FUNCTIONAL IMPAIRMENT IN ADULT BIPOLAR DISORDER WITH ADHD

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Abstract

Background: It is well established that patients with either bipolar disorder (BD) or attention-deficit/hyperactivity disorder (ADHD) present functional impairment even when in remission. Nevertheless, research on functional impairment with adult patients with bipolar disorder comorbid to ADHD (BD+ADHD) is very scarce.
The main objective of the current report was to evaluate the overall and specific domains of functioning, in patients with BD+ADHD compared to patients with pure bipolar disorder (pBD) and healthy controls (HCs).

Method: 162 subjects from 3 groups were compared: 63 pBD, 23 BD+ADHD and 76 HCs. All the patients with BD had been euthymic for at least 6 months and they were recruited at the Hospital Clinic of Barcelona. All the participants were assessed with the 17-item Hamilton Depression Rating Scale (HAM-D), the Young Mania Rating Scale (YMRS) and the Functioning Assessment Short Test (FAST). Clinical, and sociodemographic data were also recorded.

Results: Clinical groups, pBD and BD+ADHD, showed lower overall functioning ($p < 0.001$) in each domain of the FAST scale compared to the HCs. Moreover, the Tukey post hoc test revealed that the BD+ADHD group showed a worse score than pBD in the cognitive domain of the FAST. However, after controlling for potential confounding variables, only the HDRS scores ($p < 0.026$) remained significant for the cognitive domain of the FAST.

Limitations: The small sample size of the comorbid BD+ADHD group.

Conclusions: Adult patients with BD+ADHD showed the worst scores in functioning compared with the HCs, but did not show more severe functional impairment than the pBD group except for the cognitive domain. Therefore our findings suggest that depressive symptoms in adults with BD+ADHD may negatively influence cognitive functioning. Further studies are needed to confirm our findings for the management of BD+ADHD.

Key words: Bipolar disorder, Attention-Deficit/Hyperactivity Disorder, Comorbidity and Functioning.

INTRODUCTION:

Previous research has demonstrated that bipolar disorder (BD) and attention-deficit/hyperactivity disorder (ADHD) present functional impairment (Goetz et al., 2007; Rosa et al., 2008; Tohen et al., 2005; Küpper et al., 2012; Barkley and Brown, 2008). BD is a severe mental illness that affects 4.8% of the population on including the whole bipolar spectrum (American Psychiatric Association, 2013). Most patients with BD present cognitive impairment in different domains including attention, executive function, and verbal memory. Moreover, it is well established that these cognitive deficits are linked to significant psychosocial impairment (Martinez-Aran et al., 2011; Bonnin et al., 2014) even during interepisode intervals (Martinez-Aran et al., 2004). There are several factors that may have a negative impact on BD functioning such as: sociodemographic variables [male sex, older age, unmarried status, and low socio-economic status] (Rosa et al., 2009, 2007; Morriss et al., 2007; Keck et al., 1998); clinical history [subthreshold depressive symptoms, suicide attempts, substance use] (Simon et al., 2007; Kennedy et al., 2007; Kennedy and Paykel, 2004); clinical course [number of previous episodes, number of previous hospitalizations, longer duration of the illness] (Rosa et al., 2009, 2007; Keck et al., 1998) and finally, neurocognition, which has also demonstrated to play an important role in psychosocial functioning (Ferrier et al., 1999; Mur et al., 2007; Torrent et al., 2007), in particular, verbal memory impairment and executive dysfunction (Martinez-Aran et al., 2007; Torrent et al., 2006; Robinson and Ferrier, 2006). Moreover, numerous studies have underlined that functioning in BD is usually impaired in more than one area of functioning such as: work productivity, cognitive functioning, and social relationships (Rosa et al., 2008, 2007; Weinstock and Miller, 2008; Tabares-Seisdedos et al., 2008).

ADHD is an early-onset neurodevelopmental disorder characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013), that affects 5% of childhood population (Polanczyk et al., 2007) and persists into adulthood in up to 50% of the cases (Ramos-Quiroga et al., 2006). Moreover, this disorder is associated with a range of clinical symptoms and comorbid psychiatric disorders (Biederman et al., 2011; Surman et al., 2013; Sobanski et al., 2008), neurocognitive dysfunction (Silva et al., 2013; Rapport et al., 2001; Seidman et al., 1998) and psychosocial impairment (Kooij et al., 2010). The main areas of functioning affected in adults with ADHD are academic, occpational and social functioning (Silva et al., 2013; Rapport et al., 2001; Seidman et al., 1998; Mattos et al., 2007; Küpper et al., 2012; Ramos-Quiroga et al., 2013; Blikø et al., 2008). Therefore, the evaluation of functional impairment is very important for ADHD diagnosis, especially in adults not diagnosed in childhood (Faraone et al., 2008) since deficits in ADHD can be chronic and may affect overall functioning.

It is known that between 10 to 30% of adult patients with BD present comorbidity with lifetime ADHD (Wingo and Ghaemi, 2007; Torres et al., 2015). Not only clinical correlates but also treatment

approaches have evidenced the broad symptom overlap with BD and ADHD. Some studies have reported positive results in manic and depressive bipolar symptomatology in patients treated with adjunctive psychostimulants such as methylphenidate (Szmulewisz et al., 2017; Perugi et al., 2017). Moreover, several clinical studies have reported that bipolar patients with comorbid ADHD show differential clinical features such as more frequent mood episodes (Nierenberg et al., 2005; Rydén et al., 2009), earlier age of onset of bipolar illness, (Nierenberg et al., 2005; Tamam et al., 2008; Karaahmet et al., 2013; Perugi et al., 2008; Tamam et al., 2006), more suicide attempts (Nierenberg et al., 2005; Rydén et al., 2009; Torres et al., 2015) as well as higher rates of comorbid substance use disorders (Torres et al. 2015). Neuropsychological performance of adult patients with BD and ADHD is understudied and in addition, the scarce evidence available is inconsistent. Likewise, functional impairment in adults with BD+ADHD, also remains understudied with most of the studies performed to date including only patients with BD, and more recently, ADHD. In fact, only one study (Nierenberg et al., 2005) has assessed psychosocial functioning using the Gobal assessment of functioning scale which showed lower scores for the comorbid ADHD group. Therefore, taking into account that BD and ADHD are two different psychiatric conditions but which have different aspects in common, it would not only be necessary but also useful and interesting to identify which factors contribute to this disability in patients with BD+ADHD.

For this reason, our aim was to evaluate the functional impairment of BD+ADHD patients using a validated tool, the Functional Assessment Short Test (FAST) for both disorders (BD and ADHD) in an adult population. Our hypothesis was that pBD patients do not differ from BD+ADHD patients in either overall psychosocial functioning or in each specific domain of the FAST. To the best of our knowledge, this is the first study to assess overall and specific domains of functioning in a sample of BD+ADHD participants compared to healthy controls (HCs) and patients with pure BD (pBD).

METHODS

Subjects

The sample included a total of 162 adult participants: 63 of whom were pure bipolar disorder (pBD), 23 of whom were bipolar disorder with comorbid adult ADHD (BD+ADHD) and 76 healthy controls (HCs) who were recruited from a specialized program in the Bipolar Disorders Unit of the Hospital Clínic of Barcelona (Spain). The Bipolar Disorders Unit regularly follows around 700 patients, most of whom are from the hospital catchment area and about one-third are tertiary referrals, mainly from different services in Barcelona and Catalonia (Vieta, 2011a; Rosa et al., 2011; Vieta, 2013). The inclusion criteria were: (a) fulfill DSM-IV-TR criteria (American Psychiatric Association, 1994) for bipolar I or bipolar II disorder and ADHD using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 2002) and the Conners' Adult ADHD Diagnostic Interview for DSM-IV CAADID (Torres et al., 2015; Ramos-Quiroga et al.,

2012), (b) age>18 years, and (c) meeting criteria for euthymia [Young Mania Rating Scale (YMRS) < 7 (Colom et al., 2002) and Hamilton Depression Rating Scale (HDRS) ≤8 (Ramos-Brieva and Cordero, 1986)]. All the subjects were symptomatically in clinical remission at the time of assessment, based on the YMRS and HDRS score at that time. Therefore, affective symptom measurements were taken at the same assessment time as the functional measures. Besides, the patients' clinical histories were reviewed to ensure that they had not suffered any affective episode in the previous 6 months. The exclusion criteria were (a) the presence of any organic brain disorder or (b) severe organic disease.

The BD subjects included in the study had previously been screened for comorbidity with ADHD, and those with positive screening results were referred to the adult ADHD Program at the Hospital Universitari Vall d'Hebron (Barcelona) for thorough diagnostic assessment using the (CAADID) (Torres et al., 2015; Ramos-Quiroga et al., 2012). This is a tertiary program for the assessment, diagnosis and comprehensive treatment of adult patients with suspected ADHD.

All the patients included in this study were diagnosed of BD according to DSM-IV-TR. All the bipolar patients received pharmacological treatment according to the clinical guidelines for the management of bipolar disorder, whereas only 4 of the 23 BD+ADHD patients received pharmacological treatment for ADHD. Treatment as usual was then administered according to clinical judgement.

The HC group included subjects with no psychiatric or neurological history recruited from the general population in Barcelona. Moreover, it was also ensured that none in the HCs had a first-degree relative with BD. The study was approved by the Hospital Clinic of Barcelona Ethics Committee. All patients gave written consent to participate in this study.

2.2. *Assessment Measures*

Clinical and sociodemographic assessment

Different sociodemographic and clinical variables were collected using the semi-structured interview with the SCID complemented by the clinical records (Vieta, 2011a; Vieta, 2011b). The mood status of all the subjects was previously assessed with the YMRS (Colom et al., 2002) and the HDRS (Ramos-Brieva and Cordero, 1986).

Functional assessment

All the participants were tested with the FAST to assess functional impairment (Rosa et al., 2007). The FAST is a valid, reliable instrument, which is easy to apply and requires a short period of time to administer (3–6 min). This scale was developed for the clinical evaluation of the main difficulties

presented by psychiatric patients and has been validated in several languages for patients with BD (Rosa et al., 2007) and ADHD (Rotger et al., 2014). The FAST scale consists of 24 items that allow the assessment of six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Items are rated using a four-point scale: 0 = no difficulty, 1 = mild difficulty, 2 = moderate difficulty and 3 = severe difficulty. FAST scores range from 0 to 72, with higher scores indicating poor functioning (Rosa et al., 2007).

Description of 6 areas of functioning in the FAST:

1) Autonomy refers to the patient's capacity to do things alone and make his/her own decisions.
2) Occupational functioning refers to the capacity to maintain employment, efficiency of performing tasks at work, working in the field in which the patient was educated and earning according to the level of the employment position.
3) Cognitive functioning is related to the ability to concentrate, perform simple mental calculations, solving problems, learning and new information recall ability.
4) Financial issues involve the capacity of managing finances and spending in a balanced way.
5) Interpersonal relationships refer to relations with friends, family, involvement in social activities, sexual relationships and the ability to defend one's own interests.
6) Leisure time refers to the capability of performing physical activities (sport, exercise) and maintaining hobbies.

Statistical analysis

The sociodemographic, clinical and functional variables were analyzed with the Statistical Package for Social Sciences (SPSS) version 20.0.0. For quantitative variables we performed one-way analysis of variance (ANOVA), followed by the Tukey post-hoc comparison procedure when significant main effects were present to identify pair-wise differences between groups or the T-test, as appropriate. For categorical variables the Chi-square test was used, except in cases which the number of empty cells was greater than 25% of all cells, in which case the Fisher's exact test was used. The effect sizes (Cohen's d value) were calculated in FAST to estimate the magnitude of the differences between groups (0.2 = small, 0.5 = medium, 0.8 or greater = large) as shown in table 2. Finally, the potential impact of sociodemographic and clinical variables were controlled for in the analysis of variance running an ANCOVA test for each domain of the FAST and using diagnostic group pertinence (pBD, BD+ADHD and HCs) as the main factor. Statistical significances was set at a p value <0.05.

The Pearson correlation coefficient was used, as appropriate, to measure the degree of covariation between different quantitative variables.

RESULTS

Sociodemographic and clinical data

The sample comprised 162 participants: 63 (38.9%) adult euthymic pBD patients, 23 (14.2%) with comorbid ADHD (BD+ADHD) and 76 (46.9%) HCs. The demographic and clinical characteristics of the groups of patients and healthy controls are shown in Table 1.

No significant differences were observed in age or gender among the groups. With regard to the level of education, the pBD group had the highest educational level, being significantly higher than that of the BD+ADHD (p = 0.013) and HC (p= 0.020) groups. Moreover, we also found significant differences in adaptation to employment, where the two clinical groups [pBD *(p= <0.001)* and BD+ADHD *(p= <0.001)*] showed a poor work adaptation compared to the HCs.

Concerning pharmacological treatment, no significant differences were found among the groups in mood stabilizers (p = 0.501), antipsychotics (p = 0.925) and antidepressants p = 0.594). On evaluating polypharmacy no differences were observed between the pBD and BD+ADHD groups with regard to the use of polypharmacy with mood stabilizers (p = 0.434) or in the use of polypharmacy with antipsychotics (p = 0.771)

With regard to clinical characteristics, significant differences were found in the YMRS scores (p= 0.028), HDRS scores (p = <0.001) and the number of previous depressive episodes (p= 0.045) among groups. Moreover, the Tukey post hoc analysis showed significant differences among three groups. Pairwise comparisons of the YMRS scores showed that the comorbid group (BD+ADHD) had the highest scores in the severity of manic symptoms, being significantly worse than the pBD *(p= 0.028)* and HC groups (p = 0.040). Along the same line, higher scores were also detected for HDRS in the comorbid BD+ADHD (p = 0.001) group followed by pBD (p = 0.001) compared with the HCs.

Analysis of the other clinical variable showed that the pBD group presented a greater number of previous depressive episodes (p = 0.045) compared with BD+ADHD group (see table 1).

Functional data

Table 2 shows the total scores and subscores of the FAST across the three groups. Overall, ANOVA revealed significant differences in the total FAST score as well as in all the functioning domains. Post-hoc test analysis revealed that the two clinical groups (pBD and BD+ADHD) performed significantly worse than the HCs in terms of the FAST total score and most domains of functioning. Large effect sizes (Cohen's d values) were detected in all the FAST domains on comparing the pBD and BD+ADHD groups with the HC group, except for leisure time. No statistically significant differences were found between the pBD and BD+ADHD groups in relation to the autonomy, occupational functioning, interpersonal

relationships, financial issues, leisure time domains, and overall functioning. The Tukey post hoc analysis indicated that the BD+ADHD group showed the greatest impairment in the FAST cognitive domain, followed by patients with pBD and finally the HCs *(p= <0.001)*, with a medium effect size (Cohen's d = 0.50) in FAST cognitive domain. Moreover, the FAST cognitive domain was analyzed using ANCOVA analysis of covariance in order to control for potential confounders such as educational level, YMRS scores, HDRS scores and the number of depressive episodes. After controlling for these factors, only the HDRS scores (F = 5.061, df = 1, p= 0.026) remained statistically significant for the cognitive domain of the FAST.

DISCUSSION

Nowadays, clinical research has widely demonstrated that BD may present functional impairment at some point or permanently during the course of the illness (Bonnín et al., 2014, 2010; Martino et al., 2009). However, in ADHD the research on functioning is a relatively immature area, especially in adult populations, and even fewer in comorbid BD+ADHD subjects. This study aimed to compare the psychosocial functioning of adult pBD and BD+ADHD patients among these two groups and with HC subjects using a scale validated for use in adults with BD and ADHD. To our knowledge, this is the first study carried out to assess functioning comparing between these three groups using a specific functioning tool that allows the evaluation of global and different functional domains. The FAST is a simple interviewer-administered instrument able to assess specific domains of functioning and disability and requires very little time to be administered. Our findings suggest that both clinical groups (pBD and BD+ADHD) showed poorer performance in functioning in all the functional domains on comparison with the HC group, except for the FAST leisure time when compared with pBD and HCs and on comparing this domain in patients with pBD and BD+ADHD. According to the FAST scores obtained in the present study pBD patients were in an intermediate position between patients with BD+ADHD and HCs. In addition, our results showed large effect size differences in different functioning domains (autonomy, occupational, cognitive, interpersonal relationships and financial issues) for the pBD and BD+ADHD groups compared with the HC group. These results are consistent with previous literature on BD patients (Rosa et al., 2010; Tabares-Seisdedos et al., 2008; Zarate et al., 2000; Strakowski et al., 2000; Keck, 2006; Goldberg and Harrow, 2005;) and also on ADHD (Surman et al., 2013; Barkley et al., 1996, 2008; Biederman et al., 1993, 2008, 2006; Faraone et al., 2004; Kessler et al., 2005; Weiss and Hechtman 1993) in which both disorders were studied separately and both had negative effects on psychosocial functioning.

Little is known about functional impairment in patients with comorbid BD+ADHD compared with pBD and even less is known regarding this impairment in adults with ADHD. Indeed, it would be logical to think that bipolar subjects with comborbid ADHD should have lower psychosocial functioning than those without comorbidity. In fact, only one previous study has compared the functional impairment of adult patients with BD+ADHD. Nierenberg et al., (2005) showed that on comparing BD and BD+ADHD groups,

the latter presented poorer functioning evaluated by means of the Global Assessment of Functioning (GAF). However, these results should be taken with caution considering that the GAF scale does not assess all functioning areas in a subject's life, and it is influenced by clinical symptoms (Martinez-Aran et al., 2007; Martinez-Aran et al., 2004). In contrast, our results pointed that the comorbid group (BD+ADHD) showed similar functional impairment to that of the pBD group, except for the cognitive domain of the FAST, in which the BD+ADHD group scored worse than the pBD group. Some sociodemographic and clinical differences between these two clinical groups could partially contribute to poorer cognitive functioning in the comorbid group (BD+ADHD). One difference was educational level, which appeared to be superior in our study in the pBD group compared with the BD+ADHD and HC groups, and this was why it was used as a confounding factor in our analysis. Within the context of cognitive reserve formulation in patients with severe mental illness, it has recently been described that years of education and leisure activities provide more efficient cognitive networks and allow better management of some conditions associated with cognitive impairment (Amoretti et al., 2016). Moreover, in euthymic bipolar patients it has also been observed that cognitive reserve may contribute not only to neurocognition but also to psychosocial outcomes measured with the FAST scale (Forcada et al., 2015; Grande et al., 2017). In this sense, it would be congruent to think that the high educational level in these pBD patients may have helped them to develop higher cognitive reserve (Forcada et al., 2015) thereby preventing or reducing cognitive impairment. On the other hand, individuals with low reserve would be more vulnerable to the onset of symptoms, functional impairment and clinical presentation of disease (Forcada et al., 2015). Hence, the present results are in line with the literature since the presence of ADHD comorbidity in bipolar patients was associated with greater disability in cognitive functioning when an observer-based measure was used (FAST). In addition, both clinical groups (pBD and BD+ADHD) showed higher scores than HCs in terms of cognitive functioning. Therefore, these results suggest that patients with severe mental illness are more prone to presenting poorer functioning in the presence of one or more Axis I diseases (Forcada et al., 2015; Amoretti et al., 2016; Grande et al., 2017) as well as subclinical affective symptoms (Solé et al., 2011; Martinez-Aran et al., 2008).

Concerning clinical contribution to functioning impairment in our sample, both subthreshold manic (measured via YMRS) and depressive (measured via HDRS) symptoms also appeared to contribute to the presence of a poor cognitive functioning outcome measured with the FAST in comparison with HCs. Although the effect of subthreshold symptoms on functioning has not been widely studied in adult ADHD, there is greater evidence that subthreshold symptoms exert a negative impact on cognitive functioning as well as psychosocial functioning in patients with BD (Martino et al., 2009; Gitlin et al., 2011; Burdick et al., 2010; Rosa et al., 2010; Bonnín et al., 2010; Sole et al., 2015).

Regarding subthreshold manic symptoms, in our sample, the comorbid group (BD+ADHD) presented significantly higher levels of this symptomatology compared to pBD patients. Comorbidity might involve worse clinical scores because there is an existing overlap of "manic-like" symptoms between the two

disorders which might have minimally positive score in the YMRS in the two clinical groups [hyperactivity, irritability, short attention span, increased rate of production of speech, and language/thought disorder] (Torres et al., 2015; Kitsune et al., 2016). However, to date, manic subthreshold symptoms have not been related to the presence of poor functioning in BD patients or in the comordid clinical BD+ADHD population, unlike subthreshold depressive symptoms.

Regarding subclinical depressive symptoms, our results indicate that, as expected, both clinical groups (pBD and BD+ADHD) showed significantly greater subthreshold depressive symptoms compared to HCs. Therefore, after controlling for potential confounders by adjusted analysis, we should consider that subthreshold depressive symptoms play a significant role in functional outcome in pBD patients, but even greater in BD+ADHD patients and, more specifically, in cognitive functional impairment. In this sense, it should be pointed out that subdepressive symptomatology has a negative impact on overall functioning (Altshuler et al., 2006; Bonnín et al., 2012) and appears to be strongly associated with poor psychosocial functioning in BD (Martino et al., 2009; Gitlin et al., 2011; Burdick et al., 2010; Rosa et al., 2010; Bonnin et al., 2010; Solé et al., 2015) as well as ADHD (Sobanski et al., 2008; Davinson et al., 2007). Another study reported that there is a circular relationship and influence between functional outcome and subdepressive symptomatology in bipolar patients (Weinstock and Miller, 2010). On the other hand, our results showed that pBD patients had a higher number of depressive episodes than BD+ADHD patients, which is consistent with previous literature (Torres el al; 2015). As far as we know, to date, depressive episodes have been related as being a strong predictor of future recurrence and poor psychosocial functioning (MacQueen et al., 2000; Rosa et al., 2010) in BD. However there are no data on the influence between functional outcome and the number of depressive episodes in BD+ADHD patients. Therefore, these preliminary results suggest that patients with pBD present more depressive episodes than those with BD+ADHD, whereas, this latter group has more subdepressive symptomatology.

Cognitive dysfunction and psychosocial functioning impairment are core features in severe mental illness patients. When measuring cognitive performance it has to be differentiated between subjective and objective measures. The evidence regarding the association between subjective cognitive complaints, objective cognitive performance and psychosocial function is sparse and inconsistent in BD and it has not yet been studied in BD+ADHD. In fact, there are few studies addressing this issue, which some of them showing a relatively weak association between subjective cognitive measures and neuropsychological tests in BD (Burdick et al., 2005; Svendsen et al., 2012; van der Werf-Eldering et al., 2011). However, other reports have found a relationship between objective and subjective measures (Martinez-Aran et al., 2005; Arts et al., 2011; Rosa et al., 2013). A recent study by Demant and collagues, (2015) investigated the association between global and domain-specific objective and subjective cognitive function and between global cognitive function and psychosocial function in BD. They found that self-rated psychosocial difficulties were associated with subjective (but not objective) cognitive

impairment assessed with the Cognitive and Physical Functioning Questionnaire (CPFQ) (Fava et al., 2006), and the Cognitive Failures Questionnaire (CFQ) (Broadbent et al., 1982). In addition, subjective cognitive and psychosocial difficulties were predicted by depressive symptoms (Demant et al., 2015), which is consistent with previous literature (Svendsen et al., 2012; van der Werf-Elderingetal., 2011). Another reason should also be taken into account that subjective cognitive complaints do not always correspond to objective cognitive impairment, as some patients may be unable to correctly evaluate their own cognitive function (Rosa et al., 2013; Demant et al., 2015). Moreover, this association may be related to the inability of neuropsychological tests to reflect a cognitive decline from premorbid levels, whereas observer-based measures such as the FAST may better capture patients' loss of functional capacity (Sole et al., 2016). All together, the association between cognition and functional outcome is not completely understood yet. Nevertheless, recent studies suggest that cognitive functioning may be differentially related to functional outcomes depending on the severity of the cognitive impairment (Moore et al., 2015). In this regard, subjective cognitive functioning could be presented as an overall functioning modulator when cognitive impairment has been reported with objective neurocognitive testing (Moore et al., 2015).

With regard to cognitive functioning, as reported previously, some studies have found that subclinical affective symptoms may have an impact on cognitive functioning in BD (Solé et al., 2011; Martinez-Aran et al., 2008). More specifically, subthreshold depressive symptoms have been related as the best predictor of cognitive impairment and occupational impairment in BD (Rosa et al., 2010; 2009; Bonnin et al., 2010). In this sense, taking all of the above into account, it would reasonable to argue that the impact and severity of subthreshold depressive symptoms might play a modulating role in functioning not only in pBD patients but also in comorbid BD+ADHD patients, with the subsequent functional disability that this implies. In other words, the presence of a greater intensity of symptoms could implies a greater level of disability. Altogether, this specific functional disability in cognitive functioning suggests that, despite the predominant impairment is "bipolar-related", it would be possible to characterize a specific functioning profile on the BD+ADHD comorbid subjects not only a different clinical, neurocognitive, but also a different functional profile between these two clinical entities (pBD and BD+ADHD) would provide useful information. Moreover, at present, there is greater evidence that functioning assessment is a potential useful source of information for specific diagnostic and treatment approaches (Rosa et al., 2011; Torres et al., 2015). Although, we were not able to elucidate a differential functioning profile between pBD and BD+ADHD patients with the use of the FAST scale, our results suggest that the FAST cognitive domain may be used as part of the differential diagnoses process, complementing the clinical interview. The identification of groups with different levels of psychosocial functioning impairment may help to guide specific and tailored pharmacological and psychological interventions for different patient subgroups with the aim of improving not psychosocial functioning but also neurocognitive performance (Varo et al., 2017). In addition, despite the lack of data on functional impairment in comorbid patients with ADHD, there is evidence that BD patients with depressive

subthreshold symptoms might be beneficiated of specific intensive psychosocial interventions to treat subthreshold symptoms and enhance the level of functioning (Bonnin et al., 2010, 2015, 2016; Rosa et al., 2011; Sole et al., 2015; Sanchez-Moreno et al., 2017). However, this intervention evidence has not been specifically targeted to ADHD populations or those suffering from the BD+ADHD comorbidity.

Limitations

This study has several limitations which should be considered in the interpretation of the results. First, although the FAST cognitive area is not a "real" objective measure, given that patients may overestimate or underestimate their level of functioning, it should be taken account that the FAST is an interviewer-administered instrument which provides a clinician's evaluation of functional impairment considering the limitations of the patients and the expected functioning of a person of the same gender, age and sociocultural status in order to obtain an objective and reliable assessment. However, the FAST cognitive domain does not aim to replace neuropsychological assessment, but could actually be used as a proxy to assess cognitive functioning by a clinician. Second, the affected sample was recruited from a tertiary hospital and thus, the study participants are likely weighted towards those with greater illness severity and may not be readily generalizable to the wider population of individuals with BD. Third, although the sample size of the comorbid BD+ADHD group was small,it was similar to that of previous studies focused on this population (Silva et al., 2014). Fourth, we could not analyze the effect of subclinical ADHD symptoms on functioning, and, therefore, we could not determine their influence on functioning impairment. A clinical assessment of the severity of ADHD symptomatology could have been reinforced with the use of the Conners' Adult ADHD Rating Scale (CAARS) (Conners et al., 2003; Bosch et al., 2008), which has been validated to assess the severity of ADHD symptoms. Further studies are needed to analyze the influence of subthreshold ADHD symptomatology on global functioning in BD+ADHD patients. Fifth, the requirement of sustained euthymia for inclusion might exclude some severe patients, especially those with comorbid ADHD. Sixth, all the BD patients were under specific bipolar medication and only 4 of the 23 comorbid patients were on pharmacological treatment for ADHD. However, we did not analyze the effect of the medication dose on functioning, but we did provide information about the effect of mood stabilizers and antipsychotics on functioning in this sample (see table 1). As far as we know, some studies have suggested that medications may have a negative effect (Malhi et al., 2016; Porter et al., 2015; Holmes et al., 2008; Harvey et al., 2007; Henin et al., 2009) whereas other studies suggest that medication may have positive effects on functioning in BD (Kapczinski et al., 2008; Fountoulakis and Vieta, 2008) and ADHD (Biederman et al., 2012 Sobanski et al., 2007). Therefore, the effects of medication on functioning remain unclear. Finally, this was a cross-sectional study, which did not allow us to provide longitudinal data. Therefore, longitudinal studies are needed to understand the cause-and-effect relationship between specific domains of functioning, and clinical groups (pBD and BD+ADHD) as well as other commonly used measures of psychosocial functioning should be considered.

Conclusions

In conclusion, we found that both clinical groups (patients with BD+ADHD and pBD) have lower overall functioning compared to HCs. Functional assessment is a potentially useful source of information for specific diagnostic and treatment approaches (Rosa et al., 2011; Torres et al., 2015). Even though our results suggest that the FAST scale was not able to elucidate a differential functioning profile between pBD and BD+ADHD patients, the FAST cognitive domain might be considered in the differential diagnoses processes as a complementary tool to the clinical interview given that the comorbid patients (BD+ADHD) could be more impaired for attention component Along the same line, we found that patients with BD+ADHD have a similar functional disability as pBD patients. This was evident in each domain of functioning, except for the cognitive domain, in which the BD+ADHD group performed worse. The presence of subthreshold depressive symptoms (measured with HDRS scores) was related to poorer functioning in pBD. In this regard, our results provided further evidence that not only pBD but also BD+ADHD patients presented greater impairment in functioning in terms of the cognitive domain of the FAST, pointing to the need for a specific care plan approach targeting subthreshold depressive symptoms. Finally, our results could suggest that a different functional phenotype for patients with BD and BD+ADHD may account when evaluating cross-sectional severity, at least in the depressive related features.

We also consider that this is a research field that has to be replicated in larger samples, carrying out longitudinal follow-up assessments, and including response to specific treatment strategies also focused on subthreshold symptoms. Future studies should routinely assess cognitive functioning in euthymic patients with BD and BD+ADHD. Additionally, and given the variability in both cognitive and functional outcomes, it would be also of interest to determine how deficits in cognitive functioning are related to functional disability in people with BD and other Axis I comorbidities.

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Table1. Demographic and clinical variables. Comparison of pBD, ADHD + BD and HCs.

Qualitative variables N (%)	BDp (A) N=63	BD+ADHD (B) N=23	HC (C) N=76	F/X2	P	A vs. B	A vs. C	B vs. C
Gender (male)	30 (47.6)	12 (52.2)	34 (44.7)	0.413	0.814			
Educational level								
Elementary	4 (6.5)	3 (13.0)	17 (22.4)	15.441	0.004	0.013	0.020	0.058
High	17 (27.4)	13 (56.5)	22 (29.3)					
College	41 (66.1)	7 (30.4)	36 (48.0)					
Work adjustment (worse)	22 (34.9)	11 (47.8)	4 (5.3)	26.888	<0.001	0.276	< 0.001	< 0.001
Diagnosis (BD I)	51 (81.0)	17 (73.9)	-	0.504	0.478			
Diagnosis (BD II)	12 (19.0)	6 (26.1)	-					
Diagnosis ADHDc	-	5 (21.7)	-					
Diagnosis ADHDda	-	7 (30.4)	-					
Diagnosis ADHDh-i	-	1 (4.3)	-					
Mood stabilizer	50 (79.4)	19 (82.6)	-	0.112	0.501			
Antipsychotics	43 (71.7)	16 (72.7)	-	0.009	0.925			
Antidepressants	2 (3.2)	1 (4.8)	-	0.098	0.594			
Mood stabilizer polypharmacy (yes)				1.671	0.434			
No stabilizer	5 (7.9)	3 (13.0)	-					
Only one	37 (58.7)	10 (43.5)	-					
More than one	21 (33.3)	10 (43.5)	-					
Antipsychotics polypharmacy (yes)				0.521	0.771			
No antipsychotic	17 (27.4)	5 (22.7)	-					
Only one	34 (54.8)	14 (63.6)	-					
More than one	11 (17.2)	3 (13.6)	-					

Table 1. Continued

Quantitative variables, Mean (SD)				T-Student				
Age (yrs)	45.84 (10.4)	41.52 (9.6)	43.85 (13.6)	1.194	0.306			
YMRS	0.85 (1.5)	1.86 (2.1)	0.93 (1.4)	3.648	0.028	0.028	0.953	0.040
HDRS	3.15 (3.9)	4.00 (3,2)	1.33 (1.5)	10.610	<0.001	0.461	0.001	0.001
Illness duration (yrs)	16.63 (13.0)	14.86 (9.8)	-	0.578	0.565			
Age at onset of BD (yrs)	25.50 (9.2)	24.64 (10.9)	-	0.359	0.721			
Age at first hospitalization	31.65 (10.8)	28.93 (10.9)	-	0.844	0.402			
Type of episode								
- Mania	2.79 (4.9)	1.55 (1.8)	-	1.171	0.090			
- Hypomania	5.47 (7.1)	3.52 (4.1)	-	1.565	0.122			
- Depressive	9.16 (9.3)	5.83 (5.4)	-	2.042	0.045			

pBD, pure bipolar disorder; BD+ADHD, bipolar disorder with attention-deficit /hyperactivity disorder; HCs, Healthy controls; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; CAARS, Conners` Adult ADHD Rating Scale; SD, standard deviation.

BD I, bipolar disorder type I

BD II, bipolar disorder type II

ADHDc, attention-deficit /hyperactivity disorder combinated type

ADHDa, attention-deficit /hyperactivity disorder inattentive type

ADHDh-i, attention-deficit /hyperactivity disorder hyperactive-impulsive type

Table 2. Functional impairment among the pBD, ADHD + BD and HC groups.

Quantitative variables, Mean (SD)	pBD (A) N=63	BD+ADHD (B) N=23	HCs (C) N=76	ANOVA	P	A vs. B	Cohen's d	A vs. C	Cohen's d	B vs. C	Cohen's d
FAST total	18.41 (12.0)	19.30 (11.4)	3.20 (4.0)	59.413	<0.001	0.913	0.08	<0.001	1.70	<0.001	1.98
FAST autonomy	1.73 (2.1)	2.17 (3.0)	0.37 (0.9)	13.725	<0.001	0.580	0.17	<0.001	0.81	<0.001	0.81
FAST occupational	8.94 (6.9)	7.04 (6.9)	0.51 (1.9)	47.852	<0.001	0.297	0.28	<0.001	1.67	<0.001	1.29
FAST cognitive	3.27 (3.1)	4.91 (3.5)	0.92 (1.6)	27.402	<0.001	0.024	0.50	<0.001	0.98	<0.001	1.47
FAST interpersonal relationships	3.05 (2.8)	2.70 (3.2)	0.75 (1.2)	19.009	<0.001	0.802	0.13	<0.001	1.07	0.001	0.81
FAST financial issues	0.87 (1.0)	1.22 (1.9)	0.14 (0.6)	8.703	<0.001	0.520	0.23	0.003	0.89	0.002	0.77
FAST leisure time	0.94 (1.4)	1.30 (1.7)	0.47 (0.8)	5.101	0.007	0.428	0.23	0.067	0.41	0.013	0.62

pBD, pure bipolar disorder; BD+ADHD, bipolar disorder with attention-deficit /hyperactivity disorder; HCs, Healthy controls; FAST, Functioning Assessment Short Test.

Conflict of interest

Prof. Vieta has received grants, CME-related honoraria or consulting fees from Alexza, Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmith-Kline, Janssen, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer,Pierre-Fabre, Qualigen, Roche, Sanofi-Aventis, Schering-Plough, Servier, Shire, Solvay, Takeda, Teva, CIBERSAM, the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corporation and Wyeth. Dr. Martinez-Aran has served as speaker or advisor for the following companies: Bristol-Myers Squibb, Otsuka, Lundbeck and Pfizer. Dr. Jose Manuel Goikolea has been a speaker or on the advisory board for Astra-Zeneca, BristolMyers-Squibb, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag,Merck Sharpe and Dohme, Otsuka, Pfizer, Sanofi-Aventis. The other authors report no financial relationships with commercial interests.

Contributors

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