

## ASSESSMENT OF IMPULSIVITY IN BIPOLAR DISORDER (BD) IN COMORBIDITY WITH GENERALIZED ANXIETY DISORDER (GAD): REVISITING THE HYPOTHESIS OF PROTECTIVE EFFECT

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### Abstract

**Objective:** Bipolar Disorder is associated with many psychiatric comorbidities. Anxiety disorders, is diagnosed in about 50% of patients with Bipolar Disorder throughout life and contributes to a worse outcome. There are evidences that impulsivity may have an inverse relationship with anxiety and, therefore, that Anxiety Disorders could serve as a protective factor in relation to an impulsive behavior.

**Method:** This study aims to evaluate the relationship between the presence of a diagnosis of GAD and the expression of different types of impulsivity in a sample of patients affected by BD. We assessed 95 subjects diagnosed with Bipolar disorder, euthymics during the evaluation. GAD was observed in 56.84% of the sample. The two groups of patients classified accordingly to the presence / absence of Generalized Anxiety Disorder were compared in a neuropsychological battery composed by Conner's Continuous Performance Task (CPT-II) and Iowa Gambling Task (IGT) to assess motor, attentional and decision-making impulsivity.

**Results and conclusions:** There were no significant differences between groups of Bipolar Patients in any measure of impulsivity, and therefore, our data does not support the hypothesis of protective effects of anxiety in impulsivity expression.

**Key words:** bipolar disorder, anxiety disorders, Iowa gambling task, Conner's continuous performance task, generalized anxiety disorder

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**Declaration of interest:** none

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## 1. Introduction

Bipolar disorder (BD) is a chronic, clinically severe and frequent psychiatric disorder that accounts for a significant economic, social, familial and individual burden being considered the sixth leading cause of disability worldwide (Woods 2000). Prevalence rates for BD have been classically acknowledged to approximate 1 to 2% (Zarate et al. 2000, Hirschfeld 2001) in general population. Although establishing the onset of BD is difficult (because of the nature of disorder) there is general agreement that early onset age is occurring in what should be a particularly productive time of life as showed by studies carried in

different countries (Szadoczky et al. 1998, Morgan et al. 2005).

Bipolar disordered patients are more prone to have forensic problems (about 10% of them), to have very low employment and more pension or disability benefits. A large proportion never marry and a vast majority of married patients divorce or experience marital problems (Morgan et al. 2005), reflecting their overall poor social functioning. Furthermore BD is the psychiatric diagnosis more closely associated with suicidal behavior. In these patients suicide rates average approximately 1% annually, about 60 times higher than the international population rate of 0.015% annually. Their suicidal acts have also higher lethality as suggested

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by a much lower ratio of attempted suicide (approximately 3:1) than in the general population (approximately 30:1) (Baldessarini et al. 2006). Furthermore nearly one third of patients acknowledge at least one suicide attempt (Muller-Oerlinghausen et al. 2002).

BD is associated with many psychiatric comorbidities like substance abuse and/or dependence, personality disorders and anxiety disorders in a way that comorbidity is the rule, more than exception (Merikangas et al. 2007). Anxiety disorders, for example, are highly prevalent, occurring in about 50% of patients with BD throughout life (Simon et al. 2004) and contributes to a worse outcome. The generalized anxiety disorder (GAD), is associated with negative outcomes such as increased severity of mood symptoms, reducing the amount and duration of euthymic periods, higher tendency to substance abuse, functional impairment and poorer quality of life (Young et al. 1993, Cassano et al. 1999, Simon et al. 2004). Moreover, in bipolar subjects affected by GAD, it has been reported increased risk for suicidal ideation and to suicide attempts (Fawcett et al. 1990, Frank et al. 2002, Engstrom et al. 2004, Simon et al. 2004, 2007).

A pivotal characteristic in Bipolar Disorder is impulsivity. Although there is no single definition for the construct of impulsivity, it involves a predisposition to quick and unplanned reactions for internal or external stimuli without weighing the consequences of these negative reactions to themselves or others (Moeller et al. 2001). In Bipolar Disorder, higher scores of impulsivity are not circumscribed only to depressed or manic phase, being present also during euthymia (Moeller et al. 2001, Swann et al. 2001; Swann et al. 2003).

One aspect of particular interest to research is the effect of GAD in impulsivity expression in bipolar disorder. Some authors have suggested that impulsivity may have an inverse relationship with anxiety (Caci et al. 1998, Mobini et al. 2006) and, therefore, that anxiety could serve as a protective factor in relation to an impulsive behavior (Slama et al. 2004, Lee et al. 2006). The main evidence for this relationship comes from studies on the comorbidity between the anxiety phenotype and attention deficit hyperactivity disorder (ADHD) (Oosterlaan 1998, Pliszka et al. 1999, Brown 2000, Manassas et al. 2000, Garon et al. 2006) though there are results indicating the presence of anxiety as an aggravating factor in relation to the impulsivity in obsessive compulsive disorder (OCD) (Summerfeldt et al. 2004) and BD (Taylor et al. 2008). However, the results of these studies are contradictory and possible explanations may be related to differences in the definition of impulsivity construct used by the authors as well as methodological differences on impulsivity assessment.

To our knowledge, specifically addressing the question of the effect GAD on impulsivity in bipolar patients only one study was carried. Thus, the purpose of this study was to evaluate the relationship between the presence of a diagnosis of GAD and the expression of different types of impulsivity in a sample of patients affected by BD.

## 2. Methods

### 2.1. Subjects

We enrolled 95 subjects diagnosed with BD, according DSM-IV, based on a semi-structured interview (MINI-PLUS 5.0), mean age = 40.94 years, SD = 12.38. A current diagnosis of GAD was observed in 56.84% of them. At the assessment, the subjects were euthymic according to DSM-IV. Furthermore, to be included patients need to have at least 8 years of formal education, intelligence within normal limits, considering the test of Raven's Progressive Matrices and no history of neurological disorders such as head trauma and stroke. All subjects were in pharmacological therapy with at least one class of mood stabilizers during the time of assessment.

### 2.2. Assessment tools

All subjects were submitted to a neuropsychiatric interview based in DSM-IV, the MINI PLUS 5.0. This interview was used to assess the diagnosis of GAD, consider in our study as a measure of anxiety as a trait. The subjects underwent assessment of intelligence by Raven Progressive Matrices test and had the manic and depressive symptoms assessed using the Beck Depression Inventory (BDI) and the Young Mania Rating Scale (YMRS), respectively. In addition, it was used Iowa Gambling Task (IGT-Br) and Conner's Continuous Performance Task (CPT-II) for the assessment of impulsivity, as previously described by Malloy-Diniz et al. (2007).

In the Conner's CPT-II (Conners, 2002), subjects have to press the spacebar when any letter (except the letter X) appears on screen. Omission errors occur when the individual does not press the spacebar when a letter (except X) appears on screen and reflects instances when a patient is not attentive to the target stimuli. A commission error occurs when the subject presses the spacebar when the letter X appears on screen, reflecting flaws in motor response inhibition. These two concepts correspond to attentional and motor impulsiveness, respectively, of Barratt's model of impulsiveness (Malloy-Diniz et al. 2007). Thus, we used commission and omission errors as dependent measures to evaluate motor and attentional impulsivity.

In the IGT, subjects have to choose one card at a time from four available decks (A, B, C, D). The task requires the subjects to make 100 choices (100 trials), and in each trial subjects may win or lose a certain amount of money. During the instructions, subjects are told that some decks are more advantageous than others but they do not know which decks are better. After each choice, subjects receive feedback on the computer screen telling them how much money they won or lost. Using the feedback, the subject has to avoid decks that yield high immediate gains but lead to large future losses (decks A and B) and choose the decks that lead to small immediate gains but avoid substantial losses throughout the task (decks C and D). One hundred choices are divided into five blocks, with twenty choices each. This kind of register is important to verify changes in the pattern of choices during the task, such as observing

the learning curve. For each block, the net score was used (number of cards selected from the advantageous “good” decks minus the disadvantageous “bad” decks) as the dependent measure. A total net score from all blocks was also obtained. This test is a good model for studying non-planning/cognitive impulsivity (Malloy-Diniz et al. 2007).

A neuropsychologist administered the tests in a laboratory in a fixed order, beginning with CPT-II. During the administration of the tests and scales the examiner was unaware of the subject’s diagnosis and also blind to molecular results.

### 2.3. Statistical analysis

Demographic and clinical data of the sample were analyzed using descriptive statistics. Given the non-parametric distribution of some neuropsychological measures, comparisons between groups were conducted using the chi-square (categorical variables) and Mann-

Whitney test (for continuous variables). Results were considered significant if a significance level of 5% was reached.

### 3. Results

The two groups of patients classified accordingly to the presence / absence of Generalized Anxiety Disorder, were matched in age, education, gender, level of intelligence and the presence of symptoms of depression and mania. Considering psychiatric comorbidities, the group of bipolar patients diagnosed with Generalized Anxiety Disorder showed a higher frequency of panic disorder (5.49%) compared to those without comorbid GAD. Accordingly to the neuropsychological variables there were no significant differences between groups in any measure of impulsivity. **Table 1** shows comparisons in clinical and sociodemographic variables between the groups and **Table 2** compares the neurocognitive test results.

**Table 1.** Comparisons between the groups of bipolar patients with and without generalized anxiety disorder in relation to sociodemographic and clinical variables

| Bipolar disorder         |                                      |       |    |        |                                   |       |    |        |                     |        |
|--------------------------|--------------------------------------|-------|----|--------|-----------------------------------|-------|----|--------|---------------------|--------|
|                          | Without Generalized Anxiety Disorder |       |    |        | With Generalized Anxiety Disorder |       |    |        | Statistical Test    |        |
|                          | Mean                                 | SD    | n  | %      | Mean                              | SD    | n  | %      | X <sup>2</sup> ou z | p      |
| Age                      | 42,71                                | 12,21 |    |        | 39,59                             | 12,45 |    |        | 1,06                | 0,289  |
| Scholarity (highschool)  |                                      |       | 26 | 63,40% |                                   |       | 38 | 70,40% | 0,178               | 0,673  |
| Marital status (married) |                                      |       | 20 | 48,80% |                                   |       | 24 | 44,40% | 2,895               | 0,408  |
| Sex (female)             |                                      |       | 29 | 70,70% |                                   |       | 36 | 66,70% | 0,513               | 0,474  |
| Young                    | 8                                    | 6     |    |        | 7                                 | 4     |    |        | 1,201               | 0,23   |
| BDI                      | 10                                   | 5     |    |        | 10                                | 5     |    |        | 0,321               | 0,748  |
| Duration of illness      | 17,8                                 | 10,4  |    |        | 17,3                              | 9,7   |    |        | 0,144               | 0,875  |
| Panic Disorder           |                                      |       | 3  | 7,30%  |                                   |       | 14 | 25,90% | 5,493               | 0,019* |
| Borderline personality   |                                      |       | 6  | 14,60% |                                   |       | 17 | 31,50% | 3,605               | 0,058  |
| Smoking                  |                                      |       | 21 | 51,20% |                                   |       | 24 | 44,40% | 0,429               | 0,512  |
| Alcoholism               |                                      |       | 11 | 26,80% |                                   |       | 17 | 31,50% | 0,243               | 0,622  |
| Substance abuse          |                                      |       | 5  | 12,20% |                                   |       | 7  | 13,00% | 0,12                | 0,911  |
| Psychotic Disorders      |                                      |       | 12 | 29,30% |                                   |       | 13 | 24,10% | 0,324               | 0,569  |
| Eating Disorders         |                                      |       | 1  | 2,40%  |                                   |       | 4  | 7,40%  | 1,154               | 0,283  |
| Suicide Attempts         |                                      |       | 16 | 39,00% |                                   |       | 26 | 48,10% | 0,787               | 0,375  |
| No. of attempts          | 1,02                                 | 1,78  |    |        | 1,3                               | 1,85  |    |        | 0,92                | 0,357  |

\*  $p < 0.05$

**Table 2.** Comparison between the neurocognitive test results accordingly to the clinical features

| Bipolar disorder |                                      |       |   |                                   |       |   |                  |       |
|------------------|--------------------------------------|-------|---|-----------------------------------|-------|---|------------------|-------|
|                  | Without Generalized Anxiety Disorder |       |   | With Generalized Anxiety Disorder |       |   | Statistical Test |       |
|                  | Mean                                 | SD    | n | Mean                              | SD    | n | X2 ou z          | p     |
| Raven            | 44                                   | 5     |   | 45                                | 6     |   | 1,138            | 0,255 |
| IGT Net          | 1,93                                 | 20,45 |   | 5,41                              | 26,82 |   | 0,643            | 0,52  |
| CPT Omissions    | 12,61                                | 22,25 |   | 8,13                              | 9,27  |   | 0,566            | 0,572 |
| CPT Commissions  | 14,71                                | 7,96  |   | 17,2                              | 8,86  |   | 1,147            | 0,251 |
| CPT RT           | 430,68                               | 96,82 |   | 428,9                             | 84,34 |   | 0,083            | 0,934 |

Here we investigate whether the presence of anxiety symptoms in bipolar individuals may influence impulsivity as assessed by neuropsychological test. The results obtained in our study failed to find a relationship, whether positive or negative, between anxiety and impulsivity in bipolar subjects, corroborating the findings of Oosterlaan & Sergeant (1998) in a meta-analysis study. Nevertheless, other researchers found different results. Oosterlaan (1998), Pliszka et al. (1999), Brown (2000), Manassas et al. (2000), found anxiety as a protective factor for impulsiveness, whereas Summerfeldt et al. (2004), Taylor et al. (2008), found it as an aggravating factor. Differences in the definitions of impulsivity and ways to measure this complex phenotype may be at the heart of those contradictory results between these studies. Moreover, changes in impulsivity may be related to factors other than comorbidity, such as the expression of specific genetic polymorphisms. Some authors consider that the impulsive phenotype may consist of a possible endophenotype candidate polymorphisms, such as 5HTTLPR and suicidal phenotype (Malloy-Diniz et al. 2007, Rocha et al. 2008, Neves et al. 2010).

Strengths of our study is the fact we evaluate different types of impulsivity using neuropsychological tests which are direct measures of impulsive phenotype in opposition to indirect measures like questionnaires and scales of self-fulfillment. In addition, the subjects were euthymic during the evaluation, which minimizes the impact of factors related to active phases of BD, in the relationship between impulsivity and anxiety.

The study has some limitations that should be mentioned. The number of subjects studied can be considered small, limiting the generalization of the results. Besides, we did not controlled the use of medications, whose mechanism of action may affect measures of impulsivity and anxiety. However, Ancin et al. (2010) suggested that cognitive alterations in bipolar patients cannot be explained by medication because the alterations remained after controlling for medication variables in the statistical analyses of several studies (Fleck et al. 2001), as well as in drug-free euthymic bipolar patients (Goswami et al. 2009). Another limitation is the absence of measures of the anxiety intensity. Therefore, we consider that the results

presented here are related to anxiety as a trait and not as a state. Future studies should address this relationship (anxiety as state x impulsivity) in bipolar patients.

Finally, in this study although there were no differences between groups with respect to the presence of other comorbidities, we can not discount the effect of the presence of other pathologies such as attention deficit disorder and hyperactivity disorder, impulse control disease and substance abuse, influencing the relationship between impulsivity and anxiety.

Future studies in larger samples, without other comorbidities than generalized anxiety disorder and control of variables related to medication may be helpful to clarify the relationship between impulsivity and anxiety. Furthermore, longitudinal studies with repeated assessments of impulsivity and anxiety may help to elucidate whether the protective effect of anxiety appears more significantly in the active phases of the disease.

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