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ORIGINAL RESEARCH

Cognition in Euthymic Patients with Bipolar Disorder: Do Not Forget to Account for Anxiety!

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Purpose: Despite the high prevalence of anxiety disorders in BD and its known impact on cognitive performance, the presence and severity of anxious symptoms is not systematically evaluated in studies on cognition in BD. Our aim was to determine if attention and/or inhibition of cognitive interference in euthymic patients with type I Bipolar Disorder (BD-I) is affected by symptoms of anxiety.

Patients and Methods: Eighty-seven euthymic BD-I patients were included. Patients with comorbidities other than Generalized Anxiety Disorder (GAD) or Panic Disorder (PD) were excluded. State anxiety was measured with the Brief Inventory of Anxious Responses and Situations (ISRA-B). Subjective cognitive performance was evaluated with the COBRA scale, attention with the Digit-Span Forward task and inhibition of cognitive interference was assessed with the StroopTest interference score. Multiple linear regression models were used to test if anxious symptoms were associated with attention or inhibition of cognitive interference, considering other known contributors for cognitive impairment.

Results: Attention was unaffected by anxiety symptoms, but the overall regression for inhibition of cognitive interference was significant: years of schooling (β=1.12, p = 0.001), cognitive complaints (β=0.44, p = 0.008), and anxiety (β=−0.21, p = 0.017) explained 15% of the interference score of the Stroop test (R2 = 0.15).

Conclusion: Beyond residual affective symptoms, anxious symptoms seem to affect inhibition of cognitive interference. We recommend routine testing of anxiety when considering cognitive evaluations, especially when screening for cognitive deficits.

Keywords: anxiety, attention, digit span forward, cognitive interference, Stroop effect, bipolar-I disorder, comorbid

Introduction

Bipolar Disorder (BD) is a chronic, highly disabling condition, characterized by severe mood instability. This disorder is accompanied by cognitive deficits, which vary in severity, and are present in the majority of patients, even before illness onset and despite being in euthymia.[1–3] The importance of recognizing their presence lies in their link to functional and other well-being outcomes: cognitive variables are associated with functioning scores as evidenced by transversal as well as longitudinal studies.[4–9]

Several factors are related to these deficits, likely in a two-direction relationship, and are therefore systematically evaluated when studying cognitive symptoms in this population. Such is the case of age, illness duration, number and type of affective episodes and history of psychotic symptoms as all have been linked to differential cognitive performance.[10–13] Furthermore, depressive and manic symptoms have such high correlation with these deficits that studies on cognition must not only state the affective state of participants but also report the severity of residual symptoms, as important differences have been documented between performance in euthymia and performance in active episodes.[12,14] Also, as comorbid substance use disorder also affects cognitive performance and is so common in BD, participants with active substance use are systematically excluded from studies on cognition in BD (for example, see exclusion criteria of).[1,9,12,14,15]

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On the other hand, anxious symptoms, whether part of a comorbid anxiety disorder or independent, are highly prevalent in persons with BD and are risk factors of various poor outcome measures, such as relapse, hospitalizations, suicidal behavior, functioning and lower quality of life.[16–23] Also, anxiety, as a general construct, is related to diminished performance on cognitive tasks, particularly with attentional control aspects of the central executive.[24] Thus, it would be expected that the presence of anxious symptoms (whether or not sufficient to fulfill criteria for a comorbid anxiety disorder) would worsen cognitive performance of patients with BD. A few studies have addressed this question: Wu et al compared performance on memory, attention, psychomotor speed, and frontal executive function between euthymic patients with type II BD (BD-II) with and without comorbid anxiety, and non-bipolar controls.[25] Only participants from the BD group with anxiety performed worse than controls, with a more significant difference in verbal memory. Chang et al compared type I (BD-I) and BD-II patients with and without comorbid anxiety, and found that cognitive performance was poorer in those with comorbid anxiety, although the affected cognitive domains varied between BD-I and BD-II.[26] Lu et al looked at the possible interaction between cognitive performance in BD-II patients with and without comorbid anxiety and the aldehyde dehydrogenase 2 polymorphism involved in the metabolism of dopamine.[27] Cognitive performance was not affected by comorbid anxiety in their sample. Finally, Huang et al evaluated cognitive performance in BDI and II with and without comorbid anxiety across different mood states, namely depressed, (hypo) manic, mixed and euthymic. The presence of anxiety tended to worsen the performance in all mood states, reaching significance for executive tasks in the mania and depressed subgroups.[28]

Yet, despite the high prevalence of anxiety in BD and the evidence of its possible impact on cognitive performance, the assessment of anxious symptoms is not part of the recommended evaluations to perform when screening for cognitive deficits in patients with BD (see recommendations of the International Society for Bipolar Disorders (ISBD) cognition task force for assessing and addressing cognitive impairment).[29] Also, although the ISBD recommendations for clinical trials on cognition do state that patients with comorbid anxiety should not be excluded and anxiety should be evaluated and monitored, the presence and severity of anxious symptoms is not systematically evaluated in studies on cognition in bipolar disorder (for example, see measurements on important studies on cognition such as).[1,30–32] Furthermore, to the best of our knowledge, the relationship between anxious symptoms and perceived cognitive deficits (ie subjective cognition) has not been addressed (as an example, in the relevant study addressing the possible reasons for discrepancies between subjective and objective cognition in anxiety performed by Miskowiak et al, neither comorbid anxiety nor anxious symptoms were considered among the possible factors).[33]

Consequently, our objective was to determine, in a Mexican sample of euthymic BD-I patients, if the severity of anxious symptoms would affect attention and/or inhibition of cognitive interference, while accounting for other possible contributors of diminished performance on these tasks, such as age, years of schooling, residual affective symptoms and perception of cognitive deficits.

Materials and Methods

The present was a cross-sectional correlational study performed with a convenience sampling approach. All study procedures comply with the declaration of Helsinki and were approved by the Ethics and Research Committee of the *Ramón de la Fuente Muñiz* National Institute of Psychiatry (INPRFM), approval number CONBIOETICA-09-CEI-010-20170316.

Participants

Euthymic patients with a diagnosis of type I BD attending the outpatient service of the National Institute of Psychiatry "Ramón de la Fuente Muñiz" at Mexico City were invited to participate. BD diagnosis was established through the following procedure: the medical records of willing participants were retrieved. Only those who had undergone at least one evaluation by the Affective Disorders' Clinic confirming that BD was the primary psychiatric diagnosis were retained: in this clinic, a semi-structured interview following DSM-5 criteria is performed by a senior psychiatrist with more than 15-year experience in the diagnosis and treatment of patients with BD. Psychiatric comorbidities were also retrieved from this evaluation, and all participants with psychiatric comorbidities other than generalized anxiety disorder (GAD) or panic disorder (PD) were excluded. Also, patients had to be in euthymia for the past two months (six months if

the last episode had been severe enough to require hospitalization or involved a suicide attempt), confirmed on the day of evaluation with a score <9 in the Hamilton Depression 17-item scale (HAMD), a score <8 in the Young Mania Rating Scale (YMRS).[34] Those who accepted and signed an informed consent were evaluated for socio-demographic characteristics, variables related to the evolution of their BD, residual affective symptoms, presence and severity of anxious symptoms, subjective and objective cognition.

Assessment Procedure

All possible candidates who met the selection criteria received an explanation of the aims and procedures of the study and read the written informed consent. Once doubts about any procedure were answered and verbal consent was given, all participants signed the consent, and the clinical assessment was performed.

Demographic characteristics (age, current occupation, years of schooling) were assessed during a face-to-face interview with the patient. Clinical characteristics, such as the age of illness onset, previous hospitalizations, and the total number of hospitalizations were obtained from the clinical records, to avoid memory bias.

Residual symptoms of mania and depression were assessed with the Hamilton Depression 17-item scale (HAMD) and the Young Mania Rating Scale (YMRS), respectively. Both are clinician-rated instruments used for the objective evaluation of symptom severity of depression and mania. Concurrent validity of the HAMD in Mexican out-patients with depression was of 0.77.[35,36] Test-retest reliability and Cronbach´s alpha for the translation and adaptation of the YMRS in the Mexican population were high (0.93 and 0.84, respectively).[37]

Anxious symptoms were assessed with the Brief Inventory of Anxious Responses and Situations (ISRA-B) which is composed by two subscales: the first one assesses the frequency of presentation of different types of anxious symptoms (cognitive, motor or physiologic anxious responses) in a 5-point Likert scale (0 = hardly ever to 4 = almost always), thus representing state anxiety and the second assesses the type of situations able to trigger such symptoms (situations of performance evaluation, interpersonal situations, phobic, every-day situations), thus evaluating trait anxiety.[38–40] For the present study, only state anxiety is reported.

Subjective cognitive complaints were evaluated with the COBRA scale. This scale comprises 16 self-administered items rated on a 4-point Likert frequency scale (0 = never to 3 = always) which assesses subjective cognitive complaints including memory, attention, executive functions, and processing speed. A total score is obtained by the sum of the item scores, with higher scores reflecting more subjective cognitive complaints. Its internal consistency for its use in Mexican patients with type I BD was high (0.91) with an adequate construct validity (one-factor explaining 45.5% of the total variance).[41]

For objective cognitive performance, we centered on two cognitive domains: attention and inhibition of cognitive interference. Attention is a lower-order cognitive task that can be affected by a spectrum of factors; its integrity is necessary for more intricate functions. On the other hand, inhibition of cognitive interference is an executive function, thus more complex, and requiring the integrity of various lower order abilities.

Attention was measured with the Digit Span forward task, which consists of strings of digits of increasing length (3 to 9), which are read out loud by the examinator at a speed of one word per second, and that the participant must repeat orally in the correct sequence. When the subject repeats correctly, a larger string is read, continuing in this way until the subjects fails to repeat two consecutive trials or correctly repeats twice the largest string. It involves auditory attention as well as short-term retention, although it is more an indicator of attention than memory.[42]

Inhibition of cognitive interference was measured with the interference index of the Stroop test, an executive functioning measure of selective attention, cognitive flexibility, cognitive inhibition, and information processing speed.[43] This test consists of three pages, each with 100 components randomly organized into five columns. The individual has 45 seconds to read aloud, as quickly as possible, the columns from left to right. The sheet on words is formed by the words “Red”, “Green”, and “Blue” in black ink, and the score is the number of words read correctly (W score). For the sheet on colors, there are groups of four X’s (“XXXX”) printed in blue, green, and red. The score is the number of elements properly named (C score). Finally, the last list consists of the three words of the first printed page in the colors of the second, with words being incongruent with the color of the ink. The task is to name the ink color, inhibiting the reading of the word, and the score is the number of correctly named elements (WC score). Finally, an

Interference Index is calculated with the formula: WC – [(WxC) /(P + W)], and indicates the degree to which a person is able to inhibit the interference produced by the incongruence of the reading task (automatic process that must be inhibited) and color naming (a task which must be voluntarily controlled). It is therefore an indicator of resistance to cognitive interference and of inhibitory control processes.[44] For the present study, all analyses were performed using raw scores.

Statistical Analyses

All analyses were conducted using IBM SPSS statistics V. 21 for PC and were deemed significant with a *p*-value ≤0.05. Frequencies and percentages for categorical variables and means with standard deviations (S.D) for continuous variables were used to summarize the demographic and clinical features of the sample.

Selection of Variables

Given the sample size (n = 87), a significance level of 0.05, and a power of at least 0.80, six associated variables were allowed in a linear regression model to be able to detect a small effect size. Therefore, we selected the most important sociodemographic variables, ie age and years of schooling, given the fact that raw —and not standardized scores— were used; for clinical variables, we selected those which could reflect the impact of affective symptoms and mood instability on cognition, but with the least collinearity, thus retaining residual affective symptoms over the number of affective episodes or the chronicity of the disorder (which would highly depend on the age of the subject). We also decided to include subjective cognition as a measure reflecting the individual's experience with cognitive deficits. Finally, the severity of anxious symptoms was included to test the main hypothesis.

Linear Regression Models

Assumptions of normality, homoscedasticity and absence of multicollinearity were determined. The distribution of the variables exhibited acceptable values of skewness (range −0.82–1.62) and kurtosis (range −0.32–1.98). Homoscedasticity assumption was obtained by plotting the predicted values and residuals on a scatterplot (which were randomly distributed) and determining the Levene's test for each variable. The *p*-values obtained were >0.05 (range 0.07–0.96) indicative of homogeneity of variances. The variance inflation factor (VIF) values measuring multicollinearity were determined and the obtained values were between 1.06 and 1.31, indicative of lack of multicollinearity. After these assumptions were determined, stepwise backward conditional linear regression models were performed to determine the association of current anxious symptoms with attention and inhibition of cognitive interference considering demographics (age and years of schooling) and clinical features (residual manic and depressive symptoms, and subjective cognitive complaints) as variables considered to be related to diminished cognitive performance in patients with BD. Unstandardized regression coefficients (β) reflect the change in cognitive scores associated with the score changes in the associated variables. We chose a stepwise backward conditional model as it has the advantage of initially considering the effects of all variables simultaneously and removes non-significant variables until reaching those who are clearly related to the dependent variable included in the model.

Results

Demographic and Clinical Characteristics of Patients with BP in Euthymia

Eighty-seven patients were included in the study. Most of them were women (81.6%, n = 71) with a mean age of 43.5 years (S.D.=10.3), and 14.4 (S.D.=3.2) mean years of schooling. Most patients had a remunerated activity.

The age of onset was mostly in the middle of the third decade of life, and a high percentage of patients had had at least one psychiatric hospitalization. Thirty-nine patients (45%) had an additional diagnosis of GAD. No patient from our sample was diagnosed with comorbid PD. Demographics, clinical characteristics, and cognitive assessment scores are exhibited in Table 1.

Table 1 Demographics, Clinical Features and Cognitive Assessment of the Total Sample (n = 87)

Demographics		
Sex	n	%
Men	16	18.4
Women	71	81.6
Current occupation		
Non-remunerated activity	30	34.5
Remunerated activity	57	65.5
	M	*SD*
Years of schooling	14.4	3.2
Age	43.5	10.3
Clinical Characteristics		
	n	%
Psychiatric hospitalizations – Yes	73	83.9
Comorbid GAD – Yes	39	45
	M	*SD*
Number of psychiatric hospitalizations	2.4	1.6
Age of illness onset – years	24.7	8.1
Residual depressive symptoms – HAMD	2.3	2.3
Residual manic symptoms – YMRS	0.9	1.4
Anxious symptoms – ISRA-B	24.5	16.5
Cognition		
	M	*SD*
Cognitive complaints – COBRA	14.5	8.9
Digit span forward	7.4	2.0
Stroop test – Word	96.8	19.2
Stroop test – Color	62.5	13.7
Stroop tests – Interference Index	1.9	10.7

Note: No patient from our sample was diagnosed with comorbid PD.

Association of Anxious Symptoms and Cognitive Variables

The Digit Span forward task exhibited an indirect association with age and the YMRS total score and a direct association with years of schooling in the first regression model. After the backward conditional method, age and the total score of the YMRS remained significant. Anxious symptoms were not related to attention in this regression modeling (see Tables 2 and 3).

Table 2 Association of Anxious Symptoms with Attention– Regression Models (n = 87)

First Regression Model	**β coefficient**	***SE***	***95% C.I. β***		***p***
			LL	***UL***	
Age	−0.06	0.02	−0.11	−0.01	0.007
Years of schooling	0.16	0.08	0.002	0.32	0.04
Cognitive complaints – COBRA	−0.01	0.03	−0.08	0.06	0.73
Manic residual symptoms – YMRS	−0.39	0.17	−0.74	−0.05	0.02
Depressive residual symptoms - HAMD	−0.13	0.14	−0.42	0.15	0.34
Anxious symptoms – ISRA-B	0.04	0.02	−0.008	0.09	0.10
Regression model after the backward conditional method					
Age	−0.07	0.02	−0.12	−0.02	0.004
Manic residual symptoms – YMRS	−0.39	0.16	−0.72	−0.05	0.02

Notes: Adjusted R^2 of first model= 0.08; Adjusted R^2 of final model=0.11.
Abbreviations: LL, lower limit; UL, upper limit.

Table 3 Association of Anxious Symptoms with Inhibition of Cognitive Interference– Regression Models (n=87)

First Regression Model	β coefficient	*SE*	*95% C.I. β*		*p*
			LL	*UL*	
Age	−0.01	0.11	−0.23	0.20	0.90
Years of schooling	1.12	0.35	0.41	1.83	0.002
Cognitive complaints – COBRA	0.44	0.16	0.10	0.77	0.01
Manic residual symptoms – YMRS	0.11	0.77	−1.42	1.66	0.88
Depressive residual symptoms - HAMD	−0.12	0.64	−1.41	1.69	0.85
Anxious symptoms – ISRA-B	−0.20	0.11	−0.42	0.01	0.06
Regression model after the backward conditional method					
Years of schooling	1.12	0.33	0.46	1.78	0.001
Cognitive complaints – COBRA	0.44	0.16	0.11	0.76	0.008
Anxious symptoms – ISRA-B	−0.21	0.08	−0.38	−0.04	0.01

Notes: Adjusted R^2 of first model= 0.12; Adjusted R^2 of final model=0.15.
Abbreviations: LL, lower limit; UL, upper limit.

In the first linear regression model, years of schooling and cognitive complaints were related to higher interference scores assessed by the Stroop test. At this moment, anxious symptoms only show a trend towards significance. However, after the backward conditional method, years of schooling and cognitive complaints remain significant, while more severe anxious symptoms were negatively related to cognitive interference score. These results show that a better performance in inhibiting cognitive interference is seen in patients with higher schooling, higher subjective cognitive complaints, and lower anxious symptoms, as assessed by the Stroop cognitive interference index.

Discussion

Impaired cognition has been largely recognized as a central component of BD, although the source of these deficits remain elusive, with evidence indicating neurodevelopmental origins and also showing a possible scar left by previous affective episodes, although this is still a controversial topic as a meta-analysis on longitudinal course of cognitive performance found no significant differences.[45–47] Furthermore, many factors, present in a vast majority of patients, can affect performance on cognitive testing, as is the case of residual affective symptoms and anxious symptoms.

Anxiety as a construct can be divided in at least two dimensions: worry and arousal. Worry in a severe form would correspond to DSM-5's conceptualization of GAD, whereas arousal would be closer to PD, although both symptoms can be present without other necessary criteria to establish a diagnosis of a formal anxiety disorder.[24] Nonetheless, their presence can be sufficient to affect cognitive performance: according to the processing efficiency theory and the attentional control theory worry gives rise to competition between anxiety-related processes and task-related processes and affects specific executive processes such as inhibition.[48]

Our results illustrate the possibility that the severity of anxious symptoms does not affect simple cognitive processes, as attention; however, when faced with complex tasks, anxiety starts to play a role. This is in line with the findings of Wu et al who found greater differences in working memory, psychomotor speed and executive functions in BD-II with comorbid anxiety.[25] Also, in the subgroup of BD-I patients, Chang et al found differences only in working memory when comparing those with and without comorbid anxiety.[26]

Another interesting finding is the interaction between perception of cognitive deficits, years of schooling and anxiety: more years of schooling, greater subjective cognitive complaints, and less anxiety were associated with a better inhibition of cognitive interference. One possible explanation is that patients who perceive cognitive deficits but do not have severe anxiety might be attentive to the task to a sufficient degree to improve their concentration on the task without reaching a threshold where hyper-arousal and worry shifts the attention towards their performance. This is congruent with studies

on emotional acceptance, and its effect on executive control where meditators had a better performance on the Stroop test than did non meditators, an effect accounted for by heightened emotional acceptance.[49]

The limitations of this study must be mentioned and include the following: a relatively small sample impeded interesting additional analysis, such as the interaction of trait-state anxiety. Indeed, the chronicity of anxious symptoms (versus current anxiety) has a significant effect on the many clinical factors affecting cognition, for example, lifetime anxiety was associated with a two-fold increase in recurrence rate of depressive episodes, whereas current anxiety did not —unless lifetime anxiety was also present—, among other relevant outcomes, such as time spent in episodes, maximum period of continuous euthymia, presence of psychosis and response to mood stabilizers.[50,51] As well, the inclusion of other neuropsychological tests would have been interesting, but their inclusion would need correction for multiple correlations thus highly increasing type-II error. Also, we only included BD-I patients, thus cannot generalize to all types of BD. Additionally, we did not include controls; it would be interesting to determine in future research if the impact of anxiety and subjective cognitive deficits is also present in the general population.

Despite these deficits, these findings bring to light the importance of anxious symptoms, whether or not part of a formal comorbid anxiety disorder, suggesting that future research on cognition in BD would benefit from systematically measuring the presence and severity of anxious symptoms, as a possible factor contributing to deficiencies, at least when evaluating cognitive inhibition; furthermore, they remind us of the importance of considering the high prevalence and importance of anxiety in patients with BD as well as the possible interaction between anxiety and cognitive complaints, which might also be a contributing factor for the discrepancies seen in subjective vs objective cognitive measures.

Conclusion

Beyond residual affective symptoms, anxiety might affect some cognitive processes. We recommend routine testing of anxiety when considering cognitive evaluations, especially when screening for cognitive deficits.

Disclosure

The authors report no conflicts of interest in this work.

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