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Cerebral White Matter Lesions and Affective Episodes Correlate in Male Individuals with Bipolar Disorder

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Abstract

Background

Cerebral white matter lesions (WML) have been found in normal aging, vascular disease and several neuropsychiatric conditions. Correlations of WML with clinical parameters in BD have been described, but not with the number of affective episodes, illness duration, age of onset and Body Mass Index in a well characterized group of euthymic bipolar adults. Herein, we aimed to evaluate the associations between bipolar course of illness parameters and WML measured with volumetric analysis.

Methods

In a cross-sectional study 100 euthymic individuals with BD as well as 54 healthy controls (HC) were enrolled to undergo brain magnetic resonance imaging using 3T including a FLAIR sequence for volumetric assessment of WML-load using FSL-software. Additionally, clinical characteristics and psychometric measures including Structured Clinical Interview according to DSM-IV, Hamilton-Depression, Young Mania Rating Scale and Beck's Depression Inventory were evaluated.

Results

Individuals with BD had significantly more ($F = 3.968$, $p < .05$) WML (Mdn = 3710mm3; IQR = 2961mm3) than HC (Mdn = 2185mm3; IQR = 1665mm3). BD men (Mdn = 4095mm3; IQR = 3295mm3) and BD women (Mdn = 3032mm3; IQR = 2816mm3) did not significantly differ as to the WML-load or the number and type of risk factors for WML. However, in men

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only, the number of manic/hypomanic episodes ($r = 0.72$; $p < .001$) as well as depressive episodes ($r = 0.51$; $p < .001$) correlated positively with WML-load.

Conclusions

WML-load strongly correlated with the number of manic episodes in male BD patients, suggesting that men might be more vulnerable to mania in the context of cerebral white matter changes.

Introduction

The neurobiological basis of bipolar disorder (BD) is not sufficiently characterized. Structural brain abnormalities in BD are reported as a common feature in neuroimaging studies. For example, white matter lesions (WML, also termed white matter hyperintensities) are hyperintense bright spots that are detectable at T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences on Magnetic Resonance Imaging (MRI) of the brain and are one of the most consistently reported brain abnormalities in individuals with BD [1, 2]. White matter lesions have conventionally been classified by location into those that occur in the periventricular or deep white matter [3]. Individuals with BD are approximately 2.5 times more likely to have WML compared to controls, with deep WML differentially represented [1, 2].

White matter lesions are not specific to BD, as they are also found in normal aging and are more common in individuals with cardio- and cerebrovascular disease as well as in various neuropsychiatric conditions (e.g. as unipolar depression, schizophrenia, panic disorder, substance abuse/dependency, migraine and some forms of dementia) [4–12]. Two studies reported associations between WML and alcohol dependency [13, 14], while a separate study which investigated WML and alcohol intake controlling for potential confounders did not show any associations [15].

There are several possible non-mutually exclusive causes of WML, including ischemia, demyelination, edema, and gliosis. Early confluent and confluent WML have been shown to more typically represent ischemic tissue damage [3] and progress over time [16]. In otherwise healthy adults, the presence of WML is generally associated with age and cardiovascular risk factors such as hypertension or smoking [17, 18]

Adults with BD are at increased risk of cardiovascular disease and hypertension compared to non-BD adults [19]. Additionally, smoking behavior and obesity/metabolic syndrome differentially affect individuals with BD [20, 21]. Moreover, replicated evidence implicates that the occurrence of obesity and/or the metabolic syndrome is associated with a more complex BD illness presentation and course [21–26], worse cognitive function [27] and increased rate of cerebro- and cardiovascular disease in BD [21]. Available evidence suggests that cognitive dysfunction in BD may be related to WML in some circumstances [28].

White matter lesions are also predictors for depressive symptoms [17]. Confluent severe deep WML may transform into true infarcts [18]. Infarcts are in approximately 80% of ischemic origin [29] and are capable of triggering depression and in rare cases also mania. A further line of evidence is the observation that up to thirty percent of individuals with post-stroke mania might also develop BD [30–32].

Several associations between clinical characteristics and WML in BD have been described in the literature. Positive correlations with the number of hospitalizations and suicide attempts,

and poor illness outcome as well as poorer treatment response, decreased performance on neuropsychological tests and impaired insight have been reported [7, 33–38].

Investigations of WML in BD have relied on a categorical method of lesion description reporting the presence or absence of white matter lesions and grading this presence on scales of differing reliabilities and measurement characteristics [39–41].

Although volumetric analysis is common within the field of structural neuroimaging, this approach has rarely been applied for rating WML in BD [38, 42, 43].

The foregoing collection of observations provided the impetus for exploring the following hypotheses in euthymic adults with BD: (I) BD individuals exhibit a higher WML-load than healthy controls. And, (II) there are associations between clinical characteristics and WML-load in BD. A particular emphasis was given on concurrent obesity / metabolic syndrome and the moderational influence of sex.

Methods and Materials

The study was conducted at the Medical University of Graz, Department of Psychiatry. All patients took part in the ongoing single center BIPFAT study, that assesses demographic parameters, complete actual and lifetime psychiatric history using the Structured Clinical Interview according to DSM-IV (SCID I), the psychiatric rating scales Hamilton-Depression (HAM-D) [44], Young Mania Rating Scale (YMRS) [45] and Beck's Depression Inventory (BDI) [46], history of medication, anthropometric measure, blood pressure, fasting blood, cognitive testing, EEG, stool sample, different lifestyle questionnaires and magnetic resonance imaging (MRI) of the brain. All patients included were former in- or outpatients of the Medical University of Graz and had a diagnosis of BD I or BD II according to the DSM-IV criteria. Patients needed to be in the state of euthymia (HAM-D score <11 and YMRS <9) and had given written informed consent prior to participating in the study.

Exclusion criteria were the presence of chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, neurodegenerative and neuroinflammatory disorders (i.e. Alzheimer's, Huntington's and Parkinson's disorder, multiple sclerosis), hemodialysis and interferon-α-based immunotherapy. Further exclusion criteria for controls were the presence of lifetime psychiatric diagnoses (verified by SCID I) and first and second grade relationship to relatives with psychiatric disorders. For further information about the study design and preliminary results see our previous reports [47–49]

One hundred BD patients (52 male, 48 female) and 54 healthy controls (HC, 23 male, 31 female) have been included in this study.

Ethics statement

The study has been approved by the local ethics committee (Medical University of Graz, Austria) in compliance with the current revision of the Declaration of Helsinki, ICG guideline for Good Clinical Practice and current regulations (EK-number: 24–123 ex 11/12).

Magnetic resonance imaging

MRI was performed on a 3T whole body scanner (TimTrio; Siemens Healthcare, Erlangen, Germany).

The protocol included an axial FLAIR sequence (TR = 10000ms, TE = 69ms, inversion time = 2500ms, number of slices = 40, slice thickness = 3mm, in-plane resolution = 0.86x0.86 mm^2) and a high resolution T1 weighted 3D sequence with magnetization prepared rapid gradient echo (MPRAGE) and whole brain coverage (TR = 1900ms, TE = 2.19ms, inversion time = 900ms, flip angle = 9°, isotropic resolution of 1 mm).

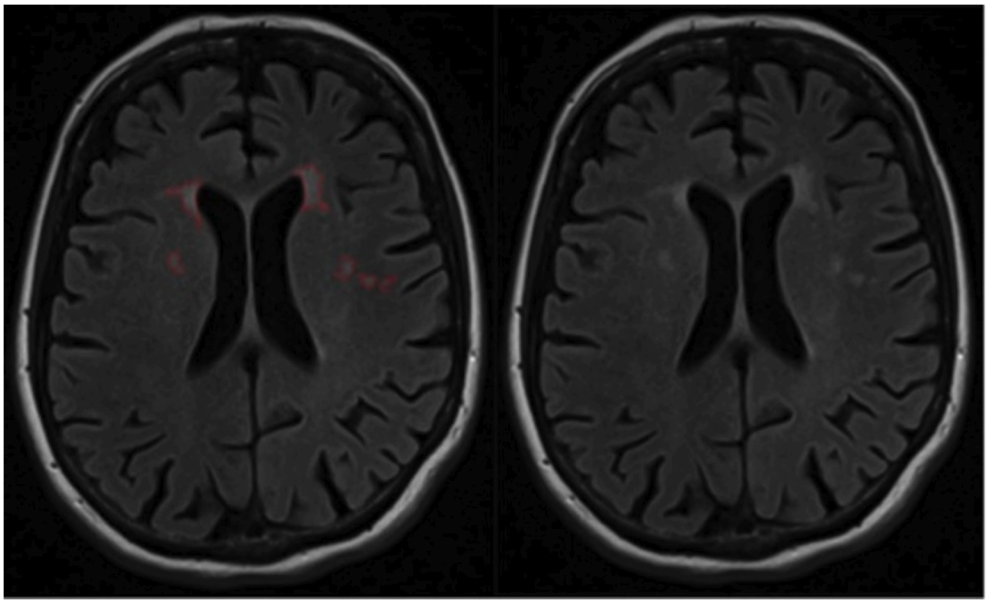

Fig 1. Representative FLAIR slice of one patient. The left image shows an example of lesion areas, outlined semiautomatically by the instructed rater using a custom written IDL program (Exelis Visual Information Solutions, USA). The right image shows the native FLAIR scan.

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Supra- and infratentorially located lesions of high signal intensity on FLAIR images were considered as WML. Silent non-lacunar infarcts and lacunes were excluded from the analysis. Non-lacunar infarcts were lesions with typical signal characteristics of infarcts following a typical vascular territory or being located in a border zone between two vascular territories. Lacunes were focal lesions involving the basal ganglia, the internal capsule, the thalamus, the brainstem or the white matter not exceeding a maximum diameter of 20 mm [50, 51].

WML were outlined on a computer using a custom written IDL program (Exelis Visual Information Solutions, USA; see Fig 1). Lesion areas were segmented by combined region growing and local thresholding following manual selection by a single instructed rater [52]. To counteract potential inter-rater variability, 15 cases from the study cohort were randomly chosen and re-rated by the instructor, a neurologist who is highly experienced in identification, volumetry and rating of WML. The neurologist was blinded to previous results and outlined WML on FLAIR scans of the 15 cases using the same procedure as the main rater. WML volumes of both raters were entered into SPSS. Subsequent intraclass correlation analysis yielded an intraclass correlation coefficient (ICC (2, 1)) of 0.938 (95%CI 0.570–0.984; $p < .001$). An ICC of 0.938 indicates high agreement and supports the reliability of WML volumetry between the two raters. Lesion volume in mm3 was calculated using the program FSLMATHS (FSL, Oxford, www.fmrib.ox.ac.uk) by multiplying the lesion area with the slice thickness and normalized by total intracranial volume (TIV). Segmentation of TIV and cortex volume from the T1-weighted high resolution MPRAGE scans was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/) [53, 54].

We decided against a separation into deep and periventricular WML as the drawing of rather random borders in the lesions themselves was often considered to be arbitrary, which was especially the case in large periventricular lesions conflating into the deep white matter.

Statistics

Student´s *t*-tests were performed for group comparisons of normally distributed variables. Categorical data sets were analyzed using chi-squared tests. Tests were two tailed and a value of $p < .05$ was considered statistically significant. For group differences normal distribution was confirmed using Kolmogorov Smirnov test. In case of violation of normality, Mann-Whitney-U-tests were performed. For differences in WML-load, BD patients and controls were analyzed using a univariate covariance analysis model (ANCOVA) controlling for the confounding factor age and additionally for BMI, smoking, and diabetes, as the groups differed in these parameters.

For partial correlation analyses, variables of interest matching the required normal distribution of residuals confirmed visually by histograms have been used for calculation (normalized WML with number of depressive episodes, number of manic episodes, illness duration, age of onset and BMI). For this purpose normalized WML volumes have been transformed by adding the number one and the use of a natural logarithm. There was no normal distribution of residuals for the rating scale variables YMRS, HAM-D and BDI forcing us to remove them from partial correlation analysis. After Bonferroni-correction for multiple comparison a value of $p < .01$ was considered statistically significant. Partial correlation analyses of WML were conducted controlling for age, hypertension, diabetes, smoking, migraine, alcohol dependency, substance dependency, anxiety disorder and medication (lithium, antiepilieptics and antipsychotics). Illness duration was additionally introduced as a control variable for number of affective episodes and age of onset.

Results

Differences BD and HC

Group differences between BD patients and controls can be seen in Table 1. ANCOVA results indicated that individuals with BD had significantly more WMLs than HC (*F(1/148)* = 3.968, $p = .048$, *Eta* = .026; Median and IQR are shown in Table 1).

Sex Differences within BD

Descriptive baseline characteristics within the BD group (males vs. females) are displayed in Table 2. In BD patients, there was no significant sex difference for demographic, clinical or vascular risk parameters.

Table 1. Demographic data.

	BD (n = 100)	HC (n = 54)	*Statistics*	*p*
Male (%)	52	42.6	χ 2 = 1.242	.265
Age (years) (M, SD)	44 (14)	41 (16)	U = -1.475	.140
Body Mass Index (M, SD)	28 (5)	25 (4)	**t = 3.695**	.000
Migraine (%)	22	27.8	χ 2 = .750	.386
Hypertension (%)	29	22.2	χ 2 = .825	.364
Smoking (%)	49	24.1	**χ 2 = 9.058**	.003
Diabetes (%)	7	0	**χ 2 = 3.960**	.047
WML (mm^3) (Mdn, IQR)[1]	3710 (2961)	2185 (1665)	**F = 3.968**	.048

Note: Results from *t*-tests (*t*), Chi square tests ($\chi 2$), Mann-Whitney-U-tests (*U*) and ANCOVA (*F*)

(1) For ANCOVA, WML volumes were normalized by individual total intracranial volume and controlled for age, diabetes, smoking and BMI.

Statistically significant effects are marked bold.

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Table 2. Clinical characteristics in BD stratified by sex.

	52 males	48 females	*Statistics*	*p*
BD I / BD II (%)	65.4 / 34.6	64.6 / 35.4	χ 2 = .007	.933
Age (years) (M, SD)	44 (14)	44 (14)	*t* = -0.24	.981
Illness Duration (years) (M, SD)	19 (13)	20 (19)	*U* = -.235	.814
Age First Episode (years) (M, SD)	25 (12)	25 (9)	*U* = -.366	.714
Manic/hypomanic Episodes (M, SD)	11 (18)	8 (9)	*U* = -.603	.547
Depressive Episodes (M, SD)	12 (12)	16 (15)	*U* = -.513	.608
History of Suicide Attempts (%)	38.5%	27.1	χ 2 = 1.462	.227
HAM-D (M, SD)	5 (4)	6 (5)	*U* = -.573	.567
Alcohol Dependency (%)	23.1	12.5	χ 2 = 1.892	.169
Substance Dependency (%)	11.5	10.4	χ 2 = .032	.858
Anxiety Disorder (%)	17.3	29.2	χ 2 = 1.840	.175
YMRS (M, SD)	1 (2)	1 (2)	*U* = -1.665	.095
BDI (M, SD)	12 (9)	15 (12)	*U* = -1.254	.210
Body Mass Index (M, SD)	28 (4)	28 (6)	*t* = -0.56	.955
Antidepressant (%)	44.2	31.3	χ 2 = 1.785	.182
Lithium (%)	23.1	10.4	χ 2 = 2.835	.092
Antiepileptic (%)	25	12.5	χ 2 = 2.534	.111
Atypical Antipsychotic (%)	42.3	39.6	χ 2 = .077	.782
Typical Antipsychotic (%)	11.5	14.6	χ 2 = .205	.651
Migraine (%)	23.1	20.8	χ 2 = .073	.787
Hypertension (%)	30.7	27.1	χ 2 = .165	.685
Smokers (%)	48.1	50	χ 2 = .037	.848
Diabetes (%)	7.7	6.3	χ^2 = .080	.778
WML (mm³) (*Mdn*, IQR)[1]	4095 (3295)	3032 (2816)	*U* = -.150	.133

Note: Results from *t*-tests (*t*), Chi square tests (χ^2) and Mann-Whitney-U-tests (*U*).

(1) WML were normalised by individual total intracranial volume for the calculations.

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Correlations of WML with clinical and demographic factors

The results of partial correlation analyses of WML with clinical and demographic characteristics within the BD group are presented in Table 3. WML-load correlated positively with manic episodes and illness duration. In BD men, the number of manic / hypomanic episodes as well as depressive episodes correlated positively with WML-load. In BD women, no significant correlations were found.

Discussion

There are several important observations that emerge from the analysis of our data. First, we found an increased total volume of WML in individuals with BD compared to HC. Secondly, the most striking result was the strong association between the number of manic and depressive episodes with the total volume of WML in men. Thirdly, illness duration was identified as a significant and independent factor associated with the volume of WML. In contrast we identified no significant correlation between BMI or age of onset and WML-load in BD.

Our results of increased WML in BD compared to HC can be understood in the context of existing literature [1,2]. We explain the higher occurrence of WML in BD by the fact that WML are simply more common in various neuropsychiatric disorders (BD being one of them) as well as in cardiovascular diseases (more likely to appear in individuals with BD). The

Table 3. Partial correlation analyses.

	WML-load		
	BD (n = 100)	***BD male (n = 52)***	***BD female (n = 48)***
Manic episodes[1]	**.405*****	**.723*****	-.075
Depressive episodes[1]	.220*	**.510*****	.067
Age of onset[1]	-.158	.093	-.316
Body Mass Index[2]	-.020	-.119	.104
Illness duration[2]	**.295****	.383*	.068

Note: WML have been normalized by total intracranial volume and have been transformed by adding the number one and the use of natural logarithm

(1) controlled for age, hypertension, diabetes, smoking, alcohol dependency, substance dependency, anxiety disorder, migraine, lithium, antiepileptics, antipsychotics and illness duration

(2) controlled for age, hypertension, diabetes, smoking, migraine, alcohol dependency, substance dependency, anxiety disorder, lithium, antiepileptics and antipsychotics; Significant results after Bonferroni correction for multiple comparison ($p < .01$) are shown in bold

*$p < .05$

$p < .01$**

$p < .001$***.

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underlying pathophysiology might involve processes of inflammation [22], oxidative stress [49], metabolic neurotoxicity [47] and vascular genesis [19–21].

Men and women in our cohort did neither differ significantly in the total volumes of WML nor in the number of affective episodes. Nevertheless the correlation between the number of affective episodes and WML was only present in men. The sex effect found in our study may be a consequence of the neuroprotective influence of estradiol and progesterone (e.g. decrease of oxidative stress) [55–58]. Estrogen and progesterone may influence DNA repair, activation of antioxidative defense and interaction with BDNF [58–61]. Furthermore, decreased estrogen levels have been associated with poor cognitive performance, especially in short term verbal memory function in women [62, 63]. Bae et al. [11] displayed a higher amount of WML in male methamphetamine abusers than in female methamphetamine abusers. They assumed that estrogen's protective effect against cerebrovascular accidents might have been responsible for this result.

Neither do we know if WML in men are responsible for a poorer illness outcome nor if WML subserve clinical symptoms of manic and/or depressive episodes. In this context it is interesting that infarcts are capable to trigger depression and in rare cases also mania. Severe WML are proposed to be of ischemic origin, and may transform into true infarcts [18]. Interestingly, a systematic review on stroke and mania involving 74 cases showed that men are approximately three times more likely to express post-stroke mania than women [64]. Stroke in general is more prevalent in men [65, 66]. However, this cannot explain the much higher occurrence of post-stroke mania in male individuals.

As a result of the foregoing observations we propose that the male brain may be more differentially vulnerable to manic affective symptoms in the context of white matter changes. On the other hand, depression after stroke is not more common in men than in women [67]. We assume that the positive correlation with depressive episodes in our study is a consequence of the direct correlation with manic episodes.

In general, sex differences in the course of BD have been repeated. In the study of Kawa et al. [68] more men than women reported mania as first illness episode at the onset of BD I. Rapid cycling might be slightly more common in women, while age at onset and number of affective episodes of each polarity did not differ between men and women in previous studies

[68–70]. Men had higher rates of comorbid substance abuse and gambling, while women reported higher rates of comorbid eating disorders, weight change, appetite change and middle insomnia during depression [68]. Interestingly, we could show that high frequencies of weight change, also called weight cycling, were independently related to the number of affective episodes in women with BD only [48].

BMI did not show a significant association with WML in the present study. BMI can be regarded as a proxy of metabolic dysfunction but is not deterministic of metabolic dysfunction. Metabolic obesity is associated with white matter changes in non-psychiatric samples [71–73]. The non-association between BMI and WMLs in our sample could be because no association exists, or because the association between BMI and WML in bipolar adults may only occur in individuals with elevated BMI and associated metabolic morbidity (e.g. dyslipidemia, hypertension etc.), which has to be explored in large samples.

Limitations

We do not know the causal relationship between WML and clinical symptoms as only correlations were studied. It is not clear whether these lesions are a result of comorbid conditions, or whether they are directly associated with the disorder, or represent a biological risk factor for BD. Age is the most important factor contributing to WML [18] which suggests that WML in young subjects might not reflect a reliable indicator as the underlying pathology might not have had enough time to develop from a micro- to a macro-structural level. In line with this, there are conflicting results concerning the presence of WML in children and adolescents with BD. Some found increased WML already in young ages [74–77] while others found BD not associated with increased rate of WMLs in young subjects without comorbid conditions [78]. Non-conventional more advanced MRI methods as DTI might have provided more detailed insights.

With volumetric analysis it is not possible to distinguish large periventricular from confluent deep WML, which puts it on a disadvantage to the more commonly used rating scales [39].

The foregoing study targets an overall assessment of the burden of white matter lesions in the brain. Consequently, conclusions about pathophysiological mechanisms are highly limited, as especially in psychiatric disorders, the precise anatomic localization of white matter lesions might be pivotal for the pathophysiological consequences [1].

The present study is also limited by its natural cross-sectional design.

Advantages of this study were the acquisition of data in a single center, the selection of all lesions with the same criteria by a single rater and the performance of the identical protocol on the same MRI scanner, as well as the volumetric quantitative lesion segmentation allowing refined statistical analyses.

Conclusions

Our results underline the increased WML-load in individuals with BD and their association with clinical illness variables. Importantly, a sex specific effect was revealed, as the number of affective episodes correlated positively with WML-load in male bipolar study participants only. The moderational influence of sex suggests a possible contribution role of endocrinological and/or pathogenic influences that affect men and women with BD differently. We propose that men are more vulnerable to mania in the context of ischaemic brain alterations as confluent sub-types of WML or stroke, which should stimulate further research into this area, preferably with longitudinal design.

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Author Contributions

Conceived and designed the experiments: AB SS NL SB LP SR CE HD HPK BR ER. Performed the experiments: AB SS NL SB MP FF RQ HD PS BR ER. Analyzed the data: AB SS NL RQ LP SR CE ER HM. Contributed reagents/materials/analysis tools: AB SS NL SB RQ FF MP LP SR CE BR HD PS HPK ER HM. Wrote the paper: AB SS NL SR CE RM HPK ER.

References

1. Beyer JL, Young R, Kuchibhatla M, Krishnan KR. Hyperintense MRI lesions in bipolar disorder: A meta-analysis and review. Int Rev Psychiatry 2009; 21(4):394–409. doi: 10.1080/09540260902962198 PMID: 20374153
2. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry 2008 Sep; 65 (9):1017–1032. doi: 10.1001/archpsyc.65.9.1017 PMID: 18762588
3. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993 Sep; 43(9):1683–1689. PMID: 8414012
4. Palm-Meinders IH, Koppen H, Terwindt GM, Launer LJ, Konishi J, Moonen JM, et al. Structural brain changes in migraine. JAMA 2012 Nov 14; 308(18):1889–1897. doi: 10.1001/jama.2012.14276 PMID: 23150008
5. Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. Cephalalgia 2010 Feb; 30(2):129–136. doi: 10.1111/j.1468-2982.2009.01904.x PMID: 19515125
6. Rivkin P, Kraut M, Barta P, Anthony J, Arria AM, Pearlson G. White matter hyperintensity volume in late-onset and early-onset schizophrenia. Int J Geriatr Psychiatry 2000 Dec; 15(12):1085–1089. PMID: 11180463
7. Grangeon MC, Seixas C, Quarantini LC, Miranda-Scippa A, Pompili M, Steffens DC, et al. White matter hyperintensities and their association with suicidality in major affective disorders: a meta-analysis of magnetic resonance imaging studies. CNS Spectr 2010 Jun; 15(6):375–381. PMID: 20625370
8. Wang L, Leonards CO, Sterzer P, Ebinger M. White matter lesions and depression: a systematic review and meta-analysis. J Psychiatr Res 2014 Sep; 56:56–64. doi: 10.1016/j.jpsychires.2014.05.005 PMID: 24948437
9. Barber R, Scheltens P, Gholkar A, Ballard C, McKeith I, Ince P, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J Neurol Neurosurg Psychiatry 1999 Jul; 67(1):66–72. PMID: 10369824
10. Bae S, Kim JE, Hwang J, Lee YS, Lee HH, Lee J, et al. Increased prevalence of white matter hyperintensities in patients with panic disorder. J Psychopharmacol 2010 May; 24(5):717–723. doi: 10.1177/0269881108098476 PMID: 18957476

11. Bae SC, Lyoo IK, Sung YH, Yoo J, Chung A, Yoon SJ, et al. Increased white matter hyperintensities in male methamphetamine abusers. Drug Alcohol Depend 2006 Jan 4; 81(1):83–88. PMID: 16005161
12. Lyoo IK, Streeter CC, Ahn KH, Lee HK, Pollack MH, Silveri MM, et al. White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. Psychiatry Res 2004 Jul 30; 131(2):135–145. PMID: 15313520
13. Gallucci M, Amicarelli I, Rossi A, Stratta P, Masciocchi C, Zobel BB, et al. MR imaging of white matter lesions in uncomplicated chronic alcoholism. J Comput Assist Tomogr 1989 May-Jun; 13(3):395–398. PMID: 2723168
14. Fein G, Shimotsu R, Di Sclafani V, Barakos J, Harper C. Increased white matter signal hyperintensities in long-term abstinent alcoholics compared with nonalcoholic controls. Alcohol Clin Exp Res 2009 Jan; 33(1):70–78. doi: 10.1111/j.1530-0277.2008.00812.x PMID: 18976350
15. Anstey KJ, Jorm AF, Reglade-Meslin C, Maller J, Kumar R, von Sanden C, et al. Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. Psychosom Med 2006 Sep-Oct; 68(5):778–785. PMID: 17012533
16. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F, Austrian Stroke Prevention Study. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet 2003 Jun 14; 361(9374):2046–2048. PMID: 12814718
17. O'Brien JT, Firbank MJ, Krishnan MS, van Straaten EC, van der Flier WM, Petrovic K, et al. White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: the LADIS study. Am J Geriatr Psychiatry 2006 Oct; 14(10):834–841. PMID: 17001023
18. Schmidt R, Schmidt H, Haybaeck J, Loitfelder M, Weis S, Cavalieri M, et al. Heterogeneity in age-related white matter changes. Acta Neuropathol 2011 Aug; 122(2):171–185. doi: 10.1007/s00401-011-0851-x PMID: 21706175
19. Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord 2009 Sep; 11(6):657–662. doi: 10.1111/j.1399-5618.2009.00735.x PMID: 19689508
20. Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J. Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. Bipolar Disord 2009 Mar; 11(2):154–165. doi: 10.1111/j.1399-5618.2009.00664.x PMID: 19267698
21. McIntyre RS, Danilewitz M, Liauw SS, Kemp DE, Nguyen HT, Kahn LS, et al. Bipolar disorder and metabolic syndrome: an international perspective. J Affect Disord 2010 Nov; 126(3):366–387. doi: 10.1016/j.jad.2010.04.012 PMID: 20541810
22. Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012 Dec 1; 141(1):1–10. doi: 10.1016/j.jad.2011.12.049 PMID: 22497876
23. Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 2003 Jan; 160(1):112–117. PMID: 12505809
24. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005 Oct; 7(5):424–430. PMID: 16176435
25. Goldstein BI, Liu SM, Schaffer A, Sala R, Blanco C. Obesity and the three-year longitudinal course of bipolar disorder. Bipolar Disord 2013 Jan 3.
26. Lackner N, Mangge H, Reininghaus EZ, McIntyre RS, Bengesser SA, Birner A, et al. Body fat distribution and associations with metabolic and clinical characteristics in bipolar individuals. Eur Arch Psychiatry Clin Neurosci 2014 Nov 8.
27. Yim CY, Soczynska JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS. The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. Eur Psychiatry 2011 May 11.
28. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 2006 Apr; 8(2):103–116. PMID: 16542180
29. Schubert MF. Schlaganfall. In: Springer, editor. Klinische Neuropsychologie. 1st ed.: Springer; 2006. p. 303–314.
30. Starkstein SE, Fedoroff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. Biol Psychiatry 1991 Jan 15; 29(2):149–158. PMID: 1995084
31. Robinson RG, Boston JD, Starkstein SE, Price TR. Comparison of mania and depression after brain injury: causal factors. Am J Psychiatry 1988 Feb; 145(2):172–178. PMID: 3341462
32. Robinson RG. Mood Disorders Secondary to Stroke. Semin Clin Neuropsychiatry 1997 Oct; 2(4):244–251. PMID: 10320468

33. Dupont RM, Jernigan TL, Butters N, Delis D, Hesselink JR, Heindel W, et al. Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging. Clinical and neuropsychological significance. Arch Gen Psychiatry 1990 Jan; 47(1):55–59. PMID: 2294856

34. 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 Feb; 178:172–176. PMID: 11157432

35. Serafini G, Pompili M, Innamorati M, De Rossi P, Ferracuti S, Girardi P, et al. Deep white matter hyperintensities as possible predictor of poor prognosis in a sample of patients with late-onset bipolar II disorder. Bipolar Disord 2010 Nov; 12(7):755–756. doi: 10.1111/j.1399-5618.2010.00867.x PMID: 21040293

36. 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 2014 Jan 10:1–12.

37. 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 Dec; 257(8):494–499. PMID: 17901999

38. 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 Nov; 10(7):753–764. doi: 10.1111/j.1399-5618.2008.00626.x PMID: 19032707

39. Kapeller P, Barber R, Vermeulen RJ, Ader H, Scheltens P, Freidl W, et al. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. Stroke 2003 Feb; 34(2):441–445. PMID: 12574557

40. Scheltens P, Erkinjunti T, Leys D, Wahlund LO, Inzitari D, del Ser T, et al. White matter changes on CT and MRI: an overview of visual rating scales. European Task Force on Age-Related White Matter Changes. Eur Neurol 1998; 39(2):80–89. PMID: 9520068

41. 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 Aug; 149(2):351–356. PMID: 3496763

42. Regenold WT, Hisley KC, Obuchowski A, Lefkowitz DM, Marano C, Hauser P. Relationship of white matter hyperintensities to cerebrospinal fluid glucose polyol pathway metabolites-a pilot study in treatment-resistant affective disorder patients. J Affect Disord 2005 Apr; 85(3):341–350. PMID: 15780705

43. Tighe SK, Reading SA, Rivkin P, Caffo B, Schweizer B, Pearlson G, et al. Total white matter hyperintensity volume in bipolar disorder patients and their healthy relatives. Bipolar Disord 2012 Dec; 14(8):888–893. doi: 10.1111/bdi.12019 PMID: 23167936

44. HAMILTON M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960 Feb; 23:56–62. PMID: 14399272

45. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978 Nov; 133:429–435. PMID: 728692

46. Hautzinger M, Bailer M, Worall H, Keller F. Beck-Depressions-Inventar (BDI). Bearbeitung der deutschen Ausgabe. Huber 1994.

47. Reininghaus EZ, McIntyre RS, Reininghaus B, Geisler S, Bengesser SA, Lackner N, et al. Tryptophan breakdown is increased in euthymic overweight individuals with bipolar disorder: a preliminary report. Bipolar Disord 2014 Jun; 16(4):432–440. doi: 10.1111/bdi.12166 PMID: 24330408

48. Reininghaus EZ, Lackner N, Fellendorf FT, Bengesser S, Birner A, Reininghaus B, et al. Weight cycling in bipolar disorder. J Affect Disord 2015 Jan; 171:33–38. doi: 10.1016/j.jad.2014.09.006 PMID: 25443762

49. Bengesser SA, Lackner N, Birner A, Fellendorf FT, Platzer M, Mitteregger A, et al. Peripheral markers of oxidative stress and antioxidative defense in euthymia of bipolar disorder-Gender and obesity effects. J Affect Disord 2014 Oct 22; 172C:367–374. doi: 10.1016/j.jad.2014.10.014 PMID: 25451439

50. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. Neurology 1999 Jul 13; 53(1):132–139. PMID: 10408549

51. Seiler S, Pirpamer L, Hofer E, Duering M, Jouvent E, Fazekas F, et al. Magnetization transfer ratio relates to cognitive impairment in normal elderly. Front Aging Neurosci 2014 Sep 25; 6:263. doi: 10.3389/fnagi.2014.00263 PMID: 25309438

52. Plummer D. DispImage: a display and analysis tool for medical images. Rev Neuroradiol 1992; 5:489–495.

53. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000 Sep 26; 97(20):11050–11055. PMID: 10984517

54. Fischl B, Salat DH, van der Kouwe AJ, Makris N, Segonne F, Quinn BT, et al. Sequence-independent segmentation of magnetic resonance images. Neuroimage 2004; 23 Suppl 1:S69–84. PMID: 15501102

55. Heron P, Daya S. 17Beta-estradiol protects against quinolinic acid-induced lipid peroxidation in the rat brain. Metab Brain Dis 2000 Dec; 15(4):267–274. PMID: 11383551

56. Kiray M, Ergur BU, Bagriyanik A, Pekcetin C, Aksu I, Buldan Z. Suppression of apoptosis and oxidative stress by deprenyl and estradiol in aged rat liver. Acta Histochem 2007; 109(6):480–485. PMID: 17698173

57. Moorthy K, Sharma D, Basir S, Baquer N. Administration of estradiol and progesterone modulate the activities of antioxidant enzyme and aminotransferases in naturally menopausal rats. Exp Gerontol 2005; 40(4):295–302. PMID: 15820610

58. Requintina PJ, Oxenkrug GF. The In Vitro Effect of Estradiol and Testosterone on Iron-Induced Lipid Peroxidation in Rat Brain and Kidney Tissues. Ann N Y Acad Sci 2005; 1053(1):400–404.

59. Dietrich AK, Humphreys GI, Nardulli AM. 17β-Estradiol increases expression of the oxidative stress response and DNA repair protein apurinic endonuclease (Ape1) in the cerebral cortex of female mice following hypoxia. J Steroid Biochem Mol Biol 2013; 138:410–420. doi: 10.1016/j.jsbmb.2013.07.007 PMID: 23907014

60. Frey BN, Dias RS. Sex hormones and biomarkers of neuroprotection and neurodegeneration: implications for female reproductive events in bipolar disorder. Bipolar Disord 2014; 16(1):48–57. doi: 10.1111/bdi.12151 PMID: 24206266

61. Spence RD, Wisdom AJ, Cao Y, Hill HM, Mongerson CR, Stapornkul B, et al. Estrogen mediates neuroprotection and anti-inflammatory effects during EAE through ERalpha signaling on astrocytes but not through ERbeta signaling on astrocytes or neurons. J Neurosci 2013 Jun 26; 33(26):10924–10933. doi: 10.1523/JNEUROSCI.0886-13.2013 PMID: 23804112

62. Shaywitz SE, Naftolin F, Zelterman D, Marchione KE, Holahan JM, Palter SF, et al. Better oral reading and short-term memory in midlife, postmenopausal women taking estrogen. Menopause 2003; 10 (5):420–426. PMID: 14501603

63. Sherwin BB. Estrogen and cognitive functioning in women. Endocr Rev 2003; 24(2):133–151. PMID: 12700177

64. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: a systematic review. Cerebrovasc Dis 2011; 32(1):11–21. doi: 10.1159/000327032 PMID: 21576938

65. Truelsen T, Piechowski-Jó wiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. European journal of neurology 2006; 13(6):581–598. PMID: 16796582

66. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. Stroke 2009 Apr; 40(4):1082–1090. doi: 10.1161/STROKEAHA.108.540781 PMID: 19211488

67. Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Prevalence of depression after stroke: the Perth Community Stroke Study. Br J Psychiatry 1995 Mar; 166(3):320–327. PMID: 7788123

68. Kawa I, Carter JD, Joyce PR, Doughty CJ, Frampton CM, Elisabeth Wells J, et al. Gender differences in bipolar disorder: age of onset, course, comorbidity, and symptom presentation. Bipolar Disord 2005; 7(2):119–125. PMID: 15762852

69. Tondo L, Baldessarini RJ. Rapid cycling in women and men with bipolar manic-depressive disorders. Am J Psychiatry 1998; 155(10):1434–1436. PMID: 9766777

70. Hendrick V, Altshuler LL, Gitlin MJ, Delrahim S, Hammen C. Gender and bipolar illness. J Clin Psychiatry 2000 May; 61(5):393–6; quiz 397.

71. Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. Arch Neurol 2005; 62:1545–1548. PMID: 16216937

72. Gustafson DR, Steen B, Skoog I. Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. Int Psychogeriatr 2004; 16:327–336. PMID: 15559756

73. Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, et al. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity 2011; 19(3):500–504. doi: 10.1038/oby.2010.312 PMID: 21183934

74. 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 Research: Neuroimaging 2002; 114(1):51–56. PMID: 11864809

75. Lyoo IK, 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(5):361–368. PMID: 12216011

76. Botteron KN, Figiel GS, Wetzel MW, Hudziak J, VANEERDEWEGH M. MRI abnormalities in adolescent bipolar affective disorder. Journal of the American Academy of Child & Adolescent Psychiatry 1992; 31(2):258–261.

77. 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. Journal of the American Academy of Child & Adolescent Psychiatry 1995; 34(6):742–749.

78. 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(1):76–82. doi: 10.1016/j.jpsychires.2010.04.019 PMID: 20488462