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Neuropsychological performance and affective temperaments in Euthymic patients with bipolar disorder type II

Ester Romero [a], Jessica N. Holtzman [a,b], Lucila Tannenhaus [a], Romina Monchablon [a], Carlo Mario Rago [a,c], Maria Lolich [a,d], Gustavo H. Vázquez [a,e,*]

[a] Department of Neuroscience, Research Center in Neuroscience and Neuropsychology, Palermo University, Buenos Aires, Argentina,
[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States
[c] Dipartimento di Psicologia Clinica, Universitá La Sapienza, Roma, Italy
[d] National Council of Scientific and Technical Research (CONICET), Argentina
[e] International Consortium for Bipolar & Psychotic Disorder Research, McLean Hospital, Belmont, MA, United States

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ABSTRACT

Affective temperament has been suggested as a potential mediator of the effect between genetic predisposition and neurocognitive functioning. As such, this report seeks to assess the extent of the correlation between affective temperament and cognitive function in a group of bipolar II subjects. 46 bipolar II outpatients [mean age 41.4 years (*SD* 18.2); female 58.9%] and 46 healthy controls [mean age 35.1 years (*SD* 18); female 56.5%] were evaluated with regard to their demographic and clinical characteristics, affective temperament, and neurocognitive performance. Crude bivariate correlation analyses and multiple linear regression models were constructed between five affective temperament subscales and eight neurocognitive domains. Significant correlations were identified in bipolar patients between hyperthymic temperament and verbal memory and premorbid IQ; cyclothymic temperament and attention; and irritable temperament, attention, and verbal fluency. In adjusting for potential confounders of the relationship between temperament and cognitive function, the strongest mediating factors among the euthymic bipolar patients were found to be residual manic and depressive symptoms. It is therefore concluded that affective temperaments may partially influence the neurocognitive performance of both healthy controls and euthymic patients with bipolar disorder type II in several specific domains.

1. Introduction

Bipolar disorder (BD) is mainly characterized by the fluctuation of mood between the two poles of depression and mania (bipolar I) or hypomania (bipolar II), passing through a period of affective remission, known as euthymia (DSM-5, American Psychiatric Association, 2013).

Along with the functional impact of this disorder, 40–60% of these patients present a specific pattern of neurocognitive impairment, both during acute mood episodes and the euthymic phase (Alshuler et al., 2008; Martínez-Arán et al., 2004b; Martino et al., 2008; Latalova et al., 2011). These impairments affect multiple cognitive domains including processing speed, verbal and visual memory, attention, and executive functions (Robinson and Ferrier, 2006; Arts et al., 2008; Bora et al., 2009; Santos et al. 2014). Demographic characteristics (i.e. age, sex, education) and clinical features (i.e. age at first episode, affective state, sub-clinical symptoms), have been identified as potentially influencing cognitive performance (Martínez-Arán et al., 2004b; Martino et al., 2008).

Though the link between BD and cognition has been well established, studies of temperament and neuropsychological test performance are scant. Temperament can be defined as relatively stable, biologically-based, individual differences in the expression of primary emotions, resulting in variable reactivity, energy levels, and self-regulation (Rothbart and Derryberry, 1981; Goldsmith et al., 1987). According to Kraepelin (1921), affective temperamental characteristics may be conceptualized in a quantitative dimension, varying from normal to pathological, and serve as the

* Corresponding author.
E-mail address: gvazquez@palermo.edu (G.H. Vázquez).

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main base for personality development. Later research delineated five specific affective temperamental domains: anxious, irritable, cyclothymic, hyperthymic, and depressive or dysthymic (Akiskal and Mallya, 1987; Akiskal et al., 1989; Akiskal, 1998), each of which may help define endophenotypes within BD (Akiskal et al., 1989; Chiaroni et al., 2005; Hantouche and Akiskal 2006; Vázquez et al., 2008). Affective temperaments are typically evaluated using the Temperament Evaluation of Memphis, Pisa, Paris and San Diego – Autoquestionnaire (TEMPS-A) (Akiskal et al., 2005), a scale developed on the aforementioned theory, translated, and validated in multiple languages (Placidi et al., 1998; Akiskal et al., 2005; Vázquez et al., 2007).

Prior studies have found that BD patients follow a specific temperamental pattern with higher scores on the hyperthymic, anxious, and cyclothymic scales, while their first-degree relatives may show an intermediate score between patients and healthy controls (HC) on the same affective temperamental subscales (Evans et al., 2005; Chiaroni et al., 2005; Vázquez et al., 2008; Mahon et al., 2013, Zeschel et al., 2015). In light of this evidence, recent studies have sought to examine the effect of predominant affective temperaments (defined as one standard deviation above the mean of each temperament) on the neurocognitive performance in BD patients, as well as any factors that may mediate this relationship. Xu et al. (2014) found that symptomatic bipolar patients with a predominant hyperthymic temperament were more impaired in the tasks of set shifting and verbal working memory, and that bipolar II patients performed significantly better than bipolar I patients with the same degrees of affective temperament. In contrast, Russo et al. (2014) found a positive correlation in bipolar patients between scores on irritable and cyclothymic subscales and processing speed, working memory, reasoning, and problem solving, along with significant negative correlations in HC between hyperthymic temperament and attention and social cognition. When the HC and bipolar patients were analyzed together, a further significant negative correlation between depressive temperament and processing speed was identified (Russo et al., 2014).

Other studies have also informed relevant associations between cognitive functions and affective traits. For example, Burdick et al. (2009) found that BD patients with depressive symptomatology showed significant impairments in processing speed tasks. Jaeger and Vieta (2007), Martínez-Arán et al. (2004a, 2004b) and Vázquez et al. (2008) have also reported that higher levels of affective temperament are associated with decreased quality of life.

The psychobiological temperamental model (Cloninger, 1986) is of particular interest for this work, the main assumption of which is that the dimensions of temperament are highly heritable and linked to specific neurobiological markers. Therefore, temperament is modulated by normal variance in brain structure and levels of neurotransmission. Research in the study of cognitive endophenotypes in BD analyzes the potential effect of temperament as a risk factor. Accordingly, differences in the dimensions of novelty seeking, harm avoidance, and reward dependence were found to be associated with variability in the level of activity of the dopaminergic, serotoninergic, and noradrenergic systems, respectively (Gerra et al., 2000; Kim et al., 2006). Further empirical support comes from neuroimaging studies that have correlated scores along Cloninger's (1998) temperamental dimensions with the data from regional brain blood flow (rCBF) analyses and brain metabolism analyses (PET, SPECT, fMRI). Such studies have identified significant alterations in numerous frontal, temporal, and occipital brain regions, in both cortical end subcortical sections (Sugiura et al., 2000; Youn et al., 2002; Gusnard et al., 2003; Hakamata et al., 2006; O'Gorman et al., 2006; Gardini et al., 2009).

Therefore, both Akiskal's (Akiskal et al., 1989; Akiskal and Mallya, 1987) and Cloninger´s (1986) models have contributed valuable insights to the study of temperament and its links to other important psychological dimensions. Though Cloninger models healthy personality and Akiskal developed his theory specifically considering affective illness characteristics, both of their influences have been crucial in the advancement of an integrated perspective of how affective temperaments impact individual psychosocial functioning. As a result, in recent years, it has also been observed that a high percentage of individuals who develop psychiatric disorders (such as schizophrenia, unipolar or bipolar mood disorders, anxiety disorders, and gambling disorder) present with personality/temperamental scores that fall at the extreme ends of the normal distribution (Ono et al., 2002; Martinotti et al., 2006; Fresan et al., 2007; Kashdan and Hofmann ,2008; Loftus et al. 2008; Pompili et al., 2008). The specific pattern of structural and functional brain impairments that these psychiatric disorders present (Sheline, 2003; Drevets et al., 2008; Freitas-Ferrari et al., 2010; Paulesu et al., 2010; Taylor et al., 2012; Haukvik et al., 2013) has pushed researchers to investigate the intricate connection between temperamental traits, brain functioning, and psychiatric disorders. Moreover, it has been stated that many cognitive functions and temperament dimensions may share common underlying neural bases. Therefore recent studies have investigated the extent to which poor development of certain temperamental traits may be associated with deficits in neuropsychological functioning (Bergvall et al., 2003).

Given the preliminary research stage regarding cognitive performance and temperament in BD, this study seeks to further assess the correlation between affective temperament and neurocognitive functioning in a variety of domains, including memory, attention, processing speed, and set shifting, in a group of BD II patients.

2. Methods

2.1. Subjects

The total sample included 92 adult (18 to 65 years old) subjects, consisting of 46 BD type II euthymic outpatients and 46 healthy controls (HC). All patients were enrolled from a private clinic and fulfilled DSM-5 diagnostic criteria for bipolar disorder type II (American Psychiatric Association, 2013).

Both groups (BD-II and HC) were evaluated through semi-structured interviews [Mini International Neuropsychiatric Interview (MINI) and Structured Clinical Interview for DSM for mood disorders (SCID)]. Healthy individuals were recruited by snowball sampling and were excluded from the study if they met criteria for any other neuropsychiatric disorder or if they reported a history of an axis I disorder among their first-degree relatives.

The mean scores on the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) of subjects with BD-II diagnosis corresponded with euthymia (symptomatic remission), as defined by the International Society for Bipolar Disorders (ISBD) nomenclature task force (Tohen et al., 2009) (total score of < 8 on the HAMD and < 5 on the YMRS). Patients with comorbid axis I disorders, current risk of suicide, neurological illness, attention deficit disorder diagnosis, history of psychotic episodes, or electroconvulsive therapy were excluded.

The protocol for subject enrollment was approved by the Institutional Review Board of our center. All subjects provided both verbal and written informed consent prior to enrollment and participation.

2.2. Measures

All subjects completed the TEMPS-A Buenos Aires, which is the locally validated version of a self-report instrument developed by Akiskal and coworkers (Vázquez and Akiskal, 2005; Vázquez et al., 2007). It consists of 110 items that measure affective temperamental traits, spanning the life course, represented in five dimensional scales: dysthymia or depression, cyclothymia, hyperthymia, irritability, and anxiety. In this work, as well as in previous studies (Vázquez et al., 2007, 2008), predominant temperaments are defined as two standard deviation (SD) above the mean of each temperament.

Neuropsychological performance was evaluated using a standardized neurocognitive battery for euthymic patients with bipolar disorder (Martínez-Arán et al., 2004a), exploring the following cognitive domains: (1) verbal memory, (2) visual memory, (3) planning/set shifting, (4) attention, (5) working memory, (6) processing speed, (7) verbal fluency, and (8) premorbid IQ. In order to evaluate these cognitive domains, the following neurocognitive tests were utilized, respectively: (1) Rey Auditory Verbal Learning Test (Rey, 1941), (2) Rey-Osterrieth Complex Figure (Osterrieth, 1944), (3) Stroop Color-Word Test (Golden, 1978) and Wisconsin Card Sorting Test (Heaton, 1981), (4) Wechsler Adult Intelligence Scale (WAIS-III) Digit Span (Wechsler, 1997) and Trail Making Test Part B (Reitan, 1958), (5) Wechsler Adult Intelligence Scale (WAIS-III) Inverse Digit Span (Wechsler, 1997), (6) Trail Making Test Part A (Reitan, 1958), (7) Verbal Fluency Task (FAS) (Benton and Hamsher, 1976), and (8) Wechsler Adult Intelligence Scale (WAIS-III) Vocabulary Subtest (Wechsler, 1997).

2.3. Statistical analysis

Statistical analyses were performed using R software version 3.1.3 (R Foundation, Vienna, Austria). Bipolar patients and HC were compared in terms of demographic characteristics (gender, age, education, and marital status), clinical characteristics (depressive and manic symptoms, as measured by the HAM-D and YMRS scales, respectively), affective temperaments (evaluated using the TEMPS-A Buenos Aires), and neurocognitive functioning in a variety of domains. Composite scores were computed for those cognitive functions that were composed of two or more measures.

Scores on the temperament scales were standardized in controls to assure that they were within one standard deviation of country-specific norm for all five temperament subscales, and therefore that no control with predominant temperament was included. Normative data from the Argentinean TEMPS-A validation study was used in order to standardize the scores. Therefore, the potential influence of predominant temperaments on cognitive performance was avoided (Vázquez et al., 2007). This strategy validates the comparisons between controls and bipolar patients, and reinforces the quality of our healthy control sample, as affective temperaments are in essence related to a dimensional model for mood disorders (Vázquez et al., 2008).

Comparisons of proportions and means were performed using Chi-Square tests and independent sample t-tests, where appropriate. To assess the relationship between affective temperaments and neurocognitive performance, bivariate and multivariate analyses were used. In the case of the latter, all investigated mediators were considered to be potentially correlated with both affective temperament and neurocognitive functioning due to clinical experience and literature review (Martínez-Arán et al., 2004b; Martino et al., 2008). Crude and adjusted regression coefficients were compared to assess the extent of effect modification between temperament and neurocognitive function.

The assumption of normality was assessed and supported by normal q-q plots and the Shapiro-Wilk test of normality. Multiple comparisons adjustments were not applied due to the small sample size. Statistical significance was accepted at $\alpha = .05$.

2.3.1. Affective temperaments and neuropsychological tasks

Crude bivariate correlation analyses were performed between TEMPS-A subscales and the aforementioned neurocognitive domains in the whole sample, as well as in bipolar patients and HCs separately, resulting in a Pearson's product moment correlation coefficient for each association. Fisher's z transformation was performed to test the significance of the difference between the correlation coefficients for the HC and bipolar subjects, making the assumption of non-overlapping correlations between bipolar patients and HC.

In an attempt to better understand the correlations between affective temperament and neuropsychological performances, the first and fourth quartiles for each affective temperament subscale in both groups were compared. As the concept of affective temperament refers to a dimensional model, studying the higher and lower extremes of their manifestation may help to better explore neuropsychological performance within these phenomenological ends. Furthermore, in a post-hoc analysis, the attentional performance was compared among bipolar patients in the first and fourth quartiles of each temperament sub-group.

A multiple linear regression model was constructed to estimate the extent of the significant associations between affective temperaments and neurocognitive domains, adjusting for age, gender, and education, as these variables have previously been reported to have a potential impact on cognition (Martínez-Arán et al., 2004b; Martino et al., 2008).

2.3.2. Affective temperaments and clinical features

To assess the extent and significance of a correlation between sub-threshold manic and depressive symptoms with the five affective temperaments, the bivariate Pearson correlation analysis was used. We constructed a second multiple linear regression model adjusting for residual manic and depressive symptoms, as measured by the YMRS and HAMD scales, as these symptoms have been shown to negatively impact a variety of domains of cognition in bipolar patients, and even during euthymia. A third further model was constructed, for bipolar subjects only, adjusting additionally for onset age, age of diagnosis, and prior number of hospitalizations, as these covariates have a potential confounding effect on the relationship between affective temperament and neurocognitive functioning (Martino et al., 2008). Finally, a composite model was constructed, adjusting for socio-demographic variables and sub-threshold affective symptoms.

3. Results

The mean age at onset for patients with BD-II was 28.93 (*SD* 11.65) years. 24 (52.2%) BD-II patients reported a positive family history for BD and the total years of bipolar illness was 15.09 (*SD* 13.75). The mean number of previous affective episodes was 7.26 (*SD* 6.23), with an average of 1.5 (*SD* 0.65) hospitalizations, and a mean age of 38.77 (*SD* 13.37) years at first hospitalization. A total of 11 patients (23.91%) presented with prior suicide attempts, 9 (19.56%) had a previous history of rapid cycling, and none presented psychotic symptoms in any prior episode.

3.1. Groups comparisons and bivariate analysis

Overall, demographic characteristics were comparable between the two groups, with no significant differences in the mean age at enrollment, gender, level of educational attainment, or marital

Table 1
Demographic, clinical, and cognitive characteristics of bipolar subjects and healthy controls.

	Bipolar II ($n=46$)	Healthy Controls ($n=46$)	p-value
Age (years) [mean (*SD*)]	41.4(18.2)	35.1(18.0)	0.100
Female [*n* (%)]	33(58.9)	26(56.5)	0.190
Education Level [*n* (%)]			0.530
Primary incomplete	0(0)	0(0)	
Secondary incomplete	10(21.7)	6(14.3)	
Higher education	36(78.3)	36(85.7)	
Marital status [*n* (%)]			0.530
Single	13(28.3)	10(31.3)	
Married	24(52.2)	18(56.3)	
Unmarried partners	3(6.5)	0(0)	
Divorced	6(13.0)	4(12.4)	
Mood symptoms [mean (*SD*)]			
Depressive symptoms (HAM-D)	7.8(3.2)	0.5(1.8)	
<0.001	Manic symptoms (YMRS)	4.7(6.0)	0.3(0.9)
<0.001			
Affective temperament [mean (*SD*)]			
Hyperthymic	10.4(4.3)	8.5(4.4)	0.060
Depressive	9.5(4.0)	5.9(3.8)	
<0.001	Cyclothymic	12.6(10.5)	5.7(5.0)
<0.001			
Irritable	8.5(4.6)	4.5(4.0)	
<0.001	Anxious	13.0(7.7)	5.9(4.2)
<0.001			
Cognitive domains [mean (*SD*)]			
Memory			
Verbal	65.4(11.4)	68.0(8.5)	0.230
Visual	14.4(6.1)	19.2(3.7)	
<0.001	Working memory	6.0(2.2)	7.5(2.1)
0.002			
Attention	20.9(6.0)	26.8(6.0)	0.004
Processing speed	42.5(19.5)	31.9(12.1)	0.020
Planning/Set shifting	205.9(39.8)	231.2 (28.5)	0.002
Verbal fluency	40.4(12.1)	40.5(7.1)	0.950
Premorbid IQ	45.8(6.8)	45.1(10.2)	0.720

status (Table 1). Though patients with BD rated significantly higher in terms of current affective mood symptoms compared than HC, including the YMRS (4.7 vs. 0.3) and HAM-D (7.8 vs. 0.5), the mean scores for manic and depressive symptoms of subjects with BD-II correspond to those of clinical euthymia (Tohen et al., 2009).

An assessment of affective temperaments in the two groups revealed higher scores on all five sub-scales for the bipolar group. Significant between-group differences were found in all temperaments except for hyperthymic temperament, which was non-significantly elevated (10.4 vs. 8.5, $p=0.060$) in the bipolar group (Fig. 1).

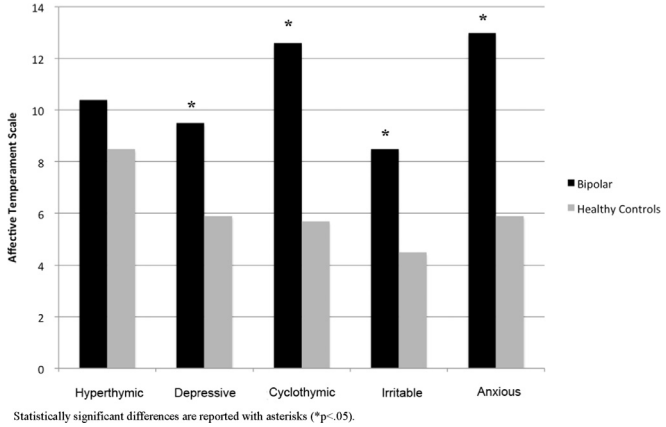


Fig. 1. Comparison between bipolar subjects ($n=46$) and healthy controls ($n=46$) in mean affective temperament scores.

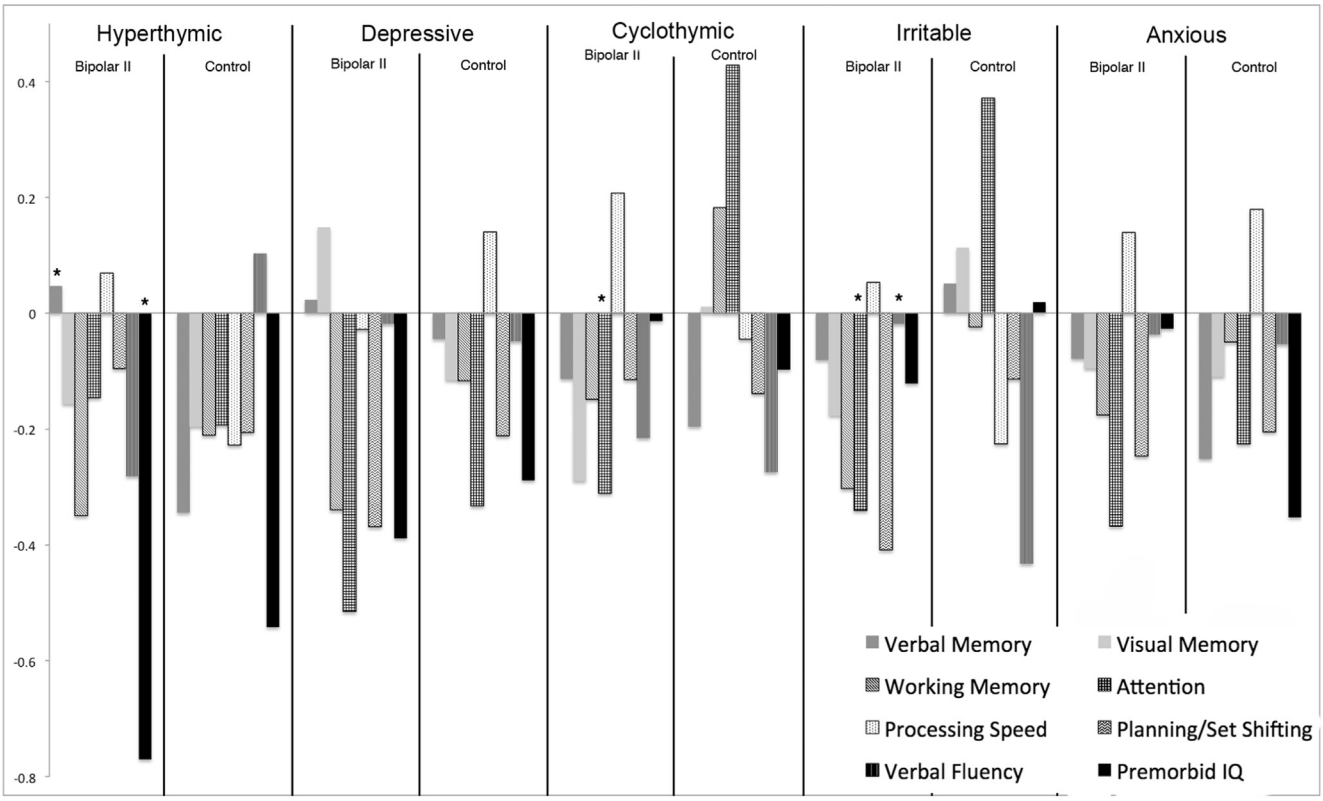
Upon standardization of the affective temperament scores of the HCs against country-specific norms, the HCs were found not to deviate significantly from the overall Argentinean population (Vázquez et al. 2007), with none of the mean temperaments deviating more than one SD outside of the accepted country-specific norm.

In terms of cognitive performance, there were several significant differences in the mean outcomes between bipolar subjects and HCs. Specifically, bipolar patients performed significantly worse in terms of visual memory, working memory, attention, processing speed, and planning/set shifting. In contrast, there were no significant differences between the two groups in terms of verbal memory ($p=0.230$), premorbid IQ ($p=0.720$), or verbal fluency ($p=0.950$).

In order to assess the extent of correlations between affective temperaments and cognitive performance, crude correlation analyses were performed on both groups separately (Fig. 2). In the bipolar subgroup, significant inverse correlations were found between hyperthymic temperament and working memory ($r^2=0.122$, $p=0.020$); dysthymic temperament and attention ($r^2=0.265$, $p<0.001$), planning/set shifting ($r^2=0.137$, $p=0.020$), working memory ($r^2=0.111$, $p=0.020$), and premorbid IQ ($r^2=0.152$, $p=0.020$); cyclothymic temperament and visual memory ($r^2=0.084$, $p=0.03$) and attention ($r^2=0.097$, $p=0.040$); irritable temperament and working memory ($r^2=0.092$, $p=0.040$), attention ($r^2=0.117$, $p=0.030$), and planning/set shifting ($r^2=0.167$, $p=0.010$); and anxious temperament and attention ($r^2=0.136$, $p=0.020$). In comparison, in the healthy control subgroup, fewer significant inverse correlations were found, only including hyperthymic temperament with premorbid IQ ($r^2=-0.542$, $p<=0.001$) and verbal memory ($r^2=-0.345$, $p=0.039$); and anxious temperament and premorbid IQ ($r^2=-0.368$, $p=0.035$).

Of particular note, when comparing the Pearson correlation coefficients between the two sample groups, several significant differences arose (Fig. 2). The bipolar subjects were found to have a stronger inverse correlation between hyperthymic temperament and premorbid IQ (r: −0.77 vs. −0.542), while a much weaker correlation was found between hyperthymic temperament and verbal memory (r: 0.047 vs. −0.345). Further, there was a highly significant difference between bipolar subjects and HCs in terms of the correlation between cyclothymic temperament and attention (r: −0.311 vs. 0.428), with bipolar patients expressing a strong inverse correlation between the two variables, whereas HC expressed a highly positive correlation. Likewise, a similar relationship was found between the two correlation coefficients for irritable temperament and attention (r: −0.341 vs. 0.371), with the bipolar subjects presenting a negative correlation and the HC presenting a highly positive correlation. Interestingly, a significantly weaker inverse correlation was found between verbal fluency and irritable temperament (r: −0.019 vs. −0.433) in the bipolar patients in comparison with controls.

When comparing temperament quartiles in the bipolar II group in a post hoc analysis, significant differences were found between the first and fourth quartiles of depressive temperament (27.7 vs. 20.2, $p<0.001$), cyclothymic (27.9 vs. 21.1, $p=0.013$), and anxious temperament (28.1 vs. 20.7, $p=0.002$). However, no significant differences were observed in hyperthymic (23.7 vs. 22.0, $p=0.500$) or irritable (24.6 vs. 20.9, $p=0.280$) temperaments. Given the observed negative correlations in bipolar patients between irritable temperament and attention, as well as anxious temperament and attention, the level of attention was compared between the first and fourth quartiles of each temperament. It is worth noting



Comparison in correlation size between neurocognitive domains and affective temperaments in healthy control subjects and bipolar II patients. Bars describe r (Pearson) resulting from the correlation analysis between the eight neurocognitive domains and the five affective temperaments in healthy control subjects and bipolar II patients. Statistically significant differences are reported with asterisks (*p<0.05).

Fig. 2. Correlations between affective temperaments and neurocognitive domains in bipolar subjects and healthy controls.

that the level of attention was elevated among bipolar patients with lower scores in all five temperament subgroups.

Interestingly, despite the observed mean differences in the sub-threshold manic and depressive symptoms between bipolar subjects and healthy controls, bivariate correlation analyses revealed no significant correlation between the sub-threshold mood symptoms and the five affective temperaments in either study group.

3.2. Multivariate assessment of affective temperaments and neurocognitive domains

As a secondary, post-hoc analysis, linear regressions were performed using the data from bipolar subjects adjusting for three sets of variables: 1) demographic characteristics (age, gender, and educational level), 2) residual manic and depressive symptoms, as measured by the YMRS and HAM-D scales, and 3) illness characteristics (illness duration, age at diagnosis, age at onset, and number of prior episodes). Additionally, another more complete model was constructed including 4) demographic characteristics and residual affective symptoms.

The inverse correlation between hyperthymic temperament and working memory in bipolar patients remained significant when adjusting for all three sets of characteristics (Supplementary Table 1). A similar pattern was observed with regard to the inverse correlation between depression and working memory, as well as depression and performance on attention tasks. For a majority of the other significant correlations observed in the crude analysis, the correlation remained significant when adjusting for demographic characteristics and illness characteristics, but became marginally insignificant when adjusting for residual mood symptoms. Lastly, the correlations between cyclothymic temperament and verbal memory and attention were only observed to be significant in the crude analysis, but not in any of the three adjusted analyses.

In a fourth, more complete, composite regression model adjusting for age, gender, educational level, and residual affective symptoms, only correlations between depressive temperament and working memory ($\beta = -0.236$, $p = 0.032$), attention ($\beta = -0.968$, $p < 0.001$), planning/set shifting ($\beta = -4.051$, $p = 0.045$), and premorbid IQ remained significant ($\beta = -0.719$, $p = 0.048$), while all other correlations with other affective temperaments were rendered non-significant (Table 2).

4. Discussion

This study examined the relationships between cognitive performance and affective temperaments in BD patients. While related research has been conducted, this study specifically targets a group of euthymic patients diagnosed with bipolar II disorder. Our findings suggest that there are unique associations between affective temperaments and cognition. Moreover, the nature of the correlations between affective temperaments and cognitive domains differed between the BD II patients and the HC subjects.

In agreement with previous studies, bipolar patients demonstrated significantly greater cognitive deficits when compared to HCs, across a wide range of cognitive domains (Martínez-Arán et al., 2004b; Martino et al., 2008; Latalova et al., 2011). It is worth noting, however, that the HCs were, as expected, significantly more normothymic, with lower and more homogenous scores on all five temperament subscales. This probably accounts for both the reduced cognitive deficits

Table 2
Crude and adjusted linear regression models including demographic characteristics and residual affective symptoms.

Affective temperament	Neurocognitive domain	Crude model			Adjusted[a] model			
		B	Standard error	*p*-value	*β*	Standard error	*p*-value	r^2
Hyperthymic	Verbal memory	0.125	0.406	0.760	0.338	0.470	0.458	0.286
	Visual memory	−0.222	0.213	0.304	−0.044	0.245	0.858	0.394
	Working memory	−0.176	0.073	0.020	−0.153	0.090	0.103	0.314
	Attention	−0.195	0.215	0.369	−0.129	0.267	0.633	0.183
	Processing speed	0.302	0.701	0.669	−0.078	0.944	0.935	0.267
	Planning/set shifting	−0.834	1.437	0.566	0.055	1.702	0.975	0.282
	Verbal fluency	−0.798	0.419	0.064	−0.645	0.572	0.270	0.256
	Premorbid IQ	−0.129	0.282	0.651	−0.070	0.354	0.844	0.293
Depressive	Verbal memory	0.066	0.432	0.880	−0.152	0.567	0.791	0.413
	Visual memory	0.223	0.228	0.331	0.272	0.2888	0.354	0.414
	Working memory	−0.186	0.079	0.0237	−0.236	0.104	0.032	0.366
	Attention	−0.801	0.217	0.0007	−0.968	0.246	0.0007	0.516
	Processing speed	−0.137	0.797	0.864	−0.233	1.126	0.838	0.268
	Planning/set shifting	−3.486	1.462	0.023	−4.051	1.895	0.045	0.415
	Verbal fluency	−0.057	0.459	0.902	−0.385	0.697	0.586	0.228
	Premorbid IQ	−0.630	0.252	0.0173	−0.719	0.343	0.048	0.415
Cyclothymic	Verbal memory	−0.124	0.165	0.457	0.050	0.185	0.788	0.414
	Visual memory	−0.168	0.084	0.053	−0.066	0.095	0.490	0.405
	Working memory	−0.031	0.032	0.335	−0.004	0.037	0.907	0.235
	Attention	−0.172	0.085	0.051	−0.072	0.102	0.489	0.193
	Processing speed	0.3711	0.280	0.193	0.332	0.357	0.362	0.294
	Planning/set shifting	−0.408	0.588	0.491	0.317	0.675	0.644	0.290
	Verbal fluency	−0.248	0.173	0.159	−0.089	0.228	0.701	0.223
	Premorbid IQ	−0.008	0.102	0.934	0.117	0.120	0.341	0.322
Irritable	Verbal memory	−0.165	0.311	0.599	−0.060	0.375	0.874	0.432
	Visual memory	−0.205	0.176	0.249	−0.281	0.211	0.195	0.423
	Working memory	−0.134	0.066	0.049	−0.063	0.089	0.489	0.275
	Attention	−0.405	0.181	0.031	−0.331	0.235	0.1728	0.243
	Processing speed	0.204	0.617	0.742	0.621	0.851	0.474	0.284
	Planning/set shifting	−2.935	1.107	0.012	−0.730	1.459	0.622	0.250
	Verbal fluency	−0.046	0.383	0.906	0.015	0.561	0.979	0.184
	Premorbid IQ	−0.158	0.222	0.479	−0.018	0.311	0.954	0.293
Anxious	Verbal memory	−0.103	0.201	0.611	−0.029	0.218	0.897	0.431
	Visual memory	−0.072	0.115	0.534	−0.129	0.124	0.309	0.407
	Working memory	−0.051	0.044	0.258	−0.018	0.052	0.734	0.264
	Attention	−0.287	0.118	0.019	−0.219	0.135	0.118	0.263
	Processing speed	0.351	0.400	0.385	0.581	0.486	0.245	0.311
	Planning/set shifting	−1.104	0.733	0.141	−0.117	0.809	0.887	0.241
	Verbal fluency	−0.058	0.241	0.812	−0.077	0.326	0.815	0.186
	Premorbid IQ	−0.023	0.143	0.874	0.028	0.168	0.869	0.294

[a] Adjusted for age, gender, educational level, and residual manic and depressive symptoms.

and the less apparent correlation between temperament and cognition in HC. It is proposed that low degrees of temperamental features, as observed in the healthy control group, likely do not interfere with cognition and may in fact benefit certain aspects of cognitive performance (Russo et al., 2014).

Though verbal fluency is often found to be impaired in several psychiatric conditions, such as depression and schizophrenia (Butman et al., 2000; Higier et al., 2014; Xu, et al. 2014), we found no significant differences between the two groups in terms of verbal fluency or premorbid IQ. The verbal fluency score derived from the vocabulary subtest from WAIS III is hence frequently used as an indicator of premorbid state and to determine baseline cognition. Furthermore, it is thought that early social experiences may influence vocabulary development, more so than formal education. As such, we conclude that the premorbid state of the two groups is likely similar. Conversely, we believe this increases the relevance of the results regarding a cognitive impairment in the BD II group.

As such, though the two groups' cognitive performances reached significant differences in several cognitive domains, this was not the case with verbal memory. As has been previously reported, verbal memory is a highly validated measure of cognitive impairment in BD (Bourne et al., 2015). Though the small sample size could have affected the sensitivity of the analysis, the clinical group demonstrated low within-group variability (BD II euthymic patients), representing an endorsement of the reliability of the results of this study. Additionally, it is worth noting that study samples frequently include either a mixture of BD I and II patients or mainly BD I subjects. However, some studies (i.e., Bourne et al., 2015; Torrent et al., 2006) have found that BD II patients may present an intermediate level of performance between BD I individuals and the control group. We therefore suggest that the lack of significant difference between the two groups in terms of verbal memory may be due to the exclusive inclusion of BD-II euthymic patients in our sample.

In performing unadjusted correlation analyses of the association between affective temperament and neurocognitive functioning in the bipolar (Fig. 1) and healthy control groups separately, several of the correlations were found to be significant. Specifically, in the BD II group, at least one significant correlation was found between each affective temperament and a corresponding neurocognitive function. However, though there were several significant individual correlations between temperament and cognition in bipolar patients, there were fewer identified significant differences between the BD and HC groups. It is possible that a bigger sample size would have provided greater statistical power to detect these differences.

Interestingly, among bipolar patients, there was a direct

correlation between hyperthymic temperament and verbal memory, while there was an inverse correlation between these two variables in the HC group. In contrast, there was a negative correlation between hyperthymic temperament and premorbid IQ in both the bipolar patients and the HC group, though the correlation within the bipolar group was significantly stronger. Though neither of these findings has been previously reported (Russo et al., 2014; Xu et al., 2014), researchers have claimed that bipolar patients with a predominant hyperthymic temperament present worse cognitive deficits in terms of verbal memory than individuals with other predominant temperaments. Furthermore, the pattern of correlations between hyperthymic temperament and verbal memory between bipolar patients and HCs is consistent with the general pattern of results found by Russo et al. (2014), though their findings were marginally non-significant. Further, Xu et al. (2014) found that BD II patients with a predominant hyperthymic temperament presented a better performance in verbal memory than BD I patients with this same temperament. Our results could suggest that those individuals with BD II that show a hyperthymic predominant temperament and are clinically euthymic may present an adequate performance in verbal memory tasks.

Another relevant difference between bipolar subjects and HCs was found in terms of the correlation between cyclothymic temperament and attention; bipolar patients expressed a strong inverse correlation between these two variables, whereas the HC group expressed a highly positive correlation. On the one hand, these results could be considered to contradict those reported by Russo et al. (2014), with BD patients that have a predominant cyclothymic temperament showing a better neurocognitive performance than BD individuals with other temperamental traits. However, this improved performance was found specifically with regard to processing speed, working memory, reasoning, problem solving, and global cognition. Additionally, though BD patients with a cyclothymic temperament presented a better performance in these functions, the Russo et al. (2014) sample was composed of both BD I and II patients, whereas our sample consisted entirely of euthymic BD II patients. Moreover, cyclothymic temperament has been proposed as a fundamental substrate from which BD II may arise (Perugi and Akiskal, 2002). According to Eich et al. (2014), this temperamental trait may explain the presence of shared features between BD and attention deficit with hyperactivity disorder. On the other hand, the lower and more homogeneous scores of the HC group on the TEMPS-A scales could explain the positive correlation found between cyclothymic temperament and attention performance. Up to a certain point, increased scores on temperament scales may be beneficial for cognition. Nonetheless, further replication in a larger sample of BD II patients is required to draw more definitive conclusions.

A comparable relationship between the two correlation coefficients for irritable temperament and attention was found, with the bipolar subjects presenting a negative association and the HC group presenting a strong positive association. As previously hypothesized by Russo et al. (2014), we believe that up to a reasonable point, the presence of certain affective temperaments may benefit cognitive performance, adequately activating the brain without becoming dominated by one specific temperament, which could instead negatively affect cognition. Further research may elucidate the specific neuropathogenic mechanisms behind the correlation of cyclothymic and irritable temperaments when present in subjects affected by BD and worse attentional outcomes.

When applying multiple linear regression analyses, demographic factors (age, gender, and educational level) had a minimal effect on the significance of the observed correlations between affective temperaments and cognitive performance. This suggests that demographic factors within our sample do not likely influence the observed relationships to a great extent. In another model adjusting for illness characteristics in the relationships between affective temperament and cognitive performance, relevant illness characteristics were identified a priori to have a potential effect on cognitive performance in BD patients (Martino et al., 2008; 2013). However, in accordance with the results of the bivariate analyses in this study, selected illness characteristics were not significant in the proposed model. Again, our restriction of the sample to BD II patients may in part explain these results, as previous studies included either a mixture of BD I and II patients or subjects that were not in a euthymic phase (Martínez-Arán et al., 2004b, Martino et al., 2013).

However, we observed a pattern of results from the adjusted analyses that suggests residual manic and depressive symptoms in euthymic patients to be the greatest confounders. The models adjusting for YMRS and HAM-D scores frequently resulted in a larger r^2 value, indicating that levels of manic and depressive symptoms may lie on the causal pathway between affective temperament and cognitive performance. This finding therefore supports the previous conception that both manic and depressive symptoms may negatively affect cognition in bipolar patients, highlighting the necessity to adequately control episodic symptomatology to the best of our abilities (Martínez-Arán et al., 2004b).

In the more elaborate multiple linear regression model, adjusting for demographic factors and residual affective symptoms, the depressive temperament remained more consistently and strongly correlated with the various neurocognitive domains than the other four temperaments. Such findings support the strength of the previously mentioned correlations between affective temperament and cognitive performance, independent of the role of illness characteristics including illness duration, age of onset, and number of prior episodes.

Overall, our findings contribute to current knowledge and understanding of the relationship between specific affective traits, temperamental levels, and cognitive performance in patients with BD type II. We believe that future research should continue to follow these new avenues of investigation, which may in turn help identify different clinical subgroups and design more tailored treatments for BD patients.

This study possesses several important strengths, perhaps most importantly that patients with significant levels of depressive or manic symptoms were excluded from the sample, preventing the influence of residual mood symptoms from substantially influencing the results. Previous studies have included bipolar I and II patients with higher average scores on sub-threshold manic and depressive symptoms, which are well known clinical factors of impairment on cognitive performance (Martínez-Arán et al., 2004b). In addition to the demographic consistency between the bipolar patients and HCs, this study possesses the additional strength of only including bipolar II patients, limiting the heterogeneity of the sample in question. To our knowledge, this is the first study that has assessed the link between affective temperament and neurocognitive performance exclusively in euthymic bipolar II patients. Finally, our analysis regards each temperament raw-score separately, rather than computing a predominant temperament for each patient, which may unnecessarily separate patients into artificially delineated subgroups.

4.1. Limitations

Despite the strengths of this study, it also possesses relevant limitations. First, the total number of subjects recruited for this study is relatively small, which may affect the power of analysis and restrict the possibility of adjusting for multiple comparisons. Second, though there is no significant difference in educational

levels between bipolar patients and HCs, both subgroups exhibit relatively high levels of education, and therefore may not be representative of the Argentinean population in general. Third, given the preliminary and cross sectional design of our study, the presence of minimal residual symptomatology may have biased our results. It is possible that sub-threshold symptoms may have affected both affective temperament and the cognitive performance. Fourth, in our analyses of the correlation between affective temperaments and neurocognitive functioning, we employed multiple linear regression analyses, which assume the linearity of the relationship in question. However, in doing so, it is possible that we were not able to detect the presence of other non-linear relationships. Yet, given the limited number of prior studies of cognition and temperament in bipolar patients, we chose to limit our analyses to a single model type. Given the continued exploratory nature of investigations seeking to link temperament and cognition in bipolar patients, further more controlled studies are warranted to define the exact nature of these relationships, as well as to identify other mediating factors that may confound a direct relationship between temperament and cognition.

Disclosures

No author or any immediate family member has financial relationships with commercial entities that might represent potential conflicts of interest in this work.

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Appendix A. Supporting information

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