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Subthreshold autism spectrum in bipolar disorder: Prevalence and clinical correlates

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ABSTRACT

Background: While few previous studies highlighted a higher prevalence of autistic traits among adults with Bipolar Disorder (BD), little is known about their clinical significance in this population.
Method: 143 subjects with BD were enrolled at the adult psychiatric inpatient clinic of the University of Pisa. Assessments included the SCID-5, the MOODS-SR, the AQ and the AdAS Spectrum.
Results: 42.7% of the sample scored positively for significant levels of autistic traits. Subjects with high autistic traits showed a greater likelihood of a very early onset of BD, greater length of current in-hospital stay, significantly higher rates of anxiety disorders and lower rates of substance use disorders compared to patients with low autistic traits. They also show significantly greater depressive symptoms and suicidality across the lifetime. Suicidality was associated with the altered responsiveness to sensory input and inversely related to adherence to routine and inflexibility.
Conclusion: The study is a first exploration of the clinical significance of autistic traits among BD patients. Our results highlight the clinical significance of autistic traits in patients with BD, supporting the usefulness of a dimensional approach to the autism spectrum.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication and social relationships as well as by restricted patterns of interests, behaviors and activities, which may show very different grades of symptom severity (American Psychiatric Association, 2013). A growing body of data stressed how ASD represents the extreme end of a set of behavioral and cognitive features that are continuously distributed in both the clinical and the general population, where they are commonly named autistic traits (Constantino and Charman, 2016; Dell'Osso et al., 2016). The expression of autistic traits has been investigated for the first time among parents of children with ASD, leading to the conceptualization of a *Broad Autism Phenotype* (BAP) (Wheelwright et al., 2010; Sucksmith et al., 2011). The BAP is characterized by a set of subclinical manifestations, similar to, although milder than, ASD typical symptoms, whose genetic and neurobiological correlates have been investigated in several studies (Losh et al., 2009; Constantino et al., 2010; Holt et al., 2014; Nayar et al., 2018; Carpita et al., 2018). More recently, a growing literature has highlighted the presence of autistic traits not only in first-degree relatives of ASD probands, but also in other high-risk groups from the general population, as well as in clinical samples of subjects with different psychiatric disorders (Dell'Osso et al., 2018a, 2018b, 2018c, 2018d, 2018e).

Bipolar Disorder (BD) is a major affective disorder with a chronic course, characterized by recurrent episodes of depression and mania/hypomania. A number of genetic, epidemiological and clinical studies highlighted a significant overlap between BD and ASD (Hofvander et al., 2009; Sullivan et al., 2012; Skokauskas et al., 2015; Selten et al., 2015), along with the recurrent hypothesis of a possible neurodevelopmental pathway for BD and other mental disorders (Sanches et al., 2008; O'Shea et al., 2016; O'Connell et al., 2018). However, the rates of comorbidity between ASD and BD have been assessed by a limited number of studies. Most of them were conducted in clinical populations of children/adolescents, reporting very different results. The prevalence of BD in clinical samples of ASD patients ranges from 3 to 27% (Ghaziuddin et al., 1998; Munesue et al., 2008), while ASD caseness in samples of subjects with BD vary from 2 to 30% depending from the study (Axelson et al., 2006; Joshi et al., 2013). Interestingly, previous data showed a significant impact of ASD on the

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clinical manifestations of BD. Borue et al. (2016) reported that in a large sample of 368 youths with BD, subjects with ASD showed a earlier onset of BD, more episodes with mixed features and a greater functional impairment compared to patients without ASD.

Conversely, only two studies have assessed autistic traits in adults with BD. Matsuo et al. (2015) evaluated 225 clinical subjects with Major Depressive Disorder (MDD), BD or Schizophrenia (Sch) and 65 healthy subjects, reporting significant autistic traits among patients with BD and Sch, independently from symptom severity, while autistic traits among subjects with MDD were associated with the severity of depressive symptoms. Abu-Akel et al. (2017) found a high prevalence of autistic and schizotypal traits (SchT) among 797 patients with BD I, also highlighting that both autistic traits and SchT were associated with better global functioning.

However, to the best of our knowledge, no study has yet investigated how autistic traits may affect clinical correlates among subjects with BD. In this framework, the present study has two main objectives: (1) to assess the expression of autistic traits in a sample of BD subjects; (2) to compare BD subjects with high versus low autistic traits focusing on some relevant clinical variables, such as the age of onset of BD, the clinical phenotype, the suicidality, and the pattern of comorbidity with other mental disorders.

2. Methods

2.1. Participants and procedures

A consecutive sample of BD subjects was enrolled between January 2017 and March 2018 at the adult psychiatric inpatient clinic of the University of Pisa (Italy), a tertiary care academic center specialized in the treatment of mood and anxiety disorders. Subjects with both BD I and BD II were eligible, with no restriction of the phase of the disorder. The BD diagnosis was confirmed by means of the Structured Clinical Interview for Psychiatric Disorders (SCID-5, First et al., 2015). Patients diagnosed with severe degenerative diseases of the central nervous system were excluded. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participants.

2.2. Measures

The SCID-5 was used to assess DSM-5 diagnosis by psychiatrists trained and certified in the use of this instrument. Assessment procedures further included the administration of the Autism-Spectrum Quotient (AQ) (Baron-Choen et al., 2001), the Adult Autism Subthreshold Spectrum (AdAS Spectrum) (Dell'Osso et al., 2017) and the Moods Spectrum (Dell'Osso et al., 2002).

2.2.1. The Autism-Spectrum Quotient (AQ)

The Autism-Spectrum Quotient (AQ) is a widely used questionnaire, which provides a self-report measure of autistic traits in adults with average IQ (Baron-Cohen et al. 2001). It features 50 items, assessing 5 different areas: social skill; attention switching; attention to detail; communication; imagination. The AQ has been used as a screening tool for ASD in the general population, as well as to evaluate autistic traits within clinical groups (Cath et al. 2008; Hoekstra et al. 2008; Spek and Wouters 2010; Wouters and Spek 2011; Mealey et al. 2014; Mito et al. 2014). According to previous studies (Wheelwright et al. 2010), subjects scoring 23 or higher on the AQ were considered as expressing a BAP.

2.2.2. The Adult Autism Subthreshold Spectrum (AdAS Spectrum)

The AdAS Spectrum is a 160-item self-report questionnaire recently developed with the aim of assessing a broad variety of symptoms and features associated with ASD. It is tailored to assess not only full-threshold symptoms, but also subthreshold and partial forms of ASD, as well as isolated autistic traits across the lifetime. Items are grouped into 7 domains: Infancy/adolescence, Verbal communication, Non-verbal communication, Empathy, Adherence to routine and inflexibility, Restricted interests and rumination, Hyper-/hyporeactivity to sensory input. In the validation study, the AdAS Spectrum showed high internal consistency, sound test-retest reliability (Kunder-Richiardson coefficient = 0.964, ICC = 0.976) and strong convergent validity with other dimensional measures of autism (Dell'Osso et al., 2017).

2.2.3. The Moods Spectrum, Self-report (MOODS-SR), life-time version

The MOODS (Dell'Osso et al, 2002; Fagiolini et al, 1999) is a 160-item questionnaire, which assesses the presence of mood disorder symptoms during the lifetime. Items are grouped in seven domains: mood-depressed, mood-manic, energy-depressed, energy-manic, cognition-depressed, cognition-manic and rhythmicity. The questionnaire showed good internal consistency, with a Kuder-Richardson's coefficient ranging from 0.79 to 0.92 among single domains.

2.2.4. Assessment of suicidality

Suicidality was assessed by means of six items of the MOODS-SR that explore suicidal ideation and behaviors. In particular, the items investigate whether the subject has ever: thought that life was not worth living (N = 102); wished he/she would not wake up in the morning, or that he/she would die in an accident or from something like a heart attack or a stroke (N = 103); wanted to die or hurt him/herself (N = 104); wanted to die and had a specific plan to hurt or kill him/herself (N = 105); actually committed a suicide attempt (N = 106); committed a suicide attempt that required medical attention (N = 107). For the purpose of this study, suicidality was scored according to the number of positive answers given on these six items by each patient (score ranging from 0 to 6).

2.3. Statistical analyses

Frequency distribution and tests of statistical significance were carried out. To perform statistical analysis, the sample of BD patients was split in two groups on the basis of the AQ score: subjects with a score $\geq$ 23 ("BAP" group) and subjects with a score $<$ 23 ("NoBAP" group). Comparisons between groups for continuous variables (such as mean total and domain scores of AQ, AdAS Spectrum, MOODS-SR) were performed by means of the independent sample Student's t-test. The Chi-square test was utilized to compare categorical variables (such as gender, psychiatric family history, previous suicide attempts) in the two groups. A multivariate linear regression was performed in order to evaluate significant predictors of suicidality with AdAS Spectrum domain scores as independent variables. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20 (IBM corp. 2011). Comparisons were considered statistically significant at the 5% ($p < .05$).

3. Results

3.1. Sample characteristics

The sample consisted of 143 adult inpatients with BD (age 46.3 ± 14.5 years; N = 97 BD I, N = 57 BD II). The recruitment process lasted for 13 months. 2 subjects (1.4%) were hospitalized for their first BD episode. The majority of the patients were Caucasian males (85; 59.4%), with a mean age of 44.8 ± 14.0 years; females were 58 (40.6%) with a mean age of 48.5 ± 15.0. BAP patients were more frequently unemployed than NoBAP, while no significant difference was found for marital status (See Table 1). The overall sample scored a mean of 21.7 ± 14.5 on the AQ, and a mean of 62.6 ± 24.8 on the AdAS Spectrum, with no difference between males and females (AQ: 21.8 ± 6.1 *vs* 21.7 ± 4.9, t = 0.126, p = .900; AdAS Spectrum: 61.2 ± 27.1 *vs* 64.6 ± 21.0, t = −0.805, p = .472). Using the AQ

Table 1
Sociodemographic characteristics of BD subjects with or without BAP

		BAP (*n*:61) N(%)	NO BAP (*n*:82) N(%)	χ^2	Sig.
Sex					
	Female Male	28(48.3) 33(38.8)	30(51.7) 52(61.2)	1.259	0.262
Employment status*					
	Employed Unemployed Other (student, housewife, retired)	19(33.9) 22(39.3) 15(26.8)	48(60.8) 21(26.6) 10(12.7)	9.946	0.007
Marital status#					
	Never married Married/cohabiting Sep./div./widowed	27(47.4) 28(49.1) 2(3.5)	42(55.3) 33(43.4) 1(1.3)	1.317	0.518
	Mean ± SD	Mean ± SD	t		
Age	45.7 ± 15.8	46.7 ± 15.8	.431	.667	
Age at onset of BD	25.4 ± 12.5	28.6 ± 12.7	1.527	.129	

*Data available for 135 subjects; #data available for 133 subjects.

cut-off ≥ 23, 42.7% of the whole sample ($N = 61$) scored positively for a BAP, while the remaining 57.3% ($N = 82$) did not (NoBAP).

3.2. Clinical correlates of BD patients with or without BAP

The two groups did not show significant differences for psychiatric family history, bipolar subtype, onset polarity, number of previous depressive and manic/hypomanic episodes, number of inpatient stays (see Table 2). Subjects in the BAP group had greater length of current in-hospital stay and greater likelihood of a very early onset (prior to age 15). Subjects in the BAP group, compared to those in the NoBAP group, reported significantly higher MOODS-SR total score. They also scored higher in all three depressive domain scores (*Depressive Mood, Depressive Cognition* and *Depressive Energy*) and in one out of three manic domain scores (*Manic energy*) and in the *Rhythmicity* domain score (see Table 2). The total number of comorbid mental disorders, as evaluated by means of the SCID-5, did not differ between BAP and NoBAP subjects (1.2 ± .83 vs 1.02 ± .71, $t = -0.984$, $p = 0.327$). BAP patients reported significantly higher rates of anxiety disorders, and significantly lower rates of substance use disorder (see Table 3).

3.3. Suicidality

Overall, 26 subjects (18.2%) attempted suicide during their lifetime, with no difference between genders (males *vs* females: 15.3% *vs* 22.4%, Chi-Square = 1.175, $p = .278$). The two groups did not differ for the presence/absence nor for the number of previous suicide attempts. BAP patients reported greater lifetime suicidality as evaluated with the MOODS-SR (see Table 2). Among BD patients who had previously attempted suicide, females were more frequently included in the BAP group than males (61.5% *vs* 23.1%, Chi-Square = 3.939, $p = .047$). Table 4 provides the results of the linear regression model for AdAS Spectrum domains predictive of MOODS-SR suicidality score. The *Hyper/hyporeactivity to sensory input* domain score was positively related to the suicidality score, while the *Adherence to routine and inflexibility*

Table 3
Lifetime frequencies of DSM-5 comorbidities of BD subjects with or without BAP.

		BAP (*n*:61) *N* (%)	NO BAP (*n*:82) *N*(%)	χ^2	Sig.
Psychiatric comorbidity					
Anxiety disorders	40(65.6)	38(46.3)	5.218	0.022	
PTSD	2(3.3)	4(4.5)	0.135	0.714	
DOC	12(20.0)	15(17)	0.209	0.648	
borderline	2(3.3)	1(1.1)	0.867	0.352	
Eating disorders	1(1.7)	7(8.3)	2.892	0.089	
Alcohol use disorder	8(13.1)	11(13.4)	0.003	0.958	
Substance use disorder	2(3.3)	11(13.4)	4.348	0.037	

Table 2
Clinical characteristics of BD subjects with or without BAP.

		BAP (*n*:61) N(%)	NO BAP (n:82) N(%)	χ^2	Sig.
Positive psychiatric family history	46(75.4)	63(76.8)	0.039	0.844	
Bipolar subtype					
	BDI BDII	57(93.4) 486.6)	76(92.7) 6(7.3)	0.031	0.860
Polarity at BD onset					
	Depressive manic/hypomanic	44(75.9) 14(24.1)	52(64.2) 29(35.8)	2.152	0.142
Early onset of BD (between 15 and 18)	17(27.9)	19(23.2)	0.410	0.522	
Very early onset of BD (prior to age 15)	10(16.4)	1(1.2)	11.343	0.001	
Number of previous hospitalizations	2.0(2.2)	2.2(2.9)	0.576	0.566	
Number of lifetime depressive episodes	3.5(2.4)	3.4(2.1)	−0.278	0.781	
Number of lifetime manic/hypomanic episodes	2.5(2.1)	3.0(2.4)	1.321	0.189	
Number of lifetime suicide attempts	0.34(.89)	0.21(.46)	−1.094	0.277	

	BAP (*n*:61) Mean ± SD	NO BAP (*n*:82) Mean ± SD	*t*	Sig.
MOODS-SR				
total	74 ± 22.7	57.6 ± 24.6	−4.159	<.001
Depressive mood	16.2 ± 4.8	12.8 ± 6.5	−3.783	<.001
Manic mood	10.1 ± 5.6	8.6 ± 6.0	−1.530	.128
Depressive energy	6.4 ± 2.2	5.0 ± 2.7	−3.489	.001
Manic energy	5.5 ± 3.2	3.6 ± 3.0	−3.702	<.001
Depressive cognitivity	15.6 ± 5.7	10.9 ± 5.5	−5.014	<.001
Manic cognitivity	6.3 ± 5.4	5.1 ± 5.3	−1.418	.158
Ritmicity	13.9 ± 5.0	11.7 ± 5.4	−2.627	.010
Length of current hospitalization	19.9 ± 13.6	14.9 ± 9.4	−2.546	.012
Suicidality	2.6 ± 2.1	1.7 ± 1.9	−2.520	.013

Table 4
Linear regression for AdAS Spectrum domains predictive of suicidality.

Coefficients Model	Unstandardized coefficients B	Std. error	Standardized coefficients Beta	*t*	Sig.
(Constant)	0.045	0.908		0.050	0.960
Age	0.004	0.013	0.031	0.338	0.736
Sex	0.423	0.350	0.101	1.210	0.229
Childhood	0.039	0.059	0.074	0.655	0.514
Verbal communication	−0.055	0.069	-0.104	−0.795	0.428
Non verbal communication	0.098	0.057	0.246	1.719	0.088
Empathy	−0.021	0.075	−0.027	−0.286	0.776
Adherence to routine and inflexibility	−0.100	0.040	−0.357	−2.479	0.015
Restricted interests and rumination	0.111	0.060	0.232	1.846	0.067
Hyper-/Hyporeactivity to sensory input	0.200	0.072	0.331	2.777	0.006

domain was inversely related to MOODS-SR suicidality score.

4. Discussion

The study aimed to assess the expression of autistic traits in a sample of subjects with BD and to compare patients with high versus low autistic traits with a specific focus on clinical features and phenotype as well as suicidality. We found that 42.7% of the overall sample of BD patients scored positively for a BAP, while the remaining 57.3% did not. BAP subjects showed a specific clinical profile, characterized by a very early onset of BD and greater length of current in-hospital stay. BAP patients also reported significantly higher rates of anxiety disorders, and significantly lower rates of substance use disorders. Moreover, they showed more severe depressive symptoms during the lifetime and greater suicidality. In particular, suicidality was positively associated with the impairment in reactivity to sensory input and inversely related to the adherence to routine and inflexibility.

Our results are in line with previous studies that evaluated the prevalence of autistic traits among BD. Matsuo et al. (2015) found a 50% rate of high autistic traits among 56 subjects with BD, as evaluated by means of the SRS scale. More recently, Abu-Akel et al. (2017) reported a 47.2% rate of subjects with significant levels of autistic traits in a sample of 797 BD patients assessed with the AQ short. Despite the use of different psychometric measures, the three studies indicate that up to 50% of BD patients may show a significant level of autistic traits. On the other hand, to the best of our knowledge, previous studies did not investigate whether the presence of autistic traits may impact the clinical profile of BD patients. Our data highlighted that BD patients with BAP, compared to those without, generally report higher lifetime depressive scores, as well as higher scores on the manic energy domain. While this may somehow indicate that BD patients with BAP would suffer from a more severe mood disorder, with particularly severe depressive states, BAP subjects did not show a higher number of depressive or manic/hypomanic episodes or hospitalization in the lifespan. In this framework, the higher depressive scores reported by the BAP group may be explained by the fact that BD patients with BAP would experience more severe depressive episodes and/or spend a longer time in a depressive mood state than BD without BAP. This hypothesis is consistent with recent data highlighting the persistence of depressive symptoms from childhood to adulthood in youths with autistic traits (Rai et al., 2018), as well as the under-recognition and undertreatment of depressive symptoms when they co-occur with ASD-like features (Chandrasekhar and Sikich, 2015). Subjects in the BAP group also reported higher scores in the domain exploring rhythmicity, which includes seasonal or circadian variations in mood and energy, changes in weight/appetite, sexual activity, sleep and physical symptoms. This finding is line with previous data about the clinical presentation of mood episodes among ASD subjects, which is often characterized by mixed features, neurovegetative symptoms and disruption of circadian rhythms (Chandrasekhar and Sikich, 2015; Borue et al., 2016). Intriguingly, recent studies pointed out that most of the susceptibility genes shared by both BD and ASD are involved into pathways regulating circadian rhythms (Ragunath et al., 2011; Khanzada et al., 2017).

Interestingly, we found that patients with BAP are more likely to have a very early onset of BD, namely before 15 years of age. This result is striking consistent with other studies conducted among youths with BD highlighting that the comorbidity with ASD was associated with an earlier onset of the mood disorder (Joshi et al., 2013; Borue et al., 2016). This data also support a dimensional approach to the autism spectrum, that would involve not only full-blown autistic symptoms, but also clinical correlates and patterns of comorbidity with other mental disorders. The similar effects of ASD and autistic traits on BD clinical features is further confirmed by the findings of a greater comorbidity with anxiety disorders and a smaller likelihood of substance use disorder among BD patients with high autistic traits, both features that have been reported by previous studies among subjects with full-blown ASD (Santosh and Mijovic, 2006; Hofvander et al., 2009; Lugnegard et al., 2011; Ramos et al., 2013). The scant association with substance use is particularly noticeable among bipolar subjects, who frequently engage in substance misuse and addiction (Sbrana et al., 2005), supporting the relevance of autistic traits to the overall clinical presentation of the mood disorder. Surprisingly, no significant difference was found between the groups for PTSD, a condition that seems to be associated with both autistic and mood spectrum according to the literature (Carmassi et al., 2013; Carmassi et al., 2018; Dell'Osso et al., 2018a).

Our findings also reported higher levels of suicidal ideation among BD patients with BAP, who conversely did not show more frequent suicide attempts, which may suggest that their greater suicidality score was mainly related to a sustained suicidal ideation. The literature about the relationship between autism spectrum symptoms and suicidality is still scant. Subjects with ASD seem to show very often suicidal thoughts (Shtayermman et al., 2007; Balfe and Tantam, 2010), but data about the extent to which thoughts may translate into suicidal behaviors are still controversial, with some studies reporting that ASD subjects are less likely to engage in suicide than the general population, and others suggesting that autistic subjects may have up to a 28-fold increase in suicide behaviors compared to the typical subjects (Hardan and Sahl, 1999; Mayes et al., 2013). A recent, population-based study investigating mortality among ASD patients found that the death from suicide is significantly greater among subjects of the autism spectrum, especially among those with no intellectual disability and among females (Hirvikoski et al., 2016). More recently some studies also reported a link between suicidality and autistic traits, in both the general and the clinical population (Dell'Osso et al., 2018b; Dell'Osso et al., 2019). Many reasons could explain the greater suicidality that we found among BD subjects with high autistic traits. First, ASD patients are at

high risk of isolation, lack of social support and depressive symptoms, which may occur, to a lesser extent, in subjects with autistic traits, and which are commonly recognized among risk factors for suicidal thoughts and behaviors. As a matter of fact, BD patients with BAP showed greater depressive symptoms in their lifetime compared to their counterparts without BAP. On the other hand, as ASD patients frequently report a broad variety of impulsive behaviors and acting-outs, BD subjects with high autistic traits might as well display greater suicidality on an impulsive basis. This is also consistent with the higher exposure and vulnerability to life adversities - from bullying to stressful events - frequently associated with autistic symptoms, that represent a common trigger of suicidal thoughts and behaviors (Shtayermman et al., 2007; Kato et al., 2013). It is noteworthy that while no gender difference was found between BAP and NoBAP groups nor between subjects who did or did not attempt suicide, among previous suicide attempters a significant greater proportion of females than males belonged to the BAP groups, suggesting that autistic traits may exert a gender-specific impact on suicidal behaviors in BD patients, as previously shown among ASD patients (Hirvikoski et al., 2016). Several limitations need to be acknowledged and may limit the impact of our findings. In particular, the use of lifetime, self-report measures, which are exposed to under-overstatement and to recall biases, as well as the enrollment of subjects in different phases of the disorder and the lack of measures of current mood state. However, in the context of these limitations, the present study is a first step towards exploring the clinical significance of autistic traits among bipolar patients. On the other hand, in line with other studies (Dell'Osso et al., 2019), it highlights the importance of recognizing autistic traits due to their impact on the course of different kinds of psychopathology, stressing the usefulness of a dimensional model for the autism spectrum.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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