Affective temperamental profiles are associated with white matter hyperintensity and suicidal risk in patients with mood disorders

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Abstract

Background: Patients with white matter hyperintensities (WMH) may be at higher risk for affective disorders and suicide. Affective temperaments may play a significant role in mood disorders. This study aimed to evaluate the eventual association between WMH, affective temperaments and suicidal behaviour in major affective disorder.

Methods: A total of 318 patients with major affective disorders were consecutively admitted as psychiatric inpatient. A total of 247 were included and given, brain magnetic resonance imaging (MRI) and assessed with the Mini International Neuropsychiatric Interview (MINI), the Beck Hopelessness Scale (BHS), the Hamilton Depression Rating Scale (HDRS17), the Young Mania Rating Scale (YMRS) and the Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A).

Results: A total of 48% of patients had periventricular WMH (PWMH) and 39% of them had deep WMH (DWMH). Patients with higher dysthymia and lower hyperthymia (H-DCIA group) were more likely to have higher BHS scores (BHS ≥ 9 = 77% vs. 52%; p < 0.001), more WMH (46% vs. 29%; χ² = 9.90; p < 0.05), higher MINI suicidal risk (54% vs. 42%; p < 0.05), and more recent suicide attempts (24% vs. 14%; p < 0.05), than patients with higher hyperthymia and lower dysthymia (H-H group).

Limitations: The small sample size did not allow the generalization of the present findings.

Conclusions: Differences among temperament groups measured by the TEMPS-A are associated with differences in their MRIs, indicating that different temperament profiles are associated with differences in the subcortical structures of the brain. The implications of the results were discussed.

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Keywords: MRI, Mood disorders, Suicidal risk, Affective temperaments, PWMH, DWMH

1. Introduction

White matter hyperintensities (WMH) appear as hyperintense signals on T2-weighted magnetic resonance images
(MRI) and represent ependymal loss and differing degrees of myelination in the brain (Thomas et al., 2002a,b). WMHs, depending on the localization, are commonly classified as periventricular white matter hyperintensities (PWMH) and deep white matter hyperintensities (DWMH) having mainly a vascular aetiology. WMH are reported to be commonly associated with older age and cardiovascular risk factors such as hypertension and diabetes (Ovbiagele and Saver, 2006; Steffens and Krishnan, 1998; Videbech, 1997). Degenerative changes in brain WM have been reported to be associated with mood disorders and suicidal behaviour both in children and young adults (Ehrlich et al., 2004, 2005; Pompili et al., 2007) while they are not specific to first episode psychotic disorders (Zanetti et al., 2008). Taylor and colleagues hypothesized that patients with WMHs may be at higher risk for developing mood disorders and suicide because of possible disruption of neuroanatomic pathways (Taylor et al., 2001). Mood regulation depends on the complex extensive connections between the prefrontal cortex, amygdala–hippocampus complex, thalamus and basal ganglia (Soares and Mann, 1997).

Those brain structures linked to mood regulation may be investigated and measured with MRI. Also, mood disorders range from subthreshold affective temperament traits measured by the TEMPS-A (Akiskal and Akiskal, 2005) through minor and major mood disorders to severe affective psychosis (Akiskal et al., 1979; Akiskal and Mallya, 1987; Parker, 2003; Rihmer et al., 2010; Oedegaard et al., 2009). Affective temperaments are also conceptualized and measured by more traditional psychometric measures such as the NEO Five Factor Inventory (McCrae and John, 1992; Costa and McCrae, 1992, 1995) and the MMPI (Trull et al., 1995) and may play a significant role in the psychopathological characteristics of mood disorders including the clinical evolution of minor/major mood episodes, the direction of polarity, the clinical symptomatology, the long-term course, suicidality and even medication adherence (Akiskal et al., 1979; Akiskal and Mallya, 1987; Rihmer et al., 2010; Oedegaard et al., 2009; Lara et al., 2006; Sayin and Aslan, 2005; Akdeniz et al., 2004; Liraud and Verdoux, 2001).

Individuals with a hyperthymic temperament are often seen as strong, energetic, productive, and well-respected, whereas the cyclothymic temperament is a pattern of alternation between hypomanic or irritable moods, and depressive moods, cognitions, and behaviours. The association between affective temperament, suicidal behaviour and MRI abnormalities is complex and largely unclear.

Rihmer et al. (2009) investigated the role of affective temperaments in suicidal behaviour using the TEMP-A and compared the affective temperament profiles of 150 consecutively non-violent suicide attempters and 302 age, sex and education matched normal controls. They found that, compared to controls, both female and male suicide attempters scored significantly higher in the more frequent depressive, cyclothymic, irritable and anxious affective temperaments. The hyperthymic temperament, characteristic for bipolar I disorder, was not significantly less common among suicide attempters, whereas the cyclothymic temperament is characteristic for bipolar II disorder and the depressive temperament prevails in unipolar major depression. Additionally, degenerative changes in brain WM have been reported to be associated both in depressed young adults and in children and adolescents with major affective disorders and suicidal behaviour (Ehrlich et al., 2004, 2005; Pompili et al., 2007). Pompili et al. (2007) have shown, after logistic regression analysis in 99 inpatients with major affective disorders, that the presence of PWMH is robustly associated with suicidal behaviour.

Based on previous evidence, we hypothesized that some temperamental traits, like depressive, cyclothymic, irritable and anxious temperaments eventually linked with WMH, may play a more significant role as endophenotypes than the hyperthymic temperament in the context of mood disorders and suicidality. The present study first aimed to evaluate whether the presence of WMH is associated with affective temperaments and suicidal behaviour in patients with major affective disorders and then whether WMH in addition to specific temperament profiles might be a useful biological predictor of suicidal behaviour. To our current knowledge, there are no data linking white matter abnormalities, affective temperaments and suicidal behaviour in mood disorders.

2. Methods

2.1. Participants and study design

From September 2007 to September 2009, a total of 318 white Italian patients were consecutively admitted to the psychiatric inpatient units of Sant'Andrea Hospital and the “Samadi Clinic” in Rome. The inclusion criterion was a DSM-IV-TR diagnosis of major affective disorders (unipolar major depressive disorder, bipolar disorder type I, bipolar disorder type II) (American Psychiatric Association, 1994). Of the 318 subjects who were eligible for the study, 45 were not included in the final sample because they had other psychiatric diagnoses; 84% of them were excluded because they were diagnosed with schizophrenia and 16% with personality disorders. 26 patients were excluded because 53.8% refused to undergo the MRI scans (they could not complete the scan as a result of claustrophobic reactions) and 46.2% because they decided not to participate in research or complete the temperament measures. Patients excluded from the study had similar demographic characteristics and did not differ significantly from the patients included in the final sample with respect to clinical variables, diagnosis or history of suicide attempts. The final sample consisted of 247 patients (118 men, 129 women). Demographic and clinical characteristics of the sample are presented in Table 1.

Clinical and socio-demographic information was taken from medical records by two researchers independently. In cases of disagreement, a third party was consulted. Blood pressure, glyceremia, triglycerides, and total cholesterol were retrieved from official medical records. Hypertension was defined as the presence of more than 140 mm Hg for systolic blood pressure, and 90 mm Hg for diastolic blood pressure and/or current use of antihypertensive medication (Joint National Committee on Detection E, and Treatment of high blood pressure, 1997).

Current severity of affective symptomatology was evaluated using the YMRS (Young et al., 1978) and the HDRS (Hamilton, 1960). Participants were additionally administered the MINI (Sheehan et al., 1998), the BHS (Beck et al.,
Table 1

Sociodemographic characteristics of the two groups (higher dysthymia, cyclothymia, irritability, and anxiety and lower hyperthymia—H-DCIA; and higher hyperthymia, and lower dysthymia, anxiety, and cyclothymia—H-H). The 2-group solution (BIC change = −127.70; ratio of distance measures = 2.23) was indicated by the Two Step Cluster Analysis procedure. Only TEMPS-A Hyperthymic trait contributed negatively to the composition of the first group compared to other traits, whereas the most significant positive trait in the composition of the group was the TEMPS-A Dysthymic trait. Conversely, TEMPS-A Hyperthymic trait contributed significantly in the positive way in the composition of the second group, while TEMPS-A Dysthymia, Anxiety, and Cyclothymia significantly contributed in a negative way the composition of the group (H-H—high hyperthymia).

<table>
<thead>
<tr>
<th>Variables</th>
<th>H-DCIA group (n = 140)</th>
<th>H-H group (n = 107)</th>
<th>Test</th>
<th>Significance</th>
<th>OR</th>
<th>Log-OR</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Men</td>
<td>50.0%</td>
<td>44.9%</td>
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<tr>
<td>Age—mean (SD)</td>
<td>48.28 (15.05)</td>
<td>48.09 (15.90)</td>
<td>t = 0.09</td>
<td>0.93</td>
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<tr>
<td>BD (BD 1)</td>
<td>72.9% (59.3%)</td>
<td>77.6% (56.1%)</td>
<td>χ² = 0.67</td>
<td>0.88</td>
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<td>Substance misuse</td>
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<td>Alcohol</td>
<td>15.7%</td>
<td>16.8%</td>
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<td>Illicit drugs</td>
<td>17.9%</td>
<td>16.8%</td>
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<td>Alcohol + Illicit drugs</td>
<td>1.4%</td>
<td>2.8%</td>
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<td>Recent suicide attempts</td>
<td>23.6%</td>
<td>14.0%</td>
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<tr>
<td>Lifetime suicide attempts</td>
<td>42.1%</td>
<td>42.1%</td>
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<tr>
<td>Lifetime suicidal ideation</td>
<td>52.1%</td>
<td>53.3%</td>
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<tr>
<td>PWMH</td>
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<tr>
<td>1</td>
<td>31.4%</td>
<td>34.6%</td>
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<tr>
<td>2</td>
<td>17.9%</td>
<td>10.3%</td>
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<tr>
<td>3</td>
<td>0.7%</td>
<td>0.9%</td>
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<td>DWMH</td>
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<td>1</td>
<td>39.3%</td>
<td>21.5%</td>
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<tr>
<td>2</td>
<td>5.0%</td>
<td>6.5%</td>
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<tr>
<td>3</td>
<td>2.1%</td>
<td>0.9%</td>
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</table>

Loglinear model statistics: likelihood ratio χ² = 12.49; p = 0.98.

1974; Beck and Steer, 1989) and the TEMPS-A (Akiskal and Akiskal, 2005).

Exclusion criteria were: presence of neurological disorder (e.g., epilepsy, multiple sclerosis, and Alzheimer’s Disease, dementia), diagnosis of other major psychiatric disorders by DSM-IV criteria; family history of dementia; presence of structural MRI findings compatible with stroke or other gross brain lesions or malformations; and history of electroconvulsive therapy in the past 6 months. Subjects participated voluntarily in the study, and each subject provided written informed consent. The study protocol received ethics approval from the local research ethics review board.

2.2. Magnetic resonance image acquisition and rating of white matter hyperintensities

Brain MRIs were performed using a Siemens Sonata, Erlangen, Germany (1.5 T). The FLAIR scan sequence was used for WSM 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 1280 T1 sag: TR 320; TE 107; thickness 5 mm; matrix 231 × 192). The presence of WMH was assessed by a neuroradiologist blind to all clinical information, using the modified Fazekas four-point rating scale which describes MRI hyperintensities on an ascending scale of intensity and frequency (Coffey et al., 1993). A second neuroradiologist, blind to all clinical information and previous ratings, reviewed all MRI films. The mean k value for interrater reliability for both PWMH and DWMH was 0.90.

2.3. Measures: clinical assessment

2.3.1. MINI

The MINI is a clinically administered tool in use in our unit, soon after the admission. One section of this instrument is developed to assess suicidal risk, with questions about past and current suicidality (Sheehan et al., 1998). The MINI is a short structured interview with high validity and reliability developed to explore 17 disorders according to DSM-III-R (Amorim et al., 1998). 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 (Sheehan et al., 1998). MINI diagnoses were confirmed by clinical DSM-IV-TR diagnoses. Clinical diagnoses were assigned by a staff psychiatrist and an attending physician who were blind to the results of MINI and MRI.

2.3.2. TEMPS-A

The TEMPS-A is a new self report measure of the affective temperament with 110 items that defines the bipolar spectrum, with depressive (D), cyclothymic (C), hyperthymic (H), irritable (I), and anxious (A) subscales (Akiskal and Akiskal, 2005). The scale is different from most other temperament scales in that it taps subaffective trait expressions as they were conceptualized in Greek psychological medicine and, in more modern times, German psychiatry. Additionally, the TEMPS-A is not affected by current mood state (e.g., depressive vs. manic) and is able to identify temperament profiles reliably in psychiatric inpatients with...
severe Axis-I psychopathology presumably combined with life crises leading to hospitalization (Akiskal et al., 2005).

2.3.3. BHS
The BHS is a 20-item scale for measuring negative attitudes about the future (Beck et al., 1974). This powerful predictor of eventual suicide addressed three major aspects of hopelessness: feelings about the future, loss of motivation and expectations. Research consistently supports a positive relationship between BHS scores and measures of depression, suicidal intent and current suicidal ideation (Beck et al., 1990). The BHS may, therefore, be used as a proxy indicator of suicide potential. In the series reported in 1985 91 of people who died by suicide had a score $\geq 10$ while only 9% had a score $\leq 9$, so the BHS cutoff score as 9 or higher (Beck et al., 1985).

2.3.4. HDRS$_{17}$ and YMRS
The HDRS$_{17}$ (Hamilton, 1960), 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 mania (Young et al., 1978). HAMD$_{17}$ and YMRS were given primarily to assess the severity of mood symptoms (Table 2).

3. Statistical analysis

In order to reveal temperament groupings (or clusters) within the data set, we used a Two Step Cluster Analysis procedure. This procedure can handle categorical and continuous variables, using a likelihood distance measure which assumes that variables in the cluster model are independent. Continuous variables are assumed to have a normal (Gaussian) distribution and categorical variables are assumed to have a multinomial distribution. Empirical internal testing indicates that the procedure is fairly robust within the data set, we used a Two Step Cluster Analysis.

### 4. Results

#### 4.1. Clinical characteristics of the sample

Patients were 185 BD (75%; 143 BD I, and 42 BD II), and 62 MDD (25%). Sixteen percent of the patients reported current alcohol misuse, 17% reported current use of illicit drugs, and 2% reported current alcohol misuse and illicit drugs use as assessed by the MINI.

All the patients had a HDRS$_{17}$ of 14 or higher indicating moderate to severe depression ($M=29.1; SD=6.2$). Patients had an average score of 10.9 ($SD=6.9; 11.4\pm7.3$ for the BD vs. $9.3\pm5.5$ for the MDD; $t_{245}=2.12; p<0.05$) on the YMRS.

#### Table 2

Psychometric characteristics of the two groups (high dysthymia, cyclothymia, irritability, and anxiety and low hyperthymia—H-DCIA; and high hyperthymia, and low dysthymia, anxiety, and cyclothymia—H-H).

<table>
<thead>
<tr>
<th>Variables</th>
<th>H-DCIA group ($n=140$)</th>
<th>H-H group ($n=107$)</th>
<th>Test</th>
<th>Significance</th>
<th>OR (Reference category is: H-H group)</th>
<th>Log-OR</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPS-A Dysthymia—mean (SD)</td>
<td>17.11 (2.97)</td>
<td>9.27 (4.29)</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
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<tr>
<td>TEMPS-A Cyclothymia—mean (SD)</td>
<td>13.98 (4.24)</td>
<td>10.80 (4.58)</td>
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<tr>
<td>TEMPS-A Hyperthymia—mean (SD)</td>
<td>3.88 (2.82)</td>
<td>12.00 (4.94)</td>
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<td>-</td>
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<tr>
<td>TEMPS-A Irritability—mean (SD)</td>
<td>10.78 (3.64)</td>
<td>8.95 (4.82)</td>
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<tr>
<td>TEMPS-A Anxiety—mean (SD)</td>
<td>17.44 (4.83)</td>
<td>12.10 (5.14)</td>
<td></td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Higher MINI suicidal risk</td>
<td>53.6%</td>
<td>42.1%</td>
<td>0.05</td>
<td>1.67</td>
<td>0.52</td>
<td></td>
<td>-0.4 to 1.06</td>
<td>0.07</td>
</tr>
<tr>
<td>BHS $\geq 9$</td>
<td>77.1%</td>
<td>52.3%</td>
<td>0.001**</td>
<td>2.88</td>
<td>1.06</td>
<td>0.49</td>
<td>1.625 to 0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>BHS—mean (SD)</td>
<td>11.50 (4.63)</td>
<td>8.48 (4.49)</td>
<td>-</td>
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<tr>
<td>HAMD$_{17}$—mean (SD)</td>
<td>29.60 (5.67)</td>
<td>28.34 (6.75)</td>
<td>0.12</td>
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<tr>
<td>YMRS—mean (SD)</td>
<td>10.21 (5.89)</td>
<td>11.76 (8.06)</td>
<td>0.08</td>
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<td></td>
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</tbody>
</table>

Loglinear model statistics: likelihood ratio $\chi^2_{n=25} = 12.49; p = 0.98$. 


Patients had a mean score of 10.2 (SD = 4.8) on the BHS with 66% of the sample reporting scores of 9 or higher.

4.2. Suicide risk

A total of 49% of the patients were at higher risk of suicide on the MINI interview among all patients with mood disorders; 42% reported lifetime suicide attempts and 53% lifetime suicidal ideation.

4.3. MRI results

The MRI indicated that 48% of patients had PWMH (more than 15% had PWMH of 2 or higher on the modified Fazekas scale), and 39% of them had DWMH (more than 7% had DWMH of 2 or higher on the modified Fazekas scale). We calculated Spearman’s rho indices for the correlations between PWMH, DWMH, hypertension, diabetes, total cholesterol, triglycerides, and number of daily cigarettes in this sample of patients; the analyses indicated that the severity of PWMH is associated only with the blood level of triglycerides (Spearman rho = 0.26; p < 0.05). All other indices were not significant.

4.4. Temperament profiles and groups composition

Subjects with BD type I were more likely to be cyclothymic compared to subjects with MDD (13.3 vs. 11.42 p = 0.05) while subjects with BD type I and II were more likely to be hyperthymic compared to subjects with MDD (7.54 vs. 9.60 vs. 5.58 p = 0.001). There were no significant associations in the descriptive analyses and multiple comparisons between WMHs and affective temperaments (data not shown).

The Two Step Cluster Analysis procedure indicated a 2-group solution (BIC change = −127.70; ratio of distance measures = 2.23). Temperament characteristics of the groups are listed in Table 1 and Figs. 1 and 2. TEMPS-A Hyperthymic trait contributed negatively to the composition of the first group, while other traits contributed positively to its composition (H-DCIA—High dysthymic, cyclothymic, irritability, and anxiety; n = 140); however, the most significant positive trait in the composition of the group was the TEMPS-A dysthymic trait. Conversely, the TEMPS-A hyperthymic trait contributed significantly in a positive way to the composition of the second group, while the TEMPS-A dysthymia, TEMPS-A anxiety, and TEMPS-A cyclothymia contributed significantly to the composition of the group but in a negative way (H-H—High hyperthymia; n = 107). Thus, the H-H group is mostly characterized by patients with higher hyperthymia and lower dysthymia, while the H-DCIA group is mostly characterized by patients with higher dysthymia and lower hyperthymia.

Furthermore, differences among the groups were confirmed by 4 (out of 13) differences on clinical and radiographic variables (see Table 1). Patients in the H-DCIA group were more likely to have higher BHS (BHS ≥ 9 = 77% vs. 52%; p > 0.001), more DWMH (46% vs. 29%; χ² n = 3 = 9.90; p < 0.05), higher MINI suicidal risk (54% vs. 42%; p < 0.05), and more recent suicide attempts (24% vs. 14%; p < 0.05), than patients in the H-H group. Even when dichotomizing the white matter intensities using Fazekas scores into absence vs. presence, the pattern of associations did not change (not reported in the

Fig. 1. Relative contribution of temperamental traits in the formation of the H-DCIA group (higher dysthymia, anxiety, cyclothymia, and irritability, and lower hyperthymia)—bars indicate contribution of each temperamental trait; the dashed vertical lines mark the critical values for determining the significance of each variable (for a variable to be considered significant, its t statistic must exceed the dashed line in either a positive or negative direction).
tables; PWMH: 50.0% and 45.8%, respectively for the H-DCIA and the H-H patients; \( p = 0.30 \). DWMH: 46.4% and 29.0%, respectively for the H-DCIA and the H-H patients; \( p < 0.01 \).

4.5. Multivariate associations with the temperament traits

We performed an independent logit loglinear analysis procedure with temperament groups as the dependent variable and variables significantly associated with the groups in the bivariate analyses as independent variables (see Table 1). The analysis fitted the data well: \( \chi^2 = 12.49 \) (df = 25); \( p = 0.98 \). Patients in the H-DCIA group were: 1) more likely to have DWMH rated as 1 on the modified Fazekas scale (OR = 2.48; \( p < 0.001 \)); and 2) more likely to have a BHS score of 9 or higher (OR = 2.88; \( p < 0.001 \)) than patients in the H-H group. We also performed an alternative analysis with the same model as the previous one, except that we entered as independent variable the presence/absence of WMHs. The H-DCIA patients were still more likely to have DWMH (LogOR = 0.77 [OR = 2.16]; \( p < 0.01 \)) than patients in the H-H group.

Thus, differences among temperament groups as measured by the TEMPS-A are supported by differences at the MRI, indicating that different temperament profiles are associated with differences in the subcortical structures of the brain. Patients with a temperament profile characterized by high scores of dysthymia, cyclothymia, anxiety, and irritability, and lower scores on Hyperthymia show a higher suicidal risk than their peers with opposite temperament profile (higher scores on hyperthymia and lower scores of dysthymia, cyclothymia, and anxiety).

Because some independent variables may be associated with the severity of depressive symptomatology, we dichotomized the participants on the basis of their HAMD_{17} score (HAMD_{17} \leq 24 for patients with mild to moderate depression, and HAMD_{17} \geq 25 for patients with severe depression). Then we tested a second model via an independent logit loglinear analysis procedure with temperament groups and depressive groups as dependent variables and the same set of independent variables as in the previous analysis (not reported in the tables). This new analysis did not change the pattern of association between the temperaments and the independent variables. Furthermore, all the third-order interactions ([temperament groups × depression groups] × [independent variable]) were nonsignificant.

5. Discussion

This was, to our knowledge, the first study investigating the association between WMH, affective temperament and suicidal risk in a population of patients with mood disorders. Our findings showed that the H-DCIA group was more likely to have higher BHS scores, higher MINI suicidal risk, more recent suicide attempts and more DWMH than H-H group.

These results replicate the findings of our prior two independent studies showing that depressive, cyclothymic, irritable and anxious temperaments are risk factors and the hyperthymic temperament is a protective factor for suicidal behaviour, at least for suicide attempters (Rihmer et al., 2009; Pompili et al., 2008a,b). The present results extended our prior findings, showing that predominantly depressive temperament profile (high dysthymia, cyclothymia, anxiety and irritability and low hyperthymia) is also significantly related to DWMHs. The most relevant biological difference...
between hyperthymic and other (dysthymic and related) temperaments has been supported previously on the basis of genetic studies showing that the short allele of the serotonin transporter gene was significantly related to depressive, cyclothymic, irritable and anxious temperaments but not to the hyperthymic temperament (Gonda et al., 2009).

Different temperament features assessed by the TEMPS-A are reflected in MRI findings, the H-DCIA group had more DWMH. In line with these findings, a recent study on elderly depressed patients showed that individuals with the short allele of the serotonin transporter gene associated with major affective disorders have more microstructural white matter abnormalities in frontolimbic and other brain regions (Alexopoulos et al., 2009).

The H-DCIA group was more likely to have only DWMH rated as 1 on the modified Fazekas scale. WMHs were predominant 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. Those brain regions are usually implicated in the normal regulation of mood and with the pathophysiology of mood disorders (Figiel et al., 1991; Greenwald et al., 1998; Steffens et al., 1999; Soares and Mann, 1997; Strakowski et al., 2000; Hwang et al., 2006; Taylor et al., 2003).

A total of 25% of bipolar patients took lithium and this was relevant because several studies have shown that mood stabilizers have neurotropic/neuroprotective effects (Manji et al., 2000). Another proposed mechanism for mood disorders is mitochondrial dysfunction and this is relevant because the finding of white matter hyperintensities on MRIs is non-specific, sometimes transient (e.g., in certain connective tissue disorders) and often has no pathologic correlate (Quiroz et al., 2010; Andreazza et al., 2010). However, we did not observe that patients with chronic lithium treatment had fewer white matter hyperintensities.

The notion that symptoms of BD might be due to vascular-related processes disrupting the connectivity between those brain structures is supported by the emergence of manic symptoms post-stroke affecting such brain areas (Celik et al., 2004; Berthier et al., 1996); however, it is still a manner of debate. DWMHs found in healthy adults often have been considered to have a vascular aetiology (e.g., degenerative processes including atherosclerosis, lacunar infarcts, atrophic demyelination and arteriolar hyalinization) (DeCarli et al., 1995). Fujikawa et al. (1995) supported the association between late-onset bipolar disorder and cerebrovascular disease, reporting a higher prevalence of silent cerebral infarcts in patients with late-onset mania compared to those with late onset major depression. Additionally, there have been reports of a significant association between the diagnosis of BD and cardiovascular risk factors, including hypertension, hypercholesterolemia, obesity, and cigarette smoking (Yates and Wallace, 1987; Kilbourne, 2005).

However, our results did not support the proposed link between vascular risk factors and the emergence of manic symptoms because after including PVMH, DWMH, hypertension, diabetes, total cholesterol, triglycerides and number of daily cigarettes as covariates in our analyses, the results indicated that the severity of PVMH is associated only with the blood level of triglycerides while all other indices were not significant.

Based on the above findings, one might have expected a greater frequency of cardiovascular and cerebrovascular risk factors in our sample. However, such negative findings may have been due to the modest size of the sample group studied. H-DCIA subjects were more likely to be men and had more recent suicide attempts, and more severe PVMHs (17.9% had a score of 2 at the Fazekas modified scale). In our recent study on 99 consecutively admitted inpatients with major affective disorder the presence of PVMHs was associated with suicidal behaviours after controlling for age (Pompili et al., 2008a,b). The rates of PVMH were similar for the H-H and the H-DCIA groups (31.4% and 34.6% respectively) consistent with results obtained in previous studies in both pediatric and adult populations (Chang et al., 2005; Sassi et al., 2003; Ahn et al., 2004; Krabbendam et al., 2000; Lyoo et al., 2002; Videbech, 1997). H-DCIA and H-H subjects did not significantly differ for the severity of depressive and manic symptomatology assessed with the HDRS; and YMRS.

These findings, suggesting an association between DWMHs, higher scores on the BHS and dysthymia reported with higher frequency both in H-DCIA and H-H groups, provide hypothetical evidence in support of the notion that in subjects with mood disorders, a dysthymic temperament profile in addition to DWMHs probably plays a critical role in the emergence of hopelessness as assessed by the BHS. The presence of DWMHs and a dysthymic temperament profile may be used for grouping subjects with mood disorder. This may potentially help in optimizing a treatment strategy.

6. Limitations

The main limitation of the present study is the small sample size which undermined generalization of our findings. In addition we could not investigate the association between the lethality or number of suicide attempts and the presence, severity or number of hyperintensities. High-lethality attempts require inpatient medical treatment. High-lethality attempts report greater suicidal intent and more previous attempts, and individuals with early severe lethal attempts more often present severe lethal attempts later (Oquendo et al., 2009). The absence of a direct comparison between lethal and non-lethal suicide attempts limited the clinical relevance of the findings.

Also, the lack of accounting for the cognitive effects of medications may be considered to be a limitation of the present study; this was due to the fact that patients complete the neurocognitive assessment which was currently used in our department (Malhi et al., 2007).

Methodological considerations should be discussed. 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 may potentially help in optimizing a treatment strategy. 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 may have yielded a much higher number and extent of white matter hyperintensities. An analysis quantifying total white matter lesion volume would strengthen the findings. Also, diffusion tensor imaging techniques may be more sensitive for detecting white matter abnormalities in association with mood disorders. In support of this possibility, a study combining diffusion tensor imaging and white matter hyperintensity measurements in healthy elderly individuals detected structural damage as evidenced by increased diffusion coefficients (as measured by diffusion tensor.
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Conflict of interest

All authors declare no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

References


Ehrlich, S., Noam, G.G., Lyoo, I.K., et al., 2004. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized imaging) in areas of normally appearing white matter surrounding foci of WMH (Firbank et al., 2003). Although the latter evidence has been found in an elderly population, in which different mechanisms may be involved in the emergence of white matter hyperintensities, it is possible that they might simply represent the ‘tip of the iceberg’ in terms of structural white matter lesions. Thus, the presence and severity of white matter hyperintensities associated with mood disorders might be understood 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 volumetric methods available.

Finally, it would be interesting to evaluate the eventual associations between differences on MRIs and differences on temperament profiles in patients with different diagnoses (e.g., schizophrenia and personality disorders).

7. Conclusion

Approximately half of the patients had PWMH and a significant percentage of them had DWMH. Also after multivariate associations with the temperament traits, patients with higher dysthymia and lower hyperthymia were more likely to have higher hopelessness, higher MINI suicidal risk and more recent suicide attempts and higher WMHs, mainly DWMHs, than patients with higher hyperthymia and lower dysthymia. Thus, different temperament features assessed by the TEMPS-A may be reflected not only in different genetic background of brain serotonin turnover in monkeys (Kraemer et al., 2008), in children (Jorm et al., 2000) and in adult females (Gonda et al., 2006), but also in different findings on MRIs, indicating that different temperament profiles are associated also with different brain alterations.

We hypothesized that genetic factors (e.g., serotonin transporter gene-linked polymorphic region (5-HTTLPR) contribute to the dysthymic temperament and this relationship is at least partially mediated by development of DWMHs. According to this hypothesis, it has been demonstrated that the short 5-HTTLPR allele has been reported to promote vascular disease (Ramasubbu et al., 2006; Otte et al., 2007; Ramasubbu et al., 2008).

Early identification of individuals with DWMHs, mood disorders and previous suicide attempts which may represent a specific sub-group at risk for highly lethal suicide attempts, is critical. WMHs in patients with major affective disorders might be useful biological markers of suicidality. We have initiated a new direction in our research into the association between WMHs, risk of high-lethal suicide attempts and outcome in mood disorders.

Prospective adjunctive studies are required to provide a better understanding of the pathophysiological processes involved in the outcome of individuals with mood disorder. We urge research the direction into the association between WMH, affective temperament features, serotonin transporter gene polymorphism, and outcome in bipolar disorder.