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Research paper

Affective temperaments mediate aggressive dimensions in bipolar disorders: A cluster analysis from a large, cross-sectional, international study

Giovanna Fico [a,b,c,d], Delfina Janiri [f,g], Marco Pinna [h,i], Maria Sagué-Vilavella [a,b,c,d], Anna Gimenez Palomo [a,b,c,d], Vincenzo Oliva [b,j], Michele De Prisco [b,e,k], Pablo Guzmán Cortez [l], Gerard Anmella [a,b,c,d], Xenia Gonda [m,o,p], Gabriele Sani [f,g], Leonardo Tondo [h,i,n], Eduard Vieta [a,b,c,d,e,*], Andrea Murru [a,b,c,d,e]

[a] Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), c. Casanova, 143, 08036 Barcelona, Spain
[b] Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, c. Villarroel, 170, 08036 Barcelona, Spain
[c] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), c. Villarroel, 170, 08036 Barcelona, Spain
[d] Institute of Neurosciences (UBNeuro), p. de la Vall d'Hebron, 171, 08035 Barcelona, Spain
[e] CIBER de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[f] Department of Neuroscience, Section of Psychiatry, Catholic University of the Sacred Hearth, Roma, Italy
[g] Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[h] Lucio Bini Mood Disorders Center, Cagliari, Italy
[i] Section of Psychiatry, Department of Medical Science and Public Health, University of Cagliari, Italy
[j] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[k] Section of Psychiatry, Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy
[l] Institut Clínic de Neurociències, Psychiatry and Psychology Service, Grup Recerca Addiccions Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic de Barcelona, Barcelona, Spain
[m] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary
[n] McLean Hospital–Harvard Medical School, Boston, USA
[o] NAP-2-SE New Antidepressant Target Research Group, Hungarian Brain Research Program, Semmelweis University, Budapest, Hungary
[p] International Centre for Education and Research in Neuropsychiatry, Samara State Medical University, Russia

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ABSTRACT

Background: Affective temperaments show potential for aggressive behavior (AB) preventive strategies in bipolar disorder (BD). We aim to define intra-diagnostic subgroups of patients with BD based on homogeneous behaviors related to AB. Subsequently, to assess whether affective temperament dimensions may contribute to the presence and severity of AB.

Methods: Patients with BD were recruited. AB was evaluated through the modified overt aggression scale (MOAS); affective temperaments were assessed with the TEMPS-A. A cluster analysis was conducted based on TEMPS-A and MOAS scores. Stepwise backward logistic regression models were used to identify the predictive factors of cluster membership.

Results: 799 patients with BD were enrolled. Three clusters were determined: non-aggressive (55.5 %), self-aggressive (18 %), and hetero-aggressive (26.5 %). Depressive, irritable, and anxious temperament scores significantly increased from the non-aggressive (lower) to the self-aggressive (intermediate) and the hetero-aggressive group (highest). A positive history of a suicide attempt (B = 5.131; OR = 169.2, 95 % CI 75.9; 377) and rapid cycling (B = −0.97; OR = 0.40, 95 % CI 0.17; 0.95) predicted self-aggressive cluster membership. Atypical antipsychotics (B = 1.19; OR = 3.28, 95 % CI 2.13; 5.06) or SNRI treatment (B = 1.09; OR = 3, 95 % CI 1.57; 5.71), psychotic symptoms (B = 0.73; OR = 2.09, 95 % CI 1.34; 3.26), and history of a suicide attempt (B = −1.56; OR = 0.20, 95 % CI 0.11; 0.38) predicted hetero-aggressive cluster membership.

Limitations: Recall bias might have affected the recollection of AB.

* Corresponding author at: Bipolar and Depressive Disorders Unit, IDIBAPS CIBERSAM, Hospital Clinic, University of Barcelona, 170 Villarroel St, 08036 Barcelona, Catalonia, Spain.
E-mail address: evieta@clinic.cat (E. Vieta).

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Conclusions: Clinical factors orientate the prevention of different ABs in BD. Affective temperaments might play a role in preventing AB since patients with more pronounced affective temperaments might have an increased risk of showing AB, in particular hetero-AB.

1. Introduction

Aggressive behaviors (AB) represent a significant public concern, being among the main causes of worldwide premature death (Wang et al., 2016), and a clinical cliché that challenges both patients and providers in mental health (Seeman et al., 2016). Several psychiatric disorders, including mood disorders, are associated with increased rates of AB, with consequences on illness outcome, course, and management (Verdolini et al., 2017; Whiting et al., 2021a), although evidence provides conflicting or unclear results on this association (Elbogen and Johnson, 2009). Notably, only a minority of patients with a psychiatric disorder present AB (Volavka, 2013). Despite widespread belief, patients affected by mental health disorders present a higher risk of being subjected to violence rather than being offenders when compared with healthy controls (Sariaslan et al., 2020). Bipolar disorder (BD) is a chronic and recurring disorder characterized, among other aspects, by wide variations in mood and energy levels, traditionally interrelated with increased rates of AB (Ballester et al., 2012; Biancosino et al., 2009; Carvalho et al., 2020). One of the main challenges in AB research in BD relates to its entangled biological (Fico et al., 2020; Manchia et al., 2019) and phenotypic nature (Ramírez and Andreu, 2006). This results in a great variety of definitions and classifications, and consequently in a great heterogeneity of predictive models (Blanco et al., 2018; Fazel et al., 2012). For instance, self-AB comprises a variety of destructive actions directed to the self, from self-injury to suicide (Skegg, 2005), and has been widely studied in BD (Hayes et al., 2016; Nordentoft et al., 2011). On the other hand, little is known about hetero-AB, an overt behavior mainly toward another object or individual which identifies an uncharted subpopulation (Plutchik, 1995). Besides significantly contributing to stigma in BD (Torrey, 2002), hetero-AB is associated with acute mood episodes (Ballester et al., 2012), especially of manic polarity (Khalsa et al., 2018), poor medication adherence (Belete et al., 2016), and substance or alcohol abuse (Corrigan and Watson, 2005). However, the possible association between hetero-AB and BD is far from automated and exemplifies the pitfalls in the management of such behaviors as well as an opportunity to improve preventive strategies. Aggression in BD might be facilitated by poor impulse control and a tendency toward unplanned responses, which is a common characteristic of both self-AB or hetero-AB, leading to poorer BD outcomes (Cassidy and Carroll, 2001; Goodwin et al., 2016; Sato et al., 2002). Also, self-AB and hetero-AB share common neurobiological pathways, including lower levels of central serotonin, chronic increase in inflammatory markers, and disruption of the hypothalamic-pituitary-adrenal activity (Fico et al., 2020; Trepci et al., 2021). Nonetheless, these shared pathways do not allow discrimination between different clinical profiles (i.e., hetero-AB vs. self-AB) and within the same clinical profile (i.e., violent vs. non-violent self-AB), calling for further research and a more homogeneous, shared definition of AB in the literature (Conner et al., 2009; Plutchik, 1995; Pompili et al., 2008). In the search for AB preventive strategies, affective temperaments have channeled growing interest, as they are considered stable traits (Gandotra and Paul, 2004) and can be a precursor or subclinical manifestations of full-blown affective disorders (Azorin et al., 2015; Goto et al., 2011). Proposed and validated affective temperaments include *anxious*, *cyclothymic*, *depressive*, *hyperthymic*, and *irritable* types (Akiskal et al., 1998), which have shown evidence of heritability and familiarity in BD (Akiskal et al., 1977; Evans et al., 2005) and might stratify BD into more clinically and genetically homogenous subtypes. Although cyclothymic and hyperthymic temperaments have been connected to a larger spectrum of aggressive behaviors in BD (Dolenc et al., 2015), temperaments have been mainly described as possible predictors of suicidal behavior (Pompili et al., 2013; Rihmer et al., 2009; Vazquez et al., 2010). Also, affective temperaments within BD seem to adjust to different profiles of illness severity (Fico et al., 2019a, 2019c).

It remains uncertain if affective temperaments and their ratings are quantitatively associated with self- or hetero-AB (Tondo et al., 2018) and to what extent self- and hetero-AB subsets of patients might differ.

To address these questions, we conducted a cross-sectional study on a large, international sample of BD patients, aiming to identify and characterize intra-diagnostic subgroups of patients based on homogeneous behaviors related to aggressiveness through cluster analysis. Subsequently, we aimed to assess whether affective-temperament dimensions may influence the emergence and severity of AB.

2. Methods

We conducted a naturalistic study including prospective data on the course of the illness and retrospective data from the electronically recorded clinical history of patients enrolled and followed in the participating centers.

2.1. Participants

Outpatients with a diagnosis of BD were recruited from three different sites in Spain or Italy from April 2019 to November 2020: 1) Bipolar and Depressive Disorders Unit of the Hospital Clínic in Barcelona, 2) Fondazione Policlinico Universitario "A. Gemelli" in Rome, and 3) Mood Disorder Centro Lucio Bini in Cagliari. Eligible participants were older than 18 years and with a diagnosis of BD type I (BDI) or II (BDII) following the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria (APA, 2013). At inclusion, all patients were euthymic, defined following consensus criteria (a score $\leq$8 on the HAM-D and $\leq$6 on YMRS for at least 3 months) (Tohen et al., 2009). Patients were excluded if having a lifetime diagnosis of any other severe mental disorder (i.e., psychoses, schizoaffective disorder, major depressive disorder), neurological disorder, brain injury, intellectual disability, severe motor or visual impairment All participants provided written informed consent, and the study was approved by the local Ethical Committees of each participating center.

2.2. Clinical assessment and psychometric tools

Patients were assessed using the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2015b) and its personality disorder version (SCID-5-PD) (First et al., 2015a) by a trained psychiatrist or clinical psychologist. The main socio-demographic and clinical characteristics were collected through an ad hoc schedule. Other several clinical variables were obtained, such as the number and polarity of previous episodes, hospitalizations, age of onset, age of the first hospitalization, the polarity of the first episode, history of rapid cycling, history of psychosis, suicidal behavior, aggressive behavior (see Section 2.3), and psychiatric co-morbidities. All the included patients are part of longitudinal cohorts, which characteristics have been previously described elsewhere (Pinna et al., 2020; Vieta, 2011). Follow-up includes monthly clinical assessments where episodes (relapse or remission) are assessed according to DSM criteria, and the severity of symptoms (and subsyndromal symptoms) is rated with the YMRS and the HAMD. These data are introduced into the electronic clinical record of each patient by trained psychiatrists. Measures of current substance use were recorded at baseline and include alcohol, tobacco, and cigarette use in the past 30 days as well as

lifetime use of other drugs (e.g., marijuana, cocaine, and methamphetamine). Current pharmacological treatment was the treatment of each patient at the clinical assessment, which was registered if maintained for at least 6 months. Mixed states were defined according to DSM-5 criteria (First et al., 2015b). Predominant polarity was defined according to previous studies (Colom et al., 2006). The absence of a rapid cycling pattern was recorded as a dichotomous variable (1 = absence, 0 = presence).

2.3. Aggressive behavior

Aggressive behavior was evaluated through the Modified Overt Aggression Scale (MOAS) (Sorgi et al., 1991). The MOAS includes four aggression sub-domains: verbal, against objects, self-harm, and against other individuals. It rates the most severe violent behaviors during the last month before the baseline assessment (i.e., during euthymia). The scores range from 0 (no aggression) to 4 (maximum grade of aggression) for each subscale. The score of each subscale is then multiplied by a predefined loading (verbal aggression = 1, aggression against objects = 2, self-harm = 3, and aggression against other individuals = 4) and the total weighted score is the sum of each subscale weighted score (range 0–40).

2.4. Affective temperaments

Affective temperaments were evaluated with the short version of the Temperament Evaluation of Memphis, Paris and San Diego Auto-questionnaire (TEMPS-A), validated both in Spanish (Jiménez et al., 2019) and Italian samples (Preti et al., 2010). This self-rated questionnaire has 39 items assessing the presence of five affective temperaments (cyclothymic, depressive, irritable, hyperthymic, and anxious) scored Yes or No. The score on each temperament is the sum of the Yes responses. Patients were instructed to respond to TEMPS-A questions based on periods of euthymia. In this study, we analyzed raw numerical scores for the five individual temperaments (*cyclothymic*, 12 items; *depressive*, *irritable*, *hyperthymic*, 8 items each; *anxious*, 3 items).

2.5. Statistical analysis

We conducted a cluster analysis across the sample using the K-means algorithm. K-means is an unsupervised method that enables the partition of n observations into k clusters, assigning each observation to the cluster with the nearest centroid. The method proceeds by iterative calculations, with an assignment step that allocates an observation to a certain cluster based on the distance to its centroid being the smallest, and a maximization step that recalculates the position of the centroids for each assignment configuration until no observation changes cluster membership. The number of clusters was defined using the elbow method which is considered an indicator of the optimal number of clusters based on the location of a bend in the plot that charts the percentage of variance explained for each cluster solution (Jain, 2010). We took a complete cases approach, including only patients without missing observations. The selected clustering variables were: 1) aggressive behavior, total- and sub-scores, estimated at the time of consultation using the MOAS, 2) affective temperaments, assessed at the time of consultation using the TEMPS-A. Cluster membership was saved as a grouping variable, and patients were grouped according to the newly identified clusters. The Kolmogorov-Smirnov test was used to assess whether continuous variables displayed a normal distribution. Parametric comparative analyses for demographic and clinical characteristics of the clusters were done with ANOVA tests followed by Bonferroni corrected *post-hoc* correction; for non-parametric distributions, a Kruskal-Wallis test was used where appropriate. Categorical data were analyzed using χ^2 tests with *post-hoc* Bonferroni adjustment. Subsequently, two stepwise backward logistic regression models were used to identify the predictive value on cluster membership of statistically and clinically relevant variables. Statistical analyses were conducted using IBM SPSS Statistics version 25 and R 3.6.1 software (R Foundation for Statistical Computing, 2022).

3. Results

A total of 799 patients (mean age 49.04 [SD = 14.23]; 454 women [56.8 %]) with BDI (544, 68.1 %), or BDII (255, 31.9 %) were enrolled.

3.1. Cluster analysis

Out of the 799 patients considered, after screening for missing values, 717 complete cases were included in the analysis. Using the elbow method, visual inspection of the plot suggested patients in our sample were best clustered into three clusters (Supplementary Fig. 1). Cluster 1 (C1) comprised 55.5 % (N = 398), Cluster 2 (C2) 18 % (N = 129) and Cluster 3 (C3) 26.5 % (N = 190) of the study population. Comparisons between continuous and dichotomic variables among clusters are shown in Tables 1 and 2.

C3 showed higher scores at the *Verbal* ($H = -323.01$, $p < 0.001$ and $H = -304.24$, $p < 0.001$), *Against-property* ($H = -249.24$, $p < 0.001$ and $H = -249.84$, $p < 0.001$) and *Against-others* aggression ($H = -323.016$, $p < 0.001$ and $H = -304.246$, $p < 0.001$) items of the MOAS compared with C2 and C1. C2 showed higher scores at the self-aggression item of the MOAS compared with C3 and C1 ($H = 471.36$, $p < 0.001$). The total MOAS weighted scores were significantly higher in C2 ($H = -344.99$, $p < 0.001$) and C3 ($H = -348.01$, $p < 0.001$) than in C1, but showed no differences between C2 and C3. Thus, we labeled the three as *Non-aggressive* (C1), *Self-aggressive* (C2), and *Hetero-aggressive* (C3) clusters (Tables 1 and 2).

When we compared these three clusters according to TEMPS-A subscales scores, the significant between-group differences were restricted to the depressive ($H = 51.969$, $p < 0.001$), irritable ($H = 143.927$; $p < 0.001$), and anxious ($H = 173.718$; $p < 0.001$) temperaments (Table 2) (Fig. 1).

The *hetero-aggressive cluster* was significantly more likely to have psychotic symptoms ($\chi^2 = 33.445$, $p < 0.001$), substance use ($\chi^2 = 21.362$, $p < 0.001$) and receive treatment with atypical antipsychotics ($\chi^2 = 44.143$, $p < 0.001$) or electroconvulsive therapy ($\chi^2 = 6.772$, $p = 0.009$) compared with *self-aggressive* or *non-aggressive* groups. Also, the same group was significantly more likely to have BDI diagnosis ($\chi^2 = 28.446$, $p < 0.001$), a rapid-cycling course ($\chi^2 = 8.766$, $p = 0.003$), and receive serotonin-norepinephrine reuptake inhibitors (SNRI) treatment ($\chi^2 = 11.294$, $p = 0.001$) compared with the *non-aggressive* group.

The *self-aggressive* group showed a statistically higher lifetime number of mixed episodes ($H = 16.075$, $p < 0.001$) and suicide attempts, both expressed as rates ($\chi^2 = 361{,}891$, $p < 0.001$) and total number ($H = 362.195$, $p < 0.001$), compared with the other groups.

The *non-aggressive* group was more likely to have BDII diagnosis ($\chi^2 = 28.446$, $p < 0.001$) compared with the *hetero-aggressive cluster* and with a seasonal pattern compared with the *self-aggressive cluster*.

3.2. Logistic regressions

Two stepwise logistic regressions were conducted using respectively *self-aggressive* and *hetero-aggressive* cluster membership as dependent variables (Supplementary Tables 1 and 2). The full models included the 10 clinical independent variables that reached statistical significance at the univariate analysis (diagnosis of BDI, lifetime number of mixed episodes and suicide attempts; psychotic symptoms, absence of rapid cycling, substance use, seasonality, and treatment with SNRI, with atypical antipsychotics, and with electroconvulsive therapy).

The final model predicting hetero-aggressive cluster membership including 5 variables, was statistically significant ($\chi2 = 93.296$ $p < 0.001$), explained between 15.8 % (Cox and Snell R square) and 23 % (Nagelkerke R squared) of the variance, and correctly classified 73.1 %

Table 1
Comparison of socio-demographics and clinical variables across the three clusters.

Variables	Non-aggressive (C1) (N = 398; 55.5 %)	Self-aggressive (C2) (N = 129; 18 %)	Hetero-aggressive (C3) (N = 190; 26.5 %)	Post-hoc comparison			F/H/χ^2	p
				1 vs. 2	2 vs. 3	3 vs. 1		
Gender (F)	236; 59.3 %	75; 58.1 %	112; 58.9 %					
Diagnosis								
BDI	229; 57.5 %	88; 68.2 %	152; 80 %			*	29.227	<0.001
BDII	169; 42.5 %	41; 31.8 %	38; 20 %			*		
Age and illness duration								
Age at assessment	49.95 ± 14.63	49.14 ± 15.03	49.47 ± 12.67					
Age at onset	27.44 ± 11.85	25.26 ± 11.53	25.37 ± 10.25				6.566	0.038
Duration of illness	22.33 ± 13.81	24.06 ± 12.8	24.23 ± 11.27					
Number of affective episodes, lifetime								
Depressive	8.58 ± 16.45	8.34 ± 14.53	7.55 ± 10.28					
Manic	2.05 ± 4.98	2.48 ± 5.17	1.92 ± 3.73					
Hypomanic	5.46 ± 13.57	3.97 ± 6.44	4.85 ± 8.44					
Mixed	1.82 ± 7.96	1.98 ± 4.8	0.85 ± 2.8	*	*		16.075	<0.001
Total	17.91 ± 30.52	16.77 ± 22.04	15.17 ± 19.45					
Number of Psychiatric admissions, lifetime	1.51 ± 2.67	2.06 ± 3.51	1.5 ± 2.53					
Clinical course variables, lifetime								
Lifetime suicide attempt (yes/no)	43; 10.8 %	118; 91.5 %	20; 10.5 %	*	*		365.617	<0.001
Number of lifetime suicide attempts	0.14 ± 0.43	1.64 ± 1.32	0.18 ± 0.57	*	*		362.195	<0.001
Psychotic symptoms	120; 42.1 %	71; 59.2 %	119; 69.2 %	*		*	33.445	<0.001
Rapid cycling	35; 9 %	20; 15.6 %	33; 17.4 %			*	9.816	0.007
Substance use	113; 28.7 %	41; 32 %	90; 48.1 %		*	*	21.644	<0.001
Alcohol Use Disorder	121; 40.2 %	31; 52.5 %	6; 40 %					
Seasonal Pattern	53; 13.5 %	7; 5.4 %	23; 12.1 %	*			6.176	0.046
Comorbidity with Personality Disorder	56; 14.1 %	21; 16.4 %	39; 21 %					
Predominant Polarity								
Depressive	96; 24.2 %	29; 22.7 %	40; 21.1 %					
Manic	61; 15.4 %	14; 10.9 %	32; 16.8 %					
Undetermined	240; 60.5 %	85; 66.4 %	118; 62.1 %					
Treatments, lifetime								
Lithium	214; 54.7 %	82; 63.6 %	115; 61.2 %					
Carbamazepine	19; 6.6 %	12; 9.8 %	17; 9.2 %					
Gabapentine	10; 3.5 %	8; 6.6 %	6; 3.3 %					
Lamotrigine	82; 28.5 %	23; 18.9 %	48; 26.1 %					
Valproate	44; 15.8 %	12; 10.6 %	21; 13.1 %					
Atypical Antipsychotics	70; 24.4 %	43; 35.2 %	104; 56.8 %		*	*	50.779	<0.001
Aripiprazole	9; 3.1 %	5; 4.1 %	13; 7.1 %					
Asenapine	1; 0.4 %	1; 1.1 %	2; 1.6 %					
Clozapine	2; 0.7 %	1; 0.8 %	6; 3.3 %					
Olanzapine	25; 8.7 %	11; 9 %	24; 13 %					
Paliperidone	0; 0 %	1; 1.1 %	1; 0.8 %					
Quetiapine	70; 24.3 %	37; 30.3 %	41; 22.3 %					
Risperidone	28; 9.7 %	9; 7.4 %	20; 10.9 %					
Ziprasidone	1; 0.3 %	2; 1.6 %	4; 0.7 %					
Antidepressant								
MAOIs	0; 0 %	1; 0.8 %	2; 1.1 %					
SNRI	17; 5.9 %	14; 11.5 %	28; 15.2 %			*	11.297	0.004
SSRI	53; 18.4 %	28; 23 %	27; 14.7 %					
TCA	29; 10.1 %	9; 7.4 %	8; 4.3 %					
Electroconvulsive Therapy	0; 0 %	1; 0.8 %	3; 1.9 %		*	*	6.726	0.035

Note: Continuous variables are expressed as mean ± standard deviation. Dichotomic variable are expressed as number of cases and percentage. * = $p < 0.05$. Abbreviations: BD = Bipolar Disorder; N = number of cases; p = statistical significance; SD = standard deviation; χ^2 = Chi-square test; F = ANOVA 1-way distribution; Independent Samples *t*-test; H = Kruskal-Wallis Test; MAOIs = Monoamine oxidase inhibitors; SNRI = Serotonin–norepinephrine reuptake inhibitors; SSRI = Selective Serotonin reuptake inhibitors; TCA = Tricyclic Antidepressants.

of cases. Treatment with atypical antipsychotics was the strongest predictor of *hetero-aggressive* cluster membership (B = 1.190; OR = 3.28, 95 % CI 2.13; 5.06), followed by treatment with SNRI (B = 1.09; OR = 3, 95 % CI 1.57; 5.71), lifetime presence of psychotic symptoms (B = 0.73; OR = 2.09, 95 % CI 1.34; 3.26), and a negative lifetime history of a suicide attempt (B = -1.56; OR = 0.20, 95 % CI 0.11; 0.38), while electroconvulsive therapy did not contribute to the model.

The final model predicting auto-aggressive cluster membership including 2 variables, was statistically significant (χ^2 = 322.861, p < 0.001), explained between 44.9 % (Cox and Snell R square), and 70.4 % (Nagelkerke R squared) of the variance, and correctly classified 79.5 % of cases. A positive lifetime history of a suicide attempt was the strongest predictor of *auto-aggressive* cluster membership (B = 5.131; OR = 169.205, 95 % CI 75.93; 377.04), followed by the presence of a rapid cycling pattern (B = −0.97; OR = 0.40, 95 % CI 0.17; 0.95).

4. Discussion

In our, large multicentrict, cross-sectional study we were able to identify three well-defined clinical clusters according to the presence of AB in a sample of patients with BD and to describe predictors of a specific AB. The three cluster were: *Non-aggressive*, which represents more than half of patients with BD in our sample, followed by *Hetero-aggressive* and *Self-aggressive* clusters which are associated with different clinical characteristics of BD.

Affective temperaments, as biologically-determined trait characteristics, might help the clinical description of AB. One of the main results of our study is that depressive, irritable, and anxious temperament scores significantly and progressively increased from the *non-aggressive* group (lowest) to the *self-aggressive* group (intermediate) and the *hetero-aggressive* group (highest). The impact of affective temperaments on the

Table 2
Mean MOAS and TEMPS-A mean scores across the three clusters.

	Non-aggressive (C1) (N = 398; 55.5 %)	Self-aggressive (C2) (N = 129; 18 %)	Hetero-aggressive (C3) (N = 190; 26.5 %)	Post-hoc comparison			H	p
				1 vs. 2	2 vs.3	3 vs.1		
MOAS (mean ± SD)					<0.001 < 0.001			
- Total weighted score	0.75 ± 1.68	12.37 ± 3.85	14.96 ± 12.11	<0.001	<0.001	<0.001	536.743	<0.001
- *Verbal* aggression	0.33 ± 0.681	0.26 ± 0.67	2.1 ± 0.82		<0.001	<0.001	393.962	<0.001
- *Against objects* aggression	0.12 ± 0.455	0.16 ± 0.63	1.63 ± 1.22			<0.001	345.475	<0.001
- *Self*-Aggression	0.03 ± 0.68	3.85 ± 1.12	1.26 ± 1.95	<0.001		<0.001	471.367	<0.001
- *Against others* aggression	0.02 ± 0.16	0.06 ± 0.3	1.46 ± 1.67			<0.001	381.499	<0.001
TEMPS-A (mean ± SD)	5.50 ± 3.6							
- Cyclothymic	3.64 ± 2.78	5.82 ± 4.09	5.98 ± 4.06				0.226	0.181
- Depressive	1.87 ± 2.37	4.71 ± 3.56	6.45 ± 1.65	0.019	0.006	<0.001	51.969	<0.001
- Irritable	4.21 ± 2.85	2.8 ± 2.88	5.43 ± 2	0.003	<0.001	<0.001	143.927	<0.001
- Hyperthymic	1.40 ± 1.14	4.79 ± 4.1	5.81 ± 2.98				3.415	0.893
- Anxious		1.55 ± 1.01	1.64 ± 1.8	<0.001	<0.001	<0.001	173.718	<0.001

Abbreviations: MOAS = Modified Overt Aggression Scale; TEMPS-A = Temperament Evaluation of Memphis, Pisa, Paris and San Diego-auto questionnaire version (TEMPS-A); N = number of cases; p = statistical significance; SD = standard deviation; H = Kruskal-Wallis Test.

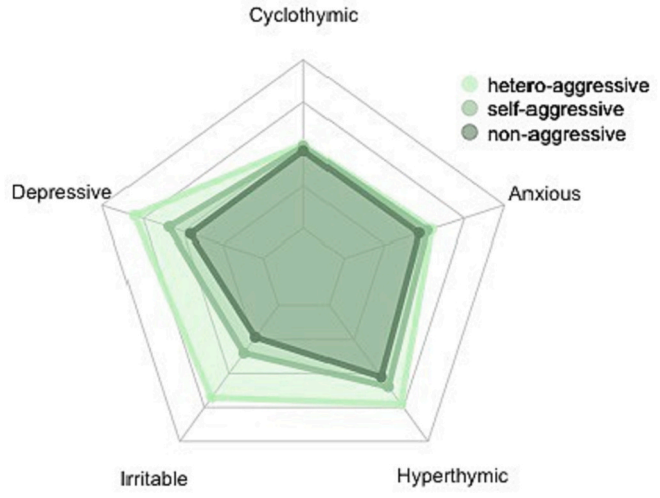

Fig. 1. Radar Chart of TEMPS-A scores for each temperament subscale according to cluster membership.

risk of aggressive behaviors is a widely explored topic in the field of mental health, especially regarding the identification of possible AB prevention strategies, focusing more on self-AB (Fico et al., 2019b; Karam et al., 2015) rather than hetero-AB (Dolenc et al., 2015). Our results indicate that a greater temperamental dysregulation may correlate to different types of AB in BD patients. Higher scores on anxious, depressive, cyclothymic, and irritable temperaments correlate with more severe mood symptoms and illness severity (Iasevoli et al., 2013). This greater intensity of depressive, anxious, or irritable traits, also reported to be associated with mood instability and impulsivity (Vázquez et al., 2018), might lead to high reactiveness toward external stimuli, as seen by their association depressive, anxious or irritable with hetero-AB in our sample. Such subpopulation of BD patients, which presents a biologically determined tendency toward severe outcomes, needs early detection and closer monitoring concerning possible hetero-AB. On the other hand, we should not underestimate the magnitude of self-AB in clinic management, which implies potentially unwanted outcomes, as a higher risk of suicide (Hayes et al., 2016; Olfson et al., 2017; Popovic et al., 2015).

Hetero-AB in our BD sample is associated with the presence of psychotic symptoms, confirming previous evidence (Elbogen and Johnson, 2009; Fazel et al., 2012; Pulay et al., 2008; Sariaslan et al., 2016; Whiting et al., 2021b). Coherently, we reported a positive association between hetero-AB and treatment with atypical antipsychotics. Hetero-AB was found to be associated with paranoia, irritability, lack of insight, impulsivity, which are considered as trait factors, but also state, potentially improved with treatment, characteristics of manic or mixed episodes (Najt et al., 2007; Perroud et al., 2011). Therefore, these patients were more likely treated with antipsychotics.

While a positive history of suicide was a negative predictor of hetero-AB, it strongly increased the risk of self-AB in our sample. Thus, the early detection of a positive history of suicide attempts might help tailor clinical interventions for the prevention of either risk behaviors.

It is well established that BD patients present an increased risk of self-AB compared to the general population (Ballester et al., 2014; Popovic et al., 2015; Schaffer et al., 2015), however, no risk factor has been considered a reliable predictor. Results from our logistic regression model point to a robust role of a prior history of self-AB in predicting subsequent similar behavior in BD. This is in line with previous evidence (Bostwick et al., 2016), suggesting that self-harm acts as an adequate proxy for more severe behavior, including death by suicide (Plans et al., 2019). Also, almost 9 % of patients with affective disorders hospitalized with suicidal ideation or after a suicide attempt will eventually die by suicide (Bostwick and Pankratz, 2000). Our results also show that a rapid cycling course increases the risk of self-AB, worsening BD long-term outcomes. Indeed, BD patients with rapid cycling are 54 % more likely to attempt suicide compared to those without rapid cycling (Hawton et al., 2005). Mixed states did not increase the risk of self-AB in our sample, despite being significantly associated with both self-AB and hetero-AB at the univariate analyses. Considering the sound, documented association between mixed states or episodes and suicidal behavior in both clinical and community samples (Pacchiarotti et al., 2011; Verdolini et al., 2017), we attributed to multicollinearity the lack of significance of mixed states on self-AB in the regression model. Clinicians should not overlook these clinical characteristics when assessing suicide risk in BD. In this light, affective temperaments might also help in suicide risk assessment, since cyclothymic temperament might associate with an increased risk, while hyperthymic with a reduced one (Fico et al., 2019a).

While is known that lithium reduces suicide risk by possibly decreasing aggression and impulsivity (Cipriani et al., 2013; del Matto et al., 2020; Fountoulakis et al., 2022), currently, there are no clear indications for the treatment of hetero-AB, commonly based on the use of antipsychotic drugs, independently from the diagnosis (Meyer et al., 2016; van Schalkwyk et al., 2018). Our results show that the use of SNRI is a marker for hetero-AB. The risk-benefit profile of antidepressant medications in BD is controversial (Pacchiarotti et al., 2013; Pacchiarotti and Verdolini, 2021): indeed, SNRI are associated with an increase in impulsivity and irritability, possible proxies for AB (Sharma et al., 2016). The use of antipsychotics for the management of hetero-AB is based on the identification of the role of dopamine and serotonin in the etiology of AB (Manchia et al., 2017) and led to the hypothesis that

antipsychotics could have a primary "anti-aggressive" effect (Meyer et al., 2016). However, a recent meta-analysis reported that antipsychotics do not show greater efficacy than other non-pharmacological treatments (such as cognitive-behavioral interventions), that the effect size is modest, and that it does not vary depending on the type of antipsychotic (van Schalkwyk et al., 2018). New pharmacological targets, such as drugs acting on the nicotinic system, which showed preclinical and early clinical efficacy in reducing hetero-AB in different diagnostic categories (Allen and Anderson, 2017; Lewis et al., 2015; Picciotto et al., 2015) or consider the association of non-pharmacological treatments for hetero-AB management (Rampling et al., 2016).

Given the conflicting evidence, future research should be able to better phenotype these subpopulations of patients (Fusar-Poli et al., 2022) and focus on clinical predictors of AB to implement strategies for AB risk prevention or treatments.

5. Limitations

There are several limitations to this study. First, the observational nature of our study prevents causal inference, especially concerning the relationship between affective temperament and aggressive behavior or pharmacological treatments and clinical outcomes. Second, we should consider that the possible underrepresentation of extremes of AB in our sample (i.e., subjects dead by suicide, convicted subjects due to hetero-AB that cannot be recruited from health care centers) and the retrospective evaluation of AB might have led to an underestimation of the AB. Obviously, some of the findings would benefit from replication in prospective, cohort studies (Vieta and Angst, 2021). Also, data on the polarity of the first episode were lacking for the majority of the patients, making it difficult to explore the role of this variable on our outcome. However, our study has some strengths, as it proposes a standardized measure of AB, and it discloses the relevant association of affective temperaments with specific phenotypes of AB in a large and international sample of patients with BD, recruited from recognized European centers, specialized in the treatment of BD and currently following-up >1000 patients, with reliable electronically clinical information recorded by trained psychiatrists.

6. Conclusions

Affective temperaments might help to cluster different profiles and severity of aggressive behavior in patients with bipolar disorder, so they might be routinely assessed to orient the clinical management. Our results could have an impact on the management of aggressive patients with bipolar disorders by providing some clinical suggestions. In particular, the evaluation of a previous history of suicide attempts or ideation should be considered from the early stages of management of patients with bipolar disorder, given its potential role as a screening tool in detecting patients at high risk for self-aggressive behavior and reduced risk for hetero-aggressive behavior. However, our results outline a gap concerning the best treatment options. Current evidence in this respect focuses on state-related factors, such as treatment adherence-enhancing strategies, rather than on the primary prevention of aggressive behavior. The evaluation of clinical variables alone still lacks in specificity to prevent aggressive behavior in bipolar disorder. Further research should explore the possibility to integrate in complex statistical models clinical with biological, behavioral, and new digital markers to develop accurate predictive algorithms of aggressive behavior.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Boehringer-Ingelheim, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Novartis, Organon, Otsuka, Sanofi-Aventis, Sunovion, and Takeda, outside the submitted work. GF has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck. GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, and Angelini, with no financial or other relationship relevant to the subject of this article.

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