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REVIEW

Brain changes in early-onset bipolar and unipolar depressive disorders: a systematic review in children and adolescents

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Abstract Pediatric bipolar disorder (BD) and unipolar disorder (UD) share common symptomatic and functional impairments. Various brain imaging techniques have been used to investigate the integrity of brain white matter (WM) and gray matter (GM) in these disorders. Despite promising preliminary findings, it is still unclear whether these alterations may be considered as common trait markers or may be used to distinguish BD from UD. A systematic literature search of studies between 1980 and September 2013 which reported WM/GM changes in pediatric and adolescent BD/UD, as detected by diffusion tensor imaging and voxel-based analysis was conducted. Of the 34 articles judged as eligible, 17 fulfilled our inclusion criteria and were finally retained in this review. More abnormalities have been documented in the brains of children and adolescents with BD than UD. Reductions in the volume of basal ganglia and the hippocampus appeared more specific for pediatric UD, whereas reduced corpus callosum volume and increased rates of deep WM hyperintensities were more specific for pediatric BD. Seminal papers failed to address the possibility that the differences between unipolar and bipolar samples might be related to illness severity, medication status, comorbidity or diagnosis. UD and BD present both shared and distinctive impairments in the WM and GM compartments. More WM abnormalities have been reported in children and adolescents with bipolar disease than in those with unipolar disease, maybe as a result of a low number of DTI studies in pediatric UD. Future longitudinal studies should investigate whether neurodevelopmental changes are diagnosis-specific.

Keywords VBM/DTI analyses · Children/adolescents · Pediatric bipolar disorder · Unipolar depressive disorder · White matter/gray matter abnormalities

Introduction

Bipolar disorder (BD) is a chronic and disabling disorder characterized by relevant impairments in social, emotional, and academic functioning in childhood and early

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adolescence [1, 2]. The prevalence rate of bipolar spectrum disorder has been estimated to be 2 % among children and adolescents in the community [3]. Early-onset BD is usually associated with poorer performance, comorbidity with substance abuse, suicide attempts, hospitalization, and legal difficulties [4–7]. Similarly, major depressive disorder (MDD) in children and adolescents is associated with a fourfold increased risk of recurrence in adulthood, long-term functional impairment and adult disability [8, 9].This poor outcome in children and adolescents with unipolar disorder (UD) or BD emphasizes the need for adequate understanding of the mechanisms underlying these affective conditions [10–14].

Although many studies attempted to elucidate the neurobiological basis of affective disorders in children and adolescents, their pathogenesis remains unclear. During the last decades, brain imaging techniques provided new approaches to detect in vivo structural and functional brain changes. Magnetic resonance imaging studies reported a wide range of morphometric alterations in both pediatric BD [15–20] and UD [21–27].

Diffused GM abnormalities have been found in patients with pediatric BD, specifically volumetric changes in the anterior limbic network (ALN), including the prefrontal regions, thalamus, striatum, amygdala, hippocampal complex, and the midline cerebellum [28].

In their meta-analysis, Arnone et al. [29] found that reduced prefrontal cortex and increased globus pallidus volumes are some of the most consistent findings in children and young adults with BD. There is also evidence that adolescents with a recent single manic episode exhibited smaller subgenual cingulate cortex volumes than healthy controls (HC) [30], whereas drug-naïve adult individuals with a first-episode depression showed reduced GM volume in the right pre-supplementary motor area [31]. Reduced GM has also been reported in the prefrontal cortex, amygdala, and hippocampi of depressed children. However, these results were inconsistent, due to heterogeneous samples and differences in terms of gender, illness duration, severity of symptoms, medication, or episode states [32–34].

A second line of studies explored white matter (WM) integrity in these disorders using diffusion tensor imaging (DTI) [35]. Studies using a region-of-interest (ROI) approach reported abnormalities in prefrontal–limbic circuits that have been associated with affective dysregulation in BD [33]. Specifically, lower fractional anisotropy (FA) has been found in the anterior corona radiata (ACR) [36] and superior frontal WM in pediatric BD [37]. Recently, studies using either voxel-based morphometry (VBM) analysis or tract-based spatial statistics (TBSS) reported WM abnormalities and lower FA in several brain regions [38–40].

Similarly, DTI studies conducted in pediatric UD reported microstructural WM abnormalities during the first episode of depression in both depressed young adults [41] and adolescents [42].

There are also some neuroimaging studies that were conducted among unaffected but high risk of BD/MDD individuals aimed to reveal WM changes [43–45].

Few studies in the current literature examined whether some VBM/DTI abnormalities may help in distinguishing individuals with UD or BD. For example, Cardoso de Almeida and Phillips [46] suggested more widespread abnormalities in WM connectivity and more WM hyperintensities in BD than UD, more habenula volume reductions in BD but not UD, and differential patterns of functional abnormalities in emotion regulation and attentional control neural circuitry in both BD and UD. There is, however, the pressing need for more neuroimaging studies using larger samples sizes, and comparing BD and UD depressed subjects.

In this context, we aimed to systematically review the current literature to determine whether pediatric/adolescent BD is associated with greater or more consistent WM or GM alterations than pediatric/adolescent UD.

Methods

Information sources, search strategy, and study selection

A detailed search strategy was used to identify relevant studies. In order to provide a new and timely critical review of VBM/DTI abnormalities and their possible involvement in children/adolescents with UD or BD, we performed a systematic PubMed/Medline, Scopus, and Science Direct search to identify all papers and book chapters in the English language during the period between 1980 and January 2014.

The search used first the following terms: “Voxel-based morphometry analysis”, OR “VBM analysis”, AND “Diffusion tensor imaging” OR “DTI” AND “White matter hyperintensities” OR “White matter lesions” OR “White matter abnormalities” OR “White matter changes signals” AND “Grey matter hyperintensities” OR “Grey matter lesions” OR “Grey matter abnormalities” to investigate “pediatric and adolescent samples with bipolar disorder” OR “PBD” OR “Bipolar disorder in children and adolescents” AND subsequently the same terms to investigate “Pediatric and adolescent samples of unipolar disorders” OR “Unipolar disorders in children and adolescents”. When a title or abstract seemed to describe a study eligible for inclusion, the full article was examined to assess its relevance based on the inclusion criteria. Two

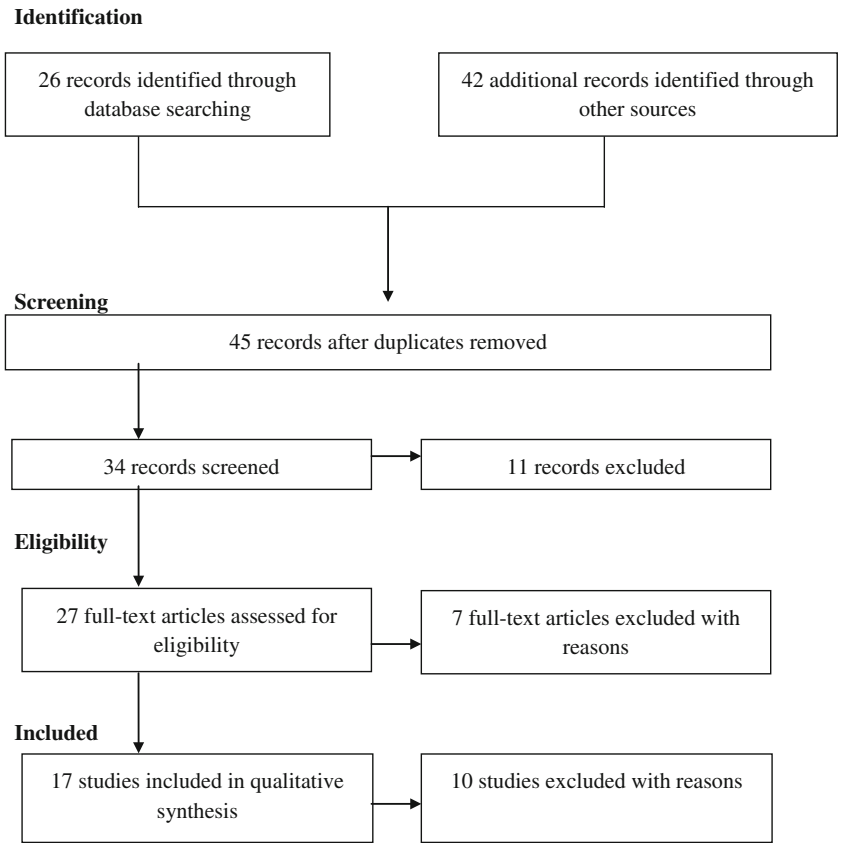

Fig. 1 Flowchart of the search and selection process

blinded, independent researchers (GS and MP) conducted a two-step literature search. Any discrepancies between the two reviewers were resolved by consultations with the senior authors (JH, MA, RJ, PG). The reference lists of the articles were also manually checked for relevant studies while other publications were cross-referenced for any additional published articles. Only English language full-text articles reporting original data about the main topic were included.

Study design and eligibility criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines [47]. Studies were included according to the following criteria: (a) being an original paper in a peer-reviewed journal and (b) containing an analysis of VBM/DTI abnormalities in samples of bipolar/unipolar disorders. Figure 1 summarizes the search strategy used for selecting studies (identification, screening, eligibility, inclusion process) in the present review. We excluded studies explicitly conducted on high-risk subjects. Papers that were not written in English, book chapters, conference abstracts, and case studies were not reviewed.

Recorded variables

We retained the following variables for each article about VBM/DTI abnormalities and their possible involvement in bipolar/unipolar disorders of children and adolescents: sample characteristics, study design, treatment-resistant definition, location of WM/GM abnormalities, main findings, limitations, and conclusions (Table 1).

Results

Number of selected studies

The combined search strategy yielded a total of 68 articles, of which 34 full-text articles were screened and 34 excluded. Articles not published in peer-reviewed journals and not in English, papers without abstracts, abstracts that did not explicitly mention the link between WM/GM abnormalities and bipolar/unipolar disorders in children and adolescents, articles published before 1980, and those with unclear data concerning materials and methods or number of patients analyzed, were excluded. Of the initial 45 papers, 34 were considered of relevance and 27 were

Table 1 Most relevant DTI studies showing neuroimaging abnormalities in samples of children and adolescents with UD

Author (s), year	Sample characteristics (mean years ± S.D.)	Study design	Location of WM	Main findings	Limitations	Conclusions
1. Cullen et al. [42]	14 adolescents with MDD (16.79 ± 1.29) compared with 14 healthy controls (16.81 ± 1.5)	Cross-sectional	WM tract connecting subgenual ACC to amygdala in the right hemisphere	Adolescents with MDD showed lower FA in the WM tract connecting subgenual ACC to amygdala in the right hemisphere	Most of the MDD subjects were undergoing treatment with medications, and they had one or more secondary comorbid diagnoses (in particular, five subjects had a history of a substance use disorder)	MDD in adolescents may be related to the altered WM microstructure in frontolimbic neural pathways

judged eligible. However, seven full-text articles were also excluded due to their low relevance (two studies were conducted on FEP patients) for the main theme, and three articles were excluded as they included high-risk subjects. This left 17 papers that fulfilled inclusion criteria, including 326 patients and 360 controls.

Types of studies selected

Several studies documented the association between WM/GM abnormalities and bipolar/unipolar disorders in children and adolescents. Table 1 summarizes the most relevant studies about DTI neuroimaging abnormalities in children and adolescents with unipolar disorder whereas Table 2 includes the nine most relevant studies about DTI neuroimaging abnormalities in children and adolescents with bipolar disorder. Table 3 summarizes the two most relevant studies about VBM neuroimaging abnormalities in children and adolescents with UD, whereas Table 4 includes the five most relevant studies about VBM neuroimaging abnormalities in children and adolescents with bipolar disorder. These studies were all cross-sectional in nature with the exception of the study of Adleman et al. [54], including an initial cross-sectional phase and a subsequent 2-year follow-up period.

DTI studies in samples of children and adolescents with BD

Nine DTI studies showed neuroimaging abnormalities in samples of children/adolescents with BD. Significantly lower FA was found by Lu et al. [33] in the anterior limb of the internal capsule (ALIC) of 35 pediatric subjects presenting with first-episode type I BD compared with 46 controls. Gao et al. [35] reported significantly lower FA values in the right anterior cingulate of pediatric bipolar children in comparison with healthy volunteers. Lower FA values were reported by Saxena et al. [49] in the callosal genu and anterior commissure of 10 bipolar adolescents than with 10 age-matched HC. James et al. [50] reported reduced GM density in the left orbito-frontal cortex, left pars triangularis, right premotor cortex, occipital cortex, right occipital fusiform gyrus, and right crus of the cerebellum of 15 bipolar subjects with psychosis, compared to 20 euthymic age- and gender-matched controls. Reduced FA values were also shown in the anterior corpus callosum associated with the prefrontal cortices. Voxel-based morphometry, tract-based spatial statistics, and probabilistic tractography were all used to analyze the DTI data.

Gönenç et al. [51] suggested that FA was reduced and radial diffusivity increased on the left side, whereas on the right side, trace was increased and T2 values were decreased in subjects with BD compared with control subjects. Significantly lower FA was found in the ACR of 13 children/adolescents with BD compared to 15 controls. Also, FA and regional fiber coherence index (r-FCI) values were significantly lower in ADHD than BD and controls in both the ALIC and superior region of the internal capsule (SRI) [36]. The authors suggested that apparent diffusion coefficient was significantly increased in specific brain areas of subjects with ADHD compared to both bipolar subjects and controls.

Kafantaris et al. [40] found that 26 adolescents with BD type I showed alterations in WM regions, including lower FA in the right orbital frontal lobe and higher apparent diffusion coefficient in the right and left subgenual region. Patients with BD manifested a significant correlation between lower FA across regions and lower visuomotor speed. Lower FA values compared to 18 age- and IQ-matched controls in the fornix, left mid-posterior cingulate gyrus, throughout the corpus callosum, in fibers extending from the fornix to the thalamus, and in parietal and occipital corona radiata bilaterally have also been reported in 21 bipolar adolescents by Barnea-Goraly et al. [39].

Finally, Frazier et al. [38] found that 10 bipolar children exhibited reduced FA in the bilateral superior frontal tracts, including the SLF I and CG-PACWM relative to eight HC and seven children at risk for BD. Furthermore, bipolar

Table 2 Most relevant DTI studies showing neuroimaging abnormalities in samples of children and adolescents with BD

Author (s), year	Sample characteristics	Study design	Location of WM	Main findings	Limitations	Conclusions
1. Lu et al. [48]	35 individuals presenting with first-episode BD type I (divided into younger and older BD subjects) and 46 HC (aged 9–42)	Cross-sectional	WM of the left anterior limb of the internal capsule (ALIC)	The ALIC was found to show significantly lower FA values in younger BD subjects than in older BD individuals. The lower FA values in BD was due to the greater radial rather than decreased axial diffusivity	The cross-sectional design and spatial resolution in the DTI acquisition that was used may be considered as major limitations. Considering that WM alterations in the ALIC are identified in many conditions, it is unlikely that the ALIC is a highly specific site of neuropathology in BD	Abnormalities in the connection of the frontal lobes with archistriatum, thalamus and medial temporal regions may contribute to mood dysregulation in BD and thus be associated with an earlier onset of illness
2. Gao et al. [35]	18 children/adolescents (six male and 12 female) with bipolar mania aged 10–18 years and 18 age- and sex-matched HC	Cross-sectional	Right anterior cingulate cortex	Significant lower FA values were detected in the right anterior cingulate in pediatric bipolar children	The sample size of each group is relatively small to allow the generalization of findings. Also, most patients are under medications when scanning (this is a potential confounding factor). The correlation between the hippocampus volume and the Young Mania Rating Scale (YMRS) score should be interpreted as exploratory (no correction has been carried out)	Extensive GM and WM structural lesions are presumably pre-existing in pediatric bipolar children. The anterior limbic network has been suggested to critically contribute to emotional and cognitive dysregulations in pediatric bipolar children
3. Saxena et al. [49]	10 adolescents (aged 7–17 years) with BD and 10 age-matched controls	Cross-sectional	Callosal genu and anterior commissure	Bipolar youth showed significantly lower FA values in the callosal genu and anterior commissure. FA values in the anterior commissure were negatively correlated with a life history of aggression in the bipolar adolescents	The sample size did not allow the generalization of findings. The bipolar sample included both adolescents with BD-I and BD not otherwise specified (NOS) with varying mood states. Also, subjects were all taking psychotropic medications. Finally, information concerning family psychopathology or head trauma for HC were not available	The callosal genu has been hypothesized to have a critical role in BD. Preliminary evidence was reported for a possible association between the structural integrity of the WM of the anterior commissure and aggression in pediatric bipolar adolescents

Table 2 continued

Author (s), year	Sample characteristics	Study design	Location of WM	Main findings	Limitations	Conclusions
4. James et al. [50]	15 bipolar subjects with psychosis (15.0 years ± 2.0) compared with 20 euthymic age- and gender-matched HC (15.3 years ± 1.0)	Cross-sectional	Anterior half of the corpus callosum	Individuals with pediatric BD had reduced FA in the anterior half of the corpus callosum compared to age- and gender-matched HC. According to a probabilistic tractography, voxels within the anterior callosal cluster were connected to the prefrontal cortex, particularly the orbito-frontal cortex, premotor cortex, pars triangularis and frontal poles	The relatively small number of subjects did not allow the generalization of findings. The study was limited to those with psychosis; therefore, findings may not be generalized to BD as a whole	Interhemispheric prefrontal tracts could be involved in pediatric bipolar patients
5. Gönenç et al. [51]	21 children/adolescents with BD (10 male, mean age 11.5 ± 3.3 years, and 11 female, mean age 11.6 ± 4.2 years) compared with 16 HC (nine male, mean age 10.9 ± 4.3 years, and seven female, mean age 13.3 ± 2.1 years)	Cross-sectional	WM hemispheric differences	Hemispheric difference was observed in the BD group, with decreased transverse relaxation time (T2) predominantly on the right side compared with the left side. With respect to DTI differences, FA was reduced and trace/radial diffusivity was increased on the left side whereas trace was increased and T2 was decreased in the BD group on the right side	The small sample size did not allow the generalization of findings. Firstly, ROI analyses are very limited in identifying global changes in the brain. Secondly, Subjects were under psychotropic medications when scanning (this is a potential confounding factor). Finally, no detailed handedness, neuropsychological testing, or socioeconomic status information were available	Myelin damage could occur on the left side determining the early-onset BD together with changes in the blood flow

Table 2 continued

Author (s), year	Sample characteristics	Study design	Location of WM	Main findings	Limitations	Conclusions
6. Pavuluri et al. [36]	13 children/adolescents with BD, 13 with attention-deficit/hyperactivity disorder (ADHD) and 15 HC	Cross-sectional	Anterior corona radiate, superior region of the internal capsule (ACR), ALIC, SRI, posterior limb of the internal capsule (PLIC); superior longitudinal fasciculus (SLF); inferior longitudinal fasciculus (ILF); cingulum (CG); splenium (SP)	Significantly lower FA was found in ACR in both BD and ADHD subjects compared to HC. Also, FA and r-FCI values were significantly lower in ADHD than in BD and HC in both the ALIC and SRI. Apparent diffusion coefficient was significantly increased in the ACR, ALIC, PLIC, SRI, CG, ILF, SLF of ADHD group compared to both the BD and HC	The sample size may be underpowered to detect modest differences in the present study. Also, the relatively low spatial resolution did not allow the findings to be generalized	Impaired fiber density or reduced myelination in the prefrontal tract reflected by the reduced FA in ACR may be involved in the pathogenesis of both BD and ADHD. Functional pathology in cortical target fields may be relatively limited to GM
7. Kafantaris et al. [40]	26 adolescents with BD type I (12 male and 14 female subjects, mean age, 16.0 years) compared with 26 HC (14 male and 12 female subjects; mean age, 15.3 years)	Cross-sectional	WM of the right orbital frontal lobe, and right and left subgenual region	Patients showed alterations in WM regions (predicted to differ a priori between groups), including lower FA in the right orbital frontal lobe and higher apparent diffusion coefficient in the right and left subgenual region compared to HC. Patients with BD reported a significant correlation between lower FA across regions and slower visuomotor speed	Any voxelwise analysis is subject to type I errors (a potential bias). Also, patients were taking antipsychotics and/or mood stabilizers when scanning. The potential of these medications to induce changes on WM integrity is still unclear	WM changes in pediatric BD have been found to have functional correlates. Alterations in the orbital frontal and subgenual WM in BD adolescents may reflect the dysregulation of affective systems and impulsivity of the illness

Table 2 continued

Author (s), year	Sample characteristics	Study design	Location of WM	Main findings	Limitations	Conclusions
8. Barnea-Goraly et al. [39]	21 BD adolescents (mean age, 16.1 ± 2.7) who were children of at least one BD parent, and 18 age- and IQ-matched HC (mean age, 14.5 ± 2.7)	Cross-sectional	WM of the fornix, left mid-posterior cingulate gyrus, throughout the corpus callosum, fibers from the fornix to the thalamus, and parietal/occipital corona radiate bilaterally	Bipolar adolescents showed lower FA values compared to HC in the fornix, left mid-posterior cingulate gyrus, throughout the corpus callosum, in fibers from the fornix to the thalamus, and parietal/occipital corona radiata bilaterally	Most participants were taking medications when scanning and/or had psychotropic medication exposure history. Also, subjects had significant ADHD symptoms (a potential confounding factor). Post hoc behavioral analyses included only a subset of the whole sample; therefore, negative results may have been obtained due to lack of power	Abnormalities in WM are present early in the course of disease in familial BD. Significant WM tract changes in bipolar adolescents may be found in those brain regions involved in emotional, behavioral and cognitive regulation
9. Frazier et al. [38]	10 bipolar children (mean age, 9.2 ± 3.0), 8 HC (mean age, 9.2 ± 2.4), and 7 age-matched children at risk for BD (AR-BPD) (mean age, 8.9 ± 3.0)	Cross-sectional	WM of the SLF I and the cingulate-paracingulate WM (CG-PACWM), left orbital frontal and the right corpus callosum body	Bipolar children reported reduced FA in the right and left superior frontal tracts, including the SLF I and CG-PACWM compared to HC. Furthermore, bipolar children showed reduced FA in left orbital frontal WM and the right corpus callosum body. Bipolar children also reported reduced FA in the right and left CG-PACWM than AR-BPD. Finally, reduced FA was found in bilateral SLF I in either the BD and AR-BPD groups compared to HC	The modest number of subjects and the cross-sectional nature of the study did not allow the findings to be generalized. Also, all subjects had attention-deficit/hyperactivity disorder (ADHD) and/or anxiety disorder. Moreover, the effects of mood state and comorbidities on the DT-MRI findings have not been evaluated. Also, individuals were taking psychotropic medications when scanning (this is a potential confounding factor)	Decreased FA in the right and left CG-PACWM in bipolar children compared to the other groups could represent a disease-state-related finding. These abnormalities could represent an endophenotype of the bipolar illness

Table 3 Most relevant VBA studies showing neuroimaging abnormalities in samples of children and adolescents with UD

Author (s), year	Sample characteristics	Study design	Location of WM/GM abnormalities	Main findings	Limitations	Conclusions
1. Shad et al. [52]	22 MDD adolescents (aged 15.0 + 2.1) and 22 age- and gender-matched HC (aged 16.0 + 2.1)	Cross-sectional	GM changes in the frontolimbic areas and caudate	Significantly lower GM volumes in the frontolimbic regions and caudate were found in depressed adolescents than HC	Among 22 depressed subjects, four patients were taking psychoactive medications. The small sample size might explain loss of significance in GM differences between the two groups	Structural deficits of GM in the frontolimbic regions and caudate may be present at the onset of depressive illness
2. Frodl et al. [53]	24 patients (aged 18–65 years) with a major depression compared to 27 HC (aged 18–65 years)	Cross-sectional	Hippocampal WM	The left prefrontal cortex was smaller in patients than in HC. Childhood stress predicted hippocampal WM abnormalities	The study is limited by the relatively small sample size and the difficulty in conducting subgroup analyses with respect to lifetime illness course. Also, abuse commonly remains underreported	Both genetic and the environmental risk factors may independently induce significant changes of the hippocampal WM reflecting the outgoing fibers of the fimbria to the additional structures of the limbic system

children showed reduced FA in left orbital frontal WM and the right corpus callosum body. Bipolar children also exhibited lower FA in the right and left CG-PACWM than for children at risk for BD (AR-BPD). In addition, lower FA relative to HC was found in bilateral SLF I in both the BD and AR-BPD groups.

DTI studies in samples of children and adolescents with UD

Only one DTI study reported brain imaging abnormalities in samples of children and adolescents with UD. Cullen et al. [42] found that 14 adolescents with MDD exhibited lower FA in the WM tract connecting the subgenual ACC to amygdala in the right hemisphere when compared with 14 healthy volunteers.

VBM studies in samples of children and adolescents with BD

Five VBM studies reported neuroimaging abnormalities in samples of children and adolescents with BD. Adleman et al. [54] reported that the GM volumes of the pre-SMA, dorsolateral prefrontal cortex (DLPFC) and insula were increased in 68 HC compared with 55 with BD and 78 with severe mood dysregulation. Regarding globus pallidus, increased GM volume in BD compared with healthy volunteers and severe mood dysregulation patients have been reported. After 2 years of follow-up, an abnormal increase in the volume of the superior/inferior parietal lobule as well as in the precuneus of 34 BD patients was found. Hajek et al. [55] also reported that 19 patients with BD who had a substantial burden of illness and a <3 months of lifetime exposure to lithium exhibited smaller right inferior frontal gyrus (rIFG) volumes when compared with 29 control subjects (having a substantial burden of long-lasting BD). This negative association was not replicated in lithium-treated BD patients.

As suggested by Jarvis et al. [56], cannabis use disorder was associated with structural differences in frontal and temporal cortical regions, as well as subcortical regions such as the caudate (hypothesized to be involved in emotional and motivational regulation); this study was performed in 14 adolescents with BD, of which seven were cannabis consumers.

Dickstein et al. [57] found that 20 bipolar subjects had reduced GM volume in the left DLPFC (Brodmann area 9) and, using a less conservative statistical threshold, in the left accumbens and left amygdala, when compared to 20 controls. Significantly greater GM volume has been also found in 10 bipolar subjects in the basal ganglia, thalamus and left temporal lobe bilaterally by Wilke et al. [58] when compared to 52 age- and gender-matched controls. In

Table 4 Most relevant VBA studies showing neuroimaging abnormalities in samples of children and adolescents with BD

Author (s), year	Sample characteristics	Study design	Location of WM/GM abnormalities	Main findings	Limitations	Conclusions
1. Adleman et al. [54]	Cross-sectionally, 201 children (78 with severe mood dysregulation (SVD), 55 BD, and 68 HC). Longitudinally, 92 children (31 SMD, 34 BD, and 27 HC) were rescanned	Cross-sectional and 2-year follow-up	Cross-sectionally, GM of the pre-supplementary motor area (pre-SMA) and globus pallidus. Longitudinally, GM of the superior/inferior parietal lobule and precuneus	Cross-sectionally, GM volume of the pre-SMA, dorsolateral prefrontal cortex (DLPFC) and insula was increased in HC compared with BD and SMD. Regarding globus pallidus, increased GM volume in BD compared with healthy volunteers and severe mood dysregulation patients has been reported. Longitudinally, an abnormal increase in volume in BD was found in the superior/inferior parietal lobule and precuneus	Differences in age between groups must also be considered as a major limitation. Also, the effects of ADHD could not be separated by those of SMD. The effects of specific medications on brain development were not been considered. Pubertal effects were not directly investigated. Finally, the high rate of comorbid illnesses did not allow the authors to obtain specific findings	Cross-sectionally, both BD and SMD are associated with structural abnormalities in frontal cortex insula, and basal ganglia. Pre-SMA and globus pallidus changes may distinguish between SMD and BD. Longitudinally, abnormal developmental trajectories in lateral parietal cortex and precuneus may also be found in the BD group
2. Hajek ey al. [55]	19 subjects with personal history of BD (aged 15-30 years) and 29 subjects with substantial burden of long-lasting BD	Cross-sectional	GM of the right inferior frontal gyrus	Patients with BD who had a substantial burden of illness and minimal lifetime exposure to lithium showed smaller right inferior frontal gyrus (rIFG) volumes than HC. This negative association has not been demonstrated in lithium-treated BD patients	The trajectories of rIFG volume changes over time have not been longitudinally tracked	Larger rIFG may represent a neuroanatomic signature of familial predisposition for BD. Lithium treatment might prevent or reverse these brain structural changes
3. Jarvis et al. [56]	14 bipolar adolescents aged 12-18 years, of which 7 have cannabis use disorder	Cross-sectional	Frontal and temporal cortical regions and some subcortical areas	Cannabis use disorder in bipolar adolescents was associated with structural differences in frontal/temporal cortical regions as well as in subcortical regions such as the caudate (supposed to be involved in emotional and motivational regulation)	The relatively small sample size did not allow the power to observe group differences. The study did not distinguish changes that precede the development of abuse from changes that might result from chronic drug exposure. Also, nicotine abuse or addiction has not been considered as an exclusion criterion	Bipolar adolescents with cannabis use disorder showed greater structural abnormalities than adolescents with BD alone in frontal/temporal cortical regions, and subcortical regions related to emotion and motivational regulation

Table 4 continued

Author (s), year	Sample characteristics	Study design	Location of WM/GM abnormalities	Main findings	Limitations	Conclusions
4. Dickstein et al. [57]	20 subjects with BD (aged 7-17 years) compared to 20 HC	Cross-sectional	GM of the left DLPFC, left accumbens and left amygdala	Bipolar subjects had reduced GM volume in the left DLPFC (Brodmann area 9) and, using a less conservative statistical threshold, left accumbens and left amygdala	The small sample size did not allow the generalization of findings. Also, 95 % of children with BD were taking psychotropic medications at the time of MR imaging	GM abnormalities in prefrontal cortex are involved in emotion dysregulation underlying BD
5. Wilke et al. [58]	10 BD adolescents compared with 52 age- and gender-matched HC	Cross-sectional	GM of the medial temporal lobe, orbito-frontal cortex, and the anterior cingulated cortex	Significantly greater GM volume was found in the bipolar group of the basal ganglia, thalamus and left temporal lobe bilaterally. Localized GM abnormalities in bipolar subjects were also reported in the medial temporal lobe, orbito-frontal and anterior cingulate cortex	Findings were derived as part of an fMRI experiment (this may determine more severe susceptibility artifacts from tissue–bone or tissue–air interfaces). Other concerns regarded z-gradient and B - field 1 linearity together with the issue of possibly incomplete coverage	A relationship between localized GM volume and altered affect processing has been hypothesized in bipolar subjects

addition, localized GM deficits in bipolar subjects were also reported in the medial temporal lobe, orbito-frontal cortex and anterior cingulate.

VBM studies in samples of children and adolescents with UD

Only two VBM studies reported brain imaging abnormalities in samples of children and adolescents with UD. Shad et al. [52] found significantly lower GM volume in the frontolimbic regions and caudate of 22 MDD adolescents when compared with 22 age- and gender-matched normal controls. Also, Frodl et al. [53] suggested that the left prefrontal cortex was smaller in 24 patients with MDD than in 27 controls. Childhood stress predicted hippocampal WM abnormalities.

Conclusions and discussion

Summary of main results

The present review is, to our knowledge, the first study examining whether pediatric/adolescent BD is associated with greater or more consistent WM/GM alterations than pediatric/adolescent UD. We aimed to investigate whether some VBM/DTI abnormalities can distinguish samples of children/adolescents with BD or UD from HC.

Only three VBM/DTI studies [42, 52, 53] investigated the existence of brain imaging abnormalities in samples of children/adolescents with UD versus fourteen VBM/DTI studies [35, 36, 38–40, 48–51, 54–58] showing neuroimaging abnormalities in pediatric/adolescent samples with BD.

Based on the main findings, more WM abnormalities have been reported in BD children/adolescents compared to those with UD. In particular, bilateral abnormalities in WM connectivity of brain regions and neural circuitry critically involved in emotion regulation and sensory processing have been reported in BD, but not UD. The bilateral findings in BD, but not UD, indicated more widespread WM connectivity alterations in BD compared to UD. WM tracts abnormalities may be related to both axonal disorganization and demyelization or apoptosis; future studies should directly investigate this important issue using recent techniques such as Magnetization Transfer Ratio or axonal calibration [59].

Main neuroimaging abnormalities in children/adolescents with BD

Several studies have suggested the existence of WM/GM abnormalities in samples of children/adolescents with BD.

In their meta-analytic study on adults, Kempton and colleagues [60] suggested that basal ganglia and hippocampal volume reductions seem to be more specific for MDD than BD, whereas reduced corpus callosum cross-sectional area and increased rates of deep WM hyperintensities seem to be more common in BD than MDD. As argued below, these findings have only partially been confirmed in samples of children and adolescents. However, alterations throughout the amygdala and basal ganglia appear poorly specific, since they have also been documented in BD [42, 54, 58] and many other neuropsychiatric disorders [42]. The presence of subcortical alterations within the amygdala and basal ganglia in childhood [61] could subsequently extend to prefrontal cortical regions continuing to develop into adulthood. These frontolimbic abnormalities occurring during childhood and early adolescence would suggest the existence of neurodevelopmental conditions [62]. Abnormalities throughout the anterior limbic system and associated prefrontal regions have been hypothesized to be involved in affective, cognitive and vegetative symptoms in BD [63–65]. In line with results in adult samples, one of the most common brain region in which abnormalities have been documented in pediatric/adolescent bipolar samples is the corpus callosum [38, 39, 50]. The corpus callosum represents the major interhemispheric commissure connecting most of the neocortical brain regions and including fundamental brain networks related to attention, memory, language and emotional states [66–72]. The corpus callosum develops during childhood/adolescence as demonstrated by the increased size [73], reduced signal intensity [72] and increased FA values [74].

Some authors [75, 76] suggested that, although the signal intensity of the corpus callosum is reduced and its shape altered in pediatric/adolescent bipolar samples, no differences in size have been reported between bipolar children/adolescents and healthy volunteers.

Barnea-Goraly et al. [39] suggested an abnormal maturation process in the corpus callosum of bipolar subjects, as reflected by the lower FA in adolescence—representing reduced coherence or aberrant myelination and increasing FA with age. This might be due to changes in the extracellular compartment related to abnormal perivascular structures [73], but might also be related to the different measurements of FA in the corpus callosum of adults and adolescents [77].

Abnormalities in the CC3-motor area of the corpus callosum interconnecting right and left paracingulate, anterior cingulate, supplementary motor areas and lateral premotor regions in the frontal lobes could be related to alterations in activity and motivation—that are frequently observed in children with BD [38].

As hypothesized, WM integrity in prefrontal limbic network has been found to be significantly altered as demonstrated by the lower FA in children with BD. Two studies suggested that there are changes in the WM of the ALIC [33, 36]. Greater alterations have been reported in the WM microstructure of the left ALIC with pediatric bipolar onset compared to adult bipolar onset [36].

Disorganized integration of prefrontal–limbic circuitry associated with affective dysregulation has been hypothesized in BD [33, 78]. The prefrontal structures appear to show dysfunctions in modulating subcortical structures. The alterations in the WM microstructure of the ALIC have also been demonstrated in another DTI tractography study [79]. This may increase the vulnerability to develop bipolar illness, by altering the processing of emotional information throughout the limbic system.

Main neuroimaging abnormalities in children/adolescents with UD

Only three VBM/DTI studies [42, 52, 53] showed the existence of brain imaging abnormalities in samples of children and adolescents with UD. Shad et al. [52] showed lower GM volumes in the frontolimbic areas and caudate of depressed adolescents than in healthy volunteers. These authors also suggested that GM changes in the striatum, especially in the caudate nucleus, may relate to the initial presentation of MDD. The involvement of frontolimbic regions in the pathogenesis of adult MDD has been extensively reported [79–83]. Dorsolateral and orbitofrontal regions of the prefrontal cortex (PFC) play a critical role in self-monitoring and executive control of the medial PFC and limbic system [84, 85].

As suggested by Frodl et al. [53], even subtle changes of the hippocampal WM may be relevant in the pathogenesis of adolescent depression. Hippocampal abnormalities have been reported in both unipolar depressed children and adolescents [53], whereas other authors suggested the existence of alterations in the WM tract connecting subgenual ACC to amygdala in the right hemisphere [42]. Consistent evidence [86–88] suggested that the subgenual ACC is a critical brain structure functionally connected with the activity of frontolimbic regions. An alteration in the ACC, including disorganized integrity of WM microstructure of the uncinate fasciculus would provide an abnormal regulatory input to the amygdala [89]. These WM changes may reflect a critical axonal reduction or cell loss in the outgoing fibers of the fimbria to the structures of the limbic system and may be responsible for the cognitive/emotional disturbances of depression. There is evidence that childhood trauma (e.g., physical or sexual abuse) may be associated with reduced hippocampal volume in subjects who subsequently develop depressive disorders in adulthood [90–92].

Cullen et al. [42] also suggested that there are lower mean FA values (reflecting reduced WM integrity) in right WM tracts connecting subgenual ACC to the amygdala in adolescents with UD. These authors stated that alterations of this connection may be involved in many neuropsychiatric disorders (e.g., bipolar disorder and schizophrenia).

Methodological differences between VBM analyses and ROI-based approaches could be fundamental in explaining some conflicting findings. This is, for example, the case of the ROI-based study of Chen et al. [23] that failed to demonstrate significant differences in OFC volume between depressed adolescents and controls.

Taken together, these few studies supported the hypothesis that dysfunctions in the microstructure of WM pathways within frontolimbic neural networks are involved in the pathophysiology of UD in children and adolescents.

Tables 5 and 6 summarize the main GM and WM abnormalities and the different brain regions that have been reported as dysfunctional in children and adolescents with BD versus UD, respectively.

Psychotic features in children and adolescents with bipolar/unipolar disorders

Whether data from first-episode psychosis (FEP) samples or BD/UD samples with psychotic features at their first presentation may help clinicians to distinguish between the subsequent (unipolar/bipolar) trajectories of affective illness is currently a matter of debate. Adolescence is an interesting period to compare the phenotypic expressions of BD with psychosis and schizophrenia.

Janssen et al. [93] analyzed data from 70 FEP adolescents and found that smaller right and left thalamus volume was positively correlated with increased severity of sensory integration neurological soft signs. In addition, smaller right caudate volume was effectively associated with increased impairment in sequencing complex motor acts. Extensive abnormalities in the left medial frontal GM volume have been also reported in bipolar patients with psychotic features at their FEP [94] when compared to bipolar patients without psychosis. Specifically, patients with GM volume abnormalities in the left medial frontal gyrus were more likely to be diagnosed with BD type I than subjects with schizophrenia.

Conversely to early-onset schizophrenia, pediatric BD with psychosis has commonly been associated with fewer cognitive deficits [95], although abnormalities in executive functioning and working memory are quite common in both these disorders. Remarkably, larger GM changes and altered WM integrity in motor control regions have been identified in patients with early-onset schizophrenia compared to those with adult-onset disease [96].

Hatton et al. [97] reported that young people with emerging anxiety, affective or psychotic disorders, had reduced left anterior insula GM volume associated with a poorer neurocognitive performance and more severe clinical symptoms compared to controls. However, no significant differences have been suggested between diagnostic groups.

A correlation between altered fornix connectivity (FA values in the right fornix), volumetric reductions in the hippocampus and self-certainty (measuring the confidence in beliefs and judgments) has been reported by Buchy et al.

Table 5 Main differences in GM abnormalities of children and adolescents with BD versus UD

GM abnormalities	Bipolar disorder	Unipolar disorder	Author(s); year
Cross-sectionally, the pre-SMA and globus pallidus; longitudinally, the superior/inferior parietal lobule and precuneus	(+)	(−)	Adleman et al. [54]
Right inferior and left medial frontal gyrus	(+)	(−)	Hajek et al. [55], Janssen et al. [94]
Frontal and temporal cortical regions and some subcortical areas	(+)	(−)	Jarvis et al. [56]
Left DLPFC, left accumbens and left amygdala	(+)	(−)	Dickstein et al. [57]
Medial temporal lobe, orbito-frontal cortex, and the anterior cingulated cortex	(+)	(−)	Wilke et al. [58], Gao et al. [35]
Left thalamus and right caudate	(+)	(−)	Janssen et al. [93], Shad et al. [52]
Changes in the frontolimbic areas	(-)	(+)	Shad et al. [52]
Left hippocampus	(-)	(+)	Cheng et al. [31], Gao et al. [35]
Callosal genu and anterior commissure	(+)	(−)	Saxena et al. [49]
Left orbito-frontal cortex, left pars triangularis, right premotor cortex, occipital cortex, right occipital fusiform gyrus, right crus of the cerebellum, and corpus callosum	(+)	(−)	James et al. [50]
Anterior corona radiate, superior region of the ACR, ALIC, SRI, PLIC; SLF; ILF; CG; SP	(+)	(−)	Pavuluri et al. [36]

Table 6 Main differences in WM abnormalities of children and adolescents with BD versus UD

WM abnormalities	BD	UD	Author(s); year
Right and left subgenual region and the tract connecting subgenual ACC to amygdala in the right hemisphere	(−)	(+)	Cullen et al. [42], Kafantaris et al. [40]
ALIC	(+)	(−)	Lu et al. [33]
Interhemispheric differences	(−)	(−)	Gönenç et al. [51]
Fornix, left mid-posterior cingulate gyrus throughout the corpus callosum, fibers from the fornix to the thalamus, and parietal/occipital corona radiate bilaterally	(+)	(−)	Barnea-Goraly et al. [39]
SLF I and CG-PACWM, left and right orbital frontal and the left/right corpus callosum body	(+)	(−)	Kafantaris et al. [40], Frazier et al. [38]
Hippocampal WM	(−)	(+)	Frodl et al. [53]

[98]. In their DTI study conducted on either affective or non-affective psychotic individuals, the authors suggested no significant differences between affective or non-affective psychotic subjects.

Also, de Azevedo-Marques Périco et al. [99], aiming to investigate structural brain differences between BD-I subjects and MDD subjects with psychotic features, found more pronounced GM reduction in the right-sided dorsolateral prefrontal cortex and a trend toward left-sided GM deficits in the dorsolateral prefrontal cortex of MDD patients (also after repeating the analysis with scanner site as a confounding covariate) when compared to BD subjects. However, the study did not focus exclusively on pediatric/adolescent samples. There are also studies that did not support the existence of differences between patients with pediatric BD with psychotic features and those with early-onset schizophrenia. Scherk et al. [100] found no significant differences in GM/WM volumes between thirty-five patients with BD who had experienced psychotic symptoms during their illness and thirty-two control subjects. Significant correlations have been observed between GM/WM volumes with number of manic or depressive episodes, duration of illness, existence of psychotic symptoms, and treatment with lithium or antipsychotics.

Also, Zanetti et al. [101] reported no statistically significant differences in the frequencies and severity scores of WM alterations when comparing the affective psychosis (psychotic BD and UD) with non-affective psychosis (schizophrenia/schizophreniform disorder) and control subgroups.

Findings are usually limited by the controversy concerning whether pediatric BD with psychosis and early-onset schizophrenia should be considered as two different diagnostic entities [102]. Also, the interpretation of differences between first-episode BD and MDD subjects may be complicated by the fact that, based on epidemiological studies, approximately 1–5 % of unipolar depressed subjects will develop a bipolar illness beyond one year after their initial identification [103, 104].

Main limitations

Findings must be interpreted in light of the following limitations. The present review allowed to identify a wider array of DTI abnormalities with BD versus UD, but this does not necessarily reflect the actual neurobiology of these disorders. To definitely disentangle this point, a meta-analysis is now required, including a search for unpublished negative findings, or using methods to evaluate whether there was a publication bias. Such a meta-analysis was judged not possible at the time of the review, due to limited and heterogeneous available data.

Also, the low number of studies, especially in UD, and the limited sample size of most studies did not allow the generalization of findings. In particular, studies may be underpowered to detect modest differences within samples. Furthermore, most studies were cross-sectional in nature and did not control for multiple comparisons. Prospective studies appear necessary to distinguish between those with trait markers of BD/UD and those at risk of conversion from MDD to BD. Indeed, follow-up studies have found that 20 to 40 % of adolescents with MDD develop BD within a period of 5 years after the onset of depression [105]. One of the most helpful future direction is to identify biomarkers underlying pathophysiological processes together with the development of symptom dimensions related to BD. Examination of the development of neural abnormalities occurring before the behavioral changes associated with BD, or other mood disorders, is crucial for clinicians.

Moreover, most of the patients included in these studies were under medication at the time of scanning, and this must be considered a confounding factor. Although lithium has been demonstrated to increase GM volume compared to placebo, MRI changes in the brain differ before and after lithium [106], and the effects of antipsychotics and mood stabilizers on WM integrity and GM volumes are still quite unclear [107]. Also, samples were often mixed, including both adolescents with varying mood states. The effects of both mood states and psychiatric comorbidities on VBM/DTI findings have been not adequately evaluated in most

studies. The presence of ADHD comorbidity in bipolar children may be interpreted as a potential confounding factor. ADHD symptoms are very frequent in samples of bipolar children—ranging to 80 % [38]; this high comorbidity induced some authors [108] to suggest that ADHD may represent a phenotypic manifestation of early-onset BD.

Also, psychosis occurs in 16 % of BD cases and is usually a marker of severity and poorer prognosis [105]; some studies analyzed bipolar subjects with psychotic features, so that the findings may not be generalized to BD as a whole.

Importantly, interpretation of WM abnormalities explored with DTI and anatomical measurement are not straightforward. Voxelwise analysis is subject to type I errors, whereas the spatial resolution of the studies using DTI acquisition may be excessively low.

As suggested by Frazier et al. [38], most DTI studies suffer from low sensitivity and could be quite sensitive only to FA differences in subsections of the most densely packed fibers.

The observation of lower FA measurement in specific brain areas could be erroneously interpreted as lower connectivity [42], leading to imprecise anatomical measurement of WM. Recent advancements in this field using meta-analytic and multimodal neuroimaging approaches should help to clarify how FA differences may reflect connectivity dysfunctions. Moreover, processing pipelines of DTI data are diverse and no clear consensus exists on how to handle DTI data.

Although ROI studies provide relevant information on regional differences, they should be similarly considered cautiously, especially in the identification of more global changes in the brain. Reliable tractography studies are also missing.

Considering that the main findings derived by the included studies are highly heterogeneous, it has not been possible to analyze some relevant issues (e.g., differences in the instruments/criteria used to diagnose BD in children; BD subtypes and bipolar polarity; duration of the illness; childhood versus adolescent onset; effects of psychoactive medications; eventual comorbidity; family history of BD; socio-demographic factors; sample size; different scans; methods to evaluate the used scans and statistics) that could have influenced the main results of the present review. All these issues may explain, at least partially, the large disparity and disorganization of the main results.

Finally, most of the correlations that were reported should be interpreted as exploratory (see Tables), since no correction for multiple comparisons has been performed or because post hoc behavioral analyses included only a subset of the entire samples. Future neuroimaging studies should be useful in elucidating pathophysiological processes underlying the differential development of BD from UD supporting to clarify the relationship between structural and functional neuroimaging findings. They will require large multicentric samples.

Implications and future directions

Overall, based on the limited studies available, more WM abnormalities have been reported in BD children/adolescents than in those with UD suggesting the possible existence of vulnerability markers for BD. More studies about WM abnormalities in youths with UD are necessary.

Future longitudinal studies should: (1) directly compare groups of children with UD and BD; (2) use multimodal imaging for cross-validation of the results and easier interpretation; and (3) combine follow-up imaging assessments to investigate whether neurodevelopmental changes may be considered specifically related to diagnostic categories. In addition, future studies should focus on dimensional approaches able to redefine "bipolarity" in terms of underlying pathophysiological processes in genetically and symptomatically at risk subjects. These studies should also be conducted using more reliable neuroimaging techniques such as tractography to provide biomarkers as well as biological targets for more selective personalized treatments. Longitudinal follow-up studies should also allow identifying differential developmental trajectories between bipolar and unipolar subjects. Finally, the combination of different neuroimaging techniques and the development of novel algorithms based on machine learning, a branch of artificial intelligence, should warrant a more detailed understanding of neural circuitry abnormalities underlying major affective disorders [109].

Conflict of interest None.

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