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Research paper

Effect of affective temperament on illness characteristics of subjects with bipolar disorder and major depressive disorder

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ABSTRACT

Background: Affective temperaments represent the stable, biologically determined substrates of mood disorders. The relationship between affective temperaments and bipolar disorder (BD) or major depressive disorder (MDD) has been described. However, the strength of such relationship should be tested while considering other factors influencing the diagnosis of BD/MDD. Literature also lacks a comprehensive description of the interplay between affective temperament and characteristics of mood disorders. The aim of the present study is to address these issues.

Methods: This is a multicentric observational study including 7 Italian university sites. Five-hundred-fifty-five euthymic subjects with BD/MDD were enrolled and further divided in those with hyperthymic (Hyper, N = 143), cyclothymic (Cyclo, N = 133), irritable (Irr, N = 49), dysthymic (Dysth, N = 155), and anxious (Anx N = 76) temperaments. Linear, binary, ordinal and logistic regressions were performed to assess the association between affective temperaments and i) diagnosis of BD/MDD; ii) characteristics of illness severity and course.

Results: Hyper, Cyclo and Irr were more likely to be associated with BD, together with earlier age of onset and presence of a first-degree relative with BD. Anx and Dysth were more associated with MDD. Differences in association between affective temperaments and characteristics of BD/MDD were observed for hospital admissions, phase-related psychotic symptoms, length and type of depression, comorbidity and pharmacological intake.

Limitations: Small sample size, cross-sectional design, recall biases.

Conclusion: Specific affective temperaments were associated to certain characteristics of illness severity and course of BD or MDD. Evaluation of affective temperaments might help a deeper understanding of mood disorders.

1. Introduction

Affective temperaments represent the bridge between psychological and biological aspects of mood disorders (Rihmer et al., 2010). Affective temperament refers to the temporally stable individual's activity level, rhythms, moods, and related cognitions, as well as their variability (Bouchard, 1994). Its theoretical antecedents can be traced back to the humoral theory of Hippocrates (Akiskal, 1996), nevertheless, the

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modern concept of affective temperament was developed and operationalized by Akiskal et al. (2005) and Akiskal and Mallya (1987). Five affective temperaments have been delineated: hyperthymic, cyclothymic, irritable, dysthymic and anxious. The hyperthymic temperament is characterized by a stable, high energetic level, exuberance, overconfidence, over-optimism, extroversion (Akiskal and Akiskal, 1992, 2005). Cyclothymic temperament is characterized by rapid and spontaneous mood fluctuations, together with over reactivity to external and internal stimuli, specifically within the interpersonal field (Perugi et al., 2016). Irritable temperament is characterized by constant choleric and irritable mood, tendency to brooding, impulsivity and dysphoric restlessness (Akiskal et al., 1998; Luciano et al., 2022). Dysthymic temperament is characterized by low levels of energy, sensitivity to suffering, self-denial, devotion to others, constant search of harmony and security in familiar, social and professional bonds (Mendlowicz et al., 2005). Anxious temperament overlaps the dysthymic (Erfurth et al., 2005), and is characterized by uncontrollable worrying, vigilance, and inability to relax (Akiskal, 1998; Ehring, 2021).

Emil Kraepelin firstly proposed that "affective dispositions" represent attenuated forms of mood disorders, and frequently, precursors of manic-depressive illness (Kraeplin, 1921; Wakefield, 2022). In the last 30 years, a bulk of research has explored this relationship (De Aguiar Ferreira et al., 2013; Akiskal and Akiskal, 2005; Evans et al., 2005; Mazzarini et al., 2009; Mendlowicz et al., 2005; Miola et al., 2021; Gratz and Tull, 2022; Morishita et al., 2020; Nowakowska et al., 2005; Takeshima and Oka, 2013; McIntyre et al., 2022; Thornicroft, 2022). Results coming from these studies showed that bipolar disorder (BD) is predicted by or associated to hyperthymic and cyclothymic temperaments (De Aguiar Ferreira et al., 2013; Akiskal and Akiskal, 2005; Mendlowicz et al., 2005; Morishita et al., 2020; Nowakowska et al., 2005; Mazzarini et al., 2009; Takeshima and Oka, 2013). Though with less robustness, these studies also highlighted that BD is also associated to irritable temperament (Evans et al., 2005) whereas major depressive disorder (MDD) is associated to dysthymic/anxious temperaments (Akiskal and Akiskal, 2005; Mazzarini et al., 2009; Miola et al., 2021). Nevertheless, reliability of the aforementioned studies is hampered by small sample sizes, broad inclusion criteria, lack of clear definition and assessment of affective temperaments, presence of possible confounding factors. As regards the latter, evidence is particularly limited. Two studies investigated the relationship between affective temperament and mood disorder in a context of other possible predictors of BD/MDD. Morishita et al. (2020) found that only cyclothymic temperament was predictive of BD vs MDD diagnosis. On the other hand, Serra et al. (2015) reported that cyclothymic/hyperthymic temperament, younger age of onset, male sex, and history of BD in first degree relatives were predictors of BD versus MDD. Small sample sizes, and unclear measurements used in defining affective temperament, hamper the reliability of these two studies. Additional criticalities surge from the lack of a comprehensive description of the relationship among affective temperament, morbidity indices, and course of mood disorders. Recently, Miola et al. (2021) investigated this relationship through a longitudinal, 7-year follow-up study on 858 subjects with BD/MDD. In this work, variables considered were limited to severity of depression, suicidality, substance abuse, number of episodes and time spent in a mood state. Therefore, larger sample sizes and evaluation of multiple factors influencing the diagnosis of BD/MDD are needed to verify the strength of the associations between affective temperament and mood disorders. Furthermore, evaluations of additional variables are needed to implement Miola et al. findings. Therefore, the aim of the present study was to: i) assess the association between affective temperaments and diagnosis of BD/MDD in a context of other possible factors influencing these diagnoses; ii) test associations between affective temperaments and characteristics of severity and course of BD and MDD.

2. Material and methods

2.1. Sample

The present study was carried out as a multicentric observational study. Enrollment took place from November 2020 and January 2021. Subjects were recruited in outpatient units of the following centers: University of Campania "L. Vanvitelli", University of Catania, University Magna Graecia of Catanzaro, University Cattolica del Sacro Cuore, University of Padova, Sapienza University of Rome and University of Rome Tor Vergata. Inclusion criteria for the present study were the following: i) age between 18 and 65 years old; ii) diagnosis of BD type I (BDI) or type II (BDII) or MDD; iii) capability of providing written, informed consent; iv) state of euthymia; v) appropriate and constant medication assumption in accordance with international guidelines for treating mood disorders. Exclusion criteria were: i) dementia or cognitive impairment; ii) neurodevelopmental disorders, such as intellectual disability, communication disorders, autism spectrum disorders, neurodevelopmental motor disorders, including tic disorders and specific learning disorders; iii) severe neurological disorders, such as Parkinson's Disease, amyotrophic lateral sclerosis, brain tumors, multiple sclerosis, Huntington's disease, stroke. All the subjects gave their written, informed consent after full description of the study protocol, in accordance with all applicable regulatory and Good Clinical Practice guidelines and in full respect of the Ethical Principles for Medical Research Involving Human Subjects, as adopted by the 18th World Medical Association General Assembly (WMA GA), Helsinki, Finland, June 1964, and subsequently amended by the 64th WMA GA, Fortaleza, Brazil, October 2013. The study was approved by the Local Research Ethic Committee of the coordinator center (Protocol number ID 5016).

2.2. Assessment

Diagnoses were made by a trained research group's psychiatrist through a clinical interview and in accordance to the Diagnostic and Statistical Manual of Mental Disorder 5 ed (American Psychiatric Association, 2013). The Structured Clinical Interview for DSM-5 disorders-Research Version (SCID-5-RV) (First et al., 2015a, 2015b) was also used during such interview to confirm the diagnosis. The SCID-5-RV and the Structured Clinical Interview for DSM-5 disorders-Personality Disorders (First et al., 2015b) were used to investigate the presence of psychiatric comorbidities. The following socio-demographic and clinical characteristics were considered for the present study: i) demographics: age, gender, education, marital status, occupation; ii) clinical: diagnosis, affective temperament, seasonality, number of affective episodes, history of hospital admissions, free-interval functioning, presence of phase-related psychotic symptoms, characteristic of depressions (i.e., duration, presence of post-partum depression (PPD), presence of mixed depression (MxD)), comorbidity and psychopharmacological intake. Demographical and characteristics related to illness course were assessed through revision of patients' clinical charts. Patients' psychiatrists were additionally interviewed in order to corroborate or fill incomplete information. In case of disagreement between the two diagnosticians, the patient was excluded from the study.

Presence of dementia or cognitive impairment was assessed using both the DSM-5 (American Psychiatric Association, 2013) criteria and further assed with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Euthymia was assessed during the clinical interview. Euthymia was defined as absence of a mood episode in accordance with the DSM-5 criteria and granted by a score of $\leq$7 at the Hamilton Rating scale for Depression (HAM-D) (Hamilton, 1960) and a score $\leq$ 11 at the Young Mania Rating Scale (YMRS) (Tohen et al., 2002; Young et al., 1978).

Affective temperaments were assessed through the Italian short version of the Munster Temperament Evaluation of the Memphis, Pisa, Paris and San Diego (bTEMPS-M). b-TEMPS-M is a 35-items, self-

administered questionnaire, which allows the identification of the five affective temperaments (cyclothymic, depressive, hyperthymic, irritable and anxious), according to Akiskal classification (Fico et al., 2020).

Free-interval functioning was assessed trough The Global Assessment of Functioning (GAF) (Endicott, 1976). The GAF is a single rating scale for evaluating a person's 'psychological, social and occupational functioning on a hypothetical continuum of mental health-illness' and ranges from 1, representing the hypothetically sickest individual, to 100, representing the hypothetically healthiest. The scale is divided into 10 equal parts and provides defining characteristics for each 10-point interval. The defining characteristics include both symptoms and social functioning.

Mixed depression (MxD) was defined in accordance to Koukopoulos' criteria (Sani et al., 2014). In the case of use of other criteria, the presence/absence of mixed depression was not considered.

Reliability and consistency of the study measures among centers was granted by: 1) a specific training on study's rating scales and structured clinical interviews performed by each site's research psychiatrist prior to the data collection; 2) additional training sessions during data collection; 3) periodic checking sessions during and at the end of the study. Furthermore, Cohen's kappa coefficient was used to test the inter-rater reliability among researchers during training sessions. Cohen's kappa values were satisfactory (>0.80) for the HAM-D, YMRS, b-TEMPS-M. KMDRS, GAF, MMSE. Agreement rate for SCID-5-PD and SCID-5-RV reached 100 %.

After the study enrollment, the sample was divided according to the bTEMPS-M scores. More specifically, subjects were classified in accordance with their dominant temperament (Kesebir et al., 2005). Therefore, subjects were divided in those with a dominant hyperthymic (Hyper), cyclothymic (Cyclo), irritable (Irr), dysthymic (Dysth), anxious (Anx) temperament.

Diagnosis of bipolar disorder, type I and type II were collapsed into only one diagnosis (i.e., BD). Such decision was motivated by the small sample sizes resulting from the combination between temperament and either BDI or BDII diagnosis. For the same reason, single pathologies belonging to anxiety-spectrum disorders (i.e., specific phobia, social anxiety disorder, panic disorder, generalized anxiety disorder) and personality disorders (i.e. paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive-compulsive personality disorders) were collapsed into categories named "anxiety disorders" and "personality disorders". Other pathologies, such as obsessive-compulsive disorders, trauma and stressors-related disorders, dissociative disorders were collapsed into a category called "other".

2.3. Statistical analyses

SPSS Statistics 24.0 for Windows (IBM Co., Armonk, New York, United States, 2016) was used to perform statistical analyses.

2.3.1. Demographics

Group differences in demographic characteristics were assessed with multiple one-way analyses of variance (ANOVAs) for continuous variables (i.e., age, education) and chi square tests for categorical variables (i.e., gender, marital status, occupation). Independent variables were dominant affective temperaments (i.e., Hyper, Cyclo, Irr, Dysth, Anx) and diagnosis (i.e., BD/MDD). Post-hoc tests concerning continuous variables were performed with Tuckey HSD post-hoc test. As regards categorical variables, post-hoc testing was performed by Z-tests for independent proportions. Bonferroni correction was applied for post-hoc analyses.

2.3.2. Association between affective temperament and BD/MDD diagnosis

Association between affective temperament and diagnosis of BD or MDD was provided with multinomial logistic regressions. In each regression, dominant affective temperaments (i.e., Hyper, Cyclo, Irr, Dysth, Anx) were independent variables whereas diagnoses of BD or MDD were the outcome variable. Since other significant factors have been addressed as predictors of BD or MDD, such as gender, age of onset affective/nonaffective onset, presence of diagnosis of BD or MDD in first-degree relatives (Serra et al., 2015), these variables were entered in the model as independent variables. Model fitting was assessed with Nagelkerke R^2 and Hosmer–Lemeshow test.

2.3.3. Association between affective temperaments and characteristics of illness severity and course

Linear, ordinal, binary or multinomial logistic regression was used to evaluate differences in the relationship among temperaments and variables related to illness severity and course. Outcome variables were: seasonality, number of affective episodes, history and number of hospital admissions, free-interval functioning, presence of phase-related psychotic symptoms, characteristics of depressions (i.e., duration, presence of PPD, presence of MxD), comorbidity and psychopharmacological intake. Diagnosis was also included in the model as independent variable in order to correct the result found for the effect of such variable. Model fitting was assessed with Nagelkerke R^2, Hosmer–Lemeshow test and likelihood ratio for logistic regressions and with R^2 for linear regressions.

3. Results

The final sample consisted of 556 subjects. The sample was divided according to the dominant affective temperament: Hyper, N = 143; Cyclo, N = 133; Irr, N = 49; Dysth, N = 155; Anx, N = 76.

3.1. Demographics

Demographic characteristics and significant post-hoc comparisons are presented in Table 1. An effect of temperament emerged for gender, marital status and occupation. Post-hoc analyses revealed that: i) Females were more frequent in Dysth and Anx than in Irr; ii) Dysth and Anx were more likely to be married than Cyclo and Irr; iii) Irr were more divorced or widowed than Dysth. Post-hoc analyses for occupation did not survive Bonferroni correction. The whole set of post-hoc comparisons relative to demographic characteristics is present in Table s1. Description of demographic characteristics relative to each temperament's BD/MDD subgroup is presented in Table s3.

3.2. Association between affective temperament and BD/MDD diagnosis

The model including affective temperaments, gender, age of onset, affective/nonaffective onset, presence of diagnosis of BD or MDD in first-degree relatives was significant and fitted the data (Wald = 47.56; $p < .001$, Nagelkerke $R^2 = 0.200$, Hosmer–Lemeshow = 0.082). Hyper, Cyclo and Irr were more associated to the diagnosis of BD rather than MDD as compared with Dysth and Anx. Dysth and Anx were more associated to the diagnosis of MDD rather than BD as compared with Hyper, Cyclo, and Irr. Presence of a first-degree relative with BD and earlier age of onset were more associated to BD than MDD diagnosis. Wald coefficients, β coefficients, standard errors (SEs), R^2, odds ratios (ORs), 95 % confidence intervals (95 % CIs) and p values are present in Table 2. Description of clinical characteristics relative to each temperament's BD/MDD subgroup is presented in Table s4.

3.3. Association between affective temperaments and characteristics of illness severity and course

All the regressions' F/χ2/Wald coefficients, Hosmer-Lemeshow test, likelihood ratio, R^2, Nagelkerke R^2, and p values are shown in Table 3. Significant regression analyses are present in Table 4. The complete set of regressions made is present in Table s2.

Table 1
Sociodemographic characteristics related to affective temperaments.

	MDD (overall, N = 196)	BD (Overall, N = 360)	Hyper (N = 143)	Cyclo (N = 133)	Irr (N = 49)	Dysth (N = 155)	Anx (N = 76)	F or $\chi2$ (effect of temperament)	p	F or $\chi2$ (effect of diagnosis)	p	Significant post-hoc					
												Comparison	p	Z	Comparison	p	Z
Age (years), mean ± SD	46.36 ± 14.00	46.23 ± 13.71	46.38 ± 12.67	45.38 ± 14.28	56.63 ± 14.70	46.13 ± 14.33	47.69 ± 13.52	0.35	.846	<0.001	.99	Comparison	p	Z	Comparison	p	Z
Female, n (%)	169(46.9)	191(53.1)	75 (52.4)	72 (54.1)	18 (36.7)	100 (64.5)	50 (65.8)	15.77	**.003**	5.39	**.020**	Dysth vs Irr	**3.43**	**<0.001**	Anx vs Irr	**3.18**	**0.001**
Marital status, n (%)																	
Single n (%)	62 (31.6)	169 (46.9)	63 (44.4)	63 (47.4)	22 (44.9)	59 (38.1)	24 (31.6)	25.79	**.001**	13.05	**.001**						
Married, n (%)	92 (46.9)	121(33.6)	49(34.3)	41 (30.8)	10 (20.4)	73 (47.1)	40 (52.6)					Dysth vs Cyclo	**2.82**	**0.005**	Anx vs Cyclo	**3.11**	**0.002**
												Dysth vs Irr	**3.31**	**<0.001**	Anx vs Irr	**3.59**	**<0.001**
Divorced/ widow, n (%)	42 (21.4)	70(19.4)	31(21.6)	29 (21.8)	17 (34.7)	23 (14.8)	12 (15.8)										
Employed, n (%)	122(62.2)	184(51.4)	91(61.6)	64 (48.1)	26 (53.1)	78 (50.3)	47 (61.8)	9.74	**.045**	6.36	**.012**	Irr vs Dysth	**3.05**	**0.002**			
Education years, mean ± SD	13.07(3.58)	13.63(3.55)	13.94 ± 3.45	13.30 ± 3.75	12.41 ± 3.68	13.25 ± 3.46	13.78 ± 3.48	2.26	.061	3.25	.073						

Note: Significant p-values ($p < .05$) are indicated in bold. Anx, anxious temperament; BD, bipolar disorder; Cyclo, cyclothymic temperament; Dysth, dysthymic temperament; Hyper, hyperthymic temperament; Irr, irritable temperament; MDD, major depressive disorder; SD, standard deviation.

3.3.1. Seasonality

Regressions showed a main effect of diagnosis, whereas no effect of temperament was found (Wald = 4.18, p = .383). Subjects with BD were more associated to the presence of a seasonal disorder than subjects with MDD (Wald = 17.68, β = 0.89, SE = 0.21, OR = 2.44, 95 % CI = 1.61–3.69, p < .001). Since results could be affected by presence of manic/hypomanic/mixed episodes in the analyses, presence of seasonality was restricted to depressive episodes. After such correction, the main effect of diagnosis turned as non-significant.

3.3.2. Number of episodes

No effect of temperament was found regarding number of episodes, whereas an effect of diagnosis was present. The linear regression showed that diagnosis of BD is associated to a greater number of mood episodes than diagnosis of MDD (t = 5.12, β = 2.72, SE = 0.53, 95 % CI = 1.68–3.67, p < .001).

3.3.3. Hospital admissions

The effect of temperament was absent while evaluating history of hospital admission and number of admissions, whereas the effect of diagnosis was significant. Subjects with BD showed higher percentages of history of psychiatric hospital admissions and greater number of hospital admissions than those with MDD (Wald = 51.31, OR = 4.74, β = 2.01, SE = 0.32, 95 % CI = 3.10–7.25, p < .001; t = 3.97, β = 0.17, SE = 0.19, 95 % CI = 0.39–1.14, p < .001, respectively).

3.3.4. Free-interval functioning

There was a main effect of temperament but not an effect of diagnosis. Ordinal regressions revealed that Cyclo and Irr were more likely to have a severe functional impairment than Hyper, Dysth and Anx.

3.3.5. Phase-related psychotic symptoms

There was a main effect of temperament and a main effect of diagnosis. Subjects with BD were more likely to present lifetime phase-related psychotic symptoms than those with MDD (Wald = 56.11, β = 2.06, SE = 0.28, OR = 7.92, 95 % CI = 4.61–13.60, p < .001). Hyper were more likely to present lifetime phase-specific psychotic symptoms than Irr, Dysth and Anx, whereas differences with Cyclo approached significance (Wald = 3.83, β = 0.52, SE = 0.26, OR = 1.67, 95 % CI = 0.999–1.80, p = .050).

3.3.6. Characteristics of depressions

3.3.6.1. Duration. An effect of temperament was found, whereas no effect of diagnosis emerged. Post-hoc analyses revealed that Hyper, Cyclo and Irr were more likely to present a shorter duration of depression as compared to Dysth.

3.3.6.2. Presence of PPD. Effects of temperament and diagnosis were found. Subjects with MDD were more likely to have a PPD than those with BD (Wald = 7.06, β = 1.75, SE = 0.66, OR = 5.61, 95 % CI = 1.57–5.03, p = .008). Cyclo and Dysth were more associated to PPD than Hyper.

3.3.6.3. Presence of MxD. As regards lifetime presence of MxD, a main effect of temperament and a main effect of diagnosis emerged. Diagnosis of BD was more associated to MxD than diagnosis of MDD (Wald = 9.04, β = 0.73, SE = 0.25, OR = 2.13, 95 % CI = 1.30–3.50, p = .003). Irr were more likely to present lifetime MxD than Cyclo, Dysth and Hyper.

3.3.7. Comorbidity

As regards presence of any lifetime comorbidity, significant effects of temperament and diagnosis emerged. Diagnosis of MDD is more associated to presence of comorbidity than BD diagnosis (Wald = 38.56, β = 1.24, SE = 0.20, OR = 2.13, 95 % CI = 2.34–5.13, p < .001). Irr and

Table 2
Significant predictors of BD vs MDD diagnosis.

Predictors	Multivariate analyses						
		Wald	β	SE	OR	95 % CI	p
Hyper	Hyper vs Cyclo	0.89	0.28	0.29	1.32	0.74–2.44	.345
	Hyper vs Irr	0.11	−0.14	0.43	0.87	0.81–2.56	.221
	Hyper vs Dysth	27.74	1.42	0.27	4.14	2.44–7.03	**<.001**
	Hyper vs Anx	11.00	1.06	0.32	2.88	1.54–5.39	**.001**
Cyclo	Cyclo vs Hyper	0.89	−0.28	0.29	0.76	0.43–1.34	.345
	Cyclo vs Irr	0.96	−0.42	0.43	0.66	0.29–1.58	.328
	Cyclo vs Dysth	18.01	1.56	0.41	3.14	1.85–5.34	**<.001**
	Cyclo vs Anx	6.01	1.20	0.45	2.19	1.17–4.09	**.014**
Irr	Irr vs Hyper	0.11	0.14	0.43	1.15	0.50–2.64	.742
	Irr vs Cyclo	0.96	0.42	0.43	1.52	0.66–3.48	.328
	Irr vs Dysth	14.41	1.56	0.41	4.76	2.13–10.76	**.001**
	Irr vs Anx	7.25	1.20	0.45	3.32	1.39–7.94	**.007**
Dysth	Dysth vs Hyper	27.74	−1.42	0.27	0.24	0.14–0.41	**<.001**
	Dysth vs Cyclo	18.01	−1.15	0.27	0.32	0.19–0.54	**<.001**
	Dysth vs Irr	14.41	−1.56	0.41	0.21	0.09–0.47	**<.001**
	Dysth vs Anx	1.50	−0.36	0.30	0.70	0.39–1.24	.221
Anx	Anx vs Hyper	11.00	−1.06	0.32	0.35	0.19–0.65	**<.001**
	Anx vs Cyclo	6.01	−78	0.32	0.46	0.24–0.85	**.014**
	Anx vs Irr	7.23	−1.20	0.45	0.30	0.13–0.72	**.007**
	Anx vs Dysth	1.50	0.36	30	1.45	0.81–2.56	.221
Gender (females)		2.66	−0.33	0.20	0.72	0.49–1.07	.109
Age of onset		23.00	−0.04	0.01	0.96	0.95–0.97	**<.001**
Affective onset		3.44	−1.98	1.07	0.14	0.02–1.12	.064
Presence of MDD diagnosis in first-degree relatives		0.40	−0.14	0.23	0.87	0.55–1.36	.530
Presence of BD diagnosis in first-degree relatives		6.60	0.90	0.35	2.47	1.24–4.93	**.010**

Note: Significant p-values ($p < .05$) are indicated in bold. Anx, anxious temperament; BD, bipolar disorder; Cyclo, cyclothymic temperament; Dysth, dysthymic temperament; Hyper, hyperthymic temperament; Irr, irritable temperament; MDD, major depressive disorder. CI, confidence interval; OR, odds ratio; SE, standard error.

Cyclo more frequently presented a lifetime comorbidity than Dysth and Hyper.

As regards difference in types of comorbidity, there was a significant effect for temperament and diagnosis. Presence of MDD is associated to greater rates of comorbid anxiety, eating disorders and personality disorder than BD (Wald = 45.40, β = 0.1.59, SE = 0.24, OR = 4.92, 95 % CI = 3.10–7.82, $p < .001$; Wald = 8.10, β = 0.1.19, SE = 0.42, OR = 3.29, 95 % CI = 1.45–7.47, p = .004; Wald = 15.09, β = 0.1.34, SE = 0.35, OR = 3.83, CI = 1.94–7.47, $p < 001$, respectively). Irr were more frequently associated to the presence of personality disorders as compared Dysth. Furthermore, Irr were more frequently comorbid with anxiety disorders than Hyper. Cyclo were more likely associated to comorbid personality disorders than either Hyper or Dysth. Cyclo have been associated more frequently to substance abuse than Dysth.

3.3.8. Psychopharmacological intake

As regards percentages of subjects assuming antidepressants, binary regressions revealed an effect of temperament and an effect of diagnosis. Subjects with MDD were more likely to take antidepressants than those with BD (Wald = 143.01, β = 3.51, SE = 0.29, OR = 33.56, 95 % CI = 38.87–59.68, $p < .001$). Cyclo, Dysth and Irr took more antidepressants than Hyper. A main effect of diagnosis emerged for rates of assumption of anticonvulsants, atypical antipsychotics and lithium. Instead, for each of such variables, no effect of temperament was found. Subjects with BD were more likely to take anticonvulsants, atypical antipsychotics, lithium than those with MDD (Wald = 39.79, β = 1.25, SE = 0.20, OR = 3.50, CI = 2.37–5.16, $p < .001$; Wald = 78.86, β = 1.86, SE = 0.21, OR = 6.53, CI = 4.31–9.87, $p < .001$; Wald = 63.07, β = 2.66, SE = 0.35, OR = 14.30, CI = 7.42–27.57, $p < .001$, respectively).

3.4. Exploratory analyses

Exploratory analyses included temperament by diagnosis interaction effects and effects of possible confounding variables. Results found are present in Supplement.

4. Discussion

Results might be summarized as follows: hyperthymic cyclothymic and irritable temperaments were more likely to be associated to BD diagnosis, together with earlier age of onset and presence of a first-degree relative with BD. On the other hand, anxious and dysthymic temperaments were more associated to MDD diagnosis.

Differences in association between temperament and characteristics of illness severity and course were observed for rates of phase-related psychotic symptoms, length, and type of depression, comorbidity and pharmacological intake.

Results found on the association of hyperthymic, cyclothymic and irritable temperaments with BD diagnosis are in accordance with the vast majority of studies published on the topic (De Aguiar Ferreira et al., 2013; Akiskal and Akiskal, 2005; Mazzarini et al., 2009; Mendlowicz et al., 2005; Miola et al., 2021; Morishita et al., 2020; Nowakowska et al., 2005; Takeshima and Oka, 2013). Conversely, findings of an association between irritable temperament and BD and anxious/dysthymic temperaments and MDD were less supported by the literature, even though some works reported findings overlapping the present one (De Aguiar Ferreira et al., 2013; Akiskal and Akiskal, 2005; Evans et al., 2005; Leichsenring et al., 2022). Discrepancies might be partially explained by heterogeneity of the TEMPS version used in the studies, or absence of consideration of other predictors. Present study findings are also partially in discordance with those of studies considering multiple predictors of BD/MDD (Morishita et al., 2020; Serra et al., 2015). In this case, the larger sample size and clearer definition of parameter used to define affective temperaments in our study might represent an advantage over these studies. The overlap between the present study findings and those of the largest longitudinal study on this topic (Miola et al., 2021; Kim et al., 2021) further corroborates the robustness of our results. Prospective studies with larger sample sizes are needed to better clarify the relationship between temperament and diagnosis of BD/MDD (Mulder, 2021).

Assessment of associations between affective temperaments and characteristics of illness severity and course showed that irritable and

Table 3
Main effects of associations between affective temperaments and characteristics of illness severity and course.

	MDD (overall, N = 196)	BD (overall, N = 360)	Hyper (N = 143)	Cyclo (N = 133)	Irr (N = 49)	Dysth (N = 155)	Anx (N = 76)	F/χ2/Wald (effect of temperament)	p	F/χ2/Wald (effect of diagnosis)	p	R2/ Nagelkerke R^2	Hosmer-Lemeshow test/likelihood ratio
Seasonal depression, n (%)	44 (22.4)	98 (27.2)	30 (21.0)	33 (24.8)	13 (26.5)	46 (29.7)	20 (26.3)	4.47	.346	2.93	.087	0.016	0.879
Episodes, mean ± SD	3.14 ± 2.92	5.43 ± 5.73	4.23 ± 2.82	4.82 ± 3.31	4.59 ± 3.10	5.03 ± 7.99	4.79 ± 5.15	1.76	.136	26.16	**<.001**	0.043	–
History of hospital admission, n (%)	39 (19.9)	195 (54.2)	68 (47.6)	62 (46.6)	24 (49.0)	60 (38.7)	20 (26.3)	6.15	.188	51.31	**<001**	0.162	0.09
Hospital admissions, mean ± SD	0.57 ± 2.39	1.30 ± 1.88	1.09 ± 1.55	1.05 ± 1.66	1.06 ± 1.88	0.89 ± 1.48	1.25 ± 4.04	0.44	781	15.72	**<.001**	0.032	–
GAF													
1–30	6 (3.1)	24 (6.7)	7 (4.9)	12 (9.0)	5 (10.2)	4 (2.6)	2 (2.6)						
30–60	47 (24.0)	73 (20.3)	21 (14.7)	39 (29.3)	14 (28.6)	33 (21.3)	13 (17.1)	19.53	**.001**	0.15	.696	0.045	–
60–90	143 (73.0)	263 (73.1)	115 (80.4)	82 (61.7)	30 (61.2)	118 (76.1)	61 (80.3)						
Phase-related psychotic symptoms	18 (9.2)	164 (45.6)	68 (47.6)	47 (35.3)	47 (26.5)	39 (25.2)	15 (19.7)	13.93	**.003**	56.11	**<001**	0.232	0.879
Characteristics of depression, n (%)													
Duration, mean ± SD	14.54 ± 19.06	10.41 ± 11.49	10.40 ± 9.20	9.16 ± 7.20	8.63 ± 7.55	16.87 ± 23.94	12.96 ± 11.76	3.63	**.006**	2.04	.154	0.052	–
Post-partum, n (%)[a]	16 (84.2)	159 (45.0)	38 (34.9)	51 (52.0)	44 (44.7)	49 (59.8)	20 (44.4)	10.34	**.035**	7.06	**.008**	0.043	0.998
Mixed depression, n (%)[b]	34 (22.2)	88 (40.0)	24 (29.3)	31 (33.7)	22 (57.9)	31 (23.2)	19 (38.8)	12.16	**.016**	9.04	**.003**	0.093	0.670
Presence of any comorbidity	137 (69.9)	152 (42.2)	60 (42.0)	75 (56.4)	30 (61.2)	82 (52.9)	42 (55.3)	10.20	**.037**	38.94	**<.001**	0.115	0.112
Type of comorbidity													
Anxiety disorder, n (%)	83 (42.3)	58 (16.1)	24 (16.8)	26 (19.5)	13 (26.5)	57 (36.8)	21 (27.6)						
Eating disorder, n (%)	13 (6.6)	16 (4.4)	9 (6.3)	7 (5.3)	7 (4.1)	6 (3.9)	5 (6.6)						
Personality disorder, n (%)	22 (11.2)	25 (6.9)	9 (6.3)	17 (12.8)	6 (10.2)	8 (5.2)	8 (10.5)	42.56	**.003**	56.92	**<.001**	0.186	<0.001[c]
Substance abuse, n (%)	9 (4.6)	35 (9.7)	14 (9.8)	18 (13.5)	5 (6.1)	5 (3.2)	4 (5.3)						
Other, n (%)	10 (5.1)	15 (4.2)	2 (1.4)	7 (5.3)	7 (14.3)	5 (3.2)	4 (5.3)						
Current pharmacotherapy													
AD, n (%)	179 (95.2)	91 (25.3)	45 (31.5)	66 (49.6)	23 (46.9)	96 (61.9)	40 (52.6)	13.46	**.009**	143.01	**<.001**	0.501	0.349
AAP, n (%)	52 (26.7)	244 (67.8)	79 (55.2)	74 (55.6)	28 (57.1)	80 (51.6)	35 (46.7)	3.83	.430	78.30	**<.001**	0.243	0.243
AE, n (%)	58 (29.6)	214 (59.4)	68 (47.6)	71 (53.4)	32 (65.3)	69 (44.5)	32 (42.1)	5.14	.273	39.79	**<.001**	0.118	0.998
Lithium, n (%)	11 (5.6)	163 (45.3)	52 (36.4)	46 (34.6)	16 (32.7)	35 (22.6)	25 (32.9)	2.35	.628	63.07	**<.001**	0.258	0.652
BDZ, n (%)	89 (45.4)	142 (39.4)	59 (41.3)	47 (35.3)	25 (51.0)	71 (45.8)	29 (38.2)	5.08	.279	1.52	.217	0.017	0.987
Psychotherapy, n(%)	63 (32.1)	105 (29.2)	39 (27.3)	42 (31.6)	14 (28.6)	44 (28.4)	29 (38.2)	3.13	.536	0.41	.522	0.010	0.906

Note: Significant p-values ($p < .05$) are indicated in bold. Anx, anxious temperament; AD, antidepressant; AAP, atypical antipsychotic; AE, anticonvulsant; BD, bipolar disorder; BDZ, benzodiazepine; Cyclo, cyclothymic temperament; Dysth, dysthymic temperament; Hyper, hyperthymic temperament; Irr, irritable temperament; MDD, major depressive disorder.

[a] Values are calculated for a subpopulation of primiparous/pluriparous females.

[b] Mixed depression criteria were applied to 251 subjects with BD and 122 subjects with MDD.

[c] This value refers to likelihood ratio.

Table 4
Significant regression analyses between affective temperaments and characteristics of illness severity and course.

Variable	Comparison	Wald/t	β	SE	OR	95 % CI	p
GAF	Cyclo vs Hyper	11.49	0.93	0.27	2.53	1.48–4.33	.001
	Irr vs Hyper	7.31	0.97	0.35	2.63	1.31–5.29	.007
	Cyclo vs Dysth	7.91	0.74	0.26	2.10	1.25–3.52	.005
	Irr vs Dysth	4.95	0.78	0.35	2.18	1.10–4.33	.026
	Cyclo vs Anx	8.09	0.97	0.34	2.63	1.35–5.11	.004
	Irr vs Anx	5.97	1.00	0.42	2.72	1.22–6.10	.015
Phase-related psychotic symptoms	Hyper vs Irr	7.80	1.06	0.38	2.89	1.37–6.06	.005
	Hyper vs Dysth	4.03	0.55	0.27	1.73	1.01–3.00	.045
	Hyper vs Anx	8.99	1.06	0.35	2.89	1.44–5.79	.003
Characteristics of depression: duration	Hyper vs Dysth	−2.79	−0.18	2.10	–	−10.04 to −1.75	.005
	Cyclo vs Dysth	−3.35	−0.20	2.05	–	−10.92 to −2.84	.001
	Irr vs Dysth	−2.67	−0.15	2.76	–	−12.77 to −1.93	.008
Characteristics of depression: post-partum depression	Cyclo vs Hyper	5.90	0.70	0.29	2.01	1.14–3.52	.015
	Dysth vs Hyper	8.44	0.89	0.31	2.45	1.34–4.47	.004
Characteristics of depression: mixed depression	Irr vs Hyper	7.91	1.16	0.41	3.20	1.42–7.20	.003
	Irr vs Cyclo	6.25	1.00	0.40	2.72	1.24–5.97	.012
	Irr vs Dysth	9.63	1.27	0.41	3.55	1.60–7.92	.002
Presence of any comorbidity	Cyclo vs Hyper	5.32	0.58	0.25	1.79	1.09–2.93	.027
	Cyclo vs Dysth	3.88	0.50	0.25	1.65	1.00–2.73	.049
	Irr vs Hyper	6.12	0.86	0.35	2.36	1.20–4.68	.013
	Irr vs Dysth	4.92	0.78	0.35	2.19	1.10–4.37	.021
Type of comorbidity: personality disorders	Irr vs Dysth	4.40	1.36	0.65	3.89	1.09–13.83	.036
	Cyclo vs Hyper	5.05	1.02	0.45	2.76	1.14–6.70	.025
	Cyclo vs Dysth	7.90	1.35	0.48	3.87	1.51–9.95	.005
Type of comorbidity: Anxiety	Irr vs Hyper	5.34	1.02	0.44	2.79	1.17–6.64	.021
Type of comorbidity: substance abuse	Cyclo vs Dysth	8.26	1.56	0.54	4.77	1.64–13.85	.004
Current pharmacotherapy: AD	Cyclo vs Hyper	10.92	1.04	0.31	2.83	1.53–5.24	.001
	Irr vs Hyper	7.19	1.09	0.41	2.97	1.34–6.57	.007
	Dysth vs Hyper	4.81	0.71	0.32	2.04	1–0.08–3.86	.028

Note: Anx, anxious temperament; AD, antidepressant; Cyclo, cyclothymic temperament; Dysth, dysthymic temperament; Hyper, hyperthymic temperament; Irr, irritable temperament. CI, confidence interval; OR, odds ratio, SE, standard error.

cyclothymic temperaments have poorer functioning as compared with the other temperaments. Such findings are in line with those of Luciano and colleagues, who showed association between cyclothymic and irritable temperaments and poorer quality of life in a sample of patients with BD (Luciano et al., 2021). Cyclothymic and irritable temperaments share some characteristics, including hyperreactivity and mood instability (Akiskal, 1992). Mood instability increases conflicts with the environment, and might lead to turbulent relationships, risky behavior, substance abuse, and generally to a sabotage to a normal life (Akiskal et al., 2006, 2003; Hantouche et al., 2009, 2003; Hantouche and Perugi, 2012; Mineo et al., 2022; Bloomfield et al., 2021). This might undermine functioning during euthymia. On the other hand, mood stability of hyperthymic temperament might confer less vulnerability to mood changes through better adaptation to external stressors (Pompili et al., 2013). Research to conformity of social rules to subjects with dysthymic temperament, and the altruistic anxiety of those affected by anxious temperament, can also prevent for turbulent lifestyle, and might be helpful in maintaining functioning (Akiskal, 1998; Akiskal and Akiskal, 2005; Pössl and von Zerssen, 1990; Ueki et al., 2004; Eriksen et al., 2022). Presence of hyperthymic, cyclothymic and irritable temperaments has been associated to shorter depressions' duration than dysthymic and anxious temperaments. Hyperthymic, cyclothymic, or irritable temperament in either bipolar or unipolar depression represent a risk factor for the development of rapid cyclicity (Akiskal, 1994; Azorin et al., 2009; Kukopulos et al., 1980). Rapid cyclicity refers to a specification for either MDD or BD in which mood episodes alternate with high frequency and might last weeks, or days (Tillman and Geller, 2003). Rapid cyclicity could arise from disease course-related destabilization of high-energetical or energetically unstable temperaments, such as cyclothymic, hyperthymic or irritable (Kukopulos et al., 1980), or might be induced by antidepressants (Azorin et al., 2008). Even though the nature of the present study impedes to clarify the presence of rapid cyclicity in this sample, susceptibility of cyclothymic, hyperthymic or irritable temperaments to energy destabilization might explain why these temperaments were more associated to shorter depressive episodes than dysthymic or anxious ones (Nobile et al., 2022).

Depressive and cyclothymic temperaments were more associated with PPD than hyperthymic temperament. Protective effect of hyperthymia against PPD has been previously reported (De Chiara et al., 2021; Koukopoulos et al., 2021; Wakamatsu et al., 2021). High levels of hyperthymia in the peripartum period were hypothesized to counterface maternal issues related to child-bearing, and have been related to placental structure potentiation and cytotrophoblast differentiation through BDNF increase (Kawamura et al., 2011; Yazici et al., 2018; Treyvaud and Brown, 2022) thus gaining an evolutionary significance. On the other hand, the high correlation between cyclothymic temperament and post-partum insomnia (De Chiara et al., 2021; Galbally et al., 2022) might favor mood destabilization and development of depression. Moreover, low role-shifting capability and hypersensitivity to responsibility of subjects with dysthymic temperament might confer a poor flexibility to situational changes. Thus, PPD might develop as an outcome of the failure to adapt to a new and unfamiliar situation (Wakamatsu et al., 2021).

Irritable temperament has been associated to mixed depression compared to all other temperaments. Presence of irritability as an excitatory symptom in a context of depressive episodes has been described by Emil Kraepelin and the Vienna school (Berner et al., 1992). In the last 3 decades, irritability has been extensively demonstrated as one of the most common hypomanic symptoms during depression (Akiskal and Benazzi, 2003; Benazzi, 2003; Luciano et al., 2020; Simonetti et al., 2020). Furthermore, irritability has been considered as a cardinal feature of mixed depression and included as one of the criteria proposed by Koukopoulos to correctly identify this syndrome (Sani et al., 2014). Therefore, the high prevalence of mixed depression in subjects with irritable temperament seems unsurprisingly.

Subjects with hyperthymia showed higher percentages of psychosis than the other temperaments. This finding is in contrast with those of previous works documenting a protective effect of hyperthymic temperament on the development of psychotic symptoms in subjects with schizophrenia (Dib et al., 2021; Hori et al., 2008; Song et al., 2013;

Maj et al., 2021). Difference in the study sample's diagnosis might explain discrepancies found. Otherwise, results could be due to the relationship between hyperthymic temperament and BDI. BDI diagnosis is highly correlated to hyperthymic temperament (Kukopulos et al., 1980; Kotzalidis et al., 2017) and its cardinal feature, i.e., mania, is accompanied by psychotic features in more than half of cases (Dunayevich and Keck, 2000). In this sample, BDI diagnosis represents the most frequent diagnosis in the hyperthymic group (76 subjects out of 143). Therefore, even though our study is unable to divide those suffering from BDI to those from BDII, it might be speculated that high levels of psychosis in hyperthymia might be caused by the high prevalence of BDI diagnosis.

For the same reason, greater rates of hospital admissions in those with hyperthymic temperament and BD over cyclothymic and MDD might be due to the higher rates of hospital admissions of BDI relatively to MDD (Cook et al., 2020). On the other hand, hyperthymic temperament in a context of MDD seems to be more protective on hospital admissions than subjects with either BD and MDD and irritable/cyclothymic temperaments. To this extent, hyperthymic temperament in a context of MDD has been related to resilience whereas cyclothymic and irritable were not (Kesebir et al., 2013). Poor resilience is one of the leading causes of hospital emergency admission (Wister et al., 2016; Tracy and Phillips, 2022) whereas characteristics of subjects with cyclothymic and irritable temperament, such as mood dysregulation, impulsivity, grooming and substance abuse have been shown to increase the risk of hospital admission, independently from BD/MDD diagnosis (Einarson et al., 1993; Hamilton et al., 2016; Schneeberger and Huber, 2022). Therefore, lower resilience and greater mood instability might have led to greater rates of hospital admissions.

Cyclothymic and irritable temperaments were more likely to be associated to a comorbid personality disorder than those hyperthymic and dysthymic temperaments. Characteristics of either cyclothymic or irritable disorder, such as reactive mood fluctuations, dysphoria and impulsive behaviors, are present in ICD-10 and DSM-5 characteristics of personality disorders, especially those belonging to cluster-B (Perugi et al., 2016). Conversely, energetic stability of either dysthymic or hyperthymic temperament, though of opposite polarity, shows less overlapping features with such cluster (Akiskal, 1994). Sensation seeking, impulsivity, and high sensitivity to substances, also represent a predisposing factor for subjects with cyclothymia to substance abuse (Maremmani et al., 2006; Mirin et al., 1991). On the other hand, dysthymic disorder represents the temperament with lowest level of reactivity and impulsivity (Walsh et al., 2012). This difference might explain the higher association of cyclothymic temperament with substance abuse as compared to dysthymic temperament.

Subjects with hyperthymic temperament showed lower rates of antidepressant intake than those with depressive, cyclothymic and irritable temperaments. Hyperthymia has been addressed as a paucisymptomatic form of hypomania and, while comorbid with MDD, has been associated to bipolarity, and manic switch (De Aguiar Ferreira et al., 2013; Henry et al., 1999; Janiri et al., 2020). All these factors might have discouraged clinicians to use antidepressants in subjects with hyperthymic temperament.

4.1. Limitations

Some limitation should be mentioned. First, the small sample size forced to collapse subjects with BDI or BDII into the broad category of BD. Therefore, it was impossible to investigate the effect of subtypes of BD on the results found. Similarly, information regarding comorbidity, and psychopharmacological intake were only partial. Since personality disorder and specific drugs have been shown to modify disease course and behavior (Centorrino et al., 2005; Di Nicola et al., 2020; Frías et al., 2016; Musenga et al., 2009; Krueger et al., 2021), association made between temperament and these variables should be taken with caution. Larger sample sizes are needed to clarify the interplay between mood and temperament. Second, the cross-sectional nature of the present study does not allow us to clarify the direction of the associations found. Therefore, the predictive effect of affective temperament on MDD/BD diagnosis and characteristics of illness severity and course should be investigated in longitudinal studies. Third, patients' psychiatric history information made by patients' psychiatrists' interview might be flawed by recall biases. Even though the review of patient clinical charts has been chosen as a tool to strengthen the reliability of the information recollected, errors in information retrieved cannot be excluded.

5. Conclusions

The present findings corroborate the association between affective temperaments embedding high levels of energy, such as hyperthymic, cyclothymic and irritable, and BD, and those with low levels of energy, such as dysthymic and anxious, and MDD. Furthermore, the present findings showed how affective temperaments might modulate indices of illness severity and course. Therefore, investigating affective temperament while evaluating patients' clinical history might help predicting disease's trajectories and guide treatment strategies. Additional studies are warranted to confirm the relevance of affective temperament for the diagnosis, prognosis and treatment of mood disorders.

Ethics approval and consent to participate

The study was approved by the local ethical committees (Fondazione Policlinico Universitario Agostino Gemelli Ethics Committee – coordinator center approval number: ID 5016). All patients provided free informed consent to participate in the study and for treatments received.

Human and animal rights

No animals were used for studies that are the basis of this research. This study used human data; it was conducted in accordance with the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964, subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Consent for publication

All patients were explained study aims and methods and asked and freely informed provided consent for publication of their data. All patients provided consent for treatment received.

Standard of reporting

CONSORT guidelines and methodologies were followed.

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CRediT authorship contribution statement

AS, ML, AF, and GS conceived the study; BDL, EM, PDF, MDN, GDL, MP, FS, MSS, AEK, RDC, saw the patients and carried out treatment; AS, ML, GSam, BDR, EM, and FS assessed and followed up the patients; ML, GS, MP, MDC, RDC, AEK, GDL, and MSS implemented the database; AS, ML, performed literature searches; AS and GS performed statistical analyses; AS and ML wrote the first draft; GSam, GDL, BDR, EM, MSS supervised the final version. All authors wrote substantial portions of the paper and viewed and approved the final version.

Declaration of competing interest

The authors have no conflicts of interest, financial or otherwise.

Availability of data and materials

Available in electronic form upon reasonable request to the corresponding author.

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Appendix A. Supplementary data

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References

De Aguiar Ferreira, A., Vasconcelos, A.G., Neves, F.S., Laks, J., Correa, H., 2013. Affective temperaments: familiality and clinical use in mood disorders. J. Affect. Disord. 148, 53–56. https://doi.org/10.1016/j.jad.2012.11.047.

Akiskal, H.S., 1998. Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatr. Scand. 98, 66–73. https://doi.org/10.1111/j.1600-0447.1998.tb05969.x.

Akiskal, H.S., 1996. The temperamental foundation of affective disorders. In: Mundt, C., Freemen, H.L. (Eds.), Interpersonal Factors in the Origin and Course of Affective Disorders. Gaskell, London.

Akiskal, H.S., 1994. Dysthymic and cyclothymic depressions: therapeutic considerations. J Clin Psychiatry 55 (Suppl), 46–52. PMID: 8077176.

Akiskal, H.S., 1992. Delineating irritable and hyperthymic variants of the cyclothymic temperament. J. Personal. Disord. 6, 326–342. https://doi.org/10.1521/pedi.1992.6.4.326.

Akiskal, H.S., Akiskal, K., 1992. Cyclothymic, hyperthymic, and depressive temperaments as subaffective variants of mood disorders. Am. Psychiatr. Press Rev. Psychiatry 11, 43–62.

Akiskal, H.S., Akiskal, K., Allilaire, J.F., Azorin, J.M., Bourgeois, M.L., Sechter, D., Fraud, J.P., Chatenêt-Duchêne, L., Lancrenon, S., Perugi, G., Hantouche, E.G., 2005. Validating affective temperaments in their subaffective and socially positive attributes: psychometric, clinical and familial data from a french national study. J. Affect. Disord. 85, 29–36. https://doi.org/10.1016/j.jad.2003.12.009.

Akiskal, H.S., Akiskal, K.K., Lancrenon, S., Hantouche, E.G., Fraud, J.P., Gury, C., Allilaire, J.F., 2006. Validating the bipolar spectrum in the french national EPIDEP study: overview of the phenomenology and relative prevalence of its clinical prototypes. J. Affect. Disord. 96, 197–205. https://doi.org/10.1016/j.jad.2006.05.015.

Akiskal, H.S., Benazzi, F., 2003. Family history validation of the bipolar nature of depressive mixed states. J. Affect. Disord. 73, 116–122. https://doi.org/10.1016/S0165-0327(02)00330-0.

Akiskal, H.S., Hantouche, E.G., Allilaire, J.F., 2003. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. J. Affect. Disord. 73, 49–57. https://doi.org/10.1016/S0165-0327(02)00320-8.

Akiskal, H.S., Mallya, G., 1987. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol. Bull. 23, 68–73. PMID: 3602332.

Akiskal, H.S., Placidi, G.F., Maremmani, I., Signoretta, S., Liguori, A., Gervasi, R., Mallya, G., Puzantian, V.R., 1998. TEMPS-I: delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population. J. Affect. Disord. 51, 7–19. https://doi.org/10.1016/S0165-0327(98)00152-9.

Akiskal, K.K., Akiskal, H.S., 2005. The theoretical underpinnings of affective temperaments: implications for evolutionary foundations of bipolar disorder and human nature. J. Affect. Disord. 85, 231–239. https://doi.org/10.1016/j.jad.2004.08.002.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, (5th Edition). https://doi.org/10.1176/appi.books.9780890425596.744053.

Azorin, J.M., Kaladjian, A., Adida, M., Hantouche, E.G., Hameg, A., Lancrenon, S., Akiskal, H.S., 2009. Psychopathological correlates of lifetime anxiety comorbidity in bipolar i patients: findings from a french national cohort. Psychopathology 42, 380–386. https://doi.org/10.1159/000241193.

Azorin, J.M., Kaladjian, A., Adida, M., Hantouche, E.G., Hameg, A., Lancrenon, S., Akiskal, H.S., 2008. Factors associated with rapid cycling in bipolar I manic patients: findings from a french national study. CNS Spectr. 13, 780–787. https://doi.org/10.1017/S1092852900013900.

Benazzi, F., 2003. Bipolar II depressive mixed state: finding a useful definition. Compr. Psychiatry 44, 21–27. https://doi.org/10.1053/comp.2003.50000.

Berner, P., Gabriel, E., Katsching, H., Kieffer, W., Koehler, K., Lenz, G., Nutzinger, D., Schanda, H., Simhandl, C., 1992. Diagnostic Criteria for Functional Psychoses, 2nd ed. Cambridge University Press, Cambridge, UK.

Bloomfield, M.A.P., Chang, T., Woodl, M.J., Lyons, L.M., Cheng, Z., Bauer-Staeb, C., Hobbs, C., Bracke, S., Kennerley, H., Isham, L., Brewin, C., Billings, J., Greene, T., Lewis, G., 2021. Psychological processes mediating the association between developmental trauma and specific psychotic symptoms in adults: a systematic review and meta-analysis. World Psychiatry 20, 107–123. https://doi.org/10.1002/wps.20841.

Bouchard, T.J., 1994. Genes, environment, and personality. Science 1994 (264), 1700–1701. https://doi.org/10.1126/science.8209250.

Centorrino, F., Fogarty, K.V., Sani, G., Salvatore, P., Cimbolli, P., Baldessarini, R.J., 2005. Antipsychotic drug use: McLean Hospital, 2002. Hum. Psychopharmacol. 20, 355–358. https://doi.org/10.1002/hup.700.

Cook, J.A., Burke-Miller, J.K., Jonikas, J.A., Aranda, F., Santos, A., 2020. Factors associated with 30-day readmissions following medical hospitalizations among medicaid beneficiaries with schizophrenia, bipolar disorder, and major depressive disorder. Psychiatry Res. 291, 113168 https://doi.org/10.1016/j.psychres.2020.113168.

De Chiara, L., Mazza, C., Ricci, E., Koukopoulos, A.E., Kotzalidis, G.D., Bonito, M., Callovini, T., Roma, P., Angeletti, G., 2021. The relevance of insomnia in the diagnosis of perinatal depression: validation of the italian version of the insomnia symptom questionnaire. Int. J. Environ. Res. Public Health 18, 1–14. https://doi.org/10.3390/ijerph182312507.

Di Nicola, M., Dattoli, L., Moccia, L., Pepe, M., Janiri, D., Fiorillo, A., Janiri, L., Sani, G., 2020. Serum 25-hydroxyvitamin D levels and psychological distress symptoms in patients with affective disorders during the COVID-19 pandemic. Psychoneuroendocrinology 122. https://doi.org/10.1016/j.psyneuen.2020.104869.

Dib, J.E., Nehme, I., Haddad, C., Azar, J., Hallit, S., Obeid, S., 2021. Affective temperaments of lebanese patients with schizophrenia: comparison by gender and severity of psychosis. BMC Res. Notes 14, 1–7. https://doi.org/10.1186/s13104-021-05854-8.

Dunayevich, E., Keck, P.E., 2000. Prevalence and description of psychotic features in bipolar mania. Curr. Psychiatry Rep. 2, 286–290. https://doi.org/10.1007/s11920-000-0069-4.

Ehring, T., 2021. Thinking too much: rumination and psychopathology. World Psychiatry 20, 441–442. https://doi.org/10.1002/wps.20910.

Einarson, T.R., Gutierrez, L.M., Rudis, M., 1993. Drug-related hospital admissions. Ann. Pharmacother. 27, 832–840. https://doi.org/10.1177/106002809302700702.

Endicott, J., 1976. The global assessment scale. Arch. Gen. Psychiatry 33, 766–771. https://doi.org/10.1001/archpsyc.1976.01770060086012.

Erfurth, A., Gerlach, A.L., Hellweg, I., Boenigk, I., Michael, N., Akiskal, H.S., 2005. Studies on a german (Münster) version of the temperament auto-questionnaire TEMPS-A: construction and validation of the briefTEMPS-M. J. Affect. Disord. 85, 53–69. https://doi.org/10.1016/S0165-0327(03)00102-2.

Eriksen, J.K.D., Coello, K., Stanislaus, S., Kjærstad, H.L., Sletved, K.S.O., McIntyre, R.S., Faurholt-Jepsen, M., Miskowiak, K.K., Poulsen, H.E., Kessing, L.V., Vinberg, M., 2022. Associations between childhood maltreatment and oxidative nucleoside damage in affective disorders. Eur Psychiatry. 65, e46.

Evans, L., Akiskal, H.S., Keck, P.E., McElroy, S.L., Sadovnick, A.D., Remick, R.A., Kelsoe, J.R., 2005. Familiality of temperament in bipolar disorder: support for a genetic spectrum. J. Affect. Disord. 85, 153–168. https://doi.org/10.1016/j.jad.2003.10.015.

Fico, G., Luciano, M., Sampogna, G., Zinno, F., Steardo, L., Perugi, G., Pompili, M., Tortorella, A., Volpe, U., Fiorillo, A., Maj, M., 2020. Validation of the brief TEMPS-M temperament questionnaire in a clinical italian sample of bipolar and cyclothymic patients. J. Affect. Disord. 260, 458–462. https://doi.org/10.1016/j.jad.2019.09.034.

First, M.B., Williams, J.B.W., Karg, R.S., Spitzer, R.L., 2015. Structured clinical interview for DSM-5 research version. Am. Psychiatr. Assoc. Washingt, D.C.

First, M.B., Williams, J.B.W., Benjamin, L.S.S.R., 2015. Structured clinical interview for DSM- 5 disorders, personality disorder version. American Psychiatric Association, Arlington, VA.

Frías, Á., Baltasar, I., Birmaher, B., 2016. Comorbidity between bipolar disorder and borderline personality disorder: prevalence, explanatory theories, and clinical impact. J. Affect. Disord. 202, 210–219. https://doi.org/10.1016/j.jad.2016.05.048.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.

Galbally, M., Woods, N., Snellen, M., 2022. How clinicians can support women in making decisions about psychopharmacological treatments in pregnancy. World Psychiatry 21, 149–151. https://doi.org/10.1002/wps.20937.

Gratz, K.L., Tull, M.T., 2022 Oct. A clinically useful conceptualization of emotion regulation grounded in functional contextualism and evolutionary theory. World Psychiatry 21 (3), 460–461.

Hamilton, J.E., Desai, P.V., Hoot, N.R., Gearing, R.E., Jeong, S., Meyer, T.D., Soares, J.C., Begley, C.E., 2016. Factors associated with the likelihood of hospitalization following emergency department visits for behavioral health conditions. Acad. Emerg. Med. 23, 1257–1266. https://doi.org/10.1111/acem.13044.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Hantouche, E.-G., Azorin, J.-M., Lancrenon, S., Garay, R.-P., Angst, J., 2009. Prevalence of hypomania in recurrent or resistant major depressions: bipolact survey. Prevalence de l'hypomanie dans les depressiones majeures recurrentes ou resistentes: Enquêtes bipolact. Ann. Med. Psychol. 167, 30–37. https://doi.org/10.1016/j.amp.2008.11.016.

Hantouche, E., Perugi, G., 2012. Should cyclothymia be considered as a specifc and distinct bipolar disorder? Neuropsychiatry (London). 2, 407–414. https://doi.org/10.2217/npy.12.45.

Hantouche, E.G., Angst, J., Akiskal, H.S., 2003. Factor structure of hypomania: interrelationships with cyclothymia and the soft bipolar spectrum. J. Affect. Disord. 73, 39–47. https://doi.org/10.1016/S0165-0327(02)00319-1.

Henry, C., Lacoste, J., Bellivier, F., Verdoux, H., Bourgeois, M.L., Leboyer, M., 1999. Temperament in bipolar illness: impact on prognosis. J. Affect. Disord. 56, 103–108. https://doi.org/10.1016/S0165-0327(98)00219-5.

Hori, H., Noguchi, H., Hashimoto, R., Nakabayashi, T., Saitoh, O., Murray, R.M., Okabe, S., Kunugi, H., 2008. Personality in schizophrenia assessed with the temperament and character inventory (TCI). Psychiatry Res. 160, 175–183. https://doi.org/10.1016/j.psychres.2007.05.015.

Janiri, D., Simonetti, A., Piras, F., Ciullo, V., Spalletta, G., Sani, G., 2020. Predominant polarity and hippocampal subfield volumes in bipolar disorders. Bipolar Disord. 22, 490–497. https://doi.org/10.1111/bdi.12857.

Kawamura, K., Kawamura, N., Kumazawa, Y., Kumagai, J., Fujimoto, T., Tanaka, T., 2011. Brain-derived neurotrophic factor/tyrosine kinase B signaling regulates human trophoblast growth in an in vivo animal model of ectopic pregnancy. Endocrinology 152, 1090–1100. https://doi.org/10.1210/en.2010-1124.

Kesebir, S., Gündoğar, D., Küçüksubaşi, Y., Tatlidil Yaylaci, E., 2013. The relation between affective temperament and resilience in depression: a controlled study. J. Affect. Disord. 148, 352–356. https://doi.org/10.1016/j.jad.2012.12.023.

Kesebir, S., Vahip, S., Akdeniz, F., Yüncü, Z., Alkan, M., Akiskal, H., 2005. Affective temperaments as measured by TEMPS-A in patients with bipolar I disorder and their first-degree relatives: a controlled study. J. Affect. Disord. 85, 127–133. https://doi.org/10.1016/j.jad.2003.10.013.

Kim, H., Turiano, N.A., Forbes, M.K., Kotov, R., Krueger, R.F., Eaton, N.R., Workgroup, HiTOP Utility, 2021. Internalizing psychopathology and all-cause mortality: a comparison of transdiagnostic vs. Diagnosis-based risk prediction. World Psychiatry 20, 276–282.

Koukopoulos, A.E., De Chiara, L., Simonetti, A., Kotzalidis, G.D., Janiri, D., Manfredi, G., Angeletti, G., Sani, G., 2021. The koukopoulos mixed depression rating scale (KMDRS) and the assessment of mixed symptoms during the perinatal period. J. Affect. Disord. 281, 980–988. https://doi.org/10.1016/j.jad.2020.08.080.

Kotzalidis, G.D., Rapinesi, C., Savoja, V., Cuomo, I., Simonetti, A., Ambrosi, E., Panaccione, I., Gubbini, S., De Rossi, P., De Chiara, L., Janiri, D., Sani, G., Koukopoulos, A.E., Manfredi, G., Napoletano, F., Caloro, M., Pancheri, L., Puzella, A., Callovini, G., Angeletti, G., Del Casale, A., 2017. Neurobiological evidence for the primacy of mania hypothesis. Curr. Neuropharmacol. 15, 339–352. https://doi.org/10.2174/1570159X14666160708231216.

Kraeplin, E., 1921. Manic-depressive Insanity and Paranoia: Translated by Barclay R.M. Chicago Medical Book Company.

Krueger, R.F., Hobbs, K.A., Conway, C.C., Dick, D.M., Dretsch, M.N., Eaton, N.R., Forbes, M.K., Forbush, K.T., Keyes, K.M., Latzman, R.D., Michelini, G., Patrick, C.J., Sellbom, M., Slade, T., South, S.C., Sunderland, M., Tackett, J., Waldman, I., Waszczuk, M.A., Wright, A.G.C., Zald, D.H., Watson, D., Kotov, R., Workgroup, HiTOP Utility, 2021. Validity and utility of hierarchical taxonomy of psychopathology (HiTOP): II. Externalizing superspectrum. World Psychiatry 20, 171–193. https://doi.org/10.1002/wps.20844.

Kukopulos, A.K., Reginaldi, D., Laddomada, P., Floris, G., Serra, G., Tondo, L., 1980. Course of the manic-depressive cycle and changes caused by treatments. Pharmakopsychiatr. Neur. Opsychopharmakol. 13, 156–167. https://doi.org/10.1055/s-2007-1019628.

Leichsenring, F., Steinert, C., Rabung, S., Ioannidis, J.P.A., 2022. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry 21, 133–145.

Luciano, M., Janiri, D., Fiorillo, A., Sani, G., 2020. Clinical picture, temperament, and personality of patients with mixed states. Psychiatr. Clin. North Am. 43, 15–26. https://doi.org/10.1016/j.psc.2019.10.002.

Luciano, M., Sampogna, G., Mancuso, E., Simonetti, A., De Fazio, P., Di Nicola, M., Di Lorenzo, G., Pepe, M., Sambataro, F., Signorelli, M., Koukopoulos, A., Delle Chiaie, R., Sani, G., Fiorillo, A., 2022. Trait-related impulsivity, affective temperaments and mood disorders: results from a real-world multicentric study. Brain Sci. 12, 1554.

Luciano, M., Steardo, L., Sampogna, G., Caivano, V., Ciampi, C., Del Vecchio, V., Di Cerbo, A., Giallonardo, V., Zinno, F., De Fazio, P., Fiorillo, A., 2021. Affective temperaments and illness severity in patients with bipolar disorder. Medicina (Kaunas). 57, 54. https://doi.org/10.3390/medicina57010054.

Maj, M., van Os, J., De Hert, M., Gaebel, W., Galderisi, S., Green, M.F., Guloksuz, S., Harvey, P.D., Jones, P.B., Malaspina, D., McGorry, P., Miettunen, J., Murray, R.M., Nuechterlein, K.H., Peralta, V., Thornicroft, G., van Winkel, R., Ventura, J., 2021. The clinical characterization of the patient with primary psychosis aimed at personalization of management. World Psychiatry 20, 4–33. https://doi.org/10.1002/wps.20809.

Maremmani, I., Perugi, G., Pacini, M., Akiskal, H.S., 2006. Toward a unitary perspective on the bipolar spectrum and substance abuse: opiate addiction as a paradigm. J. Affect. Disord. 93, 1–12. https://doi.org/10.1016/j.jad.2006.02.022.

Mazzarini, L., Pacchiarotti, I., Colom, F., Sani, G., Kotzalidis, G.D., Rosa, A.R., Sanna, L., De Rossi, P., Girardi, N., Bonnin, C.M., Sanchez-Moreno, J., Vazquez, G.H., Gasto, C., Tatarelli, R., Vieta, E., 2009. Predominant polarity and temperament in bipolar and unipolar affective disorders. J. Affect. Disord. 119, 28–33. https://doi.org/10.1016/j.jad.2009.03.016.

McIntyre, R.S., Alda, M., Baldessarini, R.J., Bauer, M., Berk, M., Correll, C.U., Fagiolini, A., Fountoulakis, K., Frye, M.A., Grunze, H., Kessing, L.V., Miklowitz, D.J., Parker, G., Post, R.M., Swann, A.C., Suppes, T., Vieta, E., Young, A., Maj, M., 2022. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry 21, 364–387.

Mendlowicz, M.V., Akiskal, H.S., Kelsoe, J.R., Rapaport, M.H., Jean-Louis, G., Gillin, J.C., 2005. Temperament in the clinical differentiation of depressed bipolar and unipolar major depressive patients. J. Affect. Disord. 84, 219–223. https://doi.org/10.1016/j.jad.2004.01.013.

Mineo, L., Rodolico, A., Spedicato, G.A., Aguglia, A., Bolognesi, S., Concerto, C., Cuomo, A., Goracci, A., Maina, G., Fagiolini, A., Amore, M., Aguglia, E., 2022. Exploration of mood spectrum symptoms during a major depressive episode: the impact of contrapolarity-results from a transdiagnostic cluster analysis on an italian sample of unipolar and bipolar patients. Eur Psychiatry 65, e30.

Miola, A., Baldessarini, R.J., Pinna, M., Tondo, L., 2021. Relationships of affective temperament ratings to diagnosis and morbidity measures in major affective disorders. Eur. Psychiatry 64, e74. https://doi.org/10.1192/j.eurpsy.2021.2252.

Mirin, S.M., Weiss, R.D., Griffin, M.L., Michael, J.L., 1991. Psychopathology in drug abusers and their families. Compr. Psychiatry 32, 36–51. https://doi.org/10.1016/0010-440X(91)90068-N.

Morishita, C., Kameyama, R., Toda, H., Masuya, J., Ichiki, M., Kusumi, I., Inoue, T., 2020. Utility of TEMPS-A in differentiation between major depressive disorder, bipolar I disorder, and bipolar II disorder. PLoS One 15, 1–10. https://doi.org/10.1371/journal.pone.0232459.

Mulder, R., 2021 Oct. The evolving nosology of personality disorder and its clinical utility. World Psychiatry 20 (3), 361–362.

Musenga, A., Saracino, M.A., Sani, G., Raggi, M.A., 2009. Antipsychotic and antiepileptic drugs in bipolar disorder: the importance of therapeutic drug monitoring. Curr. Med. Chem. 16, 1463–1481. https://doi.org/10.2174/092986709787909604.

Nobile, B., Olié, E., Dubois, J., Benramdane, M., Guillaume, S., Courtet, P., 2022 Apr 18. Characterization of suicidal depression: a one-year prospective study. Eur Psychiatry. 65 (1), 1–40.

Nowakowska, C., Strong, C.M., Santosa, C.M., Wang, P.W., Ketter, T.A., 2005. Temperamental commonalities and differences in euthymic mood disorder patients, creative controls, and healthy controls. J. Affect. Disord. 85, 207–215. https://doi.org/10.1016/j.jad.2003.11.012.

Perugi, G., Hantouche, E., Vannucchi, G., 2016. Diagnosis and treatment of cyclothymia: the "Primacy" of temperament. Curr. Neuropharmacol. 15, 372–379. https://doi.org/10.2174/1570159x14666160616120157.

Pompili, M., Innamorati, M., Gonda, X., Serafini, G., Sarno, S., Erbuto, D., Palermo, M., Elena Seretti, M., Stefani, H., Lester, D., Perugi, G., Akiskal, H., Siracusano, A., Rihmer, Z., Tatarelli, R., Amore, M., Girardi, P., 2013. Affective temperaments and hopelessness as predictors of health and social functioning in mood disorder patients: a prospective follow-up study. J. Affect. Disord. 150, 216–222. https://doi.org/10.1016/j.jad.2013.03.026.

Pössl, J., von Zerssen, D., 1990. A case history analysis of the "manic type" and the "melancholic type" of premorbid personality in affectively ill patients. Eur. Arch. Psychiatry Neurol. Sci. 239, 347–355. https://doi.org/10.1007/BF01734540.

Rihmer, Z., Akiskal, K.K., Rihmer, A., Akiskal, H.S., 2010. Current research on affective temperaments. Curr. Opin. Psychiatry 23, 12–18. https://doi.org/10.1097/YCO.0b013e32833299d4.

Sani, G., Vöhringer, P.A., Napoletano, F., Holtzman, N.S., Dalley, S., Girardi, P., Nassir Ghaemi, S., Koukopoulos, A., 2014. Koukopoulos' diagnostic criteria for mixed depression: a validation study. J. Affect. Disord. 164, 14–18. https://doi.org/10.1016/j.jad.2014.03.054Researchreport.

Serra, G., Koukopoulos, A., De Chiara, L., Napoletano, F., Koukopoulos, A.E., Curto, M., Manfredi, G., Faedda, G., Girardi, P., Baldessarini, R.J., 2015. Features preceding diagnosis of bipolar versus major depressive disorders. J. Affect. Disord. 173, 134–142. https://doi.org/10.1016/j.jad.2014.10.050.

Schneeberger, A.R., Huber, C.G., 2022. Crisis within a crisis - the fragility of acute psychiatric care delivery. World Psychiatry 21, 245–246. https://doi.org/10.1002/wps.20969.

Simonetti, A., Lijffijt, M., Swann, A.C., 2020. The neurobiology of mixed states. Psychiatr. Clin. North Am. 43, 139–151. https://doi.org/10.1016/j.psc.2019.10.013.

Song, Y.Y., Kang, J.I., Kim, S.J., Lee, M.K., Lee, E., An, S.K., 2013. Temperament and character in individuals at ultra-high risk for psychosis and with first-episode schizophrenia: associations with psychopathology, psychosocial functioning, and aspects of psychological health. Compr. Psychiatry 54, 1161–1168. https://doi.org/10.1016/j.comppsych.2013.05.015.

Takeshima, M., Oka, T., 2013. A comprehensive analysis of features that suggest bipolarity in patients with a major depressive episode: which is the best combination to predict soft bipolarity diagnosis? J. Affect. Disord. 147, 150–155. https://doi.org/10.1016/j.jad.2012.10.026.

Thornicroft, G., 2022. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts or power shifts? World Psychiatry 21, 334–335. https://doi.org/10.1002/wps.21000.

Tillman, R., Geller, B., 2003. Definitions of rapid, ultrarapid, and ultradian cycling and of episode duration in pediatric and adult bipolar disorders: a proposal to distinguish episodes from cycles. J. Child Adolesc. Psychopharmacol. 13, 267–271. https://doi.org/10.1089/104454603322572598.

Tohen, M., Baker, R.W., Altshuler, L.L., Zarate, C.A., Suppes, T., Ketter, T.A., Milton, D. R., Risser, R., Gilmore, J.A., Breier, A., Tollefson, G.A., 2002. Olanzapine versus divalproex in the treatment of acute mania. Am. J. Psychiatry 159, 1011–1017. https://doi.org/10.1176/appi.ajp.159.6.1011.

Tracy, D.K., Phillips, D.M., 2022. What is good acute psychiatric care (and how would you know)? World Psychiatry 21, 166–167. https://doi.org/10.1002/wps.20958.

Treyvaud, K., Brown, S.J., 2022. Mental health of children and parents after very preterm birth. World Psychiatry 21, 148–149. https://doi.org/10.1002/wps.20936.

Ueki, H., Holzapfel, C., Sakado, K., Washino, K., Inoue, M., Ogawa, N., 2004. Dimension of typus melancholicus on Kasahara's inventory for the melancholic type personality. Psychopathology 37, 53–58. https://doi.org/10.1159/000077578.

Wakamatsu, M., Nakamura, M., Douchi, T., Kasugai, M., Kodama, S., Sano, A., Kobayashi, H., 2021. Predicting postpartum depression by evaluating temperament during pregnancy. J. Affect. Disord. 292, 720–724. https://doi.org/10.1016/j.jad.2021.05.106.

Walsh, M.A., Royal, A.M., Barrantes-Vidal, N., Kwapil, T.R., 2012. The association of affective temperaments with impairment and psychopathology in a young adult sample. J. Affect. Disord. 141, 373–381. https://doi.org/10.1016/j.jad.2012.03.016.

Wakefield, J.C., 2022 Feb. Klerman's "credo" reconsidered: neo-kraepelinianism, Spitzer's views, and what we can learn from the past. World Psychiatry 21 (1), 4–25.

Wister, A.V., Coatta, K.L., Schuurman, N., Lear, S.A., Rosin, M., MacKey, D., 2016. A lifecourse model of multimorbidity resilience: theoretical and research developments. Int. J. Aging Hum. Dev. 82, 290–313. https://doi.org/10.1177/0091415016641686.

Yazici, E., Uslu Yuvaci, H., Yazici, A.B., Cevrioglu, A.S., Erol, A., 2018. Affective temperaments during pregnancy and postpartum period: a click to hyperthymic temperament. Gynecol. Endocrinol. 34, 265–269. https://doi.org/10.1080/09513590.2017.1393509.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.