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ORIGINAL ARTICLE

Prevalence of white matter hyperintensities is not elevated in a large sample of adolescents and young adults with bipolar disorder

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Objective: The increased prevalence rate of white matter hyperintensities is one of the most consistently reported brain abnormalities in adults with bipolar disorder. However, findings in children and adolescents with bipolar disorder are less consistent. Prior studies have been constrained by small sample sizes and/or poor age- and sex-matching of healthy controls. We examined this topic in the largest sample of adolescents with bipolar disorder to date.
Methods: T_2-weighted 3-Tesla magnetic resonance imaging data were acquired for 83 adolescents with bipolar disorder diagnosed via the Kiddie Schedule for Affective Disorders and the Schizophrenia, Present and Lifetime version semi-structured interview and 64 age- and sex-matched healthy controls. All acquired scans were examined by neuroradiologists and the presence or absence of white matter hyperintensities was determined for each participant.
Results: The prevalence of white matter hyperintensities did not differ between adolescents with bipolar disorder (13.3%) and controls (21.9%; $\chi^2 = 1.90$; $p = 0.168$).
Conclusion: In contrast to the study hypothesis, the prevalence of white matter hyperintensities was not higher in adolescents with bipolar disorder than controls. The large sample size and good matching for age and sex bolster the reliability of this negative finding. Future studies are warranted to evaluate the prevalence, incidence, and predictors of white matter hyperintensities in early-onset bipolar disorder prospectively.

Keywords: Adolescents; bipolar disorder; MRI; white matter hyperintensities

Introduction

White matter hyperintensities (WMHs) are localized foci of increased water content in the white matter of the brain that appear as bright white areas in T_2-weighted magnetic resonance imaging (MRI).[1] Depending on their localization, the lesions are classified as deep WMHs (DWMHs) or periventricular hyperintensities (PVHs). The prevalence of WMHs increases with age[2] or in the context of a number of diseases, including bipolar disorder (BD).[3]

Several studies have compared WMHs in adults with BD and healthy controls (HC).[4-11] While most studies on this topic have reported increased WMH prevalence in BD,[4-9] some studies have reported equivalent rates in BD and HC.[10-12] The reported WMH prevalence rates vary widely across studies, ranging from 18-100% in people with BD.[3] This heterogeneity is likely related in part to methodological differences regarding MRI parameters (e.g., slice thickness, magnet strength) and WMH rating systems.[4] Overall, WMHs are considered one of the most consistently reported abnormalities in BD, with a meta-analysis of 21 studies yielding an odds ratio (OR) of 2.5 (95% confidence interval [95%CI] 1.9-3.3) for WMHs in patients with BD (n=573) compared to HCs (n=850).[3]

The finding of elevated WMH prevalence rates is not exclusive to BD and has been observed in different conditions relevant to BD as well. Cardiovascular and metabolic disorders, migraine, as well as developmental disorders, which are frequently comorbid with BD, have also been associated with elevated rates of WMHs.[13] Among adults with BD, WMHs have been associated with cardiovascular and cerebrovascular disorders.[14] Relatedly, previous findings from our group showed that cardiovascular risk factors are significantly more strongly associated with brain structure and function in adolescents with BD than HCs.[15-17] Indeed, there is substantial

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genetic overlap between cardiovascular risk and WMH.[18] This clustering of medical comorbidities, particular those of a cardiovascular nature, likely contribute in part to the prevalence of WMHs in BD.[13]

Compared to the number of studies evaluating WMH prevalence in BD, far fewer have examined WMH correlates. Among individuals with BD, WMH correlates include BD-I subtype, psychiatric hospitalization, poorer neurocognitive function, and more hypomanic and depressive episodes (among males).[5,8] Additionally, some studies have reported on correlates of WMHs according to localization. DWMHs, but not PVHs, have been linked with treatment-refractory BD.[19,20] PVHs, on the other hand, have been repeatedly associated with a higher risk for suicide-related behavior,[21,22] as well as lower insight/illness awareness during mania.[23]

Contrasting these relatively substantial findings in adults with BD, the literature regarding WMHs in children and adolescents with BD is sparse. Studies on WMHs in children and adolescents or young adults with BD are summarized in Table 1.[24-29] The results of studies on WMHs in pediatric BD are highly conflicting: two studies reported that the WMH prevalence was significantly higher among patients with BD than HCs.[24,25] Three others reported statistically equivalent WMH rates between BD and HCs,[27-29] and one recent study found elevated DWMH but not PVH rates for young adults with BD.[26] Furthermore, it should be noted that due to small sample sizes and/or poor age- and sex-matching of HCs, the results of these prior studies should be interpreted with caution. Nevertheless, a meta-analysis of four of these studies[24,25,27,28] yielded an OR of 5.7 (95%CI 2.3-13.7) for children or adolescents with BD (n=99) vs. HCs (n=124), exceeding the OR of 2.2 in studies on adults only.[3]

In contrast to adult studies, no prior studies have specifically focused on the correlates of WMHs in children and adolescents with BD. One study examined the association between WMHs and suicidality in children and adolescents with psychiatric disorders (n=153).[32] Among study participants with depression, PVHs were associated with a markedly higher prevalence of suicide attempts, with an OR of 18.6 (95%CI 2.4-145.8).[32]

We set out to extend the knowledge base on the topic of WMHs in a large, well-characterized sample of adolescents with BD compared to adolescent HCs. We hypothesized that the prevalence of WMHs would be significantly greater among adolescents with BD. Based on the link between cardiovascular disorders, BD, and WMH[14] and the association of cardiovascular risk factors with brain structure and function in adolescent BD,[15-17] we further hypothesized that WMHs would be significantly associated with body mass index (BMI) and blood pressure in the BD group but not the HC group.

Methods

Sample

The current study included a sample of 147 participants (83 BD, 64 HC) between the ages of 13 and 21 years (mean [M] = 17.39, standard deviation [SD] = 1.73).

Table 1 Studies on children, adolescents, and young adults with BD

Study	BD		HC		Prevalence of WMH			MRI parameters	
	n	Mean age ± SD	n	Mean age ± SD	Location	BD n (%)	HC n (%)	Statistics χ^2, p-value	Magnet strength (T)	Rating system
Botteron[27]	8	11.3±3.1	5	11.8±2.9	DWMH	2 (25)	0 (0)	3.80, 0.28	1.5	Fazekas' visual rating scale,[30] quantitative volume measurement
Lyoo[24]	56	13.6±2.1	83	9.9±3.3	WMH	10 (18)	1 (1)	7.22, 0.007	1.5	Coffey's visual rating scale, modified[31]
Pillai[25]	15	15.0±2.4	16	16.0±1.8	WMH	10 (67)	5 (31)	3.89, 0.03	1.5	Four-point ordinal scale for severity
Chang[28]	20	14.6±2.8	20	14.1±2.8	DWMH	12 (63)	10 (50)	0.40, 0.53	3.0	Coffey's visual rating scale,[31]
					PVH	4 (20)	5 (25)	0.14, 0.71		scale for overall WMH-presence
Gunde[29]	35	21.5±4.1	49	21.5±3.5	WMH	6 (17)	11 (22)	0.44, 0.80	1.5	Fazekas' visual rating scale, modified[30]

BD = bipolar disorder; DWMH = deep white matter hyperintensities; HC = healthy controls; MRI = magnetic resonance imaging; PVH = periventricular hyperintensities; SD = standard deviation; T = Tesla; WMH = white matter hyperintensities.

Procedure

The Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL),[33] a semi-structured interview, was used to determine current and lifetime psychiatric diagnoses in interviews with both the adolescents and their parent/s. In addition, the K-SADS Depression Rating Scale[34] and the K-SADS Mania Rating Scale[35] were used to determine the presence and severity of manic and depressive symptoms. All interviews were conducted by interviewers with a bachelor's or master's degree in health science, and the diagnoses were confirmed during consensus meetings with a licensed child-adolescent psychiatrist. The Children's Global Assessment Scale[36] was administered to evaluate the participants' general level of functioning. For both the BD and the HC groups, the exclusion criteria were current cardiac conditions, autoimmune or inflammatory illness, infectious illness in the past 14 days, taking anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, or hypoglycemic agents, neurological impairment, an intelligence quotient below 80, autism, and any MRI contradictions. Additionally, HCs had to have no personal or family history of affective or psychotic disorders, no anxiety disorder, and no drug or alcohol dependence in the past 3 months.

Height, weight, waist circumference, and blood pressure were measured in accordance with standard procedures.[37] BMI was computed by dividing weight in kilograms (kg) by the square of height in meters (m^2), as previously described.[15]

MRI and WMH measurement

Brain MRIs were performed on all participants using a 3T magnet strength scanner. Fluid-attenuated inversion-recovery images were acquired using standard T2-weighted imaging with the following parameters: TE = 125 ms, TI = 2,800 ms, TR = 9,000 ms, flip angle = 90.1 $\times$ 1.1 $\times$ 3 mm^3 voxel, FOV (cm) 24, 50 axial slices, matrix size = 240 $\times$ 217, acquisition time = 5'30''. Anatomical images were acquired using standard T1-weighted imaging with the following parameters: TE = 3.29 ms, TI = 900 ms, TR = 2,200 ms, flip angle = 9, isotropic 1 mm^3 voxel, 192 axial slices, matrix size = 256 $\times$ 192, acquisition time = 7'02''.

To rate WMHs, none of the rating systems described in Table 1 were used. Instead, all MRI scans were examined by neuroradiologists who, blind to the participants' diagnoses, flagged and described all brain abnormalities in written reports. Three independent raters reviewed each of the reports and rated the presence or absence of WMHs for each participant based on the neuroradiologists' description of WMHs. There were no discrepancies between the raters.

Analyses

Statistical analysis was performed in SPSS version 25, with a significance level of $\alpha = 0.05$. Analyses assessed differences between the BD and HC groups, as well as differences between participants with and without WMHs. Chi-square tests were used to examine categorical variables and independent sample *t*-tests were used for continuous variables.

Ethics statement

Adolescents with BD were recruited from a subspecialty clinic in a tertiary academic health science center and healthy adolescents were recruited through community advertisements. Prior to participating, written informed consent was provided by all participants, as well as a parent/guardian. Approval by the local research ethics board was obtained.

Results

Demographic variables, WMH prevalence rates, and clinical characteristics for adolescents with BD and HCs are presented in Table 2. There were no significant differences between the BD and HC groups regarding age, sex, race, socioeconomic status (SES), or living with both natural parents. There were no between-group differences in the prevalence rate of WMHs (BD = 13.3%, HC = 21.9%; $\chi^2 = 1.90$, p-value = 0.168). Adolescents with BD and HC differed significantly on a number of clinical variables, such as suicide attempts and ideation, non-suicidal self-injurious behavior, comorbidities, family history, as well as current and lifetime medication (Table 2). Regarding physiological characteristics, the BD group had a significantly higher BMI (24.25 $\pm$ 4.49 vs. 21.72 $\pm$ 3.07, Mann-Whitney $U = 1{,}752$, $p < 0.001$).

In the BD group, diastolic blood pressure was significantly higher among those with WMHs (M = 71.64, SD = 4.27) than among those without WMHs (M = 66.85, SD = 6.70; F = -2.29, p = 0.02), whereas there was no difference in BMI (M = 21.88, SD = 2.87 and M = 24.61, SD = 4.60, respectively; F = 1.91, p = 0.06) or systolic blood pressure (M = 109.23, SD = 11.06 and M = 107.55, SD = 11.05, respectively; F = -0.47, p = 0.64). HCs with and without WMHs did not differ regarding BMI (M = 21.88, SD = 3.57 and M = 21.68, SD = 2.95, respectively; F = -0.22, p = 0.83), systolic blood pressure (M = 105.11, SD = 7.99 and M = 107.89, SD = 14.78, respectively; F = 0.93, p = 0.36), or diastolic blood pressure (M = 65.79, SD = 7.39 and M = 67.28, SD = 7.39, respectively; F = 0.67, p = 0.51). There was a significant interaction whereby the presence of WMHs was associated with significantly higher diastolic blood pressure in the BD group than the HC group ($\beta = 0.15$, standard error = 0.069, p = 0.04).

Discussion

This study found that the prevalence of WMHs did not differ significantly between adolescents with BD and HCs, although there were more WMHs in the HC group than the BD group. While the explanation for this unexpected finding is unclear, the pattern is not attributed to excess medical comorbidities, since common medical comorbidities were exclusion criteria for the HC group.

Table 2 Demographic variables, WMH and clinical characteristics among adolescents with BD and HC

	HC (n=64)	BD (n=83)	Statistic	Eta squared/Cramer's V
Demographics				
Age, years (±SD)	17.36±1.74	17.70±1.61	F = 0.67, p = 0.22	0.01
Female	37 (57.8)	51 (61.4)	χ^2 = 0.20, p = 0.66	0.037
Race, Caucasian	43 (67.2)	61 (74.4)	χ^2 = 0.66, p = 0.42	0.068
SES (mean rank)	4.44±0.871	4.23±0.979	F = 1.82, p = 0.18	0.007
Living with both natural parents	41 (66.1)	50 (61.0)	χ^2 = 0.40, p = 0.53	0.053
WMH				
WMH prevalence	14 (21.9)	11 (13.3)	χ^2 = 1.90, p = 0.17	0.114
Clinical characteristics				
Age of onset (±SD)	-	14.88±2.64	-	-
Duration of BD (±SD)	-	2.89±2.38	-	-
Lifetime SA	-	13 (16.0)	-	-
Lifetime SIB	-	38 (46.0)	-	-
Lifetime SI	2 (3)	47 (57.0)	χ^2 = 26.84, p < 0.001	0.479
Current mood state				
Depressed	-	22 (27.0)	-	-
Hypomanic/manic	-	6 (7.0)	-	-
Mixed	-	20 (24.0)	-	-
Euthymic	-	35 (42.0)	-	-
Lifetime comorbidities				
ADHD	8 (13.0)	38 (46.0)	χ^2 = 18.62, p < 0.001	0.358
ODD	-	23 (28.0)	-	-
CD	-	4 (5.0)	-	-
Any anxiety	5 (8.0)	63 (76.0)	χ^2 = 69.36, p < 0.001	0.694
SUD	-	20 (24.0)	-	-
Family history				
Hypomania/mania	-	22 (27.0)	-	-
Depression	12 (19.0)	58 (70.0)	χ^2 = 37.87, p < 0.001	0.508
Anxiety	12 (19.0)	43 (52.0)	χ^2 = 16.86, p < 0.001	0.339
ADHD	4 (6.0)	23 (28.0)	χ^2 = 11.10, p < 0.001	0.275
Current medication				
SGA	-	48 (58.0)	-	-
Lithium	-	18 (22.0)	-	-
SSRI	1 (2.0)	10 (12.0)	χ^2 = 5.74, p = 0.017	0.198
Non-SSRI antidepressants	-	4 (5.0)	-	-
Stimulants	3 (5.0)	8 (10.0)	χ^2 = 1.279, p = 0.258	0.093
Any medication	4 (6.0)	64 (77.0)	χ^2 = 72.98, p < 0.001	0.705
Lifetime medication				
SGA	-	53 (64.0)	-	-
Lithium	-	19 (23.0)	-	-
SSRI	2 (3.0)	26 (31.0)	χ^2 = 20.28, p < 0.001	0.378
Non-SSRI antidepressants	-	10 (12.0)	-	-
Stimulants	4 (6.0)	21 (25.0)	χ^2 = 10.36, p < 0.001	0.270
Physiological characteristics				
BMI (adjusted)	21.72±3.07	24.25±4.49	U = 1,752, p < 0.001	0.66
Resting systolic blood pressure	107.28±13.58	107.77±11.00	F = 0.24, p = 0.81	0.04
Resting diastolic blood pressure	66.95±7.36	67.48±6.61	U = 2,442, p = 0.65	0.08

Data presented as n (%), unless otherwise specified.
ADHD = attention deficit hyperactivity disorder; BD = bipolar disorder; BMI = body mass index; CD = conduct disorder; HC = healthy controls; ODD = oppositional defiant disorder; SA = suicide attempts; SD = standard deviation; SES = socioeconomical status; SGA = second-generation antipsychotics; SI = suicide ideation; SIB = self-injurious behavior; SSRI = selective serotonin reuptake inhibitor; SUD = substance use disorder; WMH = white matter hyperintensities.

Higher diastolic blood pressure was associated with WMHs among adolescents with BD, but not among HCs. While neither temporality nor causality can be inferred from this cross-sectional study, this finding aligns with our prior findings that cardiovascular risk factors are more strongly associated with brain structure and function in adolescents with BD than in HC.[15-17]

To our knowledge, this sample of 83 adolescents with BD is the largest investigation of WMH prevalence in pediatric BD to date. With our total sample of 147 participants, we were powered to detect a small effect size (Cohen's $d \geqslant 0.23$).

The low prevalence rates of WMHs in our sample is comparable to the majority of other studies investigating

the prevalence of WMHs in children, adolescents, and young adults with BD (Table 1). However, our finding that there was no significant difference in WMH prevalence rates between adolescents with BD and HCs conflicts with studies which found that adolescents with BD have a higher prevalence of WMHs[23-25] than HCs. Demographic differences between the studies' samples might have contributed to these conflicting findings regarding WMH prevalence rates. WMHs have been associated with age[2] and female sex[27] for both the general population and BD patients. In studies that found significantly higher WMH rates among children with BD, the control group had a higher average age and/or a higher percentage of females than males.[23-25] While age and/or sex were included as covariates in these studies, this approach may not have fully mitigated confounding.

So far, there is little consensus regarding the best method to determine the presence and severity of WMH. The majority of studies on the occurrence of WMH in children, adolescents and young adults with BD (Table 1) have used (modified) versions of either Fazekas' visual rating scale[26,27,29,30] or Coffey's visual rating scale,[24,28,31] which is based on Fazekas. However, since the Fazekas scale[37] was originally designed to rate the presence and severity of WMH in geriatric samples with Alzheimer's disease and WMHs are known to be much more prevalent and severe among aging individuals,[2] it is not well suited to young populations with limited variability in WMH severity/extent. Consequently, the vast majority of WMHs reported in studies on pediatric BD only met criteria for the lowest severity rating, and the gradings where either collapsed into only two grades of severity[24,27,28] or into present and absent.[25,26,29] Thus, it is unlikely that the discrepancy between prior[24-29] and current findings can be explained by the use of a WMH rating system or just the presence/absence or WMHs.

Both WMHs[38] and BD[39] have been associated with an increased risk for cardiovascular disease, and cardiovascular disorders have been found to be more prevalent in BD patients with DWMHs than in BD patients without them.[14] Relatedly, our group has previously reported reduced cardiovascular reactivity[40] and an unchanged rate of global oxygen metabolism in adolescents with BD, despite an increase in global cerebral blood flow.[41] Taking the results of prior studies and these related anomalies in cerebrovascular physiology together, we expected to find higher rates of WMHs among adolescents. Additionally, we expected that vascular risk factors, specifically blood pressure and BMI, would be significantly associated with WMHs among adolescents with BD but not among HCs. Based on the aforementioned anomalies in neurovascular physiology, we speculate that, despite the absence of between-group differences in adolescence, neurovascular dysfunction in adolescence may predate WMH and explain the excess rates of WMHs among adults with BD. Future prospective studies are warranted to test this hypothesis. The current study provides preliminary evidence that cardiovascular risk factors are more strongly associated with WMHs among adolescents with BD than HCs.

The findings of the present study should be viewed in light of several limitations. Given that our sample of adolescents with BD was recruited from a tertiary clinical setting, generalizability to the general population, as well as to community samples and other settings, may be limited. In this context, it should also be taken into account that illness severity might impact the prevalence of WMH. However, given that the majority of previous studies on WMHs in youth with BD were also based on outpatient samples,[25-29] comparability between studies should not be limited in this regard. Further, based on the low prevalence rates of WMHs, they were rated as present or absent for each participant. Consequently, differences in the location or severity of the lesions were not taken into account.

In conclusion, based on the large sample and good matching for demographics, the current study provides reliable evidence that the prevalence of WMHs is not higher among adolescents with BD. To understand the biological underpinnings of excess WMHs in adults with BD, future research is warranted to further investigate the relationship of traditional and novel cardiovascular risk factors with WMHs, ideally integrating prospective designs and neurovascular imaging approaches.

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Disclosure

The authors report no conflicts of interest.

References

1 Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Assoc. 2015;4:001140.
2 Hopkins RO, Beck CJ, Burnett DL, Weaver LK, Victoroff J, Bigler ED. Prevalence of white matter hyperintensities in a young healthy population. J Neuroimaging. 2006;16:243-51.
3 Beyer JL, Young R, Kuchibhatla M, Krishnan KR. Hyperintense MRI lesions in bipolar disorder: a meta-analysis and review. Int Rev Psychiatry. 2009;21:394-409.
4 Ahn KH, Lyoo IK, Lee HK, Song IC, Oh JS, Hwang J, et al. White matter hyperintensities in subjects with bipolar disorder. Psychiatry Clin Neurosci. 2004;58:516-21.
5 Dupont RM, Jernigan TL, Butters N, Delis D, Hesselink JR, Heidel W, et al. Subcortical abnormalities detected in bipolar affective disorder

using magnetic resonance imaging. Clinical and neuropsychological significance. Arch Gen Psychiatry. 1990;47:55-9.
6 Gulseren S, Gurcan M, Gulseren L, Gelal F, Erol A. T2 hyperintensities in bipolar patients and their healthy siblings. Arch Med Res. 2006;37:79-85.
7 Kieseppä T, Mäntylä R, Tuulio-Henriksson A, Luoma K, Mantere O, Ketokivi M, et al. White matter hyperintensities and cognitive performance in adult patients with bipolar I, bipolar II, and major depressive disorders. Eur Psychiatry. 2014;29:226-32.
8 Birner A, Seiler S, Lackner N, Bengesser SA, Queissnere R, Fellendorf FT, et al. Cerebral white matter lesions and affective episodes correlate in male individuals with bipolar disorder. PLoS One. 2015;10:e0135313.
9 Silverstone T, McPherson H, Li Q, Doyle T. Deep white matter hyperintensities in patients with bipolar depression, unipolar depression and age-matched control subjects. Bipolar Disord. 2003;5:53-7.
10 Breeze JL, Hesdorffer DC, Hong X, Frazier JA, Renshaw PF. Clinical significance of brain white matter hyperintensities in young adults with psychiatric illness. Harv Rev Psychiatry. 2003;11:269-83.
11 Macritchie KA, Lloyd AJ, Bastin ME, Vasudev K, Gallagher P, Eyre R, et al. White matter microstructural abnormalities in euthymic bipolar disorder. Br J Psychiatry. 2010;196:52-8.
12 Sassi RB, Brambilla P, Nicoletti M, Mallinger AG, Frank E, Kupfer DJ, et al. White matter hyperintensities in bipolar and unipolar patients with relatively mild-to-moderate illness severity. J Affect Disord. 2003;77:237-45.
13 Gunde E, Blagdon R, Hajek T. White matter hyperintensities: from medical comorbidities to bipolar disorders and back. Ann Med. 2011;43:571-80.
14 Deicken RF, Reus VI, Manfredi L, Wolkowitz OM. MRI deep white matter hyperintensity in a psychiatric population. Biol Psychiatry. 1991;29:918-22.
15 Islam AH, Metcalfe AW, Macintosh BJ, Korczak DJ, Goldstein BI. Greater body mass index is associated with reduced frontal cortical volumes among adolescents with bipolar disorder. J Psychiatry Neurosci. 2018;43:120-30.
16 Naiberg MR, Newton DF, Collins JE, Bowie CR, Goldstein BI. Impulsivity is associated with blood pressure and waist circumference among adolescents with bipolar disorder. J Psychiatr Res. 2016;83:230-9.
17 Naiberg MR, Newton DF, Collins JE, Dickstein DP, Bowie CR, Goldstein BI. Elevated triglycerides are associated with decreased executive function among adolescents with bipolar disorder. Acta Psychiatr Scand. 2016;134:241-8.
18 Ten Kate M, Sudre CH, den Braber A, Konijnenberg E, Nivard MG, Cardoso MJ, et al. White matter hyperintensities and vascular risk factors in monozygotic twins. Neurobiol Aging. 2018;66:40-8.
19 Moore PB, Shepherd DJ, Eccleston D, Macmillan IC, Goswami U, Mcallister VL, et al. Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. Br J Psychiatry. 2001;178:172-6.
20 Regenold WT, Hisley KC, Phatak P, Marano CM, Obuchowski A, Lefkowitz DM, et al. Relationship of cerebrospinal fluid glucose metabolites to MRI deep white matter hyperintensities and treatment resistance in bipolar disorder patients. Bipolar Disord. 2008;10:753-64.
21 Pompili M, Ehrlich S, De Pisa E, Mann JJ, Innamorati M, Cittadini A, et al. White matter hyperintensities and their associations with suicidality in patients with major affective disorders. Eur Arch Psychiatry Clin Neurosci. 2007;257:494-9.
22 Pompili M, Innamorati M, Mann JJ, Oquendo MA, Lester D, Del Casale A, et al. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1501-7.
23 Serafini G, Pompili M, Innamorati M, Girardi N, Strusi L, Amore M, et al. The impact of periventricular white matter lesions in patients with bipolar disorder type I. CNS Spectr. 2013;21:23-34.
24 Lyoo K, Lee HK, Jung JH, Noam GG, Renshaw PF. White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. Compr Psychiatry. 2002;43:361-8.
25 Pillai JJ, Friedman L, Stuve TA, Trinidad S, Jesberger JA, Lewin JS, et al. Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. Psychiatry Res. 2002;114:51-6.
26 Wadhwa R, Wen W, Frankland A, Leung V, Sinbandhit C, Stuart A, et al. White matter hyperintensities in young individuals with bipolar disorder or at high genetic risk. J Affect Disord. 2019;245:228-36.
27 Botteron KN, Vannier MW, Geller B, Todd RD, Lee BC. Preliminary study of magnetic resonance imaging characteristics in 8- to 16-year-olds with mania. J Am Acad Child Adoleesc Psychiatry. 1995;34:742-9.
28 Chang K, Barnea-Goraly N, Karchemskiy A, Simeonova DI, Barnes P, Ketter T, et al. Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. Biol Psychiatry. 2005;58:197-203.
29 Gunde E, Novak T, Kopecek M, Schmidt M, Propper L, Stopkova P, et al. White matter hyperintensities in affected and unaffected late teenage and early adulthood offspring of bipolar parents: a two-center high-risk study. J Psychiatr Res. 2011;45:76-82.
30 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149:351-6.
31 Coffey CE, Figiel GS, Djang WT, Weiner RD. Subcortical hyperintensity on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. Am J Psychiatry. 1990;147:187-9.
32 Ehrlich S, Noam GG, Lyoo IK, Kwon BJ, Clark MA, Renshaw PF. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. J Am Acad Child Adolesc Psychiatry. 2004;43:770-6.
33 Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-8.
34 Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, et al. The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. Arch Gen Psychiatry. 1985;42:696-702.
35 Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, et al. A preliminary study of the kiddie schedule for affective disorders and schizophrenia for school-age children mania rating scale for children and adolescents. J Child Adolesc Psychopharmacol. 2003;13:463-70.
36 Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry. 1983;40:1228-31.
37 Krebs NF, Himes JH, Jacobson D, Nicklas TA, Guilday P, Styne D. Assessment of child and adolescent overweight and obesity. Pediatrics. 2007;120 Suppl 4:S193-228.
38 Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham study. Stroke. 2004;35:1857-61.
39 Goldstein BI. Bipolar disorder and the vascular system: mechanisms and new prevention opportunities. Can J Cardiol. 2017;33:1565-76.
40 Urback AL, Metcalfe AW, Korczak DJ, MacIntosh BJ, Goldstein BI. Reduced cerebrovascular reactivity among adolescents with bipolar disorder. Bipolar Disord. 2019;21:124-31.
41 Karthikeyan S, Fiksenbaum L, Grigorian A, Lu H, MacIntosh BJ, Goldstein BI. Normal cerebral oxygen consumption despite elevated cerebral blood flow in adolescents with bipolar disorder: putative neuroimaging evidence of anomalous energy metabolism. Front Psychiatry. 2019;10:739.