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Total white matter hyperintensity volume in bipolar disorder patients and their healthy relatives

Sarah K Tighe^a, Sarah A Reading^{a,b,c}, Paul Rivkin^a, Brian Caffo^d, Barbara Schweizer^a, Godfrey Pearlson^{e,f}, James B Potash^g, J Raymond DePaulo^a, and Susan S Bassett^a

^aDepartment of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD

^bMental Health and Behavioral Science Service, The James A. Haley Veterans' Hospital, Tampa, FL

^cDepartment of Psychiatry and Neuroscience, University of South Florida, Tampa, FL

^dDepartment of Biostatistics, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD

^eOlin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, CT

^fDepartments of Psychiatry and Neurobiology, Yale University, New Haven, CT

^gDepartment of Psychiatry, The University of Iowa, Iowa City, IA, USA

Abstract

Objectives—White matter hyperintensities (WMH) are more common in subjects with bipolar disorder (BP) than in healthy subjects (HS). Few studies have examined the effect of the diagnostic type of bipolar illness on WMH burden, and none have approached this question through a direct measurement of volume of affected white matter in relationship to familiarity. In this pilot study, we utilized a volumetric measurement of WMH to investigate the relationship between the total volume of WMH and the familiarity and type of BP.

Methods—Forty-five individuals with bipolar I disorder (BP-I) with psychotic features, BP-I without psychotic features, or bipolar II disorder (BP-II), seven of their unaffected relatives, and 32 HS were recruited for participation. T-2 weighted magnetic resonance imaging (MRI) scans were obtained on all subjects, and total volume of all WMH for each subject was measured in cubic centimeters. The significance of difference between groups was tested using ANOVA with post-hoc adjustment for multiple comparisons. Further, we used logistic regression to test for trends between symptom load and total WMH volume.

Corresponding author: Sarah K. Tighe, M.D., Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, Alpha Commons Building, 4th Floor, 5300 Alpha Commons Drive, Baltimore, MD 21224, USA. Fax: 410-550-1407, stighe1@jhmi.edu.

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Disclosures

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Results—The mean total volume of WMH in BP-I patients with psychotic features was significantly higher ($p < 0.05$) than that of HS. Further, we observed a positive linear trend by familiarity and type of affectedness when comparing mean total WMH volume of HS, unaffected family members, subjects with BP-II, and BP-I with and without a history of psychosis ($p < 0.05$).

Conclusions—Based on a quantitative technique, WMH burden appears to be associated with familiarity and type of BP. The significance of these findings remains to be fully elucidated.

Keywords

bipolar disorder; endophenotype; illness severity; magnetic resonance; white matter hyperintensities

The presence of excessive white matter hyperintensities (WMH) on T-2 weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences is one of the most consistently replicated imaging findings in bipolar disorder (BP). WMH are areas of increased signal intensity often found in the periventricular and deep white matter and have been studied in conjunction with many psychiatric disorders. Several prior studies have found a higher rate of WMH in patients with BP in comparison to appropriate healthy subjects (HS) (1–7). Two recent meta-analyses have provided additional evidence that there is an association between WMH and BP. The first study (8) demonstrated that patients with BP were 2.5 times more likely to have WMH compared to comparison subjects [odds ratio (OR) = 2.5, 95% confidence interval (CI): 1.87–3.30]. Although there was no difference in the prevalence of global WMH, Kempton and colleagues (9) found that patients with BP had an increased odds of deep WMH compared to comparison subjects (OR = 2.49, 95% CI: 1.64–3.79).

When present in BP, WMH have been related to a number of adverse outcomes. For instance, Dupont and colleagues (10) found that WMH are associated with greater illness severity characterized by more hospitalizations and poorer performance on neuropsychological tests. Further, deep WMH have been correlated with poor illness outcome (11, 12) and greater treatment resistance (13), while periventricular WMH have been associated with suicide attempts in BP (14, 15).

Evidence has also emerged to suggest that white matter lesions may serve as an endophenotypic marker for BP. Ahearn and colleagues (16) studied a family with a strong history of BP and observed a high prevalence of WMH in both probands and their unaffected relatives, although the study was limited by the absence of a comparison group from the general population. A subsequent study revealed that BP patients and their unaffected siblings tended to have WMH in the deep white matter of the right cerebral hemisphere in contrast to comparison subjects whose lesions were isolated to the left cerebral hemisphere (17). However, a third group found no significant difference in the prevalence of WMH among affected and unaffected relatives of BP probands and HS (18).

Historically, investigations of WMH in BP 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 lengths (19). Studies of WMH in BP have

most commonly used a four-point visual-rating scale in which zero indicates the absence of lesions, and grades one through three represent the increasing presence of white matter lesions (20, 21). Although volumetric analysis is commonplace within the field of structural neuroimaging, this approach has infrequently been applied to the study of WMH in BP (13, 22).

The goal of this study was to clarify the usefulness of WMH as an intermediate marker of disease burden in relation to family status and the diagnostic type of BP. In this pilot study, we utilized a dimensional, volumetric measurement of WMH to investigate the relationship between the volume of WMH and the familiarity and type of BP. A second goal of this work was to demonstrate feasibility of this quantitative measure of WMH in a study of BP disorder. To test the familiarity of WMH, we examined the total volume of WMH in subjects with BP, unaffected family members, and HS. We compared patients with BP-I with a history psychosis, BP-I without a history of psychosis, and BP-II to study the relationship between these volumes and the diagnostic category of BP. We limited our examination to the brains of subjects age 45 or younger as there is growing evidence to suggest that WMH are common in the elderly and increase with age (23). We hypothesized that mean total volumes of WMH would be greatest in all BP subjects followed by their relatives and then HS. Further, we hypothesized that mean total WMH volumes would correlate positively with illness type.

Patients and methods

The present study was approved by the Institutional Review Board of The Johns Hopkins University School of Medicine (Baltimore, MD, USA). Study co-investigators provided a verbal description of the study and obtained written consent from all of the participants before they enrolled. Forty-five individuals with BP and their unaffected family members were recruited for participation through the Stanley Medical Research Institute Bipolar Disorders Center at Johns Hopkins (JRD, Principal Investigator). Thirty-one HS were recruited through the Aging, Brain, and Cognition (ABC) Study at Johns Hopkins [GP, Principal Investigator (24)].

Diagnostic evaluation

BP participants and unaffected family members were interviewed using either the Schedule for Affective Disorders and Schizophrenia–Lifetime version (25) or the Diagnostic Interview for Genetic Studies (26). The unaffected family members were not diagnosed with BP or any other major psychiatric disorder and were the first-degree relatives of the BP participants. Diagnoses were made by incorporating medical record and family informant data, using the Research Diagnostic Criteria (RDC), the DSM-III-R, and the DSM-IV. Those diagnosed with BP-I met all three diagnostic criteria while those diagnosed with BP-II were required to meet only the RDC criteria. A psychotic BP diagnosis was defined as the occurrence of hallucinations and/or delusions during at least one mood episode. A non-psychotic BP diagnosis was defined as the absence of hallucinations and/or delusions during all mood episodes. HS were administered the Schedules for Clinical Assessment in Neuropsychiatry (27) to rule out a history of BP.

MRI acquisition and volumetric measurement

MRI scans were obtained on a GE Signa 1.5T scanner. All subjects underwent a T-2 weighted MRI scan with the following parameters: repetition time (TR) = 2500 msec; echo time (TE) = 80 msec; slice thickness = 5 mm; inter-section gap = 0; field of view (FOV) = 24; and matrix = 256×256 . All scans were performed in the axial plane, as described by Strasser et al. (28). A neuroradiologist reviewed all scans to determine whether WMH were present, and to differentiate between WMH, strokes, artifacts, and other abnormalities. In the WMH measurement protocol [for details, see Rivkin et al. (29)], the MRI data were displayed and manipulated on computer screens using locally developed imaging software (30). Voxels within WMH were outlined with a mouse-controlled cursor. A single rater (PR), blinded to diagnosis, performed all the measurements. Isolated single-voxel hyperintensities were not included because they could not be reliably rated. Further, periventricular rims of 1–2 voxel width were not included as part of the WMH volume because they might represent a normal variant (31, 32). The sum of the volumes in cubic centimeters (cc) of the outlined voxels was computed for each subject to determine the total volume of WMH. As previously described, there was absolute intra-rater agreement regarding which scans possessed no WMH, and the intra-rater reliability for scans with non-zero WMH volumes yielded a kappa statistic of 0.952 (29).

Statistical analysis

All statistical analyses were performed using SPSS 20.0. The significance of difference in total WMH volume by group was tested using an ANOVA with post-hoc adjustment for multiple comparisons. Further, independent *t*-tests were performed to assess the statistical relationship of total WMH volume between diagnostic groups. Finally, we used logistic regression to test for trends between symptom load defined by disease type and the presence of white matter lesions, as defined by total WMH volume being greater than zero. For this analysis, orthogonal polynomials for equally spaced symptom load scores were used to evaluate trends.

Results

Demographic characteristics and mean total WMH volumes of the five patient groups are shown in Table 1. Despite the absence of an overall significant difference in total WMH volume by group ($p = 0.227$), we observed a pattern of results that revealed a positive linear trend by familiarity and type of affectedness ($p = 0.033$) (Fig. 1). As expected, comparison of groups showed a statistically significant difference in mean total volume of WMH between HS and BP-I patients with psychotic features ($p = 0.027$). Consistent with previously reported findings (33), a positive trend between increasing age and WMH load was also found ($p = 0.015$), but this was independent of the effects of disease type. Gender difference was also considered, but found to be non-significant.

Discussion

The primary findings of this study are two-fold. First, we observed a positive relationship between increasing total volume of involved white matter and diagnostic category within the

bipolar spectrum. Second, the statistical trend regarding volume of abnormal white matter extends to and includes unaffected first-degree relatives of subjects with BP.

In an MRI study of parenchymal abnormalities in BP, Dupont and colleagues (34) first noted the presence of WMH in bipolar patients. Since then, WMH have become one of the most replicated neuroimaging findings in patients with BP. The data put forth here demonstrate a greater total volume of brain tissue affected by WMH in BP subjects compared to HS. These findings are consistent with a number of prior studies (1–10).

While studies have examined the relevance of illness state in BP (5, 35), few studies have examined the effect of illness type and severity on WMH load. In a prospective study of treatment-refractory BP illness, Altshuler and colleagues demonstrated that WMH were 1.6 times more common in BP-I patients compared to BP-II patients (2). To our knowledge, these data are the first to demonstrate an association, albeit a trend, between diagnostic type of BP (i.e., BP-I with a history of psychosis, BP-I without psychosis, and BP-II), and total volume of affected white matter. The mechanism underlying the relationship between psychosis and WMH in BP patients warrants further exploration in future work, though evidence from schizophrenia suggests that white matter dysfunction may precede the onset of psychosis and worsen after the first episode of psychosis (36). Other indicators of a more severe illness course have been studied. For instance, the presence of WMH in BP subjects has been correlated with more frequent hospitalizations (10), greater treatment resistance (13), and suicide attempts (14, 15). A relationship also seems to exist between WMH and treatment outcome of patients with BP (11, 12), and it may be that the poorer outcomes that are associated with increased WMH correlate with illness type, as our data may imply.

Brain imaging findings have recently been discussed as possible endophenotypes in psychiatric disorders (37). Ahearn and colleagues first introduced the possibility that white matter abnormalities may be a biologic marker in BP after they observed an increased prevalence of WMH in patients with BP and their unaffected family members (16). More recent studies have provided conflicting results. One study found differences in the localization of WMH in patients, their healthy relatives, and comparison subjects (17), while a second study found no difference in the prevalence of WMH between these groups (18). Building on this prior literature, our observation of a positive correlation between familiarity of BP and total WMH volume provides additional evidence that WMH may be an endophenotypic marker in BP. Several factors other than familiarity may influence the relationship between WMH and BP affectedness, and thus, may explain the contradictory findings about the prevalence of WMH in BP patients compared to their unaffected family members. For instance, Gunde and colleagues included participants in early adulthood (mean ages for the three subject groups ranged from 19.8 to 21.5 years) and unipolar depression, whereas our work focused on individuals within the BP spectrum and middle adulthood (mean ages for the subject groups ranged from 31.4 to 34.7 years). Given that increasing age has been associated with WMH (3, 38, 39), the likelihood of observing WMH might have been greater in our study groups due to their older mean ages. WMH may be less common in unipolar depression than BP (40, 41), and thus, the inclusion of major depression in prior studies may have reduced the ability to detect a difference in WMH prevalence between study groups. Further, later illness onset (38, 42) and the presence of conditions

known to increase with age, such as cardiovascular disease (43), also have been associated with the occurrence of WMH in BP, and thus, may account for some of the discrepancies observed in this body of literature.

Prior investigations of WMH in BP have most commonly employed visual-rating scales to examine the presence and grade of WMH, whereas we performed a quantitative analysis of WMH volumes. This latter approach is expected to confer several advantages over the rating scales typically used. For one, the rating scales are semi-quantitative, which introduces the possibility of human error (5). Further, the Fazekas scale (20) was developed in the context of a study of patients with Alzheimer's disease, where the pathology is expected to differ considerably from BP. Given that the Fazekas scale was validated in a group of elderly patients with a variety of diagnoses (21), the utility of the scale in a younger cohort of BP subjects is called into question. This present analysis provides further evidence that the quantitative measurement of WMH is feasible in a group of bipolar spectrum patients.

Several limitations warrant consideration. First, while these data may help elucidate the mechanisms underlying WMH in BP, the study was cross-sectional and yielded correlational data. Second, we do not have measures of the BP subjects' current mood states. Therefore, we cannot comment on the possibility that WMH abnormalities are state-related phenomena. In light of the recent meta-analysis that showed BP subjects were more likely to have deep WMH than periventricular lesions, there is considerable interest in the location of WMH (9). Thus, a third limitation of this study is that we did not consider the relationship between location, including laterality, of WMH and BP familiarity and type. Other potential problems with the current study are the relatively small subject numbers, especially within the group of unaffected family members, and the fact that WMH are related to numerous risk factors for small vessel disease, including smoking, hypercholesterolemia, obesity, hypertension and substance use. These vascular factors were not covaried for in the current study as overall subject numbers were too small.

In conclusion, we found a statistically significant difference in the total volume of WMH between BP-I patients with psychotic features and healthy comparison subjects. Second, we observed a positive linear trend by familiarity and type of BP illness when comparing total WMH volume of BP-I subjects with and without a history of psychosis, BP-II subjects, unaffected family members, and HS. The significance of these findings remains to be fully elucidated, but they may relate to a specific disease etiology at a genetic level. Future studies are necessary to confirm the results of this analysis and to describe the mechanisms underlying WMH in BP. Finally, we demonstrated the practicability of a quantitative approach using a dimensional (brain volume) as opposed to categorical (scoring technique) method of WMH description in BP. Further work testing the inter-rater reliability and validity of this quantitative measure is warranted.

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Figure 1.

Mean total white matter hyperintensities (WMH) volume by diagnostic group with trend analysis line. BP-I = bipolar I disorder; BP-II = bipolar II disorder; cc = cubic centimeters.

*Significant difference between the healthy subjects and patients with BD-I with history of psychosis, $p = 0.027$.

**Significant trend by group, $p = 0.033$.

Table 1

Baseline demographic characteristics by diagnostic group

Diagnostic group	N	Age, years Mean (SEM)	Sex (Male/female)	Total WMH volume, cc Mean (SEM)
Healthy subjects	31	32.97 (1.22)	14/17	0.015 (0.009)
Unaffected family members	7	34.00 (2.28)	3/4	0.029 (0.020)
Bipolar II disorder	12	33.75 (2.35)	7/5	0.037 (0.035)
Bipolar I disorder with no psychosis	7	31.43 (2.39)	2/5	0.063 (0.046)
Bipolar I disorder with psychosis	26	34.69 (1.64)	10/16	0.085 (0.032)

SEM = standard error; WMH = white matter hyperintensities; cc = cubic centimeters