From inhibition to activation, from emotional hyporeactivity to emotional hyperreactivity: Two pathways to discriminate mood in bipolar disorders

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ARTICLE INFO

ABSTRACT

To better explore the clinical heterogeneity of bipolar mood states, we developed a dimensional scale for assessing all mood episodes (depressive, hypomanic, manic, mixed states) using the same tool. The Multidimensional Assessment of Thymic States (MATHYS) (Henry et al., 2008) provides two scores, a total score measuring a level of activation and a sub-score of emotional reactivity. The aim of this study was to establish the appropriate cut-off in total activation versus inhibition and in the emotional reactivity sub-score in bipolar disorders. Patients ($n=187$) during an acute episode and controls ($n=89$) filled in the MATHYS. Receiver Operating Characteristic (ROC) curves were obtained to estimate the sensitivity and specificity of the global score and the emotional reactivity sub-score of the MATHYS, in order to differentiate patients from controls. ROC curves showed very satisfactory sensitivity and specificity levels both for the total score and the sub-score of emotional reactivity, thus providing an appropriate cut-off. Concerning the total score between 0 and 200, patients with a score lower than 91 had significant global inhibition and those with a score higher than 109 had significant global activation. Regarding the emotional reactivity sub-score between 0 and 40, patients with a score lower than 16 had significant emotional hyporeactivity and those with a score higher than 24 had significant emotional hyperreactivity. Our results provide cut-offs for the MATHYS to identify patients in an acute phase.

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1. Introduction

Bipolar disorders are characterized by their wide clinical heterogeneity. Beyond the classical depressed, manic, hypomanic and mixed episodes defined by the Diagnostic and Statistical Manual of Mental Disorders-IV Edition-Text Revision (DSM-IV-TR) (American Psychiatric Association (APA), 2000), many authors have described a broad spectrum of mixed states ranging from depressive episodes associated with fewer than four manic symptoms to manic or hypomanic episodes associated with depressive symptoms. This heterogeneity has led investigators to propose syndromes such as agitated depression (Koukopoulos and Koukopoulos, 1999), depressive mixed states (Benazzi and Akiskal, 2006), mixed depression

(Sato et al., 2005), irritable-hostile depression (Benazzi and Akiskal, 2005) and depression with activation (Henry et al., 2010; Henry et al., 2007a,b). Concomitant manic symptoms are common in bipolar patients with depression, and occur in more than half of them according to Goldberg et al. (2009). Other studies have shown that many hypomanic or manic episodes are neither pure nor mixed states but that they include depressive symptoms (Bauer et al., 1994). For example, syndromes such as mixed hypomania (Suppes et al., 2005) and dysphoric hypomania (Akiskal and Benazzi, 2005) have been identified. Goldberg suggests that clarifying the nature of pure versus mixed bipolar depression is essential for prognostic assessment, pharmacotherapy decisions and nosologic implications.

The DSM-5 defines a generic specifier for mixed episodes. The main proposition is that "mixed state" should disappear as a syndrome by itself and be replaced by a mixed specifier. This mixed specifier characterizes "episodes where sub-threshold symptoms from the opposing pole are present during a full mood

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episode (i.e., depressive symptoms during hypo/manic episodes and vice versa)" (http://www.dsm5.org/ProposedRevisions/). Thus, the DSM-5 accepts the idea that major depressive episode can occur with or without mixed features. Similarly, hypomanic episodes may occur with or without mixed features. Moreover the DSM-5 proposes that the level of energy should be taken into account to define manic and hypomanic episodes. Indeed, patients with a mild exalted episode do not have good insight into their elevated mood (Angst et al., 2010). This new conception seems particularly relevant for clarifying the management of the disorder. Clinical investigations would therefore include mixed for all types of clinical features, which implies the need to develop an adapted methodology with tools taking into account this specificity.

To better describe the heterogeneity of symptoms in mood disorders, we proposed the Multidimensional Assessment of Thymic States (MATHYS), a scale assessing the multidimensionality of thymic states (Henry et al., 2008). The scale allows mood states to be defined by assessing symptoms on their quantitative aspects (acceleration/retardation; increase/decrease) (see Section 2 for more details). The MATHYS has been previously validated on a sample of controls and bipolar patients in various states (euthymic, manic or depressed). We have previously shown that providing a score for the inhibition/activation process and a score for emotional reactivity is clearly useful for distinguishing bipolar depressive episodes without manic symptoms from those with manic symptoms (Henry et al., 2010; Henry and Etain, 2010).

However, there is a need to identify and propose an appropriate cut-off for the purposes of clinical practice. It is useful to be able to distinguish significant global inhibition and significant global activation from the basic levels and emotional hyporeactivity and emotional hyperreactivity from basic emotional reactivity.

This study sought to identify the appropriate cut-off in global activation versus inhibition and in the emotional reactivity dimension in bipolar disorders using the MATHYS (Henry et al., 2008) by comparing acute phase bipolar patients to controls.

2. Methods

2.1. Participants and setting

A total sample of 278 participants was recruited including control subjects and bipolar patients. Control subjects were recruited through advertisements. Bipolar patients were in- and out-patients recruited in a setting specialized in bipolar consultations or patients hospitalized in a department corresponding to the catchment area of Bordeaux (France). Among participants, a part is common with the previous sample used for the validation of the MATHYS scale. For this study, we have included new participants. All bipolar patients were in an acute episode and were compared to a group of control subjects.

Two individuals, one control and one mixed bipolar patient, were excluded because they failed to answer two or more items on the MATHYS questionnaire, so the remaining 276 participants were included in the subsequent analyses. The study was conducted in accordance with international guidelines for good clinical practice. All participants provided written informed consent.

2.2. Measures

All participants were interviewed using the French version (Preisig et al., 1999) of the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) providing lifetime *DSM-I* axis I diagnoses (American Psychiatric Association (APA), 2010).

As there was no clinical tool to assess all bipolar mood states dimensionally, we developed and validated a dimensional self-rated scale: the Multidimensional Assessment of Thymic States (MATHYS). This scale was built a priori with five relevant quantitative dimensions, which vary from inhibition to activation. The goal was to generate a total score indicative of the overall level of inhibition/activation. Thus, classic dimensions such as cognition, motivation, psychomotor agitation or retardation and sensory perception, were assessed quantitatively (i.e., racing thoughts or subjectively feeling that one's thoughts occur more slowly,

physical agitation or retardation, and increase or decrease in sense perception) (Example: My brain never stops/My brain seems to be functioning in slow motion). We applied a similar concept to evaluate emotion, focusing only on the quantitative aspect (i.e., whether the patient felt emotion with normal intensity, greater intensity, or less intensity) (Example: My emotions are very intense/My emotions are not very strong).

The concept behind this scale involved exploring all bipolar mood states on a continuum using a score for inhibition/activation and exploring emotional reactivity rather than tonality of affect (euphoria/sadness). The scale is composed of a visual analog scale comprising 20 items related to how the individual feels during the previous week. Statistical analyses demonstrated a good validity for this scale and a good internal consistency (Cronbach's alpha coefficient=0.95). The MATHYS is moderately correlated with both the MADRS scale (depressive score; $r=-0.45$) and the MAS scale (manic score; $r=0.56$).

It gives a total score assessing the activation/inhibition level and a score for emotional reactivity (hyper/hyporeactivity) (the English version of the scale can be found by following this link: [http://www.biomedcentral.com/content/supplementary/1471-244X-8-82-S1.doc]) (Henry et al., 2008). The total score is based on all 20 items while the emotional score aggregates data of four items (items 3, 7, 10 and 18). We have previously shown that the MATHYS demonstrated good psychometric properties, included face validity (Henry et al., 2007a,b).

2.3. Data analysis

Analyses were performed using the SPSS®14 statistical package and the ROCR package (Sing et al., 2005) implemented in R (R Development Core Team, 2008). Data were initially screened for missing values and outliers. There were few missing values and no outlier was detected using Cook and Mahalanobis distances. Means between controls and patients were compared using one-way analysis of variance.

Receiver Operating Characteristic (ROC) curves were obtained for the total sample. The ROC curve method is a graphical technique that is usually used to estimate the accuracy of a prediction model, making it possible to determine sensitivity and specificity according to all the threshold values a test may have (Obuchowski, 2003; Vining and Gladish, 1992). Test accuracy in terms of discriminating power is given by a simple quantitative indicator, which is the area under the curve (AUC). This indicator can have any value between 0.5 and 1 (from discriminating power "not by chance" to perfect discriminating power). An AUC greater than 0.9 indicates that the test is highly discriminating (Greiner et al., 2000; Streiner and Cairney, 2007).

3. Results

3.1. Final sample

The final sample consisted of 276 participants including 89 controls (Ctl.) and 187 bipolar patients. The latter comprised patients with pure major depressive disorder (EDM, $n=114$), patients with a mixed state (MS, $n=21$) and manic bipolar patients (Ma, $n=52$). The sample was composed of 185 (67%) women and 91 (33%) men, with a mean age at interview of 39.18 (S.D. 13.16) years. There was no difference between control and patients on age, $t_{158.1}=-1.27$, $P=0.21$, $d=0.90$, 95% CI [−5.6, 1.25][1] or on gender, χ^2 (1, $N=276$)=0.21, $P=0.65$. Controls and patients differed significantly on each score of the MATHYS. On the total score, controls had a significantly lower mean score (5.5, S.D. 7.6) than patients (33.6, S.D. 23.6), $F(1, 266)=119.1$, $P<0.001$, $\eta^2=0.31$. The same was true for the emotional reactivity score, where controls had a significantly lower mean score (2.05, S.D. 2.40) than patients (11.67, S.D. 5.46), $F(1, 270)=251.7$, $P<0.001$, $\eta^2=0.48$.

3.2. ROC curve analyses

3.2.1. Sensitivity and specificity for selected MATHYS threshold

The best tradeoff between sensitivity and specificity gave a threshold value for the total score of 9.25/9.75, yielding a sensitivity ranging from 0.82 to 0.85 (meaning that 82–85% of

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[1] Degrees of freedom for the independent samples *t*-tests were corrected for unequal variances based on Levene's test for equality of variances.