al., 1997; Welch et al., 2010), whereas the volumes were similar compared to controls in the young adults HR subjects (Witthaus et al., 2009; Witthaus et al., 2010). Similar volumes were also observed in children/adolescents and in adolescents/young adults HR individuals compared to controls (Dougherty et al., 2012; Sismanlar et al., 2010).
Regarding the inclusion criteria, no difference was detected in young adults HR with attenuated psychotic symptoms and controls (Witthaus et al., 2009; Witthaus et al., 2010).
HR with genetic risk factors had smaller amygdala in adolescents and adolescents/young adults (Bhojraj et al., 2011; Keshavan et al., 1997) but similar volumes were found in children/adolescents (Dougherty et al., 2012).
Adolescents/young adults with combined symptoms/factors did not show volume differences (Velakoulis et al., 2006), but abnormal volumes were found throughout childhood and adolescence (Hendren et al., 1995; Welch et al., 2010).
Moreover, results on HRp compared to HRnp cross-sectionally (Velakoulis et al., 2006; Witthaus et al., 2010) detected no difference between HRp and HRnp.
In FE subjects aged above 16 years, all studies found abnormalities in amygdala volumes (Velakoulis et al., 2006; Witthaus et al., 2009; Witthaus et al., 2010), mainly on the left (Witthaus et al., 2009; Witthaus et al., 2010).

HR subjects with risk symptoms

We found three studies using “psychotic symptoms” as inclusion criteria for HR subjects for schizophrenia (Hendren et al., 1995; Witthaus et al., 2009; Witthaus et al., 2010) (Table 3).
Family history of HR subjects was collected in one study (Hendren et al., 1995). Information about family history was not provided in the other two papers.
In (Witthaus et al., 2010), approximately half of HR subjects had other psychiatric disorders as well as attenuated psychotic symptoms and, in the other papers, approximately 40% (Witthaus et al., 2009; Witthaus et al., 2010) were taking psychotropic drugs.
Contrary to the hippocampus, the amygdala was similar compared to controls in the young adults HR (Witthaus et al., 2009; Witthaus et al., 2010).

HR subjects with risk factors

We found four articles (Bhojraj et al., 2011; Dougherty et al., 2012; Keshavan et al., 1997; Sismanlar et al., 2010) that used the presence of genetic risk factor as inclusion criteria for HR subjects (Table 3).
In all studies, individuals who had a diagnostic of psychotic disorder or an acute psychotic episode in their lifetime were excluded. Nevertheless, in almost all studies the HR group had at least 34% of subjects with diagnosis of psychiatric disorder other than psychotic disorder or schizophrenia (Bhojraj et al., 2011; Ho

and Magnotta, 2010; Keshavan et al., 1997; Sismanlar et al., 2010). The amygdala was smaller only in the left side in adolescents (Keshavan et al., 1997) and bilaterally in older subjects (Bhojraj et al., 2011).
No differences were observed in younger HR individuals compared to controls (Dougherty et al., 2012; Sismanlar et al., 2010).

Combined symptoms/factors

We found three studies (Hendren et al., 1995; Velakoulis et al., 1999; Welch et al., 2010) in that group that studied the amygdala. In all of the studies, the presence of other psychiatric disorder in HR subjects was not reported. In two articles, at least 15% of HR subjects were taking psychatric medication (Hendren et al., 1995; Velakoulis et al., 1999).
The amygdala was smaller bilaterally in HR children and a significant negative correlation was seen between left amygdala volume and severity of negative symptoms within this HR group (Hendren et al., 1995). In the same study, all children had moderate psychotic symptoms and 33% were positive to family history of schizophrenia.
Adolescent HRs with low IQ and psychotic symptoms showed increased right amygdala volumes compared to subjects with low IQ, without psychotic symptoms (Welch et al., 2010). There were not differences in the older HR subjects (20 y.o. on average) with psychotic symptoms and/or genetic risk factors compared to controls (Velakoulis et al., 2006).

FE subjects

All studies reviewed found abnormalities in the volume of the amygdala in FE subjects aged above 16 years. The left amygdala was smaller in FE young adults compared to HR subjects (Witthaus et al., 2009; Witthaus et al., 2010) and compared to controls (Witthaus et al., 2010). Amygdala volumes were increased bilaterally in FE subjects younger (21 y.o. age mean) than healthy individuals and HR subjects who converted or not converted later (Velakoulis et al., 2006). In this study, FE subjects were divided in subgroups based on first-episode psychosis diagnostic categories. The subjects with affective psychosis and other psychosis had the bigger amygdala compared to controls.

Amygdalo-Hippocampal Complex (AHC)

Six studies investigated both structures, combining relatives of schizophrenia patients (Schreiber 1999; Keshavan 2002; Lawrie 1999; Lawrie 2001; Lawrie 2002; Welch 2011). Only one study reported the presence of other psychiatric disorders in 59% of HR subjects considered (Keshavan 2002). All studies that compared AHC volumes in controls to adolescents or adolescents/young adults HRs, except one (Lawrie 2002), observed reduced volumes in either the left side (Keashavan 2002; Lawrie 1999), the right side (Schreiber 1999), or bilaterally (Lawrie 2001).
No significant differences in volumes were detected between HR subjects with psychotic symptoms and without psychotic symptoms (Lawrie 2001; Lawrie 2002), and between HR subjects with first degree and -second degree schizophrenic relatives (Lawrie et al., 2002).
One study investigating the effect of the exposure to cannabis on AGH volumes did not find an association (Welch 2010).
The right amygdala-hippocampal complex was smaller in FE young adults individuals compared to controls, and in the left side compared to controls and HR subjects (Lawrie et al., 1999).

Summary of Findings and Conclusions

Assessment of volumetric HC and AG observations will need first to consider what criteria were used to select HR subjects, in order to understand which risk factors and/or risk symptoms were being taken into consideration during the original analysis.

Furthermore, reports of an excess in adverse events during the pre- and perinatal periods, the presence of cognitive and behavioral signs during childhood and adolescence, and the lack of evidence of a neurodegenerative process in most individuals with schizophrenia (Lewis and Levitt, 2002) all point to a neurodevelopmental pathogenesis hypothesis for schizophrenia. In this context, it is therefore important to take into account the age of HR subjects when analyzed.

Hippocampus

The reduction of hippocampal volume in patients at their first manifestation of the disease (FE subjects) seems to be well documented in all studies. This would indicate with near certainty that there is a loss of tissue in the hippocampus in the period near the onset of the disease. It would further appear that there is a greater vulnerability for the left hippocampus (Buehlmann et al., 2010; Phillips et al., 2002; Velakoulis et al., 2006), as well as in the body and tail hippocampal areas (Witthaus et al., 2010). Unsurprisingly thus, most studies analyzing HR individuals that developed schizophrenia found that their hippocampi were smaller than controls (Francis et al., 2013; Ho and Magnotta, 2010; Hurlemann et al., 2008; Keshavan et al., 1997; Mittal et al., 2013; Moorhead et al., 2013; Phillips et al., 2002; Sismanlar et al., 2010; Tepest et al., 2003; Witthaus et al., 2009; Witthaus et al., 2010; Wood et al., 2010).

In these subjects it is important to consider inclusion criteria since genetic factors and psychotic symptoms seem to have different impacts on the hippocampal volumes (Wood et al., 2005).

Studies on young adults belonging to all three categories of HR subjects (risk symptoms, risk factors, combined symptoms/factors) had smaller hippocampal volumes when compared to controls (Francis et al., 2013; Hurlemann et al., 2008; Tepest et al., 2003; Witthaus et al., 2009; Witthaus et al., 2010).

HR and FE subjects with moderate psychotic symptoms showed hippocampal volume reduction especially in the body and the tail of the hippocampus. (Hurlemann et al., 2008).

Smaller hippocampal volumes in specific hippocampal regions were also observed in young adults HR with ‘genetic risk factors’ where subicula volumes were significantly reduced in HR and correlated significantly with deficits in verbal memory (Francis et al., 2013).(Maziade et al., 2009b)

The right side seemed to be more vulnerable as evidenced by the fact that the right hippocampal volumes were smaller at baseline in HR subjects with ‘psychotic symptoms’ who converted in psychosis in a study (Witthaus et al., 2010) and correlated with verbal memory deficit in another one (Hurlemann et al., 2008).

Deficit in verbal memory in subjects with high risk for schizophrenia was well documented (Maziade et al., 2011a). A reduction located in the posterior subicula in the right side could be a specific marker of this intermediary cognitive phenotype in young adults HR.

A peculiar vulnerability of right hippocampus was also observed in adolescents with a low IQ as risk factor to develop schizophrenia. Subjects who converted to

psychosis had smaller right hippocampal volume at the baseline and bilaterally at the follow-up (Moorhead et al., 2013).
Presence of smaller hippocampi in HR adolescents was confirmed in another study considering genetic risk factor for the disease (Keshavan et al., 1997).
The results become less consistent when people belonging to different age groups are analyzed in the same sample.
Relatives did not show the normal age-related decrease in hippocampal volumes expected during late adolescence into early adulthood, and a history of obstetric complications among relatives of schizophrenia probands was further associated with smaller hippocampus volumes bilaterally (Ho and Magnotta, 2010). The lack of normal age-related hippocampus volume reductions among adolescent/young adult relatives of schizophrenia probands may be indicative of aberrant neurodevelopment and/or reduced dendritic elimination.
A moment in late adolescence that could be a “key period” in which the hippocampus begins to develop differently in HR subjects compared to controls could explain why in young adults the hippocampus was smaller than controls in all studies and the discrepancy of results in the group adolescents/young adults.
In fact, similar hippocampal volumes were detected in children with ‘combined risk and symptoms’ (Hendren et al., 1995) and results become inconsistent in the sample children/young adults with genetic risk for schizophrenia.
All of these findings need to be interpreted with caution. More definitive inference regarding abnormal hippocampal maturation in HR subjects will require additional studies and other factors must be considered, such as obstetric complications.
Indeed, a greater number of obstetric complications were significantly associated with smaller hippocampal volumes in adolescents/young adults with genetic HR (Ho and Magnotta, 2010).
The interpretation of studies on hippocampal volume differences between HRp and HRnp in adolescents/young adults HR “combined symptoms” is even more arduous, given the few and inconsistent results. This inconsistence may be explained by the large difference of age in the HR groups and in the methodology used in the different studies.
Therefore, a point to investigate would be the impact of pubertal development on hippocampal volume in HR subjects with genetic risk and risk symptoms to understand if puberty plays a role in one kind of subjects or both.
It is not yet clear if the loss of tissue is localized mainly in the posterior hippocampus in the HR subjects with psychotic symptoms and in the anterior hippocampus in HR individuals with genetic risk.
Further studies on hippocampal shape could clarify if psychotic symptoms and genetic factors have a different impact on hippocampal formation.

Amygdala

As for the hippocampus, abnormalities in amygdala volume in patients at their first manifestation of the disease (FE subjects) seem to be well documented in all studies (Velakoulis et al., 1999; Witthaus et al., 2009; Witthaus et al., 2010).
Moreover, a greater vulnerability of the left side seems to be confirmed in two studies finding smaller left amygdala in FE subjects compared to controls (Witthaus et al., 2009; Witthaus et al., 2010).
Greater amygdala volumes were found in another one (Velakoulis et al., 2006). This discrepancy with studies showed smaller amygdala in FE individuals may

be explained by the fact that amygdala volume enlargement was identified only in first-episode with non-schizophrenic psychosis.
Regarding HR subjects, smaller amygdala was detected in children with 'combined risk and factors' (Hendren et al., 1995) and in adolescents (Keshavan et al., 1997) and adolescents/young adults with genetic risk factors (Bhojraj et al., 2011).
However, these differences in amygdala volumes of HR subjects compared to controls were not observed in other studies considering children/adolescents with genetic risk factor (Dougherty et al., 2012; Sismanlar et al., 2010) and adolescents/young adults with 'combined symptoms and factors' (Velakoulis et al., 1999).
Surprisingly, in one study the amygdala was bigger in adolescents with low IQ and attenuated psychotic symptoms (Welch et al., 2010).
This result is in disagreement with the study that found less amygdala volumes in adolescents with genetic risk factors (Keshavan et al., 1997). Furthermore, it seems contra-intuitive that amygdala volumes are reduced in children (Hendren et al., 1995) while it is enhanced in adolescents.
One possible explanation could be the possibility that the Childhood Behaviour CheckList (CBCL) and Structured Interview for Schizotypy (SIS) tests used to identify HR subjects are identifying individuals within the intellectually impaired group with specific, but non-schizophrenifrom, conditions. Autism is one such possibility, and given the evidence that brain volumes are enlarged in autism (Stanfield et al., 2008), perhaps particularly in those with autism and low IQ, it is conceivable that the schizotypal population may also have autistic features. It is also possible that the measures are identifying individuals with other conditions, such as affective disorders or personality disorders.
Another possible explanation could be a mechanism of amygdala hyperactivity and subsequent atrophy, these changes potentially being triggered by events such as exposure to environmental stressors. Indeed, this explanation has previously been posited to explain amygdala volume loss with time in children with autism (Nacewicz et al., 2006). It may be that structurally abnormal amygdalae, such as the abnormally large structures found in the subjects with high score in CBCL and SIS tests, are particularly vulnerable to this process.
This is indeed what may be suggested by the second finding of this study, the significant negative correlation between left amygdala volume and severity of negative symptoms.
The same correlation was also found bilaterally in amygdala volumes of children with 'combined symptoms and factors' (Hendren et al., 1995).
In young adults with psychotic symptoms compared to controls there were not differences in amygdala volumes (Witthaus et al., 2009; Witthaus et al., 2010).
Moreover, the only two studies providing the follow-up did not find differences between HR subjects who converted in psychosis and HR subjects who did not convert (Velakoulis et al., 2006; Witthaus et al., 2010).
In conclusion, the trajectory of the changes in the hippocampus and amygdala in HR subjects from childhood to adolescence appears different.
In the hippocampus, there appears to be present an abnormal development in late adolescence and a loss of tissue in young adults individuals, whereas in the amygdala the loss of tissue begins in childhood, continues in adolescence. In early adulthood, there seems to be a recovery.
Methodological considerations

Almost all studies used a magnetic resonance scanner at 1.5 Tesla. Manual segmentation of medial temporal lobe structures is the technique most frequently used (semiautomated segmentation algorithm and automated algorithm for the others). The majority of the studies used the hippocampal tracing criteria of Cook (Cook et al., 1992). All the protocols included the whole hippocampus and the alveus and fimbria in the tracing.
For the amygdala, each study used a different protocol. Despite this, all the protocols are very similar and include the same amygdala structures.
To avoid the variability due to different protocols, there is a project aimed to harmonize the available protocols for the manual segmentation of the hippocampus on MR images in order to define a standard protocol (http://www.hippocampal-protocol.net/SOPs/index.php).
This review is an attempt merely qualitative to clarify the incoherent literature on subjects with a high risk to develop schizophrenia. At the moment, there are insufficient studies on the mediotemporal structures to use rigourous quantitative methods such as a meta-analysis.

CONCLUSIONS

In conclusion, the main points emerging from this review are summarized below:
- Studies on subjects with high risk for schizophrenia showed a great variability in methodologies, in particular: inclusion criteria, different age stages, techniques of hippocampus and amygdala detection (manual tracing, automated and semi-automated methods).
In particular, results become less consistent when different ages were considered in the same sample.
- A portion of HR subjects had psychiatric disorders that could have an impact on the hippocampus and amygdala (e.g. anxiety and depression). We must, therefore, consider that alterations in hippocampus and amygdala could be a consequence of such disease.
- Abnormalities in hippocampal and amygdala volumes in FE subjects seem well documented, especially in the left side.
- In early adulthood, hippocampus of all types of HR subjects was smaller when compared to controls. Moreover, the right hippocampus seems particularly vulnerable and could be a prodromal marker for schizophrenia disease.
- The results become inconsistent in subjects passing from adolescence to adulthood. This may be due to the great variability of the different studies but a key period in which the hippocampus of HR subjects begins to develop in a different way compared to controls could be assumed.
- Genetic factors could have an impact on anterior hippocampal regions impaired typically in schizophrenia and connected to prefrontal regions.
- Amygdala had a different trajectory compared to hippocampal changes during the maturation process. Variables less cognitive but more related to stress and affective disorders could play a role in amygdala changes.
- In light of this, studies on HR subjects should consider: inclusion criteria used for HR subjects diagnosis, range of age of HR subjects, the presence of other psychiatric disorder in HR subjects. Finally, amygdala and hippocampus should be analyzed separately and not as amygdalo-hippocampus complex.

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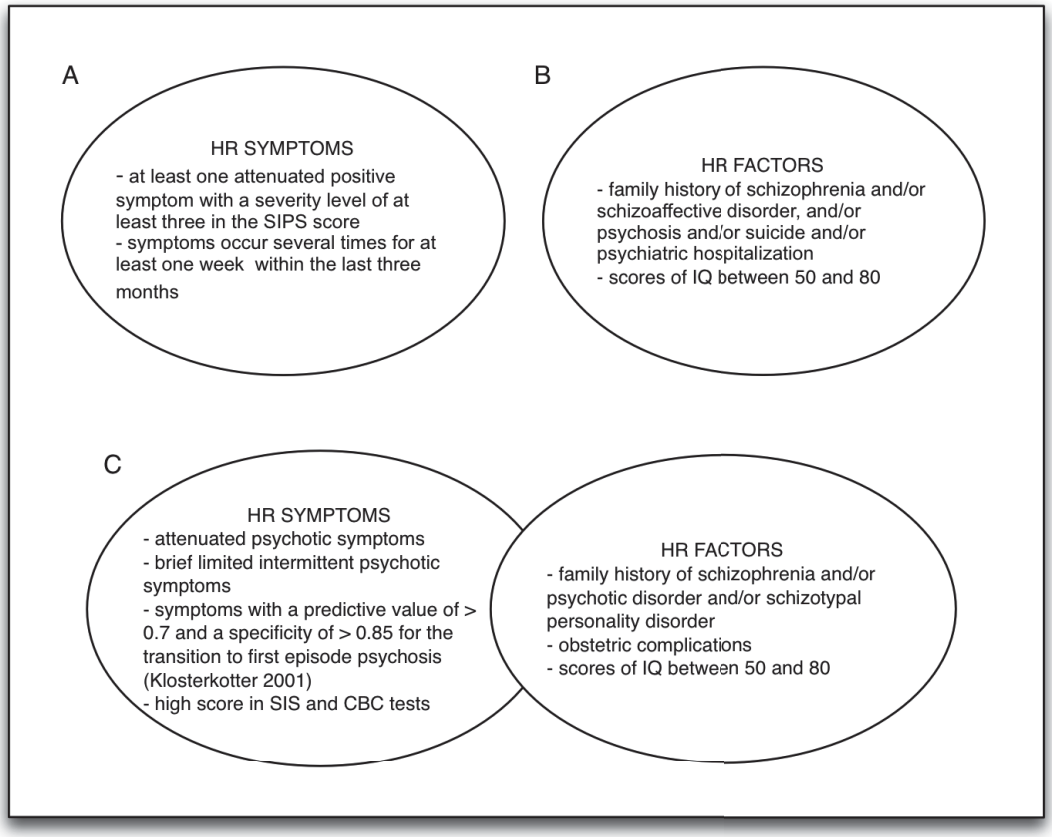
Table 1. Main findings of the 29 papers reviewed.

		Children	Children/adolescents	Adolescents	Adolescents/young adults	Young adults	Children/adolescents/young adults
HC	Risk symptoms					</</<	
	Risk factor		=/<	</<	=/<	</<	=
	Combined symptoms/factors	=			=/=/=/</</<	<	
	FE					</</<	
AG	Risk symptoms					=/=	
	Risk factor		=/=	<	<		
	Combined symptoms/factors	<		>	=		
	FE				>	</<	
AHC	Risk symptoms						
	Risk factor			<	</</<		
	Combined symptoms/factors						
	FE						

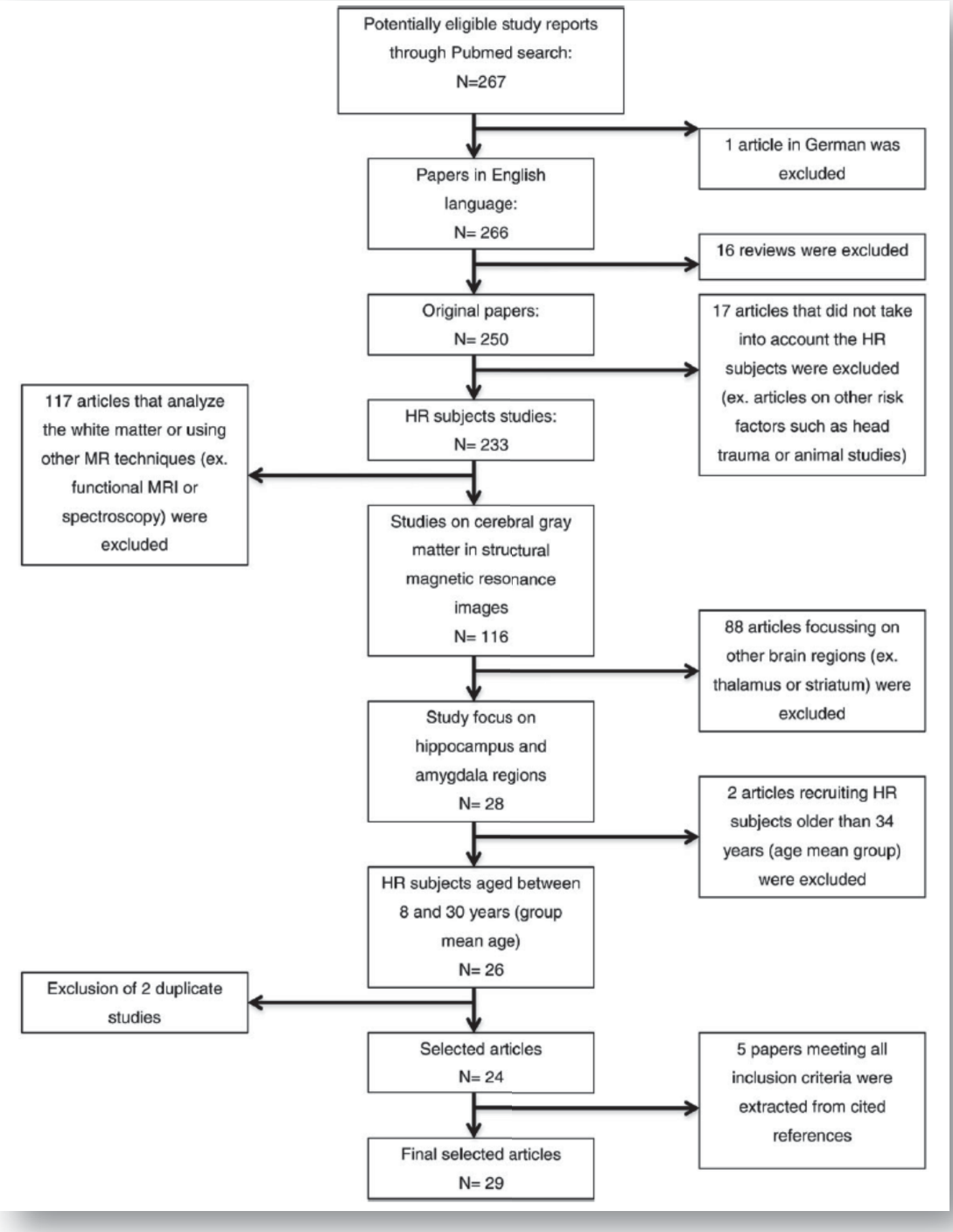
Table shows results of hippocampus (HC), amygdala (AG), and amygdalo–hippocampal complex (AHC) volume comparisons between first episode (FE) subjects and controls, high risk subjects belonging the category “risk symptoms”, or “risk factor” or “combined symptoms/factors” and controls

Figure 1. Reclassification of HR subjects.



The reclassification of HR subjects based on the presence of psychotic symptoms (A) or risk of factors (B) or both (C) in their inclusion criteria.
SIPS= Structured Interview for Prodromal Syndrome.
IQ = Intelligence Quotient. SIS = Structured Interview for Schizotypy (Kendler, 1989).
CBC= Child Behavior Checklist (Achenbach and Rescorla, 2000).

Figure 2. Flowchart for the review of literature searches.



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