Research Article

Affective Temperaments in Bipolar I Patients in Tunisia (A Study Using the Tunisian Validated Version of the TEMPS-A)

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Abstract

Background: The study of affective temperaments is of interest for psychiatrists as they have an impact on the clinical expression and the prognosis of bipolar disorder.

Method: This is a cross-sectional, descriptive and analytical study on 100 patients with Bipolar Disorder type I in clinical remission, that were recruited from 1 february 2013 to 30 June 2013 at the Department of Psychiatry A of Razi Hospital. We used the Tunisian validated version of the TEMPS-A for assessment of affective temperaments.

Results: The sex-ratio was 1,3. Average age of patients was 41 years. Highest average scores were obtained for hyperthymic temperament (12,97) and for cyclothymic temperament (10,03). Age was positively correlated with hyperthymic temperament (r=0,197; p=0,050). Average score of anxious temperament was inversely correlated with psychotic features during first affective episode. (p=0,015). A positive correlation was found between a history of mixed episodes and the average score of depressive temperament (p=0,043. The average score of cyclothymic temperament was positively correlated with the number of mixed episodes (r=0,231; p=0,021). The duration of the disorder was positively correlated with hyperthymic temperament (r=0,263; p= 0,008) and negatively correlated with anxious temperament (r=-0,201; p=0,045). The choice of therapeutic strategies was little influenced by affective temperaments.

Limitations: The cross-sectional design of the study, the small sample size, our sample consisted of former inpatients exclusively, concurrent pscychopharmacological treatment which can be a confounding factor.

Conclusion: Assessment of affective temperaments should be taken into consideration in the diagnosis, prognosis and therapeutic decision making of bipolar I patients.

Keywords: Affective temperaments; Bipolar disorder; TEMPS-A

Abbreviations

TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire version; TEMPS-I: Temperament schedule of Memphis, Pisa, Paris and San Diego, Interview version; DSM -IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; SPSS: Statistical Package for Social Sciences

Introduction

The temperament refers to individual characteristics, supposed to be of biological or genetic origin. It determines affective, relational, attentional and motor reactions to different situations and plays an important role in social functioning. The concept of affective temperaments has been studied in order to comprehend human behavior and psychopathological risk factors for different mental disorders, in particular affective disorders [1,2]. Affective temperaments can be defined as a temporally stable dimension which consists of constitutive, heritable and independent traits which largely determine the bipolar phenotype [1,3,4]. Indeed, temperaments can be understood as behavior al endophenotypes of mood disorders, or genetic predispositions to certain mood states [5]. The first types of temperaments individualized by Akiskal in 1979 were: depressive, hyperthymic, and cyclothymic temperament, followed by the irritable temperament in 1987 and the anxious temperament in 1998 [6,7]. The five factor structure of the model was confirmed when the short version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A) was validated. Several studies explored the role of affective temperaments in the onset and the clinical features of mood episodes, the prognosis of mood disorders and their comorbidities [1,8-11]. Future studies need to confirm statistically the factorial distribution of temperamental traits, and to analyse the relation ships between temperamental traits, mood states and mood disorder [12]. However, in clinical practice, the evaluation of the underlying temperament receives little attention compared to the mood episodes. So far, very few Tunisian studies have investigated this subject.

The objectives of our study were:

• to evaluate affective temperaments in patients bipolar disorder type I in remission, and

• to explore the relationship between affective temperaments and clinical as well as prognostic variables of the disorder.

Methods

This is a cross-sectional and analytical study that was conducted at the out patients clinic of Psychiatry «A» department of «Razi» Hospital from 1 February to 30 June 2013.

Participants' inclusion criteria were:

- follow up for Bipolar Disorder type I according to DSM-IV-R.

- age ≥ 18 years

- illness duration ≥1 year

- remission from last affective episode ≥ 8weeks

- informed consent of patient to participate in the study

Participants' exclusion criteria were:

- mental retardation

- Cognitive impairment (dementia)

- illness duration < 1 years

- substance induced bipolar disorder or affective disorder due to a general medical condition.

Description of the study and assessment instruments: Data was collected from the patients' medical files, and completed by face to face interviews, with the help of a pre-established questionnaire containing socio-demographic and clinical variables and the TEMPS-A questionnaire in its Tunisian-arabic validated version. All interviews were conducted by the person (WL), one of the authors of the study and Psychiatry resident. Interviews took place at the Department of Psychiatry «A» of Razi hospital, and had an approximate duration of 30 to 60 minutes. Affective temperaments were assessed with the help of the The TEMPS-A questionnaire. It was developed as a semi-structured interview (TEMPS I) at the university of Tennessee, Memphis, by Akiskal. It was initially validate din 1998 in a sample of students. On the basis of TEMPS I, Akiskal elaborated 2005 in San Diego an auto-questionnaire, the TEMPS-A. This version of the questionnaire was validated in numeruous countries and languages. In Tunisia, the TEMPS-A in its Tunisian-Arabic version was validated in 2010, as part of a doctoral thesis. This scale is composed of 110 items for females and of 109 items for males. It describes the five dimensions: depressive temperament (items 1-21), cyclothymic temperament (items 22-42), hyperthymic temperament (items 43-63), irritable temperament (items 64-84), and anxious temperament (items 85-110). The factorial score of each of the five dimensions is obtained by scoring each positive response to an item with one point. The total score for each dimension is obtained by adding up all positive responses. Therapeutic compliance during the past two years was qualified as «good» in case of complete adherence to treatment, as «medium» if patient stopped treatment not more than once in a year, and as «low» if treatment was stopped two times

Table 1: Socio-demographic profile of the studied sample.

Sex n(%)	
M	57 (57%)
F	43 (43%)
Age a±sd	41±9
Residence n(%)	
Urban	86 (86%)
Rural	14 (14%)
Schooling level n(%)	
Primary	32(32%)
Secondary	49(49%)
University	13(13%)
No schooling	6(6%)
Professional status	
Active	63(63%)
Unemployed	32(32%)
Retired	5(5%)
Marital status	
Single	48(48%)
Married	41(41%)
Divorced	11(11%)
Personal antecedent's n(%)	
Somatic	17(17%)
Anxious troubles	2 (2%)
Suicide attempt	22 (22%)
Judicial	8(8%)
Addictive behavior n(%)	
Tobacco	41(41%)
Alcohol	13(13%)
Cannabis	7(7%)
Others	6(6%)
Age of disease beginning; a±sd	25±6,7
Number of evolution years a±sd	16±9,5
Remission duration; a±sd	34±7
First episode n(%)	
Manic	49(49%)
Depressive	36(36%)
Hypomanic	2(%)
Mixed	13(13%)
a: average; sd: Standard Deviation	

or more per year.

Data analysis

Data analysis was performed using the software package SPSS in its 18th version. The impact of affective temperaments on socio-demographic and clinical variables was analysed by multivariate tests, ANOVA tests, and by calculating the Pearson correlation coefficient.

Results

Socio-demographic and clinical description of the sample: Sex ratio was 1,3 and average age of participants was 41 years. Socio-demographic data is presented in (Table 1). A family history of affective disorders was present in 52 patients (52%), of whom 63,5% (n=33) reported a family history of bipolar disorder. Somatic co-morbidity was dominated by endocrine diseases (58,8%, n=10), and psychiatric co-morbidity was found in two patients who had obsessive compulsive disorder. Suicide attempts were comitted in most cases (82,6% n=19) during an affective episode (Table 1). Substance use, abuse or dependence as found in 44% of study participants (n=44). Tobacco was the most consumed substance (41%, n=41) Table1. The principal clinical data were presented in (Table 1). The first thymic episode was principally manic and it was hard with the presence of psychotic characteristics for 60% of the cases (Table 1). The average duration of the hospitalisation for the first episode

Table 2: Number and nature of mood episodes.

Pisode nature	Average number	Min-Max	Percentage
Depressive	1,4±1,6	0-8	20,7%
Manic	4,3±3,8	0-20	61,9%
Hypermanic	0,5±1,1	0-6	9,7%
Mixed	0,7±1,4	0-10	7,7%
Total	6,9±3,8	1-20	100%

Table 3: Average scores of affective temperaments.

Affective temperament	Average score	Min-Max
Depressive	9,39±3,3	3-18
Cyclothymic	10,03±5,7	1-20
Hyperthymic	12,97±4,5	2-21
Irritable	5,37±4,2	0-18
Anxious	9,89±6,1	0-24

Table 4: Correlations between smoking and average scores of affective temperaments.

Temperament	Tobacco+	Tobacco-	P
Depressive	9,85±3,2	9,06±3,3	0,251
Cyclothymic	11,95±5,3	8,69±5,6	0,004
Hyperthymic	12,78±4,4	13,1±4,5	0,727
Irritable	6,36±4,6	4,67±3,8	0,050
Anxious	10,87±6,1	9,2±6,1	0,182

Table 5: Inter-tempéramental corrélations.

Affective temperament	Depressive	Cyclothymic	Hyperthymic	Irritable
cyclothymic	r=0,517			
	p <0,001			
Hyperthymic	r=-0,347	r=-0,195		
	p=0,013	p=0,051		
Irritable	r=0,349	r=0,624	r=0,025	
	p <0,001	p <0,001	p=0,805	
Anxious	r=0,537	r=0,659	r=-0,182	r=0,566
	p <0,001	p <0,001	p=0,069	p <0,001

was 2,68±1,3 weeks. Among the study treated patients, 2% (n=2) had rapid cycles according to the criteria of DSM-IV-R. A seasonal feature of the bipolar disease was found in 26% (n=26) of the patients. The quality of free intervals was good in the majority of cases (96%, n=96). Antecedents of mixed episodes were found for 35% (n=35) of the patients. The majority of thymic episodes was of manic nature (Table 2). The average duration of the treatment by the last prescribed moodstabiliser was of 9,25±6,8 years. The majority of patients were under the effect of Valproic Acid (75%, n=75), 17 patients were under carbamazepine, 1 patient was under lithium, 1 was under lamotrigine, the remaining patients were under the combination of moodstabilisers (4 under lithium+valproate and 1 under lithium+carbamazepine and 1 under valproate+ carbamazepine). Half of patients were under classical Neuroleptics (50%), 13 were under atypical antipsychotics (13%) and more than half (58%, n=58) were under benzodiazepine at the moment of the study. The compliance of the treatment was good

for 38% (n=38) of the cases, average for 37% (n=37) of the cases and bad for 25% (n=25) of the cases. The average scores of cyclothymic temperaments(10,03±5,7) and hyperthymic ones (12,97±4,5) were the highest (Table 3).

Analytical results:The age was positively correlated to the scores of hyperthymic temperament (r=0,197; p=0,050) (Table 4). The other socio-demographic data did not have any correlation with affective temperaments. The cyclothymic ad irritable temperaments were associated with the abuse/dependence on tobacco (p=0,004 et p=0,050 respectively) (Table 5). There were not any significant associations with tobacco for the other studied substances.The average scores of the affective temperaments were negatively correlated with the presence of psychotic characteristics during the first thymic episode for the anxious temperament (average score 8,7 in case of the presence of psychotic characteristics in contrast to 11,7 in case of their absence with p= 0,015). The average score of cyclothymic temperament was positively correlated to the number of mixed episodes (r=0,231; p=0,021). The patients who had already presented at least one mixed episode presented positive correlations with the average score of depressive temperament (score of depressive temperament 10,3 in case of the presence of mixed episode in contrast to 8,89 in case of its absence with p= 0,043). The number of evolution years of the illness was positively correlated with hyperthymic temperament (r=0,263; p= 0,008) and negatively with anxious temperament (r=-0,201; p=0,045). The study of the correlation between the different temperaments found a negative correlation, which is statically significant, between hyperthymic temperament and depressive one and a positive correlation between depressive, cyclothymic, irritable and anxious temperament (Table 5). There was any significant correlation neither between affective temperaments and personal or family history, nor with the other clinical or evolutional data of the bipolar illness. On the therapeutic level, the prescription of benzodiazepines was significantly correlated with average highest scores of irritable temperament (score 6,13 in case of prescribing benzodiazepines in contrast to 4,3 in the opposite case with p =0,033). Any significant association was found with the other prescribed treatments, nor with the compliance to treatment. The therapeutic options were weakly influenced by affective temperaments.

Discussion

Our study allowed to assess the affective temperaments in a population of patients treated for bipolar disorder type I using the questionnaire TEMPS-A. We searched for correlations between affective temperaments and clinical and evolutionary characteristics. In our study, age was positively correlated to the temperament hyperthymic scores. Thus, the more the patients got older, the more the scores of hyperthymic temperament rose. Our results do not agree with the majority of studies. Indeed, several authors have not objectified correlation between the scores of affective temperaments and the age of bipolar patients. Some authors even report negative correlations between the scores of cyclothymic and hyperthymic temperament and age. However, Brieger and al support the hypothesis that personality is altered by the affective disorder [13]. Indeed, it is now established that the residual states with persistent changes occur not only in the schizoaffective disorder or schizophrenia, but also during the development of mood disorders. Thus this leads to a

phenomenon of lasting, residual and chronic phases such as sub-chronic depressive syndromes or chronic hyperthymia. The type of residual syndrome depends on the evolution of the underlying disorder and previous episodes deviation [14]. This component has been neglected in most studies. Thus, patients who experienced mixed episodes are developing different types of residual states compared to patients who have not had this kind of episodes. Moreover, the probability of having residual states increases with duration of disease progression [13]. This could explain the increase in average scores of hyperthymic temperament with age. In our study, the type of episodes being presented was of mainly manic kind. Therefore, it would probably be chronic hyperthymia states. In our work, irritable and cyclothymic temperaments were positively correlated with smoking. Literature data concerning the correlations between affective temperaments and addictive behavior in bipolar patients are controversial [15-17]. Some authors report that the use of alcohol and other psychoactive substances are more common in bipolar I patients with cyclothymic temperament [7,16,18]. For Hantouche et al, they are the cyclothymic and hyperthymic temperaments which predispose more to substances abuse [15]. In our study, the average score of cyclothymic temperament was positively correlated with the number of mixed episodes. The average score of depressive temperament was positively correlated with previous mixed episodes. Mazzarini et al., find no correlation between the polarity of the predominant episodes in bipolar patients type I and affective temperaments. According to these authors, patients with more depressive episodes and those with more manic episodes have the same characteristics with temperamental predominance of hyperthymic and cyclothymic temperaments in both groups [19]. Affective temperaments seem to be the key to differentiating between unipolar and bipolar patients regardless of the predominant polarity of thymic episodes. On the contrary, Vöhringer et al, found a positive correlation between depressive temperament and the number of depressive episodes [20]. A similar result was reported by Henry et al, in bipolar patients I. These authors also report that the number of manic episodes is positively correlated with the hyperthymic temperament and negatively with the depressive temperament [21]. Moreover, Perugi et al, find that bipolar patients type I with cyclothymic temperament have a greater number of depressive and hypomanic episodes [22]. Indeed cyclothymic temperament rarely associates with typical manic episodes. This temperament is rather correlated with dysphoric mania [15]. Besides, according Kesebir et al, depressive and anxious temperaments are frequently noted in patients who have already experienced mixed episodes, while hyperthymic temperament is less noted in these patients [16]. Similarly, Röttig et al, report positive correlations between depressive, cyclothymic, irritable and anxious temperaments and the previous mixed episode in the bipolar I [23]. These data in the literature emphasize the link between the type of affective temperament and the nature of thymic episodes. Indeed, mania typically derives from the hyperthymic temperament while depression would result from depressive temperament. As for mixed episodes, they would come from the coexistence of a mood episode or and an opposite polarity temperament [23-25]. In our study, the average scores of affective temperaments were negatively correlated with the presence of psychotic features during the first thymic episode for the anxious temperament. In the literature, the results of different studies on the links between affective temperaments and psychotic features remain controversial [23,25-27]. Indeed, Dell'Osso et al, found a negative correlation between hyperthymic temperament and psychotic features incongruent for mood in bipolar I patients [25]. O the contrary, Gassab et al, reported an average score of hyperthymic temperament significantly higher in the presence of a last depressive episode with psychotic features in bipolar patients type I [27]. Kesebir et al, found a positive correlation between the existence of thymic episodes with psychotic features in bipolar patients type I and the presence of irritable temperament [16]. For Akiskal, psychotic features are primarily associated with cyclothymic and irritable temperaments [28]. The same author also reported an association between psychotic features and complex temperamental regulations with depressive, cyclothymic and irritable features in bipolar patients [7]. In our study, a statistically significant negative correlation was found between hyperthymic temperament and depressive temperament. A positive correlation was noted between depressive, cyclothymic, irritable and anxious temperament. These results are consistent with literature data [29-31]. Indeed, Matsumotu et al, in the validation study of the Japanese version of TEMPS-A, reported a positive correlation between depressive, cyclothymic, anxious and irritable temperaments. They reported no statistically significant correlation between hyperthymic temperament and other temperaments [31] The German study by Bloink et al, shows the existence of a statistically significant positive correlation between depressive, cyclothymic, anxious and irritable temperaments. The hyperthymic temperament is negatively correlated with depressive and anxious temperament [29]. Figuera et al, finding a negative correlation between depressive and hyperthymic dimension, conclude that these two areas are united but opposed to the temperamental scale [30]. This can be explained by the fact that affective, depressive and hyperthymic temperaments would be part of a two-phase continuum by analogy with bipolar disorder [32]. Moreover, the strong positive correlation between depressive, cyclothymic, irritable and anxious temperaments allowed to hypothesize the existence of a common superstructure comprising these four temperaments. There would be a common thread between these four temperaments, which is the depressive component, present in different degrees [33]. The hyperthymic temperament would be totally independent of this structure [34]. The works of Gonda et al, provide genetic evidence for this hypothesis. Indeed, they show a significant association between short allele (S) encoding the serotonin transport protein (5HTTLPR) and cyclothymic, anxious, irritable and depressive temperaments. These authors reported no correlation between hyperthymic temperament and this carrier (5HTTLPR) that facilitates the uptake of serotonin in the cerebral amygdala and is involved in the modulation of emotions [35,36]. The prescription of benzodiazepines was significantly correlated with higher average scores in irritable temperament. This prescription was also correlated with higher average scores in cyclothymic temperament but the differences were not significant. In the literature, the links between affective temperaments and therapeutic behaviors have been studied in only a few works. Therefore, the possibility that affective temperaments could predict the effects of different treatments remains controversial. Rybakowski et al, show that the response to lithium therapy is positively correlated to the hyperthymic temperament scores [37,38]. These authors also find a negative

correlation between this response and cyclothymic, depressive and anxious temperaments [38]. Indeed, according to Hantouche et al, it would be possible, theoretically, to stipulate that the mania results from the interaction of excessive energy of hyperthymic temperament with exogenous inducing factors. In this model, the stabilizing effect of lithium may be related to an attenuator effect of hyperthymia, thereby protecting the subject against the occurrence of manic episodes. Camacho et al, recommend anticonvulsants in bipolar having a substance abuse for their action on the underlying temperament especially in case of cyclothymic and hyperthymic temperaments [39]. Lasevoli et al, report a more frequent prescription of conventional neuroleptics in case of the cyclothymic and hyperthymic temperaments. In the same study benzodiazepines are prescribed for bipolar having hyperthymic temperament with alcohol dependence. The prescription of benzodiazepines is also more frequent in case of the most recent episode of mixed type [40]. However, these authors found that treatment choices are weakly influenced by the different temperaments and / or type of episode. Therefore, they do not identify differences in the therapeutic management of bipolar patients based on affective temperaments. Concerning the prescription of antidepressants, literature data underline a hyperthymic temperament that promotes a manic turn in bipolar patients [41,42]. Akiskal also stresses that the temperamental model of bipolar disorder is not without consequences therapeutically. The central idea in this area is that the temperament is the basis and the starting point, as well as the end point of thymic episodes. Thus the risk of a too aggressive treatment episodes is jeopardizing what is unique about such an individual patient as well as its intercritical terms of operation [43].

Study Limitations

The Cross-cutting nature: the evaluation of affective temperaments was performed after remission of the disorder without its ability to evaluate them in pre morbid. A longitudinal assessment would be interesting to objectify the stability of different temperaments.

The Selection of our hospital exclusively sample may be biased, insofar the disorders encountered in this context are probably more severe.

To Identify subjects in thymic relapse we are based on the psychiatric interview. Rating scales were not used due to the length of the questionnaire. To minimize bias in assessment, the same examiner assured the collection of epidemiological data, the passing of TEMPS-A and data entry.

References

1. Fayyazi Bordbar MR, Faridhosseini F, Kaviani H, Kazemian M, Samari AA, Kashani Lotfabadi M. Temperament and character personality dimensions in patients with bipolar I disorder. Turk Psikiyatri Derg. 2014; 25: 149-156.

2. Graham RK, Parker GB, Breakspear M, Mitchell PB. Clinical characteristics and temperament influences on 'happy' euphoric and 'snappy' irritable bipolar hypo/manic mood states. J Affect Disord. 2015; 174: 144-149.

3. Azorin JM, Fakra E, Adida M, Belzeaux R, Cermolacce M, Mazzola P, et al. Les endophenotypes tempéramentaux. L Encephale. 2012; 38: 70-74.

4. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003; 160: 636-645.

5. Perugi G, Toni C, Maremmani I, Tusini G, Ramacciotti S, Madia A, et al. The influence of affective temperaments and psychopathological traits on the definition of bipolar disorder subtypes: a study on bipolar I Italian national sample. J Affect Disord. 2012; 136: 41-49.

6. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull. 1987; 23: 68-73.

7. Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF, et al. Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). J Affect Disord. 1998; 50: 175-186.

8. Akiskal HS, Akiskal KK, Haykal RF, Manning JS, Connor PD. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J Affect disord. 2005; 85: 3-16.

9. Akiskal HS, Mendlowicz MV, Jean Louis G, Rapaport MH, Kelsoe JR, Gillin JC, et al. TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament. J Affect Disord. 2005; 85: 45-52.

10. Hantouche EG, Akiskal HS, Lancrenon S, Allilaire JF, Sechter D, Azorin JM, et al. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). J Affect Disord. 1988; 50: 163-173.

11. Zaninotto L, Souery D, Calati R, Di Nicola M, Montgomery S, Kasper S, et al. Temperament and character profiles in bipolar I, bipolar II and major depressive disorder: Impact over illness course, comorbidity pattern and psychopathological features of depression. J Affect Disord. 2015; 184: 51-59.

12. MsAbda M, Ebmeler KR. Optimising the management of bipolar disorder. Practitioner. 2015; 259: 11-15.

13. Brieger P, Roettig S, Ehrt U, Wenzel A, Blöink R, Marneros A. TEMPS-a scale in 'mixed'and 'pure'manic episodes: new data and methodological considerations on the relevance of joint anxious-depressive temperament traits. J Affect Disord. 2003; 73: 99-104.

14. Di Florio A, Hamshere M, Forty L, Green EK, Grozeva D, Jones I. Affective temperaments across the bipolar-unipolar spectrum: examination of the TEMPS-A in 927 patients and controls. J Affect Disord. 2010; 123: 42-51.

15. Hantouche EG, Akiskal HS. Troubles bipolaires précoces et tempéraments affectifs pré-bipolaires, Annales médico-psychologiques. Elsevier. 1997; 481-496.

16. Kesebir S, Vahip S, Akdeniz F, Yuncu Z. The relationship of affective temperament and clinical features in bipolar disorder. Turk Psikiyatri Derg. 2005; 16: 164-169.

17. Marquez-Arrico JE, López-Vera S, Prat G, Adan A. Temperament and character dimensions in male patients with substance use disorders: Differences relating to psychiatric comorbidity. Psychiatry research. 2016; 237: 1-8.

18. Wittchen HU, Zhao S, Kessler RC, Eaton WW. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1994; 51: 355-364.

19. Mazzarini L, Pacchiarotti I, Colom F, Sani G, Kotzalidis GD, Rosa AR, et al. Predominant polarity and temperament in bipolar and unipolar affective disorders. J Affect Disord. 2009; 119: 28-33.

20. Vohringer PA, Whitham EA, Thommi SB, Holtzman NS, Khrad H, Ghaemi SN. Affective temperaments in clinical practice: a validation study in mood disorders. J Affect Disord. 2012; 136: 577-580.

21. Henry C, Lacoste J, Bellivier F, Verdoux H, Bourgeois ML, Leboyer M. Temperament in bipolar illness: impact on prognosis. J Affect Disord. 1999; 56: 103-108.

22. Perugi G, Akiskal HS, Micheli C, Musetti L, Paiano A, Quilici C, et al. Clinical subtypes of bipolar mixed states: Validating a broader European definition in 143 cases. J Affect Disord. 1997; 43: 169-180.

23. Rottig D, Rottig S, Brieger P, Marneros A. Temperament and personality in bipolar I patients with and without mixed episodes. J Affect Disord. 2007; 104: 97-102.

24. Akiskal HS, Benazzi F. Family history validation of the bipolar nature of depressive mixed states. J Affect Disord. 2003; 73: 113-122.

25. Dell'Osso L, Placidi GF, Nassi R, Freer P, Cassano GB, Akiskal HS. The manic-depressive mixed state: familial, temperamental and psychopathologic characteristics in 108 female inpatients. Eur Arch Psychiatry Clin Neurosci. 1991; 240: 234-9.

26. Daros AR, Ruocco AC, Reilly JL, Harris MS, Sweeney JA. Facial emotion recognition in first-episode schizophrenia and bipolar disorder with psychosis. Schizophr Res. 2014; 153: 32-37.

27. Gassab L, Mechri A, Bacha M, Gaddour N, Gaha L. Tempéraments affectifs dans les troubles bipolaires et unipolaires: comparaison des profils tempéramentaux et relation avec les caractéristiques cliniques. L'Encephale. 2008; 34: 477-482.

28. Akiskal HS, Hantouche EG, Allilaire JF. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. J Affect Disord. 2003; 73: 49-57.

29. Bloink R, Brieger P, Akiskal HS, Marneros A. Factorial structure and internal consistency of the German TEMPS-A scale: validation against the NEO-FFI questionnaire. J Affect Disord. 2005; 85: 77-83.

30. Figueira ML, Caeiro L, Ferro A, Severino L, Duarte PM, Abreu M, et al. Validation of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A): Portuguese-Lisbon version. J Affect Disord. 2008; 111: 193-203.

31. Matsumoto S, Akiyama T, Tsuda H, Miyake Y, Kawamura Y, Noda T, et al. Reliability and validity of TEMPS-A in a Japanese non-clinical population: application to unipolar and bipolar depressives. J Affect Disord. 2005; 85: 85-92.

32. Akiskal H, Placidi G, Maremmani I, Signoretta S, Liguori A, Gervasi R, et al. TEMPS-I: delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population. J Affect Disord. 1998; 51: 7-19.

33. Gonda X, Juhasz G, Laszik A, Rihmer Z, Bagdy G. Subthreshold depression is linked to the functional polymorphism of the 5HT transporter gene. J Affect Disord. 2005; 87: 291-297.

34. Pompili M, Girardi P, Tatarelli R, Iliceto P, De Pisa E, Tondo L, et al. TEMPS-A (Rome): psychometric validation of affective temperaments in clinically well subjects in mid-and south Italy. J Affect Disord. 2008; 107: 63-75.

35. Gonda X, Fountoulakis K, Rihmer Z, Lazary J, Laszik A, Akiskal K, et al. Towards a genetically validated new affective temperament scale: A delineation of the temperament 'phenotype'of 5-HTTLPR using the TEMPS-A. J Affect Disord. 2009; 112: 19-29.

36. Gonda X, Rihmer Z, Zsombok T, Bagdy G, Akiskal KK, Akiskal HS, The 5HTTLPR polymorphism of the serotonin transporter gene is associated with affective temperaments as measured by TEMPS-A. J Affect Disord. 2006; 91: 125-131.

37. Rybakowski JK. Genetic influences on response to mood stabilizers in bipolar disorder: current status of knowledge. CNS drugs. 2013; 27: 165-173

38. Rybakowski JK, Dembinska D, Kliwicki S, Akiskal KK, Akiskal HH. TEMPS-A and long-term lithium response: positive correlation with hyperthymic temperament. J Affect Disord. 2013; 145: 187-189.

39. Camacho A, Akiskal HS. Proposal for a bipolar-stimulant spectrum: temperament, diagnostic validation and therapeutic outcomes with mood stabilizers. J Affect Disord. 2005; 85: 217-230.

40. Iasevoli F, Valchera A, Di Giovambattista E, Marconi M, Rapagnani MP, De Berardis D, et al. Affective temperaments are associated with specific clusters of symptoms and psychopathology: a cross-sectional study on bipolar disorder inpatients in acute manic, mixed, or depressive relapse. J Affect Disord. 2013; 151: 540-550.

41. Kesebir S, Unubol B, Tatlidil Yaylaci E, Gundogar D, Unubol H. Impact of childhood trauma and affective temperament on resilience in bipolar disorder. Int J Bipolar Disord. 2015; 3: 3.

42. Van Den Bulke D, Henry C. Intérêt de l'analyse du tempérament chez les sujets bipolaires. L'Encephale. 2005; 31: 207-211.

43. Akiskal KK, Akiskal HS. The theoretical underpinnings of affective temperaments: implications for evolutionary foundations of bipolar disorder and human nature. J Affect Disord. 2005; 85: 231-239.