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Research report

White matter hyperintensities in bipolar and unipolar patients with relatively mild-to-moderate illness severity

Roberto B. Sassi[a,b], Paolo Brambilla[a,c,d], Mark Nicoletti[a,c], Alan G. Mallinger[a,e], Ellen Frank[a,f], David J. Kupfer[a,g], Matcheri S. Keshavan[a], Jair C. Soares[a,c,*]

[a] *Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[b] *Department of Psychiatry, Institute of Psychiatry, University of Sao Paulo School of Medicine, Sao Paulo, Brazil*
[c] *Division of Mood and Anxiety Disorders, Department of Psychiatry, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA*
[d] *Department of Psychiatry, University of Pavia School of Medicine, Pavia, Italy*
[e] *Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[f] *Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA*
[g] *Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA*

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Abstract

Background: Increased rates of white matter hyperintense lesions have been reported in mood disorder patients. However, the potential effects of age and illness severity on reported findings are not fully established. We examined the rates of hyperintense lesions in adult, non-elderly bipolar and unipolar patients, with a relatively mild-to-moderate illness severity, and in matched healthy controls. *Method:* We examined brain MRI images in 24 bipolar (19–56 years, mean ± S.D. = 34.2 ± 9.9 years) and 17 unipolar patients (24–59 years, 42.8 ± 9.2 years), and 38 healthy controls (21–59 years, 36.8 ± 9.7 years). T2-weighted and proton-density axial MRI images were obtained at 1.5 Tesla. The lesions were rated by two independent raters, using a semi-quantitative rating scale. *Results:* There were no significant differences in the frequency of hyperintensities between bipolar or unipolar patients and healthy controls. Age was related to the presence of subcortical gray matter hyperintensities for the whole sample. Among the unipolar patients, length of illness and presence of mood disorder in a first-degree relative were related to deep and periventricular white matter lesions, respectively. *Limitations:* The methodology utilized for measurement of the white matter hyperintensities was semi-quantitative. *Conclusions:* Increased rates of white matter hyperintensities do not appear to be present in a group of relatively young mood disorder patients, with relatively mild to moderate illness severity. These brain lesions may be more directly related to late-life and more severe cases of these illnesses.

Keywords: Neuroimaging; White matter hyperintensities; Affective disorders; Bipolar disorder; Unipolar disorder; MRI

1. Introduction

White matter hyperintense lesions, also known as subcortical leukoencephalopathy, are among the ear-

* Corresponding author. Tel.: +1-210-567-5492; fax: +1-210-567-3759.
E-mail address: soares@uthscsa.edu (J.C. Soares).

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liest and most consistently reported structural brain changes in psychiatric disorders. These lesions are typically seen as hyperintense areas in T2-weighted magnetic resonance images (MRI) in periventricular and deep white matter, but can also be described in subcortical gray matter regions. Although the exact neuropathological process underlying these lesions is not clear, it is believed that they represent areas of increased water density, possibly due to minor cerebrovascular damage (Awad et al., 1986; Fazekas et al., 1991). Not surprisingly, clinical conditions that are linked to vascular lesions, such as hypertension and diabetes, are associated with increased rates of brain hyperintense lesions (Fukuda and Kitani, 1995; Veldink et al., 1998; Ylikoski et al., 1995). Furthermore, an important increase in the frequency and intensity of hyperintense lesions is seen with age, even in otherwise healthy elderly subjects (Ylikoski et al., 1995).

Among mood disorder patients, several researchers reported increased frequency of hyperintense lesions in late-onset compared to early-onset depressed subjects (Figiel et al., 1991a; Krishnan and Gadde, 1996). Also, late-onset mania seems to be related to increased rates of subcortical hyperintensities (McDonald et al., 1991). On the other hand, studies with younger populations or early-onset mood disorder patients are more controversial, with both positive and negative findings in either unipolar or bipolar disorders (Dupont et al., 1995b; Guze and Szuba, 1992; Strakowski et al., 1993; Videbech, 1997). The presence of increased rates of hyperintense lesions in late-onset or elderly mood disorder subjects, but not in early-onset or younger patients, might be related to distinct neuropathological processes. However, the potential role of confounding variables such as age or illness severity in the findings of increased hyperintense lesions in mood disorder subjects should be systematically examined, as the actual relationship between clinical variables and hyperintense lesions is not clear.

In the present study, we examined the frequency of hyperintense lesions in non-elderly, mild-to-moderately ill unipolar and bipolar mood disorder outpatients and in matched healthy controls. We hypothesized that the prevalence of subcortical and periventricular hyperintensities would be increased in bipolar and unipolar mood disorder subjects compared to healthy individuals.

2. Methods

2.1. Subjects

Seventy-nine subjects were studied (age: 19–59 years, mean age ± S.D. = 37.3 ± 10 years; 40 M, 39 F), of which 24 were bipolar disorder patients (19–56 years, mean ± S.D. = 34.2 ± 9.9 years; 15 M, 9 F), 17 unipolar disorder patients (24–59 years, mean age ± S.D. = 42.8 ± 9.2 years; 1 M, 16 F), and 38 healthy controls (21–59 years, mean ± S.D. = 36.8 ± 9.7 years; 24 M, 14 F). All subjects provided signed informed consent, after having understood all issues involved in participation in the study protocol. This research study was approved by the University of Pittsburgh Biomedical IRB. The patients were recruited at the outpatient facilities of the University of Pittsburgh Medical Center, or through advertisements in the local media. The inclusion criteria were a diagnosis of either bipolar or unipolar disorder, with ages between 18 and 65 years, and without any psychotropic drug use other than lithium (or off all psychotropic medications) for at least 2 weeks before the scan. All patients met the DSM-IV diagnostic criteria for bipolar or unipolar disorder, as determined by the Structured Clinical Interview for DSM IV (SCID-IV) (First et al., 1996), and confirmed in a clinical evaluation conducted by an attending psychiatrist. At the time of participation in the study, 10 bipolar patients (38.4 ± 11.5 years; 6 BP I, 4 BP II; 6 M, 4 F) were off all psychotropic drugs for at least 2 weeks, and off lithium for at least 1 month; and 14 patients (31.3 ± 7.9 years; 13 BP I, 1 BP II; 9 M, 5 F) were on lithium monotherapy, and off all other psychotropic medications for at least 1 month. All unipolar patients were off psychotropic medications for at least 2 weeks. All subjects had no current significant medical problems, and had no history of neurological problems. Patients with axis I comorbid psychiatric disorders, current medical problems, or alcohol or substance abuse within the 6 months preceding the study were also excluded. Information about clinical variables and medication history were retrieved from patients' psychiatric interviews and medical charts. Healthy controls had no DSM-IV axis I disorders, as determined by the SCID-IV non-patient version (SCID-NP), no current medical

problems, and no history of psychiatric disorders among first-degree relatives.

2.2. MRI procedure

MRI scans were acquired with a 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI). A T1-weighted sagittal scout image was obtained for graphic prescription of the coronal and axial images. 3D gradient echo imaging (spoiled gradient recalled acquisition, SPGR) was performed in the coronal plane (TR = 25 ms, TE = 5 ms, nutation angle = 40°, FOV = 24 cm, slice thickness = 1.5 mm, NEX = 1, matrix size = 256 × 192) to obtain 124 images covering the entire brain. Additionally, a double echo-spin echo sequence was used to obtain T2 and proton density (PD) images in the axial plane, covering the whole brain (Fig. 1). These images were 5 mm thick, with no inter-slice gap, totaling 28 slices for each acquisition (T2 and PD), which were utilized to screen and rate the hyperintense signals.

2.3. Hyperintensities measurement

All MRI scans were independently analyzed by two trained raters (JCS and RBS), blind to the subjects' diagnosis, using the software MEDx 3.2 (Sensor Systems, Sterling, VA, USA). In order to be scored, the hyperintense lesions had to be present in both acquisitions, i.e., T2 and PD. A semiquantitative rating scale (Fazekas modified by Coffey et al., 1990) was used to rate the hyperintense lesions in three different locations and to classify them according to its severity using a categorical system:

(1) *Periventricular hyperintensity:* (0) absent, (1) 'caps' or pencil-thin lining, (2) smooth 'halo', (3) irregular periventricular hyperintensity extending into the deep white matter.
(2) *Deep white matter hyperintensity:* (0) absent, (1) punctuate foci, (2) beginning confluence of foci, (3) large confluent areas.
(3) *Changes in the subcortical gray matter:* (a) punctuate, (b) multipunctuate, (c) diffuse.

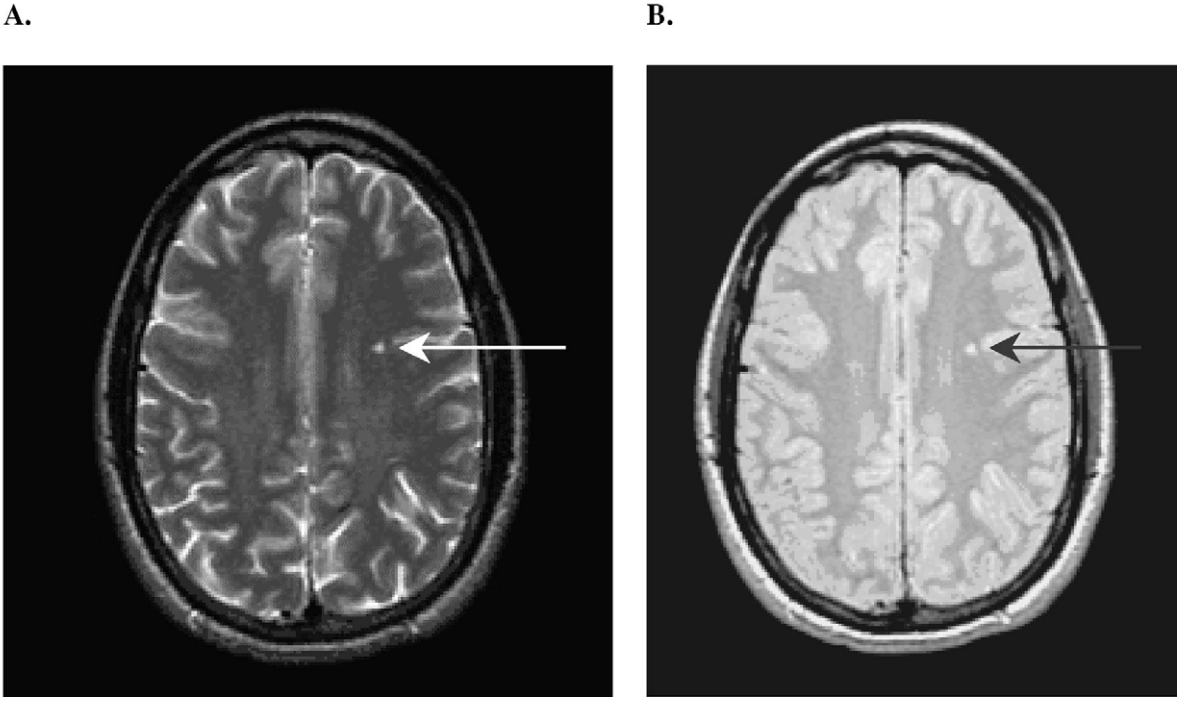

Fig. 1. An illustration of a single and small hyperintensity (arrows) near the lateral ventricles, as observed in the axial T2 (A) and proton-density (B) images.

Initial interrater reliability for the two raters was $r = 0.7$ (intraclass correlation coefficient). Since the reliability achieved was modest, in all the cases where a disagreement occurred in any item of the scale, the individual scans were reassessed, and a consensus rating was obtained.

2.4. Statistical analyses

All analyses were conducted using the SPSS for Windows software, version 10.0.5 (SPSS, Chicago, IL), and two-tailed statistical significance level was set at $P < 0.05$. Pearson χ^2 was used to compare the frequencies of hyperintensities among the groups. For further analysis, the groups were also stratified for age, length of illness, and number of previous affective episodes. The significance of these clinical variables within groups was also assessed using nonparametric Mann–Whitney *U*-test, to contrast the subjects with and without lesions.

3. Results

Bipolar and healthy control groups did not differ significantly regarding age ($F = 0.31$, df = 60, $P = 0.3$) or gender ($\chi^2 = 0.003$, df = 1, $P = 0.9$). The unipolar patients, however, were significantly older than the healthy controls ($F = 0.71$, df = 53, $P = 0.03$) and bipolar patients ($F = 0.8$, df = 39, $P = 0.008$). Also, the

Table 1
Frequency and severity of hyperintense lesions

Location of the lesion	Healthy controls ($n = 38$)	Bipolar patients ($n = 24$)	Unipolar patients ($n = 18$)
Periventricular hyperintensity:[a]			
0	17 (44.7%)	14 (58.3%)	11 (64.7%)
1	20 (52.7%)	10 (41.7%)	5 (29.4%)
2	–	–	1 (5.9%)
3	1 (2.6%)	–	–
Deep white matter:[b]			
0	34 (89.4%)	22 (91.6%)	14 (82.3%)
1	4 (10.6%)	2 (8.4%)	3 (17.7%)
2	–	–	–
3	–	–	–
Subcortical gray:[c]			
Absent	35 (92.1%)	23 (95.8%)	15 (88.2%)
Punctuate	3 (7.9%)	1 (4.2%)	2 (11.8%)
Multipunctuate	–	–	–
Diffuse	–	–	–
At least one periventricular lesion[d]	21 (55%)	10 (41.6%)	6 (35.3%)
At least one lesion, in any subregion[e]	22 (57.8%)	12 (50%)	7 (41.2%)

No significant differences were found in any of the variables tested:
Comparing the three groups: [a]$\chi^2 = 7.2$, df = 6, $P = 0.3$; [b]$\chi^2 = 0.9$, df = 2, $P = 0.6$; [c]$\chi^2 = 0.8$, df = 2, $P = 0.6$; [d]$\chi^2 = 2.2$, df = 2, $P = 0.3$; [e]$\chi^2 = 1.3$, df = 2, $P = 0.5$.
Comparing only bipolar and healthy control groups: [a]$\chi^2 = 1.5$, df = 2, $P = 0.4$; [b]$\chi^2 = 0.1$, df = 1, $P = 0.7$; [c]$\chi^2 = 0.3$, df = 1, $P = 0.5$; [d]$\chi^2 = 1.1$, df = 2, $P = 0.3$; [e]$\chi^2 = 0.4$, df = 1, $P = 0.5$.
Comparing only unipolar and healthy control groups: [a]$\chi^2 = 4.9$, df = 3, $P = 0.2$; [b]$\chi^2 = 0.5$, df = 1, $P = 0.4$; [c]$\chi^2 = 0.2$, df = 1, $P = 0.6$; [d]$\chi^2 = 1.8$, df = 2, $P = 0.2$; [e]$\chi^2 = 1.3$, df = 1, $P = 0.2$.
Comparing only bipolar and unipolar groups: [a]$\chi^2 = 1.9$, df = 2, $P = 0.3$; [b]$\chi^2 = 0.8$, df = 1, $P = 0.4$; [c]$\chi^2 = 0.8$, df = 1, $P = 0.3$; [d]$\chi^2 = 0.2$, df = 1, $P = 0.6$; [e]$\chi^2 = 0.3$, df = 1, $P = 0.5$.

Table 2
Frequencies of hyperintense lesions across sub-groups

Subgroups	Periventricular white matter N present/total (scale score)	Deep white matter N present/total	Subcortical gray matter N present/total
Age			
Up to 30 y.o. (n = 27):			
Control: 13/38	4/13 (1)	–	2/13
Bipolar: 12/24	6/12 (1)	1/12	–
Unipolar: 2/17	1/2 (1)	–	–
31–50 y.o. (n = 42):			
Control: 21/38	14/21 (1); 1/21 (3)	4/21	–
Bipolar: 10/24	3/10 (1)	1/10	–
Unipolar: 11/17	4/11 (1)	2/11	1/11
*51 years or more (n = 10):**			
Control: 4/38	2/4 (1)	–	1/4
Bipolar: 2/24	1/2 (1)	–	1/2
Unipolar: 4/17	–	1/4	1/4
Gender			
Male (n = 40):			
Control: 24/38	12/24 (1); 1/24 (3)	4/24	1/24
Bipolar: 15/24	7/15 (1)	2/15	–
Unipolar: 1/17	–	–	–
Female (n = 39):			
Control: 14/38	8/14 (1)	–	2/14
Bipolar: 9/24	3/9 (1)	–	1/9
Unipolar: 16/17	5/16 (1); 1/16 (2)	3/16	2/16
Age at onset of illness			
Early onset (n = 21):			
Bipolar (up to 20 y.o.): 14/24	6/14 (1)	1/14	–
Unipolar (up to 30 y.o.): 7/17	2/7 (1); 1/7 (2)	2/7	1/7
Late onset (n = 20):			
Bipolar (after 21 y.o.): 10/24	4/10 (1)	1/10	1/10
Unipolar (after 30 y.o.): 10/17	3/10 (1)	1/10	1/10
Length of illness			
Shorter (n = 22):			
Bipolar (up to 14 years): 12/24	6/12 (1)	1/12	–
Unipolar (up to 10 years): 10/17	4/10 (1)	–	–
Longer (n = 19):			
Bipolar (15 or more years): 12/24	4/12 (1)	1/12	1/12
Unipolar (11 or more years): 7/17**	1/7 (1); 1/7 (2)	3/7	2/7

(continued on next page)

Table 2 (*continued*)

Subgroups	Periventricular white matter N present/total (scale score)	Deep white matter N present/total	Subcortical gray matter N present/total
Number of previous affective episodes			
Few (n = 21):			
Bipolar (up to 6 previous episodes): 12/22	5/12 (1)	1/12	1/12
Unipolar (up to 3 previous episodes): 9/17	2/9 (1); 1/9 (2)	2/9	2/9
Several (n = 18):			
Bipolar (7 or more previous episodes): 10/22	5/10 (1)	–	–
Unipolar (4 or more previous episodes): 8/17	3/8 (1)	1/8	–
Mood disorders in the family[a]			
Present (n = 19):			
Bipolar: 12/24	4/12 (1)	2/12	1/12
Unipolar: 7/12***	3/7 (1); 1/7 (2)	1/7	1/7
Absent (n = 17):			
Bipolar: 12/24	6/12 (1)	–	–
Unipolar: 5/12	–	–	–
Bipolar subtype			
Bipolar 1 (19/24)	7/19 (1)	2/19	1/19
Bipolar 2 (5/24)	3/5 (1)	–	–
Medication status (only bipolar)			
Lithium monotherapy (14/24)	4/14 (1)	2/14	–
Drug-free (10/24)	6/10 (1)	–	1/10

*Subjects (bipolar, unipolar and controls) who were more than 51 years old had a significantly increased frequency of subcortical gray matter lesions than the other age groups ($\chi^2 = 8.8$, df = 2, $P = 0.01$). Among the healthy controls, the ones with at least one positive periventricular hyperintense signal tended to be older than the ones without any periventricular lesion (39.3 ± 8.5 and 33.8 ± 10.5 years, respectively; Mann–Whitney *U*-test, $Z = -1.95$, $P = 0.051$). Furthermore, for the entire patient group, the patients presenting subcortical gray matter lesions were significantly older than the other patients (51 ± 4.3 and 36.7 ± 10 years, respectively; Mann–Whitney *U*-test, $Z = -2.3$, $P = 0.018$).

**Unipolar patients with longer illness duration presented significantly more deep white matter hyperintensities ($\chi^2 = 5.2$, df = 1, $P = 0.02$) and a trend towards more subcortical gray matter hyperintensities ($\chi^2 = 3.2$, df = 1, $P = 0.07$) when compared with unipolar patients with shorter illness duration. Compared with healthy controls, this same sub-group of unipolar patients (7/17) presented significantly more deep white matter lesions ($\chi^2 = 4.7$, df = 1, $P = 0.03$) and a trend towards more subcortical gray matter lesions ($\chi^2 = 2.6$, df = 1, $P = 0.1$). Also, among the unipolar patients, the subjects with deep white matter lesions had significantly more years of illness than the subjects without deep white hyperintensities (25 ± 8.5 and 9 ± 7.4 years, respectively; Mann–Whitney *U*-test, $Z = -2.27$, $P = 0.023$).

***The subgroup of unipolar patients with positive family history of mood disorder presented significantly more periventricular white matter lesions, regardless of its severity ($\chi^2 = 4.2$, df = 1, $P = 0.03$), and were more likely to present at least one hyperintense lesion, regardless of its anatomical localization ($\chi^2 = 4.2$, df = 1, $P = 0.03$) than the unipolar patients without mood disorder in their families.

No influences of gender, age at onset, number of previous affective episodes, bipolar subtype (type I or type II), or medication status were found on the frequency of hyperintense lesions.

[a] Five unipolar patients where the presence of mood disorder in the family was uncertain were excluded from this analysis.

unipolar group was comprised mostly of women (16 F, 1 M), and therefore had a significantly larger number of females than the control ($\chi^2 = 15.5$, df = 1, $P < 0.001$) or bipolar ($\chi^2 = 13.4$, df = 1, $P < 0.001$) groups. Bipolar patients presented a significantly younger age at onset of illness when compared to unipolar patients (20 ± 6.8 and 30 ± 11.8 years old, respectively; $F = 8.5$, df = 39, $P = 0.001$), although length of illness was comparable between the two groups (14.6 ± 9 and 12 ± 9.6 years; $F = 0.2$, df = 39, $P = 0.4$). We were not able to obtain accurate information on the number of previous affective episodes

for two bipolar patients; thus, only 22 bipolar patients were stratified for this comparison. Bipolar patients had significantly more previous affective episodes than unipolar patients (16 ± 17 and 4.8 ± 4 episodes; $F=25$, df$=37$, $P=0.015$). Excluding five unipolar patients where the presence of mood disorder in the family was uncertain, mood disorders were present in at least one first-degree relative in 50% of bipolar and 40% of our unipolar sample ($\chi^2=0.2$, df$=1$, $P=0.6$).

The frequencies of hyperintense abnormalities found among the different groups are presented in Table 1. In the present sample, no subject received a score greater than 1 on the item deep white matter hyperintensities, or more intense than 'punctuate' for subcortical gray matter. No significant effects of psychiatric diagnosis were found for any of the measurements across the three subject groups (see Table 1). We then stratified the groups for age, age at onset of illness, length of illness, and number of previous affective episodes (see Table 2). In order to provide a reasonable number of subjects in each subgroup, we utilized the median to divide the bipolar and unipolar subjects into two sub-groups, for age at onset of illness, length of illness, and number of previous affective episodes. Because bipolar and unipolar subjects differed on these variables, the selection criteria were different between the two groups. Table 2 presents the rates of hyperintensities among all subgroups and the statistically significant effects of specific clinical variables on the frequency of lesions.

4. Discussion

The most relevant finding in our study is the lack of significant differences in the rates of occurrence of hyperintensities between bipolar and unipolar mood disorder patients and healthy controls. Previous studies have shown increased frequency and/or severity of hyperintense lesions in bipolar and unipolar patients compared to age-matched healthy individuals. A relationship between increased age and presence of hyperintense lesions has been found in most (Aylward et al., 1994; Dupont et al., 1995b; McDonald et al., 1991), although not in all prior studies (McDonald et al., 1999). Furthermore, a relationship between hyperintensities and poor performance in neuropsychological tests (Dupont et al., 1990, 1995b), higher number of previous hospitalizations (Dupont et al., 1995a), family history of psychiatric disorders (Dupont et al., 1995b), and diagnosis of bipolar type I (as opposed to bipolar II) (Altshuler et al., 1995) has been reported. Other studies, however, did not find significant relationship between the rates of hyperintense lesions and these specific clinical variables (Figiel et al., 1991b).

Our study is not the first negative report regarding rates of hyperintense lesions in bipolar patients (Persaud et al., 1997; Brown et al., 1992). Negative findings were also reported in studies involving young bipolar patients (8–16 years old) (Botteron et al., 1995), or adult patients with first-episode mania (Strakowski et al., 1993). More recently, Moore et al. (2001) observed an increase in the frequency and severity of deep white matter lesions that was restricted only to a group of bipolar patients with a poor treatment outcome. Bipolar disorder patients with good outcome did not differ from healthy controls in measurements of hyperintensities. Although this issue is still controversial, the available literature findings suggest that increased rates of hyperintense lesions in bipolar disorder patients may be more directly related to age and severity of the illness than to the illness diagnosis itself.

Consistent with these findings, we were not able to find significant differences in the occurrence of hyperintense lesions between mild-to-moderately ill non-elderly adult mood disorder bipolar and unipolar patients and healthy controls. However, due to the relatively small sample size, other clinical variables conceivably associated with severity of illness and outcome could not be adequately examined in our study. For that reason, our findings should be seen as preliminary. The relationship we found in the unipolar sample between increased frequency of deep white matter lesions and longer length of illness, and the relationship between presence of mood disorders in first-degree relatives and periventricular lesions should be interpreted with caution. These findings suggest that increased rates of hyperintense lesions among non-elderly unipolar patients might be present primarily in specific sub-groups, in particular patients with a history of mood disorders on a first-degree relative, and possibly a more severe illness course. However, it is important to emphasize that these findings are preliminary, as statistical significance would not persist after a Bonferroni correction for

multiple comparisons, and therefore should be further examined in larger patient samples.

Some methodological limitations in our study design should be considered when interpreting the results. First, the unipolar group was not similar to the bipolar and healthy control groups in regard to gender and age distribution; more specifically, the unipolar group was significantly older, and primarily composed of women. We sought to minimize any potential confounding effects from these variables by taking these factors in consideration for our group comparisons. Second, most of our MRIs had been previously acquired in the context of a different study, and adding a FLAIR acquisition, which would be advantageous for detection of hyperintense brain lesions in MRIs was not a possibility. Another limitation relates to the fact that, although we carefully excluded any medical conditions that could be related to hyperintense lesions, our groups were not matched for cigarette smoking. Tobacco has been suggested to increase the risk of hyperintense lesions, although this putative relationship is not fully clear (Dager and Friedman, 2000).

In summary, this study provides a comparison of the occurrence of hyperintense lesions among non-elderly bipolar patients, unipolar patients, and healthy controls. Our findings do not support the hypothesis that hyperintensities are more frequently found in non-elderly bipolar patients or unipolar patients compared to healthy controls. Similar rates of hyperintensities between healthy controls and non-elderly mood disorder patients with mild-to-moderate illness severity suggests that increased rates of lesions reported in other studies might be more related to clinical variables other than the diagnosis of mood disorder itself, and perhaps be more characteristic of specific illness sub-groups.

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