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**Mood or energy/activity symptoms in bipolar mania: which are the most informative?**

Short title: Mood versus energy/activity symptoms in mania

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**ABSTRACT**

**Introduction:** Bipolar disorder (BD) in DSM-III and DSM-IV is classified as a mood disorder and requires the presence of a mood change, i.e., euphoria or irritability. Differently, DSM-5 states that there must be some increase in energy or motor activity in addition to the mood change.

**Objective:** Our aim was to identify which types of symptoms (i.e., mood- or energy/activity-related symptoms) are the most informative in a manic episode.

**Method:** Symptoms of manic episodes in 106 outpatients with BD were assessed through the Young Mania Rating Scale between November 2002 and November 2015 in a naturalistic study. The items of the scale were divided into three groups according to clinical criteria: mood, energy/activity, and other. The Samejima Graded Response Model of the Item Response Theory was computed as well as the Test Information Function for comparisons between groups. Chi-squared tests were used to verify the association between the groups of symptoms by comparing the area under the curve of the TIF results.

**Results:** The information accounted for energy/activity represents 77% of the proportion of the total TIF; about 23% is related to mood and other groups of symptoms. Both proportions are statistically different ( $\chi^2(1) = 30.42, p < 0.001$ )

**Conclusion:** On average, changes in energy/activity tend to be more informative than mood changes during the manic phases of BD.

**Keywords:** *bipolar disorder, motor activity, energy, mood changes, Young Mania Rating Scale.*

## Introduction

Kraepelin<sup>1</sup> defined manic and depressive syndromes based on three elements – mood, thought, and activity –, giving the same weight to the three kinds of symptoms. However, from the DSM-III,<sup>2</sup> on, bipolar disorder (BD) was classified as a mood disorder similarly to major depressive disorder, to the detriment of thought and activity.

In contrast to the view of BD as a mood disorder, Akiskal et al.<sup>3</sup> proposed criteria for the diagnosis of mania that favored increased motor activity. Besides, several studies have shown the importance of motor activity changes in mania. Factor analyses of manic symptoms found that the “hyperactivity” factor was the most heavily loaded factor.<sup>3- 6</sup> Additionally, some actigraphic studies have shown that patients with BD exhibit increased motor activity during manic episodes.<sup>7-10</sup>

Probably as a result of the findings of these studies, the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5),<sup>11</sup> brought an important change in criterion A for the diagnosis of a manic or hypomanic episode. Until the DSM-IV-TR,<sup>12,13</sup> euphoria or irritability were mandatory. Nevertheless, increased energy or motor activity must now be accounted for in addition to mood symptoms. This obviously implied a modification in the concept of BD.

It is still debatable whether changes in mood and energy/motor activity have the same level of importance in BD, particularly in mania. In the present study, we compared the two kinds of symptoms during manic episodes in outpatients with BD. We used Test Information Function (TIF) analysis to identify the degree to which each group of symptoms informed different levels of syndrome severity.

## Method

### *Participants*

The present study was conducted in an outpatient research center at the Institute of Psychiatry, Federal University of Rio de Janeiro (IPUB-UFRJ), Brazil, from November 2002 to November 2015. This was a naturalistic study. Patients were not specifically recruited to take part in it, being already under regular treatment there. Not all the patients were involved in the study at the same time, and they were not necessarily assessed during the entire period of 13 years. The inclusion criteria were a diagnosis of BD types 1 or 2;  $\geq 18$  years old; written informed consent; and the occurrence of at least one manic or hypomanic episode, at least one depressive episode and at least one period of euthymia during the course of the study. Notwithstanding, our study specifically addressed manic episodes. Depressive episodes and comparisons between the different phases of BD would be the object of other studies. This study has been carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

### *Instruments*

Diagnoses of BD and affective episodes were established according to DSM-IV-TR criteria<sup>13</sup> using the Structured Clinical Interview for the DSM.<sup>14</sup> When a manic or hypomanic episode was detected, the Brazilian version of the Young Mania Rating Scale (YMRS)<sup>15,16</sup> was routinely administered. The scale was not applied during episodes of depression and periods of euthymia.

The YMRS, with 11 items, is one of the most frequently utilized rating scales to assess manic symptoms. It is based on the patient's subjective report of his/her clinical condition and in the objective evaluation carried out by the examiner regarding the previous 48 hours. Each item is graded into five levels of severity: seven (elevated mood, increased motor activity-energy, sexual interest, sleep, language-thought disorder, appearance and insight), have scores

ranging from 0 to 4 and the remaining four (irritability, speech, content and disruptive-aggressive behaviour) have scores ranging from 0 to 8.<sup>16</sup> The original scale,<sup>17,18</sup> as well as the version adapted to Brazilian Portuguese,<sup>19</sup> showed high levels of validity and reliability.

Demographic and retrospective clinical data were also obtained from interviewing the patients.

### *Procedures*

Several patients had more than one manic or hypomanic episode throughout the clinical follow-up, but only one of them was considered in our study. We chose each patient's episode with the highest total score on YMRS. In case of a tie, the oldest episode was chosen.

The YMRS items were divided into three groups according to the types of symptoms: mood, energy/activity, and other. The mood symptom group consisted of item 1 (Elevated Mood) and item 5 (Irritability). The energy/activity symptom group consisted of item 2 (Increased Motor Activity/Energy), item 3 (Sexual Interest), item 4 (Sleep), and item 6 (Speech-Rate and Amount). The other symptom group consisted of: item 7 (Language-Thought Disorder), considered heterogeneous regarding the changes evaluated; item 9 (Disruptive-Aggressive Behavior), related to both mood and energy; and item 8 (Content), item 10 (Appearance), and item 11 (Insight), not related to mood or energy. Such organization followed clinical criteria, based on definitions of symptoms and the authors' personal experiences. Other studies that compared energy or activity symptoms with mood symptoms also influenced this arrangement.<sup>20-22</sup> Considering that each group of symptoms was composed of a different number of items, we calculated the average of each of these items to make comparisons possible.

*Statistical analyses*

Data were initially preprocessed to identify errors and inconsistencies. No outlier was removed, and data was complete, with no missing case. To verify which item groups were the most informative, a unidimensional version of the Samejima Graded Response Model<sup>23,24</sup> was used as an Item Response Theory (IRT) trait estimate.

The Graded Response Model is an extension of the two-parameter dichotomous model, developed for polytomous items. In this model, a single discrimination (slope) and several threshold (location) parameters are computed under the assumption that responses are graded on an ordinal scale.<sup>25</sup> To identify the model, Ramsay acceleration was used along with the Broyden-Fletcher-Goldfarb-Shanno algorithm.<sup>26</sup> After identification of the IRT model, the Test Information Function (TIF) was computed. TIF is a measure of the amount of information provided by the item responses on a test about latent traits (aka  $\theta$ ), which is computed by the sum of the information function of all the items. This statistics enables to check the degree to which such item groups contributed to understanding symptoms across the latent trait spectrum. The TIF returns Fisher information for the latent trait ( $\theta$ ) after summing item information functions (IIFs). Pragmatically, TIF ranges from -4 to 4, and a higher TIF indicates a better estimate of the precision of the results. Akaike and Bayesian Information Criteria, both raw and adjusted, were computed to determine the relative quality of the statistical models. Chi-squared tests were used to check the association between the types of symptoms during the manic phase by comparing the area under the curve of the TIF results. All the analyses were performed using R 4.1 software and the mirt package.<sup>26</sup>

## Results

### *Sample*

Along the study period, 243 patients were evaluated, but only 106 had at least one episode of mania or hypomania, at least one depressive episode, and at least one period of euthymia. No patient refused to participate in the study. There was no record regarding the number of times in which, despite the occurrence of a manic or hypomanic episode, it was not possible to apply the clinical scale. Thus, a total of 106 manic or hypomanic episodes, one for each patient, were evaluated with YMRS. The patients were followed for an average of 5.5 years (SD = 3.1 years). Among them, 74 were women (69.8%). The mean age of the participants was 52.5 years (SD = 11.7 years).

A total of 102 patients were classified as type 1 BD, and four were classified as type 2 BD. The mean age at the first episode of BD was 24.2 years (SD = 9.8 years). The total disease duration was an average of 24.1 years (SD = 12.6 years). Fifty-seven patients (53.8%) had been hospitalized at least once. The mean number of hospitalizations was 2.5 (SD = 4.0). Thirty-four patients (32.1%) had attempted suicide at least once. The mean number of suicide attempts was 0.8 (SD = 1.5). The average total score on the YMRS was 20.79 (SD = 8.44). There was no record regarding psychiatric comorbidities or the total number of manic and depressive episodes.

### *Test Information Function*

The IRT model converged after 49 EM interactions. The Akaike information criterion (AIC) was 859.2018, and the Bayesian information criterion (BIC) was 901.8169. These indices demonstrated the adequacy of the model preliminarily.

The discrimination parameters (i.e., slopes) of the mood, energy/activity, and other groups were 1.34, 1.90, and 1.29, respectively. The latent trait varied between -4 and 4. This



index allows determining how well the items discriminate different levels of the trait. Table 1 presents these results. The TIF curves for the three suggested clinical classification criteria (mood, energy/activity, and other symptoms) during manic episodes were computed (Figure 1). Energy/activity symptoms were more essential during the manic phase of BD. The TIF curves with the highest peaks provided more information about one specific point in the latent trait, whereas the TIF curves with the longest lengths and peaks above the other curves were the most informative about the severity of one stage. The information regarding energy/activity represents 77% of the proportion of the total TIF and about 23% is related to mood and other groups of symptoms. These two proportions are statistically different ( $X^2(1) = 30.42, p < 0.001$ ), suggesting that the manic phase of BD is associated with symptoms related to energy/activity. Only at the extremes related to the severity of the manic episode, that is, when the condition was very mild or very severe, the group of changes in energy or motor activity was not the most informative.

Figure 1 - Test information function (TIF) of the group of symptoms during manic episodes

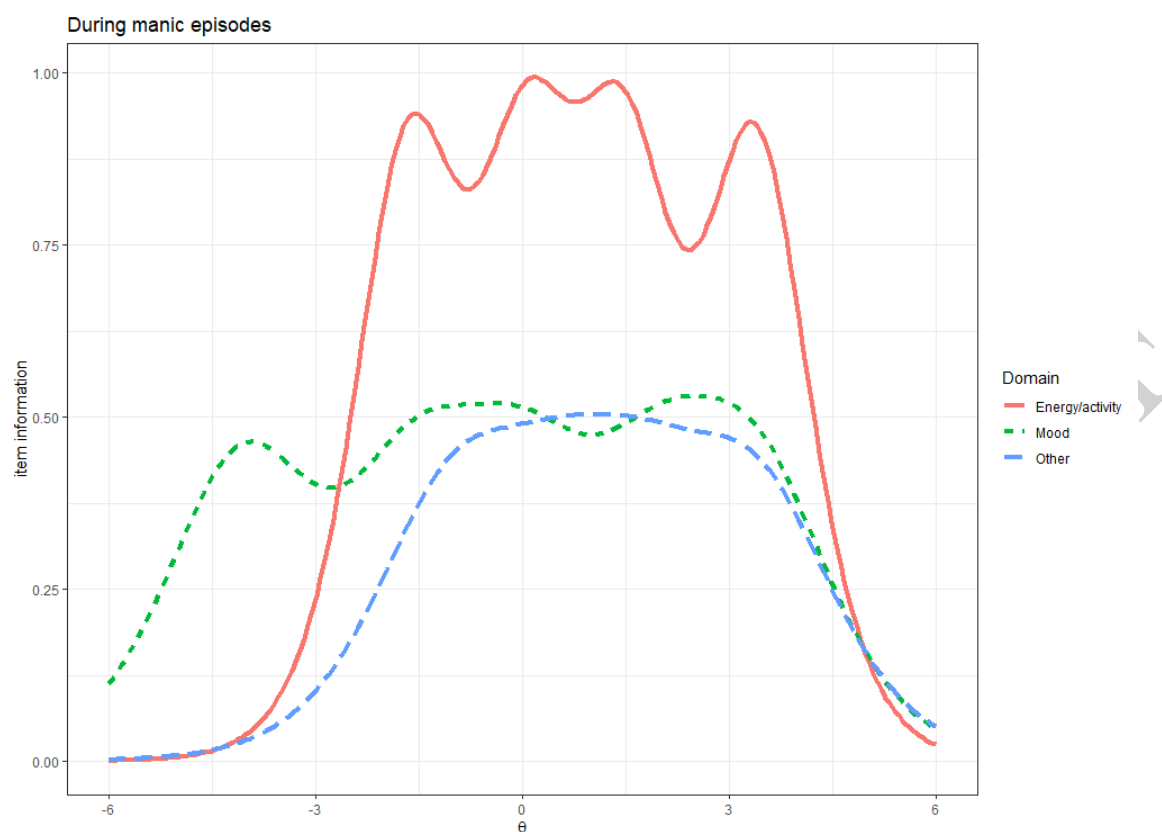


Table 1 - Results of the IRT analysis using the GRM model with values of factor loadings, discrimination, and thresholds

| Items' groups   | $\lambda$ | a1    | d1    | d2     | d3     | d4     | d5     |
|-----------------|-----------|-------|-------|--------|--------|--------|--------|
| Mood            | 0.619     | 1.34  | 5.415 | 2.014  | -0.03  | -2.693 | -4.462 |
| Energy/Activity | 0.745     | 1.903 | 3.12  | -0.14  | -2.76  | -6.428 | NA     |
| Other           | 0.603     | 1.286 | 1.212 | -0.692 | -2.257 | -4.29  | NA     |

Full-information item factor analysis

AIC = 859.2018; AICc = 865.3142

BIC = 901.8169; SABIC = 851.2671

SS Loadings: 1.302

Proportion of variance: 0.434

$\lambda$  = standardized factor loadings, a1 = discrimination, d = difficulty parameter

## Discussion

Symptoms of manic episodes were assessed in 106 bipolar outpatients using the YMRS. The items on this clinical scale were divided into three groups according to clinical criteria: mood,

energy/activity, and other. Using the TIF analysis, we found that energy/activity symptoms were the most informative in manic episodes. Compared to the mood changes and other symptoms groups, the difference was statistically significant.

It should be noted that we observed that increased energy and motor activity were more informative than mood changes in manic episodes diagnosed according to DSM-IV-TR criteria.<sup>13</sup> These criteria require the occurrence of euphoria or irritability but not changes in the energy of motor activity. Thus, there was some sample bias in favor of mood changes in our study.

The average age of the patients was high and the average duration of the illness was relatively long. This may have occurred because of the inclusion criteria that required the occurrence of at least one manic episode, one depression episode, and one period of euthymia. Furthermore, the study was carried out at a university hospital, where more severe patients are commonly referred to. It is not clear how these sample aspects could have influenced the results. Only two patients were diagnosed with type 2 BD. As the proportion between type 1 and type 2 patients was not known prior to the study, it was decided not to exclude any subject from the sample.

A previous study<sup>20</sup> also used a TIF analysis to establish comparisons between changes in mood and changes in energy/motor activity during an episode of bipolar mania and obtained results that were similar to the present one. However, unlike the present study, their sample was formed of hospitalized patients, and the assessment of manic symptoms was based on six items extracted from the Schedule for Affective Disorders and Schizophrenia-Changed version.<sup>27,28</sup>

Two other studies also investigated which symptoms would be the most important in BD. Nevertheless, differently from that study with inpatients,<sup>20</sup> however, the samples consisted of outpatients, and, in addition to the manic phases, the depressive and euthymic phases were evaluated. One of these studies<sup>21</sup> used Canonical Discriminant Analysis and found that items

that evaluated increased motor activity (i.e., item 2 [increased motor activity/energy] on the YMRS and item 9 [agitation] on the Hamilton Depression Scale)<sup>29</sup> were the ones that best distinguished mania, depression, and euthymia. Items that were related to mood symptoms on both scales were less important for this differentiation. The other study<sup>22</sup> evaluated the same sample but applied only the Hamilton Depression Scale. According to their IRT analysis, items that were related to energy and motor activity were more informative than items that were related to mood.

Some factor analysis studies of manic symptoms have been performed. Bauer et al.<sup>4</sup> evaluated a sample of patients with BD or unipolar depression and healthy controls. They found that “activation” was the factor that correlated most with YMRS total scores. In a sample of patients who were hospitalized with mania, Akiskal et al.<sup>3</sup> used the Beigel-Murphy Manic State Rating Scale<sup>30</sup> and obtained the same results. Benazzi and Akiskal<sup>5</sup> applied the Mood Disorder Questionnaire<sup>31</sup> in patients who were diagnosed with type 2 BD or unipolar depression and identified two main factors: “energized activity” and “irritability-racing thoughts”. Benazzi<sup>32</sup> evaluated a similar sample and identified three factors: “elevated mood,” “mental activation,” and “behavioral activation.” In summary, in all four of these studies, factors that were related to increased energy/activity were among the most important, but only two of these studies found a mood-related factor (irritability in one study and euphoria in the other).

Clinical practice also seems to reveal an association between hyperactivity and mania or hypomania. Benazzi<sup>6</sup> found that hyperactivity was the most common symptom among patients with BD type 2, surpassing elevated mood, and was the symptom most associated with the diagnosis. Some authors<sup>33,34</sup> proposed that the presence of increased motor activity during a depressive episode would indicate the occurrence of a mixed state. In a study with 7,689 patients who were currently experiencing a major depressive episode, Barbuti et al.<sup>35</sup> found that psychomotor agitation was more associated with bipolar spectrum features when compared

with psychomotor retardation. Psychomotor retardation has classically been considered the cardinal symptom of depression.<sup>36,37</sup>

Motor activity can be objectively assessed by actigraphy. Some actigraphic studies show that patients with mania or hypomania have higher levels of motor activity than other depressed or euthymic bipolar patients, schizophrenia patients, and healthy controls.<sup>7-10,38</sup> In contrast, other actigraphic studies have found a decrease in motor activity in patients with depression when compared with normal controls.<sup>38-40</sup> They also found that the remission of this change was associated with the clinical improvement of depressive symptoms.<sup>41-43</sup>

Other studies found that the occurrence of elation or irritability did not clearly define a manic episode. In a review of 16 clinical studies of mania, Goodwin and Jamison<sup>44</sup> found that a weighted average of 46% of manic patients presented sadness. In another review, Cassidy<sup>45</sup> noted that anxiety was an especially common symptom in mixed mania episodes. According to Henry et al.<sup>46,47</sup> mania is better characterized by the intensity of affective expression, which they referred to as hyperreactivity, than by mood quality (i.e., euphoria, irritability, or sadness). Modification of the criteria for diagnosing a manic or hypomanic episode in the DSM-5<sup>11</sup> significantly affected the clinical prevalence of BD. When the new criteria were applied to patients who were previously diagnosed with BD based on DSM-IV-TR criteria,<sup>13</sup> the number of cases dropped by at least one third.<sup>48-51</sup> Additionally, Fredskild et al.<sup>50</sup> reported that patients who were diagnosed with a manic episode according to the DSM-5 criteria<sup>11</sup> had higher scores on the YMRS compared with patients who met only the DSM-IV-TR criteria.<sup>13</sup>

Akiskal et al.<sup>3</sup> proposed a more radical change to the diagnostic criteria of a manic episode, in which criterion A should include only psychomotor activation. Mood changes would be in criterion B, but would not be restricted to elation and irritability (i.e., sadness and anxiety could also be accepted). **The conception that changes in energy and motor activity would be more relevant than changes in mood could be extrapolated from BD, with at least three consequences**

from the perspective of nosography. The first consequence would be an even more radical change in the diagnostic criteria for mania, which aligns with the proposal presented by Akiskal et al.<sup>3</sup> The second consequence would be a change in the criteria for the diagnosis of a major depressive episode, favoring motor changes over mood changes. Finally, BD and major depressive disorder would no longer be considered mood disorders and would instead be reclassified as energy and motor activity disorders. Obviously, these ideas are merely speculative and require additional scientific proof.

The present study has limitations. First, the choice of items that would comprise the symptom groups (energy/activity vs. mood), despite being based on common observations in clinical practice, was arbitrary to some extent. The division of symptoms was not based on groups derived from factor analysis, which can certainly be criticized. Second, the choice of the YMRS may also be subject to criticism. The YMRS is the most widely used assessment of manic episodes, but it has significant psychometric problems. According to an item response theory evaluation, several YMRS items provide little or no information.<sup>52</sup> Another limitation was the decision to evaluate just the most severe episode of mania since it may not be the most representative one.

## Conclusion

The present results indicate that, on average, energy or motor activity changes tend to be more informative than mood changes in mania. Previous studies that made this comparison between these two symptom groups reported similar results.<sup>21,22</sup> Results of factor analyses of manic symptoms, assessments of motor activity using clinical observation scales, and actigraphic studies point in the same direction.

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