



## The role of overlapping excitatory symptoms in major depression: are they relevant for the diagnosis of mixed state?

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### ABSTRACT

**Background:** DSM-5 and ICD-11 define mixed depression as the presence of non-overlapping symptoms of opposite polarity during a major depressive episode. However, such a definition has generated controversy.

**Methods:** 2720 patients with major depression, enrolled in BRIDGE–II–MIX cross-sectional study, were subdivided in clusters using a k-medoids algorithm based on 32 clinical features. Clinical variables were compared among clusters. Stepwise logistic regression and random forest predictor importance estimates were used to identify which features best predicted cluster membership. Data-driven criteria were compared with DSM-5 mixed specifier and previously proposed research-based criteria (RBDC).

**Results:** Two clusters were identified (MDE ± MX), mainly reflecting differences in current manic symptoms. As expected, MDE + MX showed higher rates of comorbidities and bipolar features, more previous depressive episodes and suicide attempts, shorter duration of current MDE and lower age at onset. Seven clinical features among the original 32 proved to be the best predictors of cluster membership. Derived criteria perfectly allocated subjects in clusters, requiring at least four features out of the following seven: irritability, emotional lability, psychomotor agitation, distractibility, mood reactivity, absence of reduced appetite, and absence of psychomotor retardation. RBDC showed a better performance than DSM-5 in identifying MDE + MX subjects.

**Conclusion:** Our results strongly suggest a predominant role for overlapping “manic” symptoms in defining mixed depressive states. Mixed depression is better identified by the presence of excitatory features shared with mania and atypical features rather than by non-overlapping manic symptoms.

### 1. Introduction

Mixed state was first defined by Emil Kraepelin as the core feature of manic-depressive illness, in which the coexistence of symptoms of opposite polarity were hypothetically explained by a dyssynchrony between patterns of change in the three areas of psychic function, namely mood, thought, and volition. Two major mixed states were described as fundamentally depressive in the final categorization presented within the eighth edition of Kraepelin's textbook (1913): excited or agitated depression, where hyperactivity replaces abulia, and depression with flight of ideas, which replaces poverty of thoughts. Interestingly, a depressive mood is not sufficient, according to Kraepelin, to define depression, as a combination of flight of ideas, hyperactivity and depressive mood is actually labelled depressive or anxious mania (Kraepelin, 1913).

When looking at current nosography, the scenery has radically changed. According to both DSM-5 (American Psychiatric Association, 2013) and ICD-11 (World Health Organization, 2018), psychomotor agitation should be, counter-intuitively, subsumed into the depressive symptomatologic domain. Consequently, DSM-5 criteria for mixed features specifier, which require the inclusion of at least three non-overlapping symptoms of the opposite polarity in depressive episode, exclude psychomotor agitation from the criteria. Similarly, irritable mood, distractibility and emotional lability have been excluded, despite being among the most frequent manic symptoms during depression (Goldberg et al., 2009; Maj et al., 2006; Perugi et al., 2015; Sato et al., 2003). This solution has been little criticized despite being not sensitive enough, nor evidence-based and for misrepresenting the clinical entity which it aims to define (Koukopoulos and Sani, 2014). Indeed, some authors have provided more inclusive criteria, allowing for overlapping

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symptoms to be represented (Kim et al., 2016; Perugi et al., 2015; Sani et al., 2014) and new non-DSM-based diagnostic instruments (Henry et al., 2013; Sani et al., 2018).

For its part, ICD-11, though recognizing the high prevalence of symptoms such as irritability and psychomotor agitation during mixed states, still defines mixed episodes based on the simultaneous occurrence or the rapid alternation of manic and depressive symptoms (American Psychiatric Association, 2013). This solution strictly follows the same combinatory model presented in DSM-5 and has been criticized as redundant and not original (Perugi, 2019).

The objective of the Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE-II-MIX) naturalistic study was to provide a reliable estimate of the frequency of mixed features in a large international sample of patients diagnosed with major depressive episode (MDE) according to several sets of criteria (Perugi et al., 2015). In our re-analysis of BRIDGE-II-MIX data, we aim to identify mixed patients using an unsupervised learning method, not requiring *a priori* criteria. This approach not only allows us to compare performances of DSM-5 mixed specifier criteria and the research-based diagnostic criteria previously proposed, but also enables new completely data-driven criteria which define a clinically homogenous subgroup of patients to be identified.

## 2. Methods

### 2.1. Participants

The BRIDGE-II-MIX study was a multinational (involving eight countries in three continents, i.e., Egypt and Morocco for Africa, Bulgaria, the Netherlands, Portugal, and Spain for Europe, and Russia and Turkey for both Asia and Europe), naturalistic (noninterventive), cross-sectional diagnostic enterprise conducted in 239 hospital-based or community centres by one psychiatrist for each. From the 239 psychiatrists involved in the study, 237 returned their site questionnaires. From June 2009 to July 2010, each centre enrolled for three consecutive months 10–20 consecutive adult patients (aged  $\geq 18$  years) who sought help for a DSM-IV-TR major depressive episode (MDE) in three-month periods. A structured case report was completed for each patient, including, among others, sociodemographic variables, MDE criteria, features of the current depressive episode, history of psychiatric symptoms, previous psychiatric hospitalizations, previous response to antidepressants, psychiatric comorbidity. The study was conducted according to the Declaration of Human Rights, as adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequently amended by the 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; (<http://www.wma.net>); the Good Epidemiology Practice and the International Epidemiologic Association (IEA) European Federation Guidelines (<http://ieaweb.org>) were followed. Written, informed consent was obtained from each patient. In each country, the protocol was approved by local ethical committees.

In the present study, we performed a post hoc analysis including 2720 subjects out of the 2811 patients included in the original dataset. 91 subjects were excluded due to missing data needed for clustering procedures. For major details, data collection was previously described in the original paper (Perugi et al., 2015).

### 2.2. Statistical analysis

#### 2.2.1. Clustering

A k-medoids clustering algorithm using the Hamming distance measure was performed in Matlab R2018b, based on the presence or absence of each of the 32 clinical features of current MDE listed in Table 1, in order to identify clinically homogenous subgroups of patients in an unsupervised manner. K-medoids clustering is a partitioning method used to divide a set of measurements into k subsets or clusters

so that the subsets minimize the sum of distances between each measurement and the centre of its cluster. In the k-medoids algorithm, the centre is a real member of the cluster, called a medoid. Medoids could thus be interpreted as prototypes of subjects included in a cluster. Partitioning around medoids (PAM) algorithm was used to find medoids.

The number of clusters was determined as  $k = 2$  using the silhouette criterion comparing the two-to eight-cluster solutions. The two-cluster solution was also found to be the best one according to Davies-Bouldin and Calinski-Harabasz criteria. To avoid local minima, 100 algorithm reiterations were performed.

#### 2.2.2. Clusters characterization

Differences between clusters in gender, clinical features, comorbidities according to DSM-IV-TR and bipolar features were assessed using chi-squared test. Comorbidities included in the analysis were obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, anorexia, bulimia, binge-eating disorder, ADHD, and borderline personality disorder. Bipolar features included bipolar disorder diagnosis according to DSM-IV-TR criteria (history of manic/hypomanic episode), bipolarity specifier proposed by Angst et al. (2013, 2011), history of manic/hypomanic switches under antidepressant treatment, and hypomania/mania or bipolar disorder among first degree relatives (parents, siblings, children). Bipolarity specifier differ from DSM-5 criteria in that: 1) it requires a period of elevated mood or irritable mood OR (not and) increased activity; 2) no minimum duration is required 3) it requires at least three symptoms under criterion B when mood is irritable (instead of four required by DSM-5); 4) it requires one out of three negative consequences (unequivocal and observable change in functioning, marked observable social or occupational impairment, requiring hospitalization or outpatient treatment); 5) it does not apply the exclusion criteria D for manic and F for hypomanic episodes (not due to the direct physiological effects of a substance or a general medical condition). Data concerning psychotic features for the diagnosis of previous manic episodes according to DSM-5 were not collected.

Wilcoxon rank sum tests was used to assess differences in age, age at first depressive diagnosis, duration of current episode, number of previous depressive episodes, number of lifetime suicide attempts, and number of previous hospitalizations, after normality was excluded for each variable using Kolmogorov-Smirnov test. Statistical significance level was settled at a Bonferroni-corrected level of  $P < 0.00098$  for both categorical and continuous variables comparisons. To assess whether differences in current age could be confounded by differences in age at first diagnosis of MDE, a logistic regression model was developed using cluster as response variable and age and age at first diagnosis as predictors.

#### 2.2.3. Cluster membership predictors

To identify which of the 32 clinical features used in the clustering algorithm better predicted which cluster each subject belonged to, two different strategies were developed. First, a stepwise logistic regression model using cluster label as response variable and the 32 clinical features as possible predictors was designed. Terms were added to the model if the p-value of chi-squared statistic of the change in deviance after each term was added was smaller than 0.001. Secondly, a random forest of 200 regression trees using the 32 clinical features as possible predictors was trained. To grow unbiased trees, the curvature test was used for splitting predictors, selecting the split predictor that minimizes the p-value of chi-square tests of independence between each predictor and the response. Thereafter, estimate predictor importance was measured by permuting out-of-bag observations. Best predictors were selected as those features preceding the greatest gap between estimate importance values sorted in descending order.

### 2.2.4. Criteria comparison

Based on the results, data-driven diagnostic criteria (DDC) distinguishing clusters were formulated and a cut-off was identified computing Receiver Operating Characteristic (ROC) curve. ROC curve was also computed to verify if previously proposed cut-off of three for a *priori* research-based diagnostic criteria (RBDC) for mixed states (Perugi et al., 2015) and DSM-5 cut-off of three for mixed features specifier were the optimal cut-offs to distinguish between the two clusters. Thereafter, DSM-5 criteria for mixed features specifier, RBDC and DDC were used to subdivide subjects and their performance in identifying cluster membership were tested computing sensitivity, specificity, positive and negative predictive values. Data concerning DSM-5 mixed specifier criterion seven, “decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted to insomnia)”, were not available due to data collection before DSM-5 publication. In its place, we used a more inclusive criterion consisting of absence of both insomnia and hypersomnia. Thus, we will refer to DSM-5 adapted criteria shown in Table 3.

## 3. Results

### 3.1. Clusters characteristics

Two clusters were identified based on the k-medoids clustering algorithm. Clusters did not differ for gender distribution (chi-squared = 3.2;  $p = 0.07$ ). Since symptomatologic features differences (Table 1) mainly involved current manic symptoms, we will refer to the first cluster ( $N = 2029$ , 75%) as MDEs without mixed features (MDE-MX), to the second cluster ( $N = 691$ , 25%) as MDEs with mixed features (MDE + MX). In order of effect size, MDE + MX significantly more frequently presented with irritable mood, emotional lability,

psychomotor agitation, distractibility, impulsivity, racing thoughts, increased talkativeness, aggression, mood reactivity, hyperactivity, risky behaviour, increased energy, elation, grandiosity, hypersexuality, and hyperphagia, but, interestingly, also with psychotic features, thoughts of death or suicidal ideation/attempts, panic attacks, anxiety, and memory problems. Conversely, MDE-MX showed significantly more frequently psychomotor retardation, reduced appetite, hyposexuality, and fatigue or loss of energy.

Both MDE + MX and MDE-MX clusters medoids, which actually represent the prototypical patient of each cluster, presented depressed mood, diminished interest or pleasure, fatigue or loss of energy, feelings of worthlessness/guilt, diminished ability to think or concentrate, insomnia, hyposexuality, anxiety and memory problems. The MDE-MX medoid also showed psychomotor retardation and reduced appetite. The MDE + MX medoid, instead, presented psychomotor agitation, irritable mood, emotional lability, distractibility and mood reactivity.

When looking at comorbidities, MDE + MX group interestingly showed a significantly increased rate of borderline personality, generalized anxiety, binge-eating, panic, bulimia, and social anxiety disorders (Table 2). MDE + MX cluster also showed significantly greater rates of bipolar disorder diagnosis according to DSM-5 criteria, bipolarity specifier (Angst et al., 2013, 2011), history of manic/hypomanic switches under antidepressant treatment, and bipolar disorder among first degree relatives (Table 2). Notably, bipolarity specifier had the greatest effect size, thus being the best discriminant between clusters among bipolar features, while diagnosis of bipolar disorder according to DSM-5 showed the lowest effect size.

The two clusters also significantly differed for age, age at first depressive diagnosis, duration of current episode, number of previous depressive episodes, and number of lifetime suicide attempts (Table 2). While MDE + MX cluster presented with significantly shorter duration

**Table 1**

Differences in symptoms distribution between clusters (MDE ± MX). Clustering algorithm was based on symptoms listed in the first column.

Symptoms	MDE + MX (N = 691)		MDE-MX (N = 2029)		OR	LI	UI
	N	%	N	%			
Depressed mood	685	99.1	2014	99.3	0.85	0.33	2.20
Diminished interest or pleasure	670	97.0	1949	96.1	1.31	0.80	2.13
Fatigue or loss of energy*	631	91.3	1930	95.1	0.54	0.39	0.75
Feelings of worthlessness/guilt	506	73.2	1359	67.0	1.35	1.11	1.63
Diminished ability to think or concentrate	627	90.7	1813	89.4	1.17	0.87	1.57
Thoughts of death or suicidal ideation/attempts*	309	44.7	683	33.7	1.59	1.34	1.90
Psychomotor agitation*	377	54.6	61	3.0	38.74	28.82	52.06
Psychomotor retardation*	174	25.2	1453	71.6	0.13	0.11	0.16
Hypersomnia	128	18.5	310	15.3	1.26	1.00	1.58
Insomnia	496	71.8	1440	71.0	1.04	0.86	1.26
Hyperphagia*	173	25.0	221	10.9	2.73	2.19	3.41
Reduced appetite*	300	43.4	1333	65.7	0.40	0.34	0.48
Hypersexuality*	54	7.8	18	0.9	9.47	5.51	16.27
Hyposexuality*	373	54.0	1351	66.6	0.59	0.49	0.70
Irritable mood*	599	86.7	291	14.3	38.89	30.22	50.04
Racing thoughts*	238	34.4	80	3.9	12.80	9.74	16.82
Emotional/mood lability*	551	79.7	259	12.8	26.90	21.44	33.74
More talkative/pressure to keep talking*	232	33.6	78	3.8	12.64	9.59	16.66
Distractibility*	466	67.4	197	9.7	19.26	15.51	23.92
Increased energy*	129	18.7	48	2.4	9.47	6.71	13.37
Aggression*	264	38.2	124	6.1	9.50	7.49	12.05
Hyperactivity*	163	23.6	53	2.6	11.51	8.32	15.92
Grandiosity*	80	11.6	22	1.1	11.94	7.39	19.31
Elation*	94	13.6	32	1.6	9.83	6.51	14.83
Impulsivity*	283	41.0	110	5.4	12.10	9.47	15.46
Risky behaviour*	146	21.1	53	2.6	9.99	7.19	13.87
Lead paralysis	203	29.4	516	25.4	1.22	1.01	1.48
Psychotic features*	91	13.2	133	6.6	2.16	1.63	2.87
Mood reactivity*	507	73.4	639	31.5	5.99	4.94	7.27
Anxiety*	583	84.4	1566	77.2	1.60	1.27	2.01
Panic attacks*	142	20.5	283	13.9	1.60	1.28	1.99
Memory problems*	464	67.1	1204	59.3	1.40	1.17	1.68

\*Bonferroni-corrected significant differences ( $p < 0.00098$ ).

**Table 2**

Differences in comorbidity and other demographic and clinical variables between the clusters (MDE ± MX) Odds ratios are presented for categorical and z-stat for dimensional variables.

Comorbid condition (according to DSM-IV-TR)	MDE + MX (N = 691)		MDE-MX (N = 2029)		95% CI		
	N	%	N	%	OR	LI	UI
Panic attack disorder*	103	14.9	176	8.7	1.84	1.42	2.39
Obsessive-compulsive disorder	47	6.8	88	4.3	1.61	1.12	2.32
Social anxiety disorder*	73	10.6	136	6.7	1.64	1.22	2.22
Generalized anxiety disorder*	213	30.8	273	13.5	2.87	2.33	3.52
Anorexia	49	7.1	86	4.2	1.72	1.20	2.48
Bulimia*	23	3.3	26	1.3	2.65	1.50	4.68
Binge-eating disorder*	35	5.1	34	1.7	3.13	1.94	5.06
Attention deficit and hyperactivity disorder	24	3.5	31	1.5	2.32	1.35	3.98
Borderline personality disorder*	111	16.1	71	3.5	5.28	3.86	7.21
Other demographic and clinical variables	N	%	N	%	OR	LI	UI
Bipolar disorder (according to DSM-IV-TR)*	177	25.6	265	13.1	2.29	1.85	2.84
Bipolarity specifier*	473	68.5	649	32.0	4.61	3.83	5.55
(Hypo)manic switch under antidepressant treatment*	196	28.4	259	12.8	2.71	2.19	3.34
First degree familiarity for manic/hypomanic episodes*	153	22.1	248	12.2	2.04	1.63	2.55
	Mean	SD	Mean	SD	z-stat		
Age	41.9	13.5	44.7	13.8	4.8		
Age at first MDE diagnosis*	31.4	11.4	36.6	12.7	9.4		
Duration of current episode (days)*	86.9	114.7	99.2	134.8	3.4		
Previous depressive episodes*	5.4	6.6	4.4	5.6	-4.7		
Lifetime suicide attempts*	0.7	2.4	0.4	1.0	-5.0		
Previous hospitalizations	1.5	4.6	1.7	3.4	3.1		

\* Bonferroni-corrected significant differences ( $p < 0.00098$ ).

of current episode, but increased number of previous depressive episodes and lifetime suicide attempts. MDE + MX showed significantly lower age at first depression diagnosis and current age. However, in the logistic regression model including both the latter (Supplementary Table 1), increasing age at first episode was significantly negatively associated with MDE + MX membership ( $p = 6.7 \times 10^{-19}$ ), while increasing current age was instead significantly positively associated with mixed features ( $p = 0.0017$ ).

### 3.2. Predictors

Clinical features predicting cluster label were identified using a stepwise logistic regression model (Supplementary Table 2) and estimate predictor importance based on a random forest of 200 regression trees (Fig. 1). Both methods converged on the same seven symptoms that differed between medoids, namely irritable mood, emotional/mood lability, psychomotor agitation, distractibility, mood reactivity, reduced appetite and psychomotor retardation.

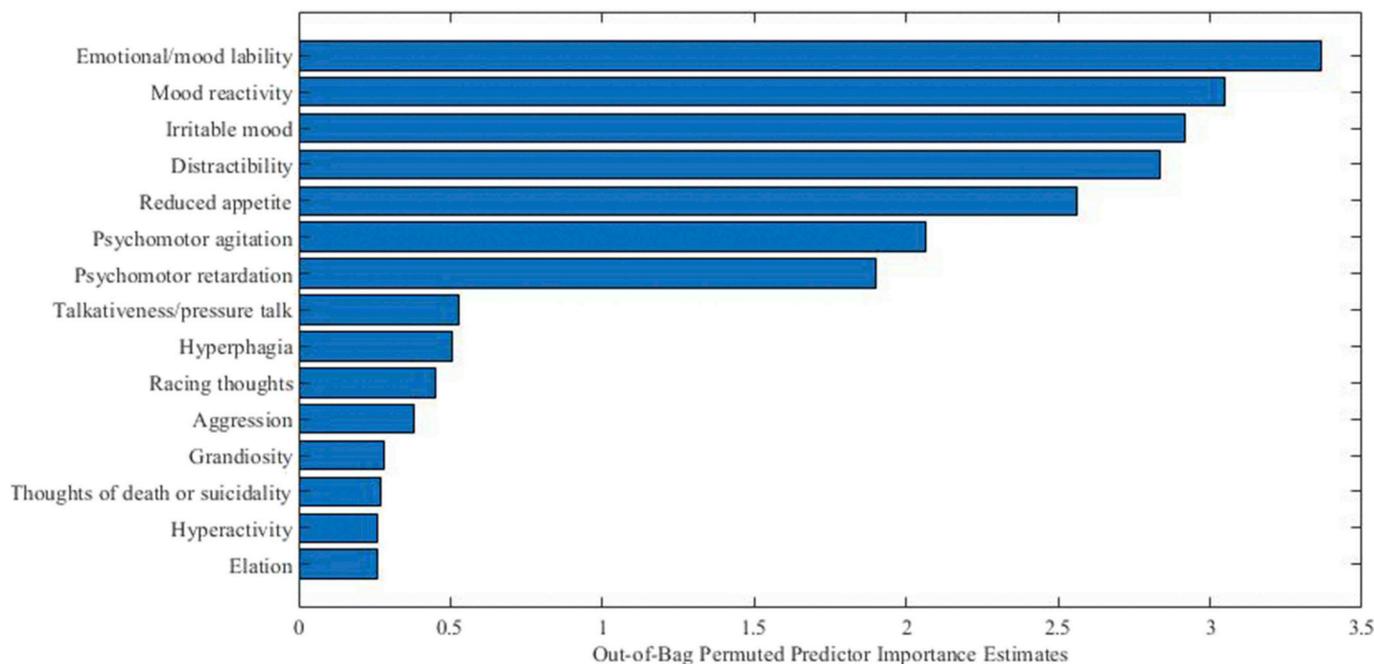
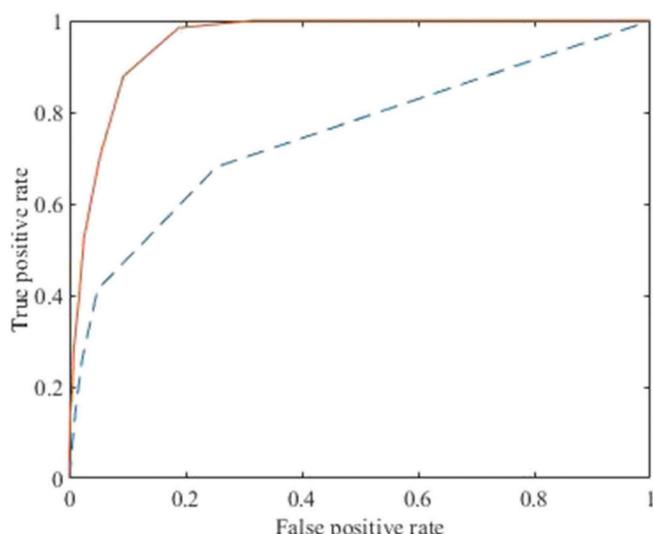


Fig. 1. Out-of-bag permuted predictor importance estimates based on random forest. The first 15 predictors of MDE + MX cluster membership are shown in descending order. The greatest gap presented between the 7th and the 8th predictor, thus suggesting the first seven features as best predictors.



**Fig. 2.** Receiver Operating Characteristic (ROC) curves of research-based diagnostic criteria (RBDC, solid red) and DSM-5 mixed features specifier criteria (dashed blue) performances in allocating subjects to their cluster. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.).

**3.3. Data-driven diagnostic criteria and criteria comparison**

Data-driven diagnostic criteria (DDC) were formulated based on the clinical features predicting cluster membership. The latter two predictors were included as negative criteria (i.e. absence of). A cut-off of four was identified computing ROC curve (AUC = 1). ROC curve also confirmed that previously *a priori* proposed cut-off of three for RBDC (AUC = 0.96, Fig. 2) was the best to identify MDE + MX subjects. Conversely, DSM-5 mixed features specifier adapted criteria cut-off of three was not the optimal one and a lower threshold of two resulted in a better performance (AUC = 0.75, Fig. 2). All criteria are shown in Table 3. Contingency tables were constructed using the original cut-offs for RBDC and DSM-5 criteria and the newly identified cut-off of at least four out of seven new data-driven criteria. DDC perfectly classified each subject in each cluster, thus showing 100% sensitivity, specificity, positive and negative predictive values. Among the remainder, DSM-5 adapted criteria showed greater specificity (97.83% (1985/2029) vs. 90.73% (1841/2029)) and positive predictive value (80.27% (179/223) vs 76.35% (607/795)), but lower negative predictive value (79.50% (1985/2497) vs. 95.64% (1841/1925)) and much lower sensitivity (25.90% (169/691) vs. 87.84% (607/691)). Data for DSM-5 subthreshold criteria (cut-off = 2) are presented in Supplementary Table 3.

**Table 3**

Compared criteria. DSM-5 criteria have been adapted due to lack of data: the 7th criterion (“decreased need for sleep (feeling rested despite sleeping less than usual to be contrasted with insomnia)”) has been substituted in a more inclusive way.

DSM-5 adapted mixed features specifier <i>At least 3 out of the following 7:</i>	RBDC for depressive mixed states <i>At least 3 out of the following 14:</i>	Data-driven diagnostic criteria <i>At least 4 out of the following 7:</i>
Elation	Irritable mood	Irritable mood
Grandiosity	Distractibility	Emotional/mood lability
More talkative/pressure to keep talking	Psychomotor agitation	Psychomotor agitation
Racing thoughts	Emotional/mood lability	Distractibility
Increased energy or hyperactivity	Aggression	Mood reactivity
Risky behaviour	Hyperactivity	Absence of reduced appetite
Absence of insomnia and hypersomnia	Hypersexuality	Absence of psychomotor retardation
	Impulsivity	
	Elation	
	Grandiosity	
	Increased energy	
	Racing thoughts	
	More talkative/pressure to keep talking	
	Risky behaviour	

**4. Discussion**

In our study, a large sample of patients affected by a major depressive episode were subdivided in clusters using a k-medoids unsupervised algorithm based on clinical features, mainly including current depressive and manic symptoms. The two clusters we identified strongly differed for prevalence rates of each of the manic symptoms assessed during depression, thus suggesting the identification of a subgroup of patients as mixed depressives (MDE + MX). One in four subjects were included in this cluster (691/2720), confirming a previous result of 23.8% of major depressive patients classified as mixed by Azorin et al. (2012).

The proposed label was further supported by external validators. In accordance with previous reports (Akiskal and Benazzi, 2003; Azorin et al., 2012; Benazzi, 2008, 2002; Bottlender et al., 2004; Goldberg et al., 2009; Maj et al., 2006; Tondo et al., 2018), our mixed patients more frequently showed anxiety, psychotic features, and suicidality during current episode, more frequently presented with comorbid conditions, bipolar disorder diagnosis, bipolarity specifier, history of manic/hypomanic switch under antidepressant treatment, and first degree familiarity for bipolarity, and showed a lower age at onset and more lifetime depressive episodes and suicide attempts in comparison with non-mixed patients.

Although non-overlapping symptoms required for DSM-5 mixed specifier were all significantly more represented among MDE + MX, seven overlapping excitatory symptoms and non-melancholic depressive features were identified as best predictors of cluster membership. Based on these results and ROC analysis, new data-driven diagnostic criteria, perfectly allocating patients, were formulated, requiring at least four features out of the following seven: irritable mood, emotional/mood lability, psychomotor agitation, distractibility, mood reactivity, absence of reduced appetite and absence of psychomotor retardation. Interestingly, none of these correspond to DSM-5 criteria for mixed specifier, which could identify as mixed only about one out of four (179/691) of our MDE + MX subjects, against the 88% (607/691) of patients identified by previously proposed research-based diagnostic criteria, including overlapping symptoms (Perugi et al., 2015).

Aiming to avoid overdiagnosis, DSM-5 decided to exclude overlapping “manic” symptoms from mixed specifier criteria. However, many authors have commented on how overlapping symptoms, such as psychomotor agitation, mood lability, irritability, and distractibility are the most frequently observed in mixed patients and may actually represent the core features of mixed depression (Koukopoulos and Sani, 2014; Maj, 2012; Malhi et al., 2016a; Perugi et al., 2014b). Intriguingly, Bertschy et al. (2007) identified through principal component analysis a “dysphoric” dimension, comprising, among the others, motor agitation, irritability, emotional lability, and distractibility, and whose score where highest in mixed patients and lowest in pure mood episodes. More recently, distractibility, irritability, and psychomotor agitation

during depression (so-called *dip* symptoms) were respectively related to an earlier age of onset and higher rates of bipolarity, an earlier age of onset and higher rates of non-melancholic depression, and more and longer previous hypomanic episodes (Malhi et al., 2016b). Moreover, the inclusion of *dip* symptoms among mixed depression criteria was found useful to discriminate bipolar disorder from major depressive disorder, while DSM-5 criteria were considered too restrictive (Takeshima and Oka, 2015). Notably, both depression with psychomotor agitation and depression with irritability have been previously conceptualized as bipolar depressive mixed states, respectively labelled agitated depression (Koukopoulos et al., 2007) and irritable-hostile depression (Benazzi and Akiskal, 2005). Indeed, as Koukopoulos et al. (2005) proposed, irritability could be a possible manifestation of inner unrest, when psychomotor agitation is absent. Similarly, among mixed patients without psychomotor agitation, identified through Koukopoulos' diagnostic criteria, absence of psychomotor retardation and mood lability or marked reactivity have been found to be the most frequent features (Sani et al., 2014). Accordingly, “rapidly alternating swings in affectivity, emotional resonance, or drive” have been previously proposed as defining “unstable mixed states” (Berner et al., 1992) and, in a dimensional approach, emotional reactivity has also been reported to define a broad mixed state entity (Henry et al., 2007). More recently, Verdolini et al. (2019) highlighted how affective lability, defined as sudden, unpredictable, endogenous changes in mood, and mood reactivity, which refers to the amplitude of emotional responses to environmental stimuli, probably lie on the same continuum.

In this regard, it is noteworthy that atypical depression, which is, by definition, characterized by mood reactivity, has been previously strongly associated with mixed features, with half of atypical depressions also satisfying criteria for mixed depression (Akiskal and Benazzi, 2003; Benazzi, 2001). This link probably accounts for the inclusion of the absence of reduced appetite among our best predictors of mixed cluster membership: as increased appetite or weight gain were not specifically assessed, absence of reduced appetite best represents another atypical feature which characterizes our MDE + MX cluster. The lack of a specific cluster for atypical depression could thus be hypothetically explained in terms of blurred boundaries between mixed and atypical presentations, which both differ substantially from more typical and melancholic depressive episodes. Even though further studies are needed to elucidate the role of differences in appetite between mixed and non-mixed depressive patients, a spectrum between melancholic depression and mixed states, possibly encompassing atypical depression, is suggested. Similarly, mixed states, specifically when defined by the presence of overlapping symptoms, probably represent the core of a wider spectrum ranging from mania to melancholia.

Some limitations should be acknowledged. First, as the original BRIDGE-II-Mix Study was not intended to include a cluster analysis looking for depression subtypes, but to estimate the prevalence of mixed features among depressive patients, psychopathological domains other than excitatory symptoms were not assessed at the same level of detail, thus preventing us from possibly identifying other clinically relevant subgroups. However, our re-analysis aimed to unveil a homogenous group of patients showing higher rates of mixed features in an unsupervised manner which did not depend from previous controversial definitions of mixed depression, and to find out which symptoms could be employed to identify such mixed patients. Indeed, a major strength of this work lies in the wide range of excitatory features explored, without *a priori* excluded symptoms. Furthermore, the unsupervised approach proposed here represents a novel way to shed light on a long-debated question such as that of mixed depression criteria. In future studies, it will be certainly interesting to examine more in depth other psychopathological dimensions, including more specific symptoms such as anxiety, cognitive and motor indecisiveness, emotional perplexity, perceptual disturbances, sense of external interference, depersonalization, and grossly disorganized behaviour which have been previously associated with severe mixed states phenomenology (Perugi

et al., 2014a).

In conclusion, our results strongly suggest a predominant role for overlapping “manic” symptoms and non-melancholic features in defining mixed depressive states. More properly, since the concept of mania, traditionally identified with psychomotor excitation, has been progressively replaced by a view based on mood polarity, we agree with Koukopoulos and Sani's (Koukopoulos and Sani, 2014) proposal to label such symptoms “excitatory” instead of “manic”, given their qualitative difference from symptoms presenting during currently-defined mania (Koukopoulos et al., 2005). Actually, the special attention paid to mood polarity is not compatible with mixed states, whose existence challenges current models of mood disorders (Malhi et al., 2018). Instead, clinical symptoms subsumed under activity and cognition domains, but also regarding fluctuations in mood rather than mood tonality, represent better landmarks to discriminate between mixed and non-mixed depression (Henry et al., 2007; Malhi et al., 2018). Features such as psychomotor agitation or absence of psychomotor retardation, distractibility, irritability, mood lability and reactivity should be really considered as highly suggestive of mixed depression and should be carefully taken into consideration by clinicians to avoid a worsening of patient conditions because of inappropriate treatments (Fornaro et al., 2012). The proper identification of mixed features has relevant treatment implications. In particular, in these patients, antidepressant drugs, which might worsen mixed symptomatology, should be utilized with due caution and mood stabilizers that might be particularly effective should not go underutilized. Indeed, a history of hypomanic or manic switch under antidepressant treatment was present in 28.4% (196/691) of mixed depressive patients identified by our new data-driven diagnostic criteria, while only 12.8% (259/2029) of non-mixed patients presented previous switches. Moreover, in a longitudinal perspective, it is noteworthy that more than two thirds of mixed patients (68.5%, 473/691) satisfied evidence-based criteria for subthreshold bipolarity proposed by Angst et al. (2013, 2011), thus suggesting the need to thoroughly evaluate patients for a history of previous (hypo)manic episodes when our criteria for mixed depression are met. For further guidance concerning treatment, these patients would benefit from therapies as those supported by recent treatment guidelines (Stahl et al., 2017; Verdolini et al., 2018).

Finally, even though future studies are certainly needed to further establish validity and reliability of our proposal, our results provide a useful basis to rethink the current definition of mixed depression. From a theoretical point of view, the prominence of overlapping excitatory symptoms and atypical symptoms, namely irritability, distractibility, mood lability and reactivity, psychomotor agitation or absence of retardation, absence of reduced appetite, supports the hypothesis of an underlying “persistent presence of a drive state contradictory to the mood state and/or the emotional resonance” (Berner et al., 1992). In this perspective, overlap or superposition of opposite drives resulting in symptoms which are not clearly ascribable to a given polarity, as opposed to combination or juxtaposition of symptoms which are specific of an opposite polarity, could possibly better explain mixed phenomenology and probably help unveil new more specific psychopathological features and neurobiological determinants.

## 5. Conclusion

Re-analysis of BRIDGE-II-MIX data from 2720 patients with an MDE using an unsupervised clustering method was able to distinguish a group of patients showing higher rates of mixed features, based on current symptomatology, without *a priori* criteria. Clusters labels were confirmed by external validators including other current symptoms, illness course, bipolarity and risk factors for bipolar disorder. Feature selection methods allowed to identify new data-driven criteria describing the mixed cluster. At least four features out of the following seven were identified to discriminate among mixed and non-mixed patients: irritable mood, emotional/mood lability, psychomotor

agitation, distractibility, mood reactivity, absence of reduced appetite and absence of psychomotor retardation. DSM-5 criteria for mixed features specifier, excluding overlapping symptoms, were able to identify as mixed only about one out of four patients in mixed cluster. Our results support the hypothesis of a predominant role of overlapping excitatory symptoms in defining mixed depression.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychires.2019.05.014>.

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