CNS Spectrums (2013), 00, 1–12. © Cambridge University Press 2013
doi:10.1017/S1092852913000825

ORIGINAL RESEARCH

The impact of periventricular white matter lesions in patients with bipolar disorder type I

*Gianluca Serafini, * Maurizio Pompili, Marco Innamorati, Nicoletta Girardi, Leonardo Strusi, Mario Amore, Leo Sher, Xenia Gonda, Zoltan Rihmer, and Paolo Girardi*

[1] Department of Neurosciences, Mental Health and Sensory Organs–Suicide Prevention Center, Sant'Andrea Hospital, Rome, Italy
[2] Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy
[3] Casa di Cura "Samadi", Rome, Italy
[4] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genova, Genova, Italy
[5] Department of Psychiatry, Columbia University College of Physicians and Surgeons, and New York State Psychiatric Institute, New York, New York, USA
[6] Department of Clinical and Theoretical Mental Health, Semmelweis University, Budapest, Hungary
[7] Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary
[8] Neuropsychopharmacology and Neurochemistry Research Group, National Academy of Sciences and Semmelweis University, Budapest, Hungary
[9] National Institute of Psychiatry and Addictions, Laboratory for Suicide Research and Prevention, Budapest, Hungary

Introduction. White matter hyperintensities (WMHs) are one the most common neuroimaging finding in patients with bipolar disorder (BD). It has been suggested that WMHs are associated with impaired insight in schizophrenia and schizoaffective patients; however, the relationship between insight and WMHs in BD type I has not been directly investigated.

Methods. Patients with BD-I (148) were recruited and underwent brain magnetic resonance imaging (MRI). Affective symptoms were assessed using Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale ($HDRS_{17}$); the presence of impaired insight was based on the corresponding items of YMRS and $HDRS_{17}$.

Results. A total of 49.3% reported multiple punctate periventricular WMHs (PWMHs) and 39.9% had deep WMHs (DWMHs). Subjects with lower insight for mania had significantly more PWMHs (54.6% vs 22.2%; $p < 0.05$) when compared to BD-I patients with higher insight for mania. The presence of PWMHs was independently associated with lower insight for mania: patients who denied illness according to the YMRS were 4 times more likely to have PWMHs (95% CI: 1.21/13.42) than other patients.

Conclusions. Impaired insight in BD-I is associated with periventricular WMHs. The early identification of BD-I subjects with PWMHs and impaired insight may be crucial for clinicians.

Received 8 July 2013; Accepted 25 September 2013

Key words: Affective symptoms, BD-I, insight, MRI, periventricular WMHs.

Introduction

White matter hyperintensities (WMH) are hyperintense signals on T2-weighted magnetic resonance images (MRI) that suggest ependymal loss and altered brain myelination.[1,2] According to their localization, WMHs are divided into periventricular white matter hyperintensities (PWMHs) and deep white matter hyperintensities (DWMHs) of a predominant vascular aetiology.[1] WMHs are known to be commonly associated with older age and risk factors such as arterial hypertension and diabetes.[3–5] Several studies have suggested that WMHs are associated with mood disorders and suicidal behavior in different populations (eg, children, young adults, etc).[6–8] Patients with WMHs, particularly with abnormalities in

*Address for correspondence: Gianluca Serafini, MD, PhD, Department of Neurosciences, Mental Health and Sensory Organs, Sant'Andrea Hospital, Sapienza University of Rome, 1035-1039 Via di Grottarossa, 00189, Rome, Italy.
(Email gianluca.serafini@uniroma1.it)

Xenia Gonda is recipient of the János Bolyai Research Fellowship of Hungarian Academy of Sciences.

the prefrontal cortex, amygdala–hippocampus complex, thalamus, and basal ganglia, the integrity of which is necessary for adequate mood regulation,[9] may be at a higher risk for developing mood disorders because of possible disruption of neuroanatomic pathways.[10]

Among mood disorders, bipolar disorder (BD), particularly BD type I (BD-I) is a serious mental illness that affects approximately 1% of the adult population.[11] Several structural changes may be found in the brains of patients with BD, but establishing correlations between neuroimaging findings and measures of illness exposure or age in cross-sectional studies requires caution.[12]

Studies investigating the eventual volumetric abnormalities in some brain structures have indicated possible involvement of the frontal cortex, temporal lobes, basal ganglia, and cerebellum in BD[13] and, recently, the subgenual cingulate cortex in both adult[14] and pediatric populations.[15] Table 1 summarizes the most relevant MRI studies of WMHs in adult patients with major psychiatric disorders.

WMHs are, no doubt, the most common neuroimaging finding that have been found in patients with BD, regardless of age.[52] Furthermore, there are differences between BD-I and bipolar II (BD-II) patients, as PWMH are more common in BD-I patients compared to BD-II and healthy controls,[53,54] indicating that these neuroimaging findings may be a sensitive and even subtype-selective diagnostic tool.

Interestingly, WMH location may be critical in the expression of certain bipolar symptoms. For example, the presence of DWMHs has been associated with poorer response to treatment in bipolar patients, less favorable outcome, and more frequent relapse[55]; also, a relevant association between increased rates of PWMHs and previous suicide attempts has also been suggested.[8]

Among all clinical manifestations, insight into illness may be widely considered as a relevant factor in coping with and treating patients with BD.[56,57] Understanding the neural mechanisms underlying insight and illness awareness may have important implications for the development of targeted treatments. Some previous findings have reported an association between WMHs and insight in schizophrenic and/or schizoaffective populations.[58–61]

Our previous studies concerning WMHs found an association between PWMHs and lower depression severity as assessed by the Center for Epidemiologic Studies Depression Scale[62]; an association between WMHs and older age with late-onset BD[63]; an association between affective temperamental profiles, WMHs, and suicidal risk in patients with mood disorders[64]; an association between WMHs and suicide attempts in patients with bipolar disorders and unipolar depression[8,25,65]; and an association between deep WMHs and poor prognosis in a sample of patients with late-onset bipolar II disorder.[20]

Here we hypothesized that those with WMHs compared to those without may be at a higher risk of impaired insight as assessed using the item 17 of the $HDRS_{17}$ and item 11 of the YMRS, respectively. The present study aimed to evaluate whether the presence of WMHs is associated with impaired insight in patients with BD-I. To our current knowledge, there are no data that link white matter abnormalities and insight in BD-I.

Methods

Subjects and study design

A total of 193 white Caucasian patients consecutively admitted to the psychiatric inpatient units of Sant'Andrea Hospital and the "Samadi Clinic" in Rome from September 2007 to September 2009 participated in the study. Inclusion criterion was a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR) diagnosis of BD-I.[66] Exclusion criteria were as follows: other DSM-IV-TR major psychiatric disorders; the presence of any neurological disorders (eg, epilepsy, multiple sclerosis, Alzheimer's disease, dementia); history of brain concussion; family history of dementia; presence of structural MRI findings compatible with stroke, including lacunar infarcts or other gross brain lesions or malformations; history of electroconvulsive therapy in the past 6 months; and conditions affecting the ability to participate in the assessment, including mental retardation. Based on inclusion criteria, 45 (23.3%) patients were not included because they had a diagnosis of BD-II. BD-II patients who were excluded from the study had similar socio-demographic characteristics and did not differ significantly from the patients included in the final sample with respect to clinical variables (eg, diagnosis or history of suicide attempts). The final sample consisted of 148 patients (77 men and 71 women). The mean age was 47.9 years (SD = 16.1; range: 19–83 years). Around 13% of the patients reported alcohol abuse; 6.1% reported illicit drug abuse, most commonly cannabis; and 2.0% reported concurrent abuse of alcohol and illicit drugs. Demographic and clinical characteristics of the sample are presented in Table 2. Clinical and socio-demographic information was taken from medical records by 2 researchers independently.

Current severity of affective symptoms was evaluated using the Young Mania Rating Scale (YMRS)[67] and the Hamilton Depression Rating Scale ($HDRS_{17}$).[68] Participants were additionally administered the Mini International Neuropsychiatric Interview (MINI)[69] and the Beck Hopelessness Scale (BHS).[70,71]

Subjects participated voluntarily in the study, and each subject provided written informed consent. The study protocol received approval from the local research

TABLE 1. MRI studies of WMHs in adult patients with major psychiatric disorders

Author (s), references	Sample characteristics	WMH evaluation	Most relevant location of WMHs	Main findings and implications
Tighe *et al*[16]	45 BD-I or -II subjects (with or without PS), and 32 HC	No psychometric instrument	Total volume of WMH	The mean total volume of WMHs in BD-I patients with psychotic features was significantly higher than that of HS.
Serafini *et al*[17]	85 CH adult outpatients	Modified Fazekas scale	Not specified	40% had PWMHs and 98% DWMHs. Patients with PWMHs were more likely to have lower CES-D scores than patients without; patients with more severe DWMHs were more likely to be older than those with mild or any DWMHs.
Oudega *et al*[18]	81 elderly MDD patients	No psychometric instrument	Total volume of WMH	No differences in change of MADRS scores were found for WMHs. WMHs did not contribute to poor response to ECT.
Serafini *et al*[19]	143 BD-I, 42 BD- II, and 62 MDD patients	Modified Fazekas scale	Centrum semiovale (24.4%), corona radiate (20.2%), frontal (17.6%), parietal (15.1%), temporal, and subcortical (8.4%) DWMHs	48% of patients had PWMHs and 39% had DWMHs. Patients with higher dysthymia and lower hyperthymia were more likely to have increased DWMHs than patients with lower dysthymia and higher hyperthymia. Different temperament profiles are associated with differences in the subcortical brain structures.
Serafini *et al*[20]	54 elderly LO BD patients. (76% BD-I, 24% BD-II)	Modified Fazekas scale	Centrum semiovale (22%), corona radiate (15%), paratrigonal (6%), frontal (46%), parietal (24%), and subcortical DWMHs	Confluence of DWMH lesions was found in 17% of the patients whereas confluent PWMHs in 28%. BD-II patients with DWMHs had a poorer quality of life than BD-I subjects. MRI findings of DWMHs could be a useful biological predictor of severity in patients with BD-II.
Gunning-Dixon *et al*[21]	42 elderly non-psychotic MDD and 25 HC subjects	A semi-automated method	WMHs and subcortical nuclei	Depressed subjects had greater total WMH burden compared to non-depressed controls. Patients who failed to remit with escitalopram had significantly greater WMH burden than patients who remitted and HC. WMHs may confer a vulnerability or perpetuate LL depression.
Köhler *et al*[22]	35 subjects aged $\geq$ 60 years with MDD and 29 HC	Scheltens scale	Total volume of WMH (both DWMHs and PWMHs)	More severe PWMHs and DWMHs were associated with greater deficits in memory and executive functions at follow-up compared with HC.
Bae *et al*[23]	24 PD patients and 24 matched HC	Composite Fazekas/Coffey scale	Frontal DWMHs	A greater severity of total WMH was associated with a diagnosis of PD in a dose-dependent pattern. WMHs may play a role in the pathogenesis of PD.
Fein *et al*[24]	51 LTAA and 46 HC	An automated algorithm	DWMHs and PWMHs	LTAA had more WMHs than HC. WMHs increase with age in LTAA. WMH load was independently associated with alcohol burden and age.
Pompili *et al*[25]	99 patients: 40.4% BD-I, 21.2% BD-II, and 38.4% MDD	Modified Fazekas scale	Corona radiate (N = 10), centrum semiovale (N = 6), and frontal subcortical WM (N = 18)	27.3% showed PWMHs, 36.4% DWMHs, and 14.1% of patients had WMHs in both locations. Subjects with PWMHs were more likely to have attempted suicide than individuals without PWMHs, even after controlling for potential confounding variables
Sheline *et al*[26]	83 LL depression subjects and 32 HC	Modified Fazekas scale	Superior/inferior longitudinal, and fronto-occipital/uncinate fasciculus, extreme capsule	Depressed subjects had greater WMHs in the investigated brain regions. Whole brain WMHs correlated with executive functions in depressed subjects; whole brain WM correlated with episodic memory, processing speed, and executive functions.
Regenold *et al*[27]	20 BP, 15 SCH patients, and 15 with TNS	An automatic volume computation	DWMHs	BD (and not schizophrenic) patients had significantly greater volumes of DWMHs compared to neurologic controls. Treatment resistance and poor outcome correlated significantly with DWMH volume in BD subjects.

Q3

Table 1. Continued

Author (s), references	Sample characteristics	WMH evaluation	Most relevant location of WMHs	Main findings and implications
Takahashi *et al*[28]	52 MD patients and 14 HC	Modified Fazekas scale	Bilateral frontal areas and the left parieto-occipital region	LO affective disorder patients showed higher ratings of DWMHs than EO patients. Significant between-group differences were detected in the investigated brain regions.
Zanetti *et al*[29]	129 individuals with FEP and 102 controls	Scheltens scale	Total volume of WMH	There were no statistically significant between-group differences in WMH frequency or severity scores.
Iosifescu *et al*[30]	65 MDD patients	Modified Fazekas scale	Subcortical and total WMHs	After logistic regression analyses, MDD with anger attacks was associated with higher severity of subcortical WMHs and total WMHs.
Pompili *et al*[8]	65 AD patients (44.6% with prior SA)	Modified Fazekas scale	Not specified	After logistic regression analyses, the prevalence of WMHs was significantly higher in subjects with past SA. WMHs might be useful biological markers of suicidality.
Patankar *et al*[31]	50 LO MDD patients and 35 HC	Scheltens scale	Basal ganglia	29 patients were responders, and 21 non-responders to monotherapy. Subjects with greater VRS dilation were more likely to be non-responders than those without.
Bae *et al*[32]	33 MA abusers and 32 HC	Modified Fazekas scale	DWMHs and PWMHs	Male MA abusers had greater severity of DWMHs and PWMHs than female MA and HC. Severity of DWMHs correlated with cumulative dose of MA inducing brain perfusion deficits.
Iosifescu *et al*[33]	84 MDD patients and matched HC	Modified Fazekas Scale	Subcortical WMHs	No significant difference was found in the prevalence of WMHs between the depression and the HC group. Left-hemisphere subcortical WMHs correlated with lower rates of treatment response.
Anstey *et al*[34]	385 adults with WAU	No psychometric instrument	Total volume of WMH	After regression analyses, WAU was not associated with WMHs.
Jorm *et al*[35]	475 subjects aged 60–64 years	Modified Fazekas Scale	Frontoparietal and PWMHs	Depressive symptoms were related to total brain WMHs but not to basal ganglia hyperintensities (the association is not significant when adjusted for physical disability and smoking).
Ehrlich *et al*[7]	102 young psychiatric MDD inpatients	Modified Coffey scale	PWMHs	After logistic regression analyses, the prevalence of PWMHs was significantly higher in subjects with past SA compared to those without.
Lin *et al*[36]	37 elderly LL MDD patients, and 18 HC	Modified Fazekas Scale	PWMHs	Over 60% of patients had significant WMHs. Relative to HC, patients with LL MDD showed more severe PWMHs. WMHs were correlated with later onset of depression.
Hickie *et al*[37]	47 MDD patients and 21 HC	Modified Fazekas Scale	DWMHs	There was no difference in lesion severity between patients and HC. After controlling for age, vitamin B12 levels were predictive of DWMHs in patients with MDD.
Heiden *et al*[38]	31 MDD patients (21 re-assessed after 5 years)	Modified Fazekas Scale	Frontal WMHs	Subjects with greater extent of WMHs had significantly higher Hamilton Depression Rating Scale scores, more severe depression at follow-up, and a lower Mini-Mental State Examination score.
Lyoo *et al*[39]	32 patients with CD, 32 with OD and HC	Composite Fazekas/Coffey scale	Frontal WMHs	Patients with cocaine dependence had greater severity of DWMHs and insular WMHs than those with opiate dependence and HC. Cocaine may induce more ischemia via vasoconstriction than opiates.

Table 1. Continued

Author (s), references	Sample characteristics	WMH evaluation	Most relevant location of WMHs	Main findings and implications
Firbank *et al*[40]	29 elderly depressed patients and 32 HC of similar age	Modified Fazekas Scale	Frontal WMHs	Depressed subjects had a significantly greater frontal-lobe WM volume than HC.
Taylor *et al*[41]	133 MDD subjects aged 60 years or older	No psychometric instrument	Total volume of WMH	After regression analyses, a greater change in WMH volume was significantly associated with a failure to remit even when controlling for confounding factors.
Breeze *et al*[42]	Over 600 psychiatric patients	No psychometric instrument	Total volume of WMH	Subjects with BD were not more likely to have WMH than other psychiatric patients. Lithium use may be subtly associated with WMHs.
Agid *et al*[43]	37 MDD patients and 27 age- and sex-matched HC	No psychometric instrument	Basal ganglia, temporal lobe, cerebellum, and brainstem	Mean volume of WMHs was significantly greater in depressed subjects. Depressed patients with WMHs in the basal ganglia may represent a clinically distinct at-risk subgroup within MDD.
Taylor *et al*[44]	86 LL depression patients and 47 HC	A semi-automated method	Fronto-striatal WMHs	A significant association between age and WMHs was found in bilateral frontal and left parietal regions.
Silverstone *et al*[45]	13 depressed BP patients, 11 unipolar depression, and 19 HC	Modified Fazekas Scale	DWMHs	More BP patients had higher DWMHs scores than both unipolar patients and HC.
Pillai *et al*[46]	15 bipolar adolescents, 19 with SCH and 16 HC	No psychometric instrument	Total volume of WMH	WMHs were present in 67% of bipolar patients, 37% of those with schizophrenia and 31% of HC. Bipolar patients had significantly increased WMHs than HC and schizophrenic subjects.
Ahearn *et al*[47]	20 unipolar subjects with prior SA matched with those without	Boyko scale, Coffey scale	Subcortical WMHs	A trend toward significance in PWMHs between unipolar patients with a history of SA compared to those without was found.
Rivkin *et al*[48]	12 LO and 10 EO SCH patients, and 31 HC	Explicit WMH volume	Total volume of WMH	No significant differences in WMH volume were found between the 3 groups. A trend towards increased WMH volume in the LO schizophrenia group was also found.
Sachdev *et al*[49]	27 LO and 30 EO SCH patients, and 34 HC	No psychometric instrument	Total volume of WMH	LO subjects had more PWMHs and subcortical nuclei WMHs than HC.
Sachdev and Brodaty[50]	25 LO and 24 EO SCH patients, and 30 HC	No psychometric instrument	Widths of periventricular rims and frontal/occipital caps	Subjects with LO schizophrenia had greater WMHs than the two other groups. LO schizophrenia patients had more WMHs in the thalamus than HC. PWMHs had significant negative correlations with intelligence, memory, and frontal-executive functioning.
Symonds *et al*[51]	30 EO and 24 LO SCH patients, 15 with OP, and 41 HC	A scale similar to the modified Fazekas	Total volume of WMH	There were no significant differences between psychotic patients and HC or EO and LO schizophrenic subjects in terms of frequency, type, or severity of structural abnormalities.

Note: AD = affective disorders; BD-I = bipolar disorder type I; BD-II = bipolar disorder type II; CD = cocaine dependence; CH = chronic headache; DWMHs = deep WMHs; ECT = electroconvulsive therapy; EO = early-onset; FEP = first-episode psychosis; HC = healthy control; LL = late-life; LO = late-onset; LTAA = long-term abstinent alcoholics; MA = methamphetamine; MADRS = Montgomery–Asberg Depression Rating Scale; MDD = major depressive disorder; MRI = magnetic resonance imaging; OD = opiate dependence; OP = other psychoses; PD = panic disorder; PS = psychotic symptoms; PWMHs = periventricular WMHs; SA = suicide attempts; SCH = schizophrenia; TNS = transient neurologic symptoms; VRS = Virchow Robin spaces; WAU = weekly alcohol use; WMHs = white matter hyperintensities.

TABLE 2. Differences between groups with different levels of insight

	BD-I with higher insight for mania (N = 18)	BD-I with lower insight for mania (N = 130)	T-test (DF = 146)	P<	BD-I with higher insight for depression (N = 55)	BD-I with lower insight for depression (N = 93)	T-test (DF = 146)	P<
Women	22.2%	51.5%		**0.05**	43.6%	50.5%		0.26
Age – M ± SD	50.06 ± 15.12	47.60 ± 16.25	0.61	0.55	46.93 ± 16.26	48.47 ± 16.05	–0.56	0.57
Suicide attempts	38.9%	43.1%		0.47	38.2%	45.2%		0.47
Lifetime suicidal ideation	55.6%	47.7%		0.35	47.3%	49.5%		0.47
BHS – M ± SD	8.17 ± 3.92	9.78 ± 4.73			9.13 ± 4.16	9.86 ± 4.93		
BHS ≥ 9	38.9%	66.2%		**0.05**	52.7%	68.8%		**0.05**
PWMHs	22.2%	54.6%		**0.01**	45.5%	53.8%		0.21
DWMHs	27.8%	41.5%		0.20	45.5%	36.6%		0.19
$HDRS_{16}$	23.67 ± 8.64	27.05 ± 6.54	–1.98	**0.05**	25.18 ± 6.98	27.51 ± 6.72	–2.00	**0.05**
$HDRS_{17} \geq 18$	83.3%	94.6%	–	–	90.9%	94.6%	–	–
$YMRS_{10}$	8.33 ± 5.69	9.33 ± 8.16	–0.50	0.62	8.84 ± 7.93	9.43 ± 7.90	–0.44	0.66

Note: BHS = Beck Hopelessness Scale; DWMHs = deep white matter hyperintensities; $HDRS_{16}$ = sum of items 1–16 of the Hamilton Scale for Depression (item 17 was excluded to avoid the strong correlation between measures of depression and insight); PWMHs = periventricular white matter hyperintensities; $YMRS_{10}$ = sum of items 1–10 of the and Young Mania Rating Scale (item 11 was excluded to avoid the strong correlation between measures of mania and insight); mean HDRS total score in the total sample = 25.4; mean YMRS total score in the total sample = 8.8.

Q4

ethics review board. Clinical interviews were conducted on average 5 days after admission.

Magnetic resonance image acquisition and rating of white matter hyperintensities

Brain MRIs were performed using a Siemens Sonata MRI scanner (Erlangen, Germany; 1.5 T). The FLAIR scan sequence was used for WMH measurement (ax: TR 10000; TE 125; thickness 5 mm; matrix 144 × 256). Proton density and T2-weighted images were obtained (PD and T2 ax: TR 2870; TE 13/107; thickness 5 mm; matrix 147 × 256) in the axial and the coronal planes. Axial and sagittal T1-weighted images were also obtained (T1 ax: TR 647; TE 17; thickness 5 mm; matrix 128 × 192 T1 sag: TR 552; TE 17; thickness 5 mm; matrix 231 × 192). The presence of a WMH was assessed by a neuroradiologist who was blind to all clinical information, using the modified Fazekas 4-point rating scale, which describes MRI hyperintensities on an ascending scale of intensity and frequency.[72] A second neuroradiologist, who was blind to all clinical information and previous WMH ratings, independently reviewed all MRI films. In the present study, the 4-point assessment of the modified Fazekas scale was collapsed into a dichotomous variable that measured the presence or absence of WMHs. The mean k value for inter-rater reliability for both PWMHs and DWMHs was 0.90.

Measures: clinical assessment

MINI

The MINI is a clinically administered, short, structured interview with high validity and reliability that was developed to explore 17 disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised (DSM-III-R),[73] and is routinely used in our unit soon after admission. One section of this instrument was developed to assess suicidal risk, it includes questions about past and current suicidality.[69]

Although the MINI should not be a substitute for a psychiatric clinical interview, validation studies confirm the validity of this instrument as a reliable tool in psychiatry.[69] MINI diagnoses were confirmed by clinical DSM-IV-TR diagnoses. Clinical diagnoses were assigned by a psychiatrist and an attending physician who were blind to the results of the MINI and MRI scans.

BHS

The BHS is a 20-item scale for measuring attitudes about the future.[70] Research consistently supports a positive relationship between BHS scores and measures of depression, suicidal intent, and current suicidal ideation.[74] The BHS may, therefore, be used as a proxy indicator of suicide potential. In the study reported in 1985, 91 of people who died by suicide had a score ≥ 9, while only 9% of suicide victims had a score < 9, establishing the BHS cut-off score as 9 or higher as predictive of higher suicide risk.[75]

$HDRS_{17}$ and YMRS

The $HDRS_{17}$,[68] a 17-item clinician-rated scale, was used to evaluate depressive symptom severity. The YMRS is an 11-item rating scale for mania that explores manic symptoms and is considered the gold standard for evaluating the concurrent validity of bipolar mania with newer scales.[67] The item of the $HDRS_{17}$ that assesses

insight (item 17) is measured on a 3-point Likert-type scale [from 0 (acknowledges being ill and depressed) to 2 (denies being ill at all)]. The item of the YMRS that assesses insight (item 11) is measured on a 5-point Likert-type scale [from 0 (present; admits illness; agrees with need for treatment) to 4 (denies any behavior change)]. Both variables were dichotomized, and patients were included in any of the following groups: (1) patients who admitted even only the possibility of being ill at the YMRS (higher insight for mania), and those who denied illness or behavior change (lower insight for mania); (2) patients who admitted to being depressed and ill at the $HDRS_{17}$ (higher insight for depression) and those who completely denied being ill (lower insight for depression).

To avoid the strong correlation between measures of depression/mania and insight, we estimated depressive ($HDRS_{16}$) and mania ($YMRS_{10}$) severity by omitting items of the scales measuring insight.

Statistical Analysis

One-sided Fisher exact tests and t-tests were used for bivariate analyses. All variables that were significant in the bivariate analyses were entered as independent variables into 2 logistic regression analyses with groups with different levels of insight as the criterion. Chi-squared tests (χ^2), Nagelkerke R^2, and -2 Log likelihood statistics are reported as statistics of model fit. Odds ratios (OR) and their 95% confidence intervals (CI) are reported as measures of association. Patients were stratified into 2 groups (having similar severity of bipolar illness): those having lower insight (having a > 1 as assessed by YMRS item 11) and those with higher insight (having a ≤ 1 as assessed by YMRS item 11). Among these groups, subjects were subsequently divided in those with lower or higher insight for mania and depression, respectively. All the analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows 19.0.

Results

Clinical characteristics of the sample

At the time of assessment, 62.8% of the patients had scores of 9 or higher on the BHS, denoting elevated hopelessness and suicide risk. Approximately 88% and 63% of BD-I patients denied being ill according to item 11 of the YMRS and item 17 of the $HDRS_{17}$, respectively.

Suicide risk

Around 43% of the patients (42.6%) had attempted suicide at least once in the past, and 48.6% of them had reported suicidal ideation.

MRI findings

A total of 73 subjects (49.3%) had PWMHs and 59 (39.9%) had DWMHs. Overall, 41 (27.7%) subjects had both PWMHs and DWMHs. Of those with PWMHs, 49 (67.1%) had multiple punctate lesions, 23 (31.5%) had beginning confluency of lesions, and only 1 (1.4%) had large confluent lesions as assessed by the modified Fazekas scale. Of those with DWMHs, 47 (79.7%) had multiple punctate lesions, 10 (16.9%) had beginning confluency of lesions, and 2 (3.4%) had large confluent lesions.

Insight ratings

Groups with different levels of insight differed in several variables (see Table 2). BD-I patients with lower insight for mania were more frequently women (51.5% vs 22.2%; $p = 0.05$), had significantly more PWMHs (54.6% vs 22.2%; $p < 0.05$), significantly higher scores on the $HDRS_{16}$ (27.05 ± 6.54 vs 23.67 ± 8.64; $t_{146} = -1.98$; $p < 0.05$), and a significantly more frequent BHS score ≥ 9 (66.2% vs 38.9%; $p < 0.05$) when compared to BD-I patients with higher insight for mania.

On the contrary, BD-I patients with higher insight for depression differed only for BHS ($p < 0.05$) and $HDRS_{16}$ ($t_{146} = -2.00$; $p < 0.05$) scores. BD-I patients with lower insight for depression had greater depressive severity (27.51 ± 6.72 vs 25.18 ± 6.98) and more frequently had scores of 9 or higher on the BHS (68.8% vs 52.7%).

Two logistic regression models assessed multivariate associations between groups and variables significant at the bivariate analysis when controlling for the presence of other variables. Both models fit the data well (see Table 3). The first model explained 20% of the variability of the data, and groups with different levels of insight in the YMRS differed significantly only for PWMHs ($p < 0.05$). The presence of PWMHs was independently associated with lower insight for mania: Patients who denied illness according to the YMRS were 4 times more likely to have PWMHs (95% CI: 1.21/13.42) than other patients.

The second model explained only 9% of the variability of the data, but none of the variables inserted in the model was independently associated with lower insight for depression ($HDRS_{16}$: OR = 1.05; $p = 0.15$; BHS ≥ 9: OR = 2.62; $p = 0.07$).

Discussion

To our knowledge, this was the first study to investigate the association between WMHs and insight as assessed by 1 item of the YMRS in a population of patients with BD-I. Subjects with lower insight for mania had significantly more PWMHs when compared to BD-I

TABLE 3. Logistic regression models (groups with different levels of insight as criterion)

		B	S.E.	Wald	df	Sig.	OR	95%CI for OR Lower	95%CI for OR Upper
Model 1									
BD-I with lower insight for mania	Women	1.19	0.63	3.53	1	0.06	3.28	0.95	11.35
	PWMHs	1.40	0.61	5.18	1	**0.05**	4.04	1.21	13.42
	$HDRS_{16}$	0.04	0.04	1.26	1	0.26	1.04	0.97	1.12
	BHS $\geq$ 9	0.61	0.58	1.13	1	0.29	1.85	0.60	5.74
	Constant	–0.39	0.95	0.16	1	0.69	0.68		
Model 2									
BD-I with lower insight for depression	$HDRS_{16}$	0.05	0.04	2.09	1	0.15	1.05	0.98	1.13
	BHS $\geq$ 9	0.96	0.54	3.24	1	0.07	2.62	0.92	7.46
	Constant	–0.79	0.69	1.31	1	0.25	0.46		

Model 1 fit: $\chi^2_4 = 16.56$; $P < 0.01$; –2 Log likelihood = 93.00; Nagelkerke $R^2 = 0.20$.
Model 2 fit: $\chi^2_2 = 6.94$; $P < 0.05$; –2 Log likelihood = 102.63; Nagelkerke $R^2 = 0.09$.
Note: BHS = Beck Hopelessness Scale; $HDRS_{16}$ = sum of items 1–16 of the Hamilton scale for depression; PWMHs = periventricular white matter hyperintensities.

Q6

patients with higher insight for mania. These results indicate that differences in white matter abnormalities, as assessed using the modified Fazekas scale, are associated with differences in insight levels.

The present findings extended some previous results of studies that investigated the association between WMHs and insight in different psychiatric populations (eg, schizophrenic and/or schizoaffective patients).[58–61] For example, Antonius *et al*[58] suggested that white matter deficits in fronto-temporal brain regions are linked to symptom unawareness, and reduced white matter integrity in temporal and parietal regions is implicated in the misattribution of symptoms. Similarly, Palaniyappan *et al*,[60] in a sample of predominantly male subjects, found a significant decrease in right posterior insular area in patients with poor insight relative to healthy controls; a negative correlation between insight and local white matter volume of the right posterior insula; and a positive association between the lower surface area of the right posterior insula and the lower degree of insight.

Not all studies, however, reported a relationship between frontal lobe atrophy and impaired insight. Bassitt *et al*[59] found no significant inverse correlations between insight impairment and gray or white matter volumes in the prefrontal region. Similarly, Rossell *et al*[61] reported no significant correlations between the whole brain, white and gray matter volumes, and the degree of insight in a sample of 78 male patients with schizophrenia and 36 normal male comparison subjects.

According to our results, different levels of insight as assessed by the YMRS are associated with MRI findings. BD-I patients with impaired insight on the YMRS were more likely to have PWMHs. WMHs were observed mostly in the centrum semiovale (24.4%) and corona radiata (20.2%) regions and higher in cortical and subcortical deep frontal (17.6%), parietal (15.1%), and temporal (8.4%) areas. These brain regions are involved in the regulation of mood and may contribute to the emergence of impairments in insight.[9,76–82] It is unlikely that impairments in insight are related to a single brain area. Most likely, symptom unawareness is linked to complex abnormalities in the network of fronto-temporal brain regions.

The assumption that some bipolar symptoms might be due to vascular-related processes (eg, degenerative processes including atherosclerosis, lacunar infarcts, atrophic demyelination, and arteriolar hyalinization)[83] that alter the connectivity between these brain structures is intriguing and is supported by the observed post-stroke emergence of mania.[84,85] However, here we did not find any association between the presence of DWMHs (usually having a vascular etiology) and impaired insight; therefore, manic symptoms other than impaired insight would be affected by these vascular processes as previously reported.[64]

The association between bipolar disorder and cardiovascular risk factors, including hypertension, hypercholesterolemia, obesity, and cigarette smoking,[86,87] is well known. However, our findings did not support this link between vascular risk factors and the emergence of manic symptoms, because after including PWMHs, DWMHs, hypertension, diabetes, total cholesterol, triglycerides, and number of daily cigarettes as covariates in our analyses, the results did not indicate any significant association.

In contrast with our previous findings,[8,25] our study did not currently find any association between PWMHs and suicidal behavior as assessed using the BHS. However, here we investigated a sample of BD-I patients, whereas the previous findings[8,25] were found in a mixed sample of bipolar and major depressed patients. The association between PWMHs and suicidal behavior is presumably significant only in some subgroups

of patients with major affective disorders, such as those with a BD type II or major depression.

Overall, these findings provide hypothetical evidence in support of the notion that the presence of PWMHs may significantly predict the presence of impaired insight in subjects with BD-I. Therefore, the presence of PWMHs might be used for grouping those subjects with BD-I who will manifest a more pronounced impairment in insight during hospitalization than other bipolar individuals, which will potentially help to optimize alternative treatment strategies.

Limitations

The present study must be considered in the light of the following limitations. First, the small sample size did not allow for generalization of the present findings. In addition, all our patients were admitted to a psychiatric hospital, which may indicate more severe affective symptoms and poorer insight at admission compared to that usually found in outpatients. This is a potential confounder of the present results according to some recent studies,[88,89] which suggests that, at least at functional level, some white matter abnormalities may be state-related. However, the present sample did not include bipolar subjects with current psychotic symptoms, nor severely depressed/manic patients as confirmed by the HDRS and YMRS mean total scores (see Table 2). Therefore, we sustained that the observed white matter abnormalities in our sample were trait-related rather than state-related features.

Also, the present study did not include a formal measure of insight. The measurement of insight through item 11 of the YMRS and item 17 of the $HDRS_{17}$ may be considered questionable, as the variance is not likely to be high. It is also difficult to make a fair comparison with the one item having a 0–4 range for mania and the other 0–2 for depression. However, our results are in line with those of Shad *et al*[90] and Ha *et al*[91] and with other authors,[92] which suggests that insight is a multidimensional domain. Factor analytic studies have often identified that different insight dimensions significantly overlap and may be represented by a single component able to explain approximately 80% of the variance.[93–96] In addition, it has been demonstrated that a good degree of agreement exists between single- and multiple-item measurement of insight.[97]

Moreover, although all our inpatients were taking psychoactive medications and most had a history of substance abuse, we did not analyze the effects of these variables on insight ratings and image processing.

It is reasonable to inquire whether the use of psychotropic medications could influence the presence and maintenance of WMHs. To date, there is no evidence that WMH rates could be influenced by the use of lithium, tricyclic antidepressants, or antiepileptic medications.[5,53,98,99] Conversely, findings concerning the possible influence of antipsychotic drugs is very limited, which suggests that caution should be used when interpreting the significance of WM lesions in patients with major affective disorders who were treated with psychoactive medications. However, most of the subjects included in the present sample were at their first hospitalization, presumably reflecting a short history of exposure to antipsychotic drugs. Also, the lack of accounting for the cognitive effects of medications was due to the fact that these patients did not complete a specific neurocognitive assessment.

Other methodological issues concern the procedure. The MRI studies were of quite low spatial resolution and done on only a 1.5 T scanner. Studies at 3 T and with higher resolution would have likely yielded a much higher number and extent of WMHs. An analysis to quantify total white matter lesion volume would strengthen the findings. In addition, diffusion tensor imaging techniques may be more sensitive for detecting white matter abnormalities in association with mood disorders. Also, although we found that WMHs were predominant in some brain regions, we could not perform regional analysis showing specific regional relationship of WMHs to insight.

Importantly, although WMHs are frequently found in populations of bipolar patients, and different mechanisms are considered in the emergence of WMHs, it is possible that WMHs may represent the "tip of the iceberg" that might be interpreted as an extreme consequence of underlying microstructural processes that affect brain connectivity, and which may be more specifically investigated using diffusion tensor imaging methods. Additionally, the Fazekas rating scale as a lesion assessment method was limited because visual rating scales, even where details of where lesions occur are provided, are a less objective method than many of the volumetric methods that are available.

Conclusions

More than half of our BD-I patients had PWMHs and a significant percentage of them had DWMHs. BD-I patients with impaired insight were more likely to have PWMHs than those without.

Prospective additional studies are needed in order to provide a better understanding of the biological processes that are involved in bipolar illness outcome.

Disclosures

Dr. Serafini has consulted and engaged in research with Janssen-Cilag, Bristol-Myers Squibb Corporation,

Astra-Zeneca, Innova Pharma, Eli Lilly, and he received travel grants from Servier and Lundbeck. Dr. P. Girardi has served as a consultant to, or has engaged in research collaborations with, Organon, Eli Lilly, Janssen, Merck, Bristol-Myers Squibb, Pfizer, and AstraZeneca Corporations. Dr. Rihmer has received speaker honoraria from AstraZeneca, GlaxoSmithKline, Eli Lilly and Co., Krka, Lundbeck GmbH, Montrose Kft, Organon, Pfizer, Richter Gedeon Ltd, Sanofi-Aventis, Schering-Plough, Servier-EGIS, Solvay-Pharma, Wörwag Pharma, and Wyeth Pharmaceuticals. During this time he also received honoraria as a member of scientific advisory boards of AstraZeneca, Eli Lilly and Co., Organon, Pfizer, Richer Gedeon Ltd, Sanofi-Aventis, Shering-Plough and Servier-EGIS. Dr. Gonda has received travel grants from Servier, Richter, Janssen, Lilly, GSK, Sanofi-Aventis, Krka and Organon. Drs. Innamorati, N. Girardi, Sher, Amore, and Strusi have no relevant disclosures.

REFERENCES:

1. Thomas AJ, Perry R, Barber R, Kalaria RR, O'Brien JT. Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Ann N Y Acad Sci*. 2002; **977**: 333–339.
2. Thomas AJ, O'Brien JT, Davis S, *et al*. Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. *Arch Gen Psychiatry*. 2002; **59**(9): 785–792.
3. Ovbiagele B, Saver JL. Cerebral white matter hyperintensities on MRI: current concepts and therapeutic implications. *Cerebrovasc Dis*. 2006; **22**(2–3): 83–90.
4. Steffens DC, Krishnan KR. Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. *Biol Psychiatry*. 1998; **43**(10): 705–712.
5. Videbech P. MRI findings in patients with affective disorder: a metaanalysis. *Acta Psychiatr Scand*. 1997; **96**(3): 157–168.
6. Ehrlich S, Noam GG, Lyoo IK, *et al*. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2004; **43**(6): 770–776.
7. Ehrlich S, Breeze JL, Hesdorffer DC, *et al*. White matter hyperintensities and their association with suicidality in depressed young adults. *J Affect Disord*. 2005; **86**(2–3): 281–287.
8. Pompili M, Ehrlich S, De Pisa E, *et al*. White matter hyperintensities and their associations with suicidality in patients with major affective disorders. *Eur Arch Psychiatry Clin Neurosci*. 2007; **257**(8): 494–499.
9. Soares JC, Mann JJ. The anatomy of mood disorders–review of structural neuroimaging studies. *Biol Psychiatry*. 1997; **41**(1): 86–106.
10. Taylor WD, Payne ME, Krishnan KR, *et al*. Evidence of white matter tract disruption in MRI hyperintensities. *Biol Psychiatry*. 2001; **50**(3): 179–183.
11. Ishak WW, Brown K, Aye SS, *et al*. Health-related quality of life in bipolar disorder. *Bipolar Disord*. 2012; **14**(1): 6–18.
12. Schneider MR, DelBello MP, McNamara RK, Strakowski SM, Adler CM. Neuroprogression in bipolar disorder. *Bipolar Disord*. 2012; **14**(4): 356–374.
13. Beyer JLKrishnan KR. Volumetric brain imaging findings in mood disorders. *Bipolar Disord*. 2002; **4**(2): 89–104.
14. Singh MK, Chang KD, Chen MC, *et al*. Volumetric reductions in the subgenual anterior cingulate cortex in adolescents with bipolar I disorder. *Bipolar Disord*. 2012; **14**(6): 585–596.
15. Baloch HA, Hatch JP, Olvera RL, *et al*. Morphology of the subgenual prefrontal cortex in pediatric bipolar disorder. *J Psychiatr Res*. 2010; **44**(15): 1106–1110.
16. Tighe SK, Reading SA, Rivkin P, *et al*. Total white matter hyperintensity volume in bipolar disorder patients and their healthy relatives. *Bipolar Disord*. 2012; **14**(8): 888–893.
17. Serafini G, Pompili M, Innamorati M, *et al*. White matter hyperintensities and self-reported depression in a sample of patients with chronic headache. *J Headache Pain*. 2012; **13**(8): 661–667.
18. Oudega ML, van Exel E, Wattjes MP, *et al*. White matter hyperintensities, medial temporal lobe atrophy, cortical atrophy, and response to electroconvulsive therapy in severely depressed elderly patients. *J Clin Psychiatry*. 2011; **72**(1): 104–112.
19. Serafini G, Pompili M, Innamorati M, *et al*. Affective temperamental profiles are associated with white matter hyperintensity and suicidal risk in patients with mood disorders. *J Affect Disord*. 2011; **129**(1-3): 47–55.
20. Serafini G, Pompili M, Innamorati M, *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; **12**(7): 755–766.
21. Gunning-Dixon FM, Walton M, Cheng J, *et al*. MRI signal hyperintensities and treatment remission of geriatric depression. *J Affect Disord*. 2010; **126**(3): 395–401.
22. Köhler S, Thomas AJ, Lloyd A, *et al*. White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. *Br J Psychiatry*. 2010; **196**(2): 143–149.
23. Bae S, Kim JE, Hwang J, *et al*. Increased prevalence of white matter hyperintensities in patients with panic disorder. *J Psychopharmacol*. 2010; **24**(5): 717–723.
24. 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; **33**(1): 70–78.
25. Pompili M, Innamorati M, Mann JJ, *et al*. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; **32**(6): 1501–1507.
26. Sheline YI, Price JL, Vaishnavi SN, *et al*. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry*. 2008; **165**(4): 524–532.
27. Regenold WT, Hisley KC, Phatak P, *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**(7): 753–764.
28. Takahashi K, Oshima A, Ida I, *et al*. Relationship between age at onset and magnetic resonance image-defined hyperintensities in mood disorders. *J Psychiatr Res*. 2008; **42**(6): 443–450.
29. Zanetti MV, Schaufelberger MS, de Castro CC, *et al*. White-matter hyperintensities in first-episode psychosis. *Br J Psychiatry*. 2008; **193**(1): 25–30.
30. Iosifescu DV, Renshaw PF, Dougherty DD, *et al*. Major depressive disorder with anger attacks and subcortical MRI white matter hyperintensities. *J Nerv Ment Dis*. 2007; **195**(2): 175–178.
31. Patankar TF, Baldwin R, Mitra D, *et al*. Virchow-Robin space dilatation may predict resistance to antidepressant monotherapy in elderly patients with depression. *J Affect Disord*. 2007; **97**(1-3): 265–270.
32. Bae SC, Lyoo IK, Sung YH, *et al*. Increased white matter hyperintensitiesin male methamphetamine abusers. *Drug Alcohol Depend*. 2006; **81**(1): 83–88.

33. Iosifescu DV, Renshaw PF, Lyoo IK, *et al*. Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *Br J Psychiatry*. 2006; **188**: 180–185.
34. Anstey KJ, Jorm AF, Réglade-Meslin 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; **68**(5): 778–785.
35. Jorm AF, Anstey KJ, Christensen H, *et al*. MRI hyperintensities and depressive symptoms in a community sample of individuals 60-64 years old. *Am J Psychiatry*. 2005; **162**(4): 699–705.
36. Lin HF, Kuo YT, Chiang IC, Chen HM, Chen CS. Structural abnormality on brain magnetic resonance imaging in late-onset major depressive disorder. *Kaohsiung J Med Sci*. 2005; **21**(9): 405–411.
37. Hickie I, Naismith S, Ward PB, *et al*. Vascular risk and low serum B12 predict white matter lesions in patients with major depression. *J Affect Disord*. 2005; **85**(3): 327–332.
38. Heiden A, Kettenbach J, Fischer P, *et al*. White matter hyperintensities and chronicity of depression. *J Psychiatr Res*. 2005; **39**(3): 285–293.
39. Lyoo IK, Streeter CC, Ahn KH, *et al*. White matter hyperintensities in subjects with cocaine and opiate dependence and healthy comparison subjects. *Psychiatry Res*. 2004; **131**(2): 135–145.
40. Firbank MJ, Lloyd AJ, Ferrier N, O'Brien JT. A volumetric study of MRI signal hyperintensitiesin late-life depression. *Am J Geriatr Psychiatry*. 2004; **12**(6): 606–612.
41. Taylor WD, Steffens DC, MacFall JR, *et al*. White matter hyperintensity progression and late-life depression outcomes. *Arch Gen Psychiatry*. 2003; **60**(11): 1090–1096.
42. 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**(5): 269–283.
43. Agid R, Levin T, Gomori JM, Lerer B, Bonne O. T2-weighted image hyperintensities in major depression: focus on the basal ganglia. *Int J Neuropsychopharmacol*. 2003; **6**(3): 215–224.
44. Taylor WD, MacFall JR, Steffens DC, Payne ME, Provenzale JM, Krishnan KR. Localization of age-associated white matter hyperintensities in late-life depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; **27**(3): 539–544.
45. 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**(1): 53–57.
46. Pillai JJ, Friedman L, Stuve TA, *et al*. Increased presence of white matter hyperintensities in adolescent patients with bipolar disorder. *Psychiatry Res*. 2002; **114**(1): 51–56.
47. Ahearn EP, Jamison KR, Steffens DC, *et al*. MRI correlates of suicide attempt history in unipolar depression. *Biol Psychiatry*. 2001; **50**(4): 266–270.
48. Rivkin P, Kraut M, Barta P, *et al*. White matter hyperintensity volume in late-onset and early-onset schizophrenia. *Int J Geriatr Psychiatry*. 2000; **15**(12): 1085–1089.
49. Sachdev P, Brodaty H, Rose N, Cathcart S. Schizophrenia with onset after age 50 years. 2: Neurological, neuropsychological and MRI investigation. *Br J Psychiatry*. 1999; **175**: 416–421.
50. Sachdev P, Brodaty H. Quantitative study of signal hyperintensities on T2-weighted magnetic resonance imaging in late-onset schizophrenia. *Am J Psychiatry*. 1999; **156**(12): 1958–1967.
51. Symonds LL, Olichney JM, Jernigan TL, *et al*. Lack of clinically significant gross structural abnormalities in MRIs of older patients with schizophrenia and related psychoses. *J Neuropsychiatry Clin Neurosci*. 1997; **9**(2): 251–258.
52. Vasudev A, Thomas A. 'Bipolar disorder' in the elderly: what's in a name? *Maturitas*. 2010; **66**(3): 231–235.
53. Altshuler LL, Curran JG, Hauser P, *et al*. T2 hyperintensities in bipolar disorder: magnetic resonance imaging comparison and literature meta-analysis. *Am J Psychiatry*. 1995; **152**(8): 1139–1144.
54. Vieta E, Suppes T. Bipolar II disorder: arguments for and against a distinct diagnostic entity. *Bipolar Disord*. 2008; **10**(1 Pt 2): 163–178.
55. Moore PB, Shepherd DJ, Eccleston D, *et al*. Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. *Br J Psychiatry*. 2001; **178**: 172–176.
56. Cassidy F. Insight in bipolar disorder: relationship to episode subtypes and symptom dimensions. *Neuropsychiatr Dis Treat*. 2010; **6**(1): 627–623.
57. Van Der Werf-Eldering MJ, Van Der Meer L, Burger H, *et al*. Insight in bipolar disorder: associations with cognitive and emotional processing and illness characteristics. *Bipolar Disord*. 2011; **13**(4): 343–354.
58. Antonius D, Prudent V, Rebani Y, *et al*. White matter integrity and lack of insight in schizophrenia and schizoaffective disorder. *Schizophr Res*. 2011; **128**(1–3): 76–82.
59. Bassitt DP, Neto MR, De Castro CC, Busatto GF. Insight and regional brain volumes in schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2007; **257**(1): 58–62.
60. Palaniyappan L, Mallikarjun P, Joseph V, Liddle PF. Appreciating symptoms and deficits in schizophrenia: right posterior insula and poor insight. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; **35**(2): 523–527.
61. Rossell SL, Coakes J, Shapleske J, Woodruff PW, David AS. Insight: its relationship with cognitive function, brain volume and symptoms in schizophrenia. *Psychol Med*. 2003; **33**(1): 111–119.
62. Serafini G, Pompili M, Innamorati M, *et al*. Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation. *Eur Rev Med Pharmacol Sci*. 2012; **16**(10): 1389–1398.
63. Pompili M, Serafini G, Innamorati M, *et al*. White matter hyperintensities, suicide risk and late-onset affective disorders: an overview of the current literature. *Clin Ter*. 2010; **161**(6): 555–563.
64. Serafini G, Pompili M, Innamorati M, *et al*. Affective temperamental profiles are associated with white matter hyperintensity and suicidal risk in patients with mood disorders. *J Affect Disord*. 2011; **129**(1–3): 47–55.
65. Pompili M, Rihmer Z, Akiskal HS, *et al*. Temperament and personality dimensions in suicidal and nonsuicidal psychiatric inpatients. *Psychopathology*. 2008; **41**(5): 313–321.
66. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text rev. Washington, DC: American Psychiatric Association; 1994.
67. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978; **133**(5): 429–435.
68. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; **23**(1): 56–62.
69. Sheehan DV, Lecrubier Y, Sheehan KH, *et al*. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSMIV and ICD-10. *J Clin Psychiatry*. 1998; **59**(Suppl 20): 22–33; quiz 34–57.
70. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. *J Consult Clin Psychol*. 1974; **42**(6): 861–865.
71. Beck AT, Steer RA. Clinical predictors of eventual suicide: a 5- to 10- year prospective study of suicide attempters. *J Affect Disord*. 1989; **17**(3): 203–209.
72. Coffey CE, Wilkinson WE, Weiner RD, *et al*. Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. *Arch Gen Psychiatry*. 1993; **50**(1): 7–16.

Q7

73. Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D. DSM-IH-R psychotic disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. *Eur Psychiatry*. 1998; **13**(1): 26–34.
74. Beck AT, Brown G, Berchick RJ, Stewart BL, Steer RA. Relationship between hopelessness and ultimate suicide: a replication with psychiatric outpatients. *Am J Psychiatry*. 1990; **147**(2): 190–195.
75. Beck AT, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry*. 1985; **142**(5): 559–563.
76. Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol*. 2003; **13**(4): 500–505.
77. Figiel GS, Krishnan KR, Doraiswamy PM, Nemeroff CB. Caudate hyperintensities in elderly depressed patients with neuroleptic-induced parkinsonism. *J Geriatr Psychiatry Neurol*. 1991; **4**(2): 86–89.
78. Greenwald BS, Kramer-Ginsberg E, Krishnan KR, *et al*. Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression. *Stroke*. 1998; **29**(3): 613–617.
79. Hwang J, Lyoo lk, Dager SR, *et al*. Basal ganglia shape alterations in bipolar disorder. *Am J Psychiatry*. 2006; **163**(2): 276–285.
80. Steffens DC, Helms MJ, Krishnan KR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke*. 1999; **30**(10): 2159–2166.
81. Strakowski SM, Delbello MP, Adler C, Cecil DM, Sax KW. Neuroimaging in bipolar disorder. *Bipolar Disord*. 2000; **2**(3 Pt 1): 148–164.
82. Taylor WD, Macfall JR, Steffens DC, *et al*. Localization of age-associated white matter hyperintensities in late-life depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; **27**(3): 539–544.
83. DeCarli C, Murphy DG, Tranh M, *et al*. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. 1995; **45**(11): 2077–2084.
84. Berthier ML, Kulisevsky J, Gironell A, Fernández Benitez JA. Poststroke bipolar affective disorder: clinical subtypes, concurrent movement disorders, and anatomical correlates. *J Neuropsychiatry Clin Neurosci*. 1996; **8**(2): 160–167.
85. Celik Y, Erdogan E, Tuglu C, Utku U. Post-stroke mania in late life due to right temporoparietal infarction. *Psychiatry Clin Neurosci*. 2004; **58**(4): 446–447.
86. Kilbourne AM. The burden of general medical conditions in patients with bipolar disorder. *Curr Psychiatry Rep*. 2005; **7**(6): 471–477.
87. Yates WR, Wallace R. Cardiovascular risk factors in affective disorder. *J Affect Disord*. 1987; **12**(2): 129–134.
88. Liu J, Blond BN, van Dyck LI, *et al*. Trait and state corticostriatal dysfunction in bipolar disorder during emotional face processing. *Bipolar Disord*. 2012; **14**(4): 432–441.
89. Van der Schot A, Kahn R, Ramsey N, Nolen W, Vink M. Trait and state dependent functional impairments in bipolar disorder. *Psychiatry Res*. 2010; **184**(3): 135–142.
90. Shad MU, Muddasani S, Prasad K, Sweeney JA, Keshavan MS. Insight and prefrontal cortex in first-episode schizophrenia. *Neuroimage*. 2004; **22**(3): 1315–1320.
91. Ha TH, Youn T, Ha KS, *et al*. Gray matter abnormalities in paranoid schizophrenia and their clinical correlations. *Psychiatry Res*. 2004; **132**(3): 251–260.
92. David AS, Buchanan A, Reed A, Almeida O. The assessment of insight in psychosis. *Br J Psychiatry*. 1992; **161**: 599–602.
93. Birchwood M, Smith J, Drury V, *et al*. A self-report insight scale for psychosis: reliability, validity and sensitivity to change. *Acta Psychiatr Scand*. 1994; **89**(1): 62–67.
94. Cuesta MJ, Peralta V, Zarzuela A. Reappraising insight in psychosis: multi-scale longitudinal study. *Br J Psychiatry*. 2000; **177**(3): 233–240.
95. Drake RJ, Lewis SW. Insight and neurocognition in schizophrenia. *Schizophr Res*. 2003; **62**(1–2): 165–173.
96. Lincoln TM, Lüllmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia: a systematic review. *Schizophr Bull*. 2007; **33**(6): 1324–1342.
97. Sanz M, Constable G, Lopez-Ibor I, Kemp R, David AS. A comparative study of insight scales and their relationship to psychopathological and clinical variables. *Psychol Med*. 1998; **28**(2): 437–446.
98. Sassi RB, Brambilla P, Nicoletti M, *et al*. White matter hyperintensities in bipolar and unipolar patients with relatively mild-to-moderate illness severity. *J Affect Disord*. 2003; **77**(3): 237–245.
99. Persaud R, Russow H, Harvey I, *et al*. Focal signal hyperintensities in schizophrenia. *Schizophr Res*. 1997; **27**(1): 55–64.