Activation levels, cardiovascular risk and functional impairment in remitted bipolar patients: Clinical relevance of a dimensional approach

- Supplementary methods and results –

Method

Participants

A total of 979 BD outpatients aged between 18-65 years were recruited from 1300 outpatients evaluated in the French Network of FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) from January 2010 to June 2015. This Network integrates research and clinical practice into community-based outpatient psychiatric care centers in France [1]. Primary diagnosis was confirmed by psychiatrists using DSM-IV Axis I Disorders (SCID) [2]. Eligible patients had diagnosed BD type I, II or Not Otherwise Specified (NOS); had no major mood episode according to DSM-IV criteria within the past 3 months; had a score ≤ 15 on the Montgomery–Åsberg Depression Rating Scale (MADRS) [3] and a score ≤ 8 on the Young Mania Rating Scale (YMRS) [4]. Of the 1300 BD patients evaluated, 321 patients were excluded on account of not being in remission and/or having medical comorbidities, including autoimmune diseases, inflammatory bowel diseases, hepatic illness, cancer or other known conditions with peripheral inflammation, or not having results for selected biomarkers, including systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, and high sensitivity C-reactive protein (hsCRP) [5] levels available. The Human Research Ethics Committee, CPP-Ile de France IX, approved the study and all participants received an information letter about this study.

Assessments

Severity of depressive and manic symptoms at the time of the assessment was evaluated using MADRS and YMRS, respectively. Anxiety symptoms were assessed by the State-Trait Anxiety Inventory (STAI) – a 20-item instrument rated on a 4-point scale, ranging from almost

never to almost always, with higher scores indicating greater anxiety [6]. Overall functioning was evaluated using the Functioning Assessment Short Test (FAST), which encompasses 24 items to evaluate six functional domains: autonomy, occupational functioning, financial issues, interpersonal relationships, leisure time, and cognitive functioning. Items are rated using a four-point scale from 0 (no difficulty) to 3 (severe difficulty). FAST scores range from 0 to 72, and higher scores indicate poorer functioning and greater disability [7]. A questionnaire detailing self-reported comorbidities, lifestyle and medication use was also administered to all participants.

Activation levels

Levels of activation were measured using the Multidimensional Assessment of Thymic States (MAThyS), a 20-item self-rated scale that assesses levels of activation uncoupled from mood during the preceding week. It evaluates quantitatively five dimensions, including emotional reactivity, sensory-perception, psychomotor activity, motivation and cognition, each of which can vary from hypo-activation to hyper-activation. Items are rated using a continuous scale ranging from 0 to 10, taking into account the intensity of emotions and the environmental context (for example: “My emotions are very intense/My emotions are attenuated”) [8]. Considering that the five dimensions are composed by different number of items, we divided the score of each dimension by its number of constituent items in order to standardize the data for further comparisons. The MAThyS score ranges from 0 to 200: scores <92 indicate hypo-activation/behavior inhibition, 92-108 = normal activation, and scores >108 indicate hyper-activation/behavior activation, across mood states. The MAThyS has good validity and internal consistency (Cronbach’s alpha coefficient=0.95)

Biological markers and anthropomorphic measurements

A fasting blood sample was taken from all patients between 7:00 and 9:00 a.m., and hsCRP and fasting glucose levels were measured. Blood samples were centrifuged at 2016 g

for 15 min, and serum was collected and stored at 80°C. Patients' height and weight were measured and used to calculate adjusted body mass index (BMI, kg/m2). Blood pressure was assessed after 10 min rest period and before the psychiatric assessment.

Statistical analysis

The results of participant's assessment for dimensions of behavior (emotional reactivity, sensory-perception, psychomotor activity, motivation and cognition) were used to perform K-means cluster analysis in order to identify subgroups based on activation levels. We selected the standard global partitioning method, K-means, over other clustering methods because K-means is an iterative cluster approach, which allows movement of subjects among clusters, thus constructing a more stable cluster solution, and the solution for more clusters is not constrained by solutions with less clusters. Cluster centers were plotted from 10 000 repeated subsamples to assess robustness of the clustering solution [10]. Missing data (approx. 3%) was imputed using factorial analysis for mixed data. The optimal number of clusters was determined by silhouette method [11]. This approach measures the quality of a clustering by determining how well each individual lies within its cluster. A high average silhouette width indicates a good clustering. The optimal number of clusters was obtained by maximizing the average silhouette over a set of numbers of clusters.

Comparisons of clinical and biological variables between clusters were performed using analysis of variance (ANOVA) adjusted for age, gender, mood symptoms, BMI and smoking status or chi-squared tests. Post-hoc Wald tests with Benjamini-Hochberg correction were conducted to examine pairwise relationships between clusters. For all statistical analysis, a p value ≤ 0.005 was considered statistically significant. All analyses were performed using R packages factoextra (v1.0.5) and missMDA (v1.11).

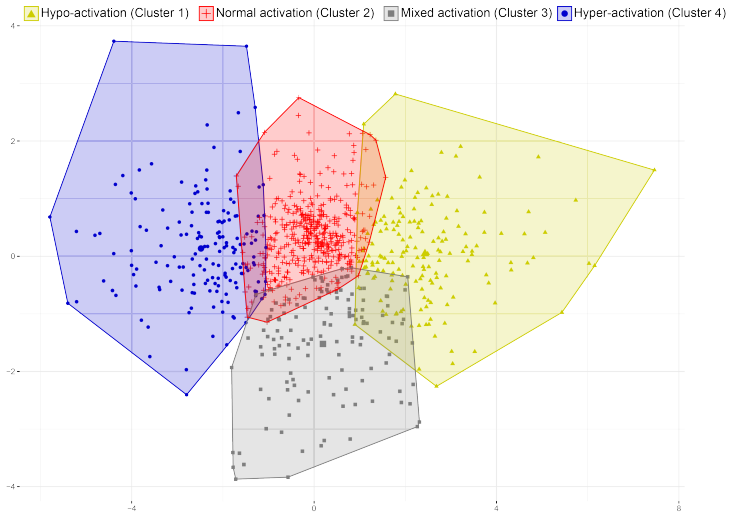
Results

Of the 979 remitted BD patients included in the study, 582 (59.4%) were female and the mean age was 41.2 (SD=12.4) years. Fifty percent of patients were diagnosed with BD type I, 34.5% with BD type II and 15.6% with BD NOS (Table S1).

Cluster analysis

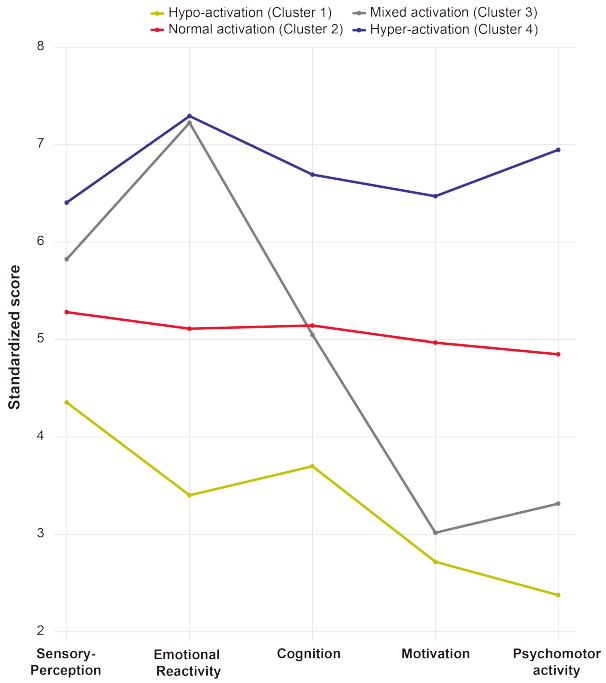
The cluster analysis using the five dimensions of the MAThyS (emotional reactivity, sensory-perception, psychomotor activity, motivation and cognition) found a four-cluster solution to be most stable, thus identifying four clusters of patients characterized by different levels of activation (Figure S1). The four-cluster solution was therefore retained for all subsequent analyses.

Figure S1: Agglomeration of patients using the four clusters emerging from the k-means cluster analysis



The five dimensions vary in different directions across the four clusters. In Cluster (C) 1, all dimensions are hypo-activated, in C2 they are in the range of normal activation, and in the C4 BD all dimensions are hyper-activated. In C3 however, there is divergence in the way the dimensions vary - emotional reactivity and sensory-perception follow the same pattern as hyper-activation, while motivation and psychomotor activity are hypo-activated (Figure S2).

Figure S2: Activation levels across clusters based on five dimensions of behavior



Demographic and further clinical characteristics of clusters are presented in Table S1. There were no significant differences between the four clusters with respect to age, age at BD onset, illness duration, and total number of previous mood episodes.

In terms of type of BD by cluster, the proportion of patients with BD type II was higher in the C4 (hyper-activation). Patients with abnormal levels of activation presented higher levels of subsyndromal mood symptoms compared to patients with normal activation. C1 (hypo-activation) had higher depressive/anxiety subsyndromal symptoms, while patients with hyper-activation had increased levels of hypomanic symptoms. Compared to C2 (normal activation), C3 (mixed activation) had significantly higher MADRS, YMRS, and STAI scores ($p<0.0001$) and greater number of suicide attempts ($p<0.0001$). In terms of medication, patients with increased levels of activation (C3 and C4) were more likely to receive antidepressants, and the proportion of patients receiving lithium was higher in C2 (normal activation).

Table S1. Demographic and clinical characteristics of 979 remitted bipolar patients with different levels of activation.

Variables	Hypo-activation (n = 170)	Normal activation (n = 503)	Mixed activation (n = 141)	Hyper-activation (n = 165)	F/χ2	p	p adjusted
Male, n (%)	73 (42.9)	215 (42.7)	42 (29.8)	67 (40.6)	8.183	0.042	0.132
Age, years mean (SD)	42.08 (12.37)	41.62 (13.22)	40.15 (11.77)	39.72 (13.39)	1.474	0.220	0.385
Education, mean (SD)	16.89 (2.79)	16.84 (2.84)	16.58 (2.85)	16.43 (2.93)	1.170	0.320	0.426
Occupation, n (%)							
Unemployed	38 (22.4)	98 (19.5)	25 (17.7)	33 (20.0)	1.113	0.774	0.833
Marital status, n (%)					8.558	0.200	0.373
Married	99 (58.2)	287 (57.1)	76 (53.9)	81 (49.1)			
Type BD, n (%)					36.171	**<0.0001**	**<0.0001**
BD Type I	85 (50.0)	288 (57.3)	63 (44.7)	52 (31.5)			
BD Type II	58 (34.1)	145 (28.8)	58 (41.1)	77 (46.7)			
BD Type NOS	27 (15.9)	70 (13.9)	20 (14.2)	36 (21.8)			
Age at onset, mean (SD)	25.26 (9.57)	25.19 (10.28)	24.59 (9.14)	23.01 (9.02)	2.238	0.082	0.177
Illness duration, mean (SD)	16.39 (10.91)	16.21 (11.36)	15.57 (9.87)	16.53 (11.73)	0.215	0.886	0.893
Number episodes, mean (SD)	6.50 (5.53)	6.41 (5.29)	6.77 (5.65)	6.67 (5.92)	0.204	0.893	0.893
Number of hospitalizations, mean (SD)	2.81 (3.60)	2.95 (2.90)	3.30 (3.56)	2.37 (2.48)	2.494	0.059	0.137
Number of suicide attempts, mean (SD)	1.43 (2.30)	1.29 (1.64)	2.35 (2.14)	2.09 (2.04)	15.772	**<0.0001**	**<0.0001**
Rapid cycling, n (%)	15 (8.8)	52 (10.3)	16 (11.3)	24 (14.5)	3.197	0.362	0.457
MADRS score, mean (SD)	9.27 (4.32)	3.99 (3.70)	8.91 (4.09)	6.30 (4.62)	103.560	**<0.0001**	**<0.0001**
YMRS score, mean (SD)	1.17 (1.86)	1.23 (1.92)	1.69 (2.29)	3.55 (2.88)	51.935	**<0.0001**	**<0.0001**
STAI score, mean (SD)	45.92 (13.48)	33.93 (11.34)	45.22 (14.05)	40.01 (14.09)	55.603	**<0.0001**	**<0.0001**
MAThyS total score, mean (SD)	69.16 (10.34)	99.28 (7.68)	102.14 (13.04)	134.69 (15.01)	101.768	**<0.0001**	**<0.0001**
MAThyS emotional reactivity	13.60 (5.55)	20.44 (3.60)	28.90 (4.28)	29.17 (4.28)	75.603	**<0.0001**	**<0.0001**
MAThyS sensory-perception	21.77 (6.05)	26.40 (3.51)	29.12 (6.81)	32.03 (5.27)	65.130	**<0.0001**	**<0.0001**
MAThyS psychomotor activity	7.13 (3.65)	14.54 (2.58)	9.94 (4.36)	20.84 (5.17)	55.603	**<0.0001**	**<0.0001**
MAThyS motivation, mean (SD)	10.87 (4.97)	19.87 (2.89)	12.06 (5.10)	25.88 (5.18)	59.398	**<0.0001**	**<0.0001**
MAThyS cognition, mean (SD)	14.79 (5.76)	20.57 (2.76)	20.20 (5.37)	26.77 (4.37)	56.603	**<0.0001**	**<0.0001**
Comorbidities, n (%)							
Anxiety disorders	68 (40.0)	185 (36.8)	81 (57.4)	77 (46.7)	21.195	**<0.0001**	**<0.0001**
Substance use disorders	50 (29.4)	142 (28.2)	37 (26.2)	57 (34.5)	3.109	0.375	0.457
Current smoking, n (%)	94 (55.3)	287 (57.1)	82 (58.2)	75 (45.5)	7.506	0.057	0.137
Body mass index (kg/m^2), mean (SD)	26.03 (4.63)	25.30 (4.49)	26.27 (5.19)	25.21 (4.28)	2.550	0.054	0.125
Medications, n (%)							
Anticonvulsants	59 (34.7)	160 (31.8)	45 (31.9)	59 (35.8)	1.189	0.756	0.833
Antidepressants	37 (21.8)	96 (19.1)	33 (23.4)	42 (25.5)	3.570	0.312	0.426
Antipsychotics	25 (14.7)	86 (17.1)	16 (11.3)	17 (10.3)	6.110	0.106	0.213
Benzodiazepine	17 (10.0)	74 (14.7)	23 (16.3)	27 (16.4)	3.644	0.303	0.426
Lithium	30 (17.6)	105 (20.9)	26 (18.4)	23 (13.9)	4.133	0.247	0.408

C: cluster; FAST: Functioning Assessment Short Test; MAThyS, Multidimensional Assessment of Thymic States; MADRS, Montgomery–Asberg Depression Rating Scale; STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale; p adjusted for age, gender, mood symptoms, body mass index, and smoking status with Benjamini-Hochberg's

BD patients presenting similar levels of subsyndromal mood symptoms measured by classical mood assessments had significantly different levels of activation, ranging from global hypo-activation to hyper-activation, cardiovascular and suicide risk, and functional impairment.

Although all BD patients were in remission, as defined by the categorical, symptom-based approach for criteria of remission [12], about half of them presented subclinical symptoms and abnormal levels of activation, which were characterized mainly by emotional dysregulation, altered sensory-perception, and abnormal psychomotor activity, as well as differences in the number of suicide attempts. When considering these results, it is important to note that the classical symptom-based tools MADRS and the YMRS were not always able to distinguish these patients with different levels of activation. That is, our results indicate that there is heterogeneity in clinical profiles among patients with similar scores using these mood rating scales currently used in clinical practice. In contrast, assessment of dimensions of behavior, including emotional reactivity, sensory-perception, and psychomotor activity, motivation and cognition using the MAThyS tool appear to have greater discriminative ability than the categorical mood-based scales.

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