

Irritability Associated with Major Depressive Episodes: Its Relationship with Mood Disorders and Temperament



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SUMMARY

Objective: Irritability is a well-known feature of some mood states. Within the framework of major depressive episodes (MDEs) irritability has been associated with subtypes of depressive mood, personality traits, depressive mixed states, and a bipolar diathesis. This study aimed to assess the symptomatology of irritable depression and the effect of personality.

Materials and Methods: The study included 93 patients with MDEs, with and without other diagnoses. The characteristics and severity of depressive, manic, and anxious symptoms were assessed. Irritability was determined using the Irritability, Depression and Anxiety Scale outwardly directed irritability subscale (IDA-out). The patients were also administered the Multidimensional Assessment of Thymic States and the Irritability Questionnaire. Personality was assessed using the Temperament and Character Inventory-125 (TCI-125) and the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEMPS-A).

Results: More of the MDE patients with irritability (32.3%) had atypical features (i.e. weight gain and rejection sensitivity), guilt, hypomanic symptoms, depressive mixed states, and a personal and family history of bipolar disorder than the MDE patients without irritability. Irritability was moderately correlated with depression, hypomania, anxiety, and emotional reactivity. More of the irritable MDE patients exhibited increased novelty seeking, irritable and hyperthymic temperament scores, and had lower TCI-125 and TEMPS-A cooperation and harm avoidance scores than those that were not irritable. Forward logistic regression analysis showed that there was a strong independent association between irritability, and weight gain, irritable temperament, depressive mixed states, novelty seeking, and depression.

Conclusions: MDE-related irritability was strongly associated with atypical and mixed features, which may be indicative of a bipolar diathesis, as well as specific temperament characteristics that may be indicative of trait activation.

Keywords: Irritable mood; hostility; depression; temperament; personality; bipolar disorder

INTRODUCTION

The word *irritabilitas* was first used by Apuleius (2nd century) in reference to Plato's "irascible part" of the soul. Although irritability is referred to in numerous psychiatry textbooks, its definition remains equivocal. It can be best defined as, "a feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioral outbursts" (Snaith and Taylor 1985), or, "a tendency to react impulsively, controversially, or rudely at the slightest provocation or disagreement" (Caprara et al. 1985). It remains unclear if irritability should be considered a mood state, an emotion, or

a temperamental feature. It can be conceptualized as a transitory (irritable mood) or persistent (irritable temperament) disposition towards the basic emotion of anger (Power and Dalglish 2005). Irritable (or choleric) temperament has existed in the medical literature since Antiquity.

Temperament theory was updated by several modern researchers, including Kraepelin and Akiskal. According to the latter, irritable temperament is characterized by a tendency to brood, moodiness with infrequent euthymia, ill-humored joking, dysphoric restlessness, and impulsivity (Akiskal and Mallya 1987). According to psychobiological models of personality,

Received: 08.01.2013 - Accepted: 25.06.2013

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anger is associated with the mesolimbic dopaminergic pathway and dimensions of activation, such as Cloninger's novelty seeking, Zuckerman's impulsive sensation-seeking, Eysenck's psychoticism, and some facets of Gray's behavioral activation system (BAS) (Mardaga and Hansenne 2007; Lara and Akiskal 2006). Fear has been associated with serotonergic pathways and dimensions of inhibition, such as Cloninger's harm avoidance, Eysenck's neuroticism, and Gray's behavioral inhibition system. It was posited that these dimensions of inhibition might be involved in the control of impulsive and anger-related behaviors, whereas the dimensions of activation may be indicative of the drive that makes anger possible, if not anger itself (Cooper et al. 2008; Lara and Akiskal 2006).

Within the framework of a bidimensional approach of personality, Lara and Akiskal proposed that irritable temperament could be the result of high anger and moderate fear (Lara and Akiskal 2006). Irritability could also be a short-term disposition (irritable mood) towards anger, especially when associated with depressive and manic symptoms. Where irritability exists within the spectrum of mood disorders remains unclear. Irritability has long been recognized as a major feature of manic and mixed states (Kraepelin 1909), and some researchers have suggested that manic dysphoria is the result of the association between mania, and irritability-hostility and depression (Akiskal et al. 2003). The presence of intradepressive symptoms during manic episodes or intramanic symptoms during depressive episodes calls into question the appropriate clinical threshold for mixed states.

According to DSM-IV-TR criteria, mixed episodes are diagnosed only if they meet the criteria for both manic and depressive episodes simultaneously; however, several researchers have suggested that mixture could be revealed by the presence of 2-3 symptoms of the opposite polarity, as in the case of depressive mixed states, with 3 superimposed manic symptoms (DMX3) (Benazzi 2002). Others advocate a more dimensional approach to mood states based on the assessment of variations in emotional reactivity, regardless of the emotional valence of stimuli (Henry et al. 2003). Fava et al. (2000, 1996) examined anger and irritability within the framework of unipolar MDEs with anger attacks (AA). They sought to determine the primary symptomatic and biological characteristics of these depressive episodes and reported that, among other things, MDEs with AA were associated with a blunted prolactin response to fenfluramine challenge, suggesting serotonergic dysregulation.

More recent studies have examined the link between irritable depression and bipolar disorder. Benazzi and Akiskal (2005) showed that irritable depression and bipolar disorder could be related to each other via hypomanic symptoms (such as an increase in risk-taking behavior, distractibility, and racing thoughts), atypical features (such as weight gain and leaden paralysis), and other bipolar validators (young age at onset

and family history of bipolar disorder) in patients with unipolar MDEs, suggesting the influence of a bipolar diathesis in such patients. In a sample of bipolar-II depressed patients, irritability was also strongly associated with intra-MDE hypomanic symptoms and atypical features, suggesting that MDEs with irritability could exist along a continuum linking major depressive disorder (MDD) and bipolar-II (Benazzi and Akiskal 2005). In this study irritability was defined according to various definitions and no validated instrument was used. Although since Kraepelin is has been widely accepted that irritability could result from the admixture of manic and depressive symptoms, the exact nature of the association remains unclear. Some researchers have posited that mixed states could result from the combination of a rather pure mood state (such as mania or depression) and a temperament of the opposite polarity (e.g. dysthymic temperament or hyperthymic temperament) (Akiskal et al. 1998). Although such a model cannot be valid for all situations, it could sometimes apply to irritability. Taking temperamental features into account is, indeed, of great heuristic interest.

Although irritability has been studied as a core feature of mixed states, few studies have examined the distinctive features of irritable MDEs and none has considered the relationship between personality dimensions and irritable MDEs. We hypothesized that irritable MDE patients would exhibit specific MDE clinical features (such as markers of bipolar disorder) or specific constitutional traits (such as high activation scores). The present study aimed to assess the symptomatology of irritable depression, and to explore the temperamental features associated this subtype of depression by comparing MDE patients with and without irritability.

MATERIALS and METHODS

This cross-sectional study was carried out between November 2011 and April 2012 at Esquirol Psychiatric Hospital, Limoges, France. The study included 93 consecutive patients with MDEs—regardless of other psychiatric diagnoses, such as bipolar disorder and personality disorders—that voluntarily presented for hospitalization or consultation. Those with severe organic diseases, cognitive deficiency, and addictions were excluded. During the initial assessment the following data were collected: sociodemographic characteristics (age, gender, level of education, employment status, and parental status), clinical features (DSM-IV criteria for MDE, and mixed, atypical, and melancholic features), and personal and family history of mood disorders and attempted suicide. The severity of depressive symptoms was evaluated using the Montgomery and Asberg Depression Rating Scale (MADRS), the severity of manic symptoms using the Young Mania Rating Scale (YMRS), and anxious symptoms using the Hamilton Anxiety Rating Scale (HAM-A). At the end of the interview a set of questionnaires was administered to

the patients. The Multidimensional Assessment of Thymic States (MATHyS) (Henry et al. 2008) was used for dimensional evaluation of mood, and the French versions of the Temperament and Character Inventory (TCI-125) (Pelissolo and Lepine 2000; Cloninger 1994) and 39-item version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A) (Akiskal et al. 2005, Krebs et al. 2006) were used to assess dimensions of personality. The Irritability Questionnaire (IRQ) (Craig et al. 2008), and inwardly directed irritability (IDA-in) and outwardly directed irritability (IDA-out) subscales of the Irritability, Depression and Anxiety Scale (IDA) (Snaith et al. 1978) were translated into French and used to assess irritability. In contrast to the IDA-in subscale, the IRQ and the IDA-out subscale have shown good internal consistency and reliability (Craig et al. 2008). In the present study irritability was defined by an IDA-out subscale cut-off score ≥ 8 , according to Snaith (1978). A preliminary test was performed to confirm that the IDA-out subscale score had a normal distribution in the study sample. P values obtained via Kolmogorov-Smirnov, Shapiro-Wilk, and Jarque-Berra tests were 0.45, 0.054, and 0.23, respectively, which indicated normal distribution of the scores.

XLSTAT 2012* (Addinsoft, Paris, France) statistical software was used for data analysis. Proportions and means were compared between the patients that were irritable and not irritable using the two-sample z-test for comparing proportions and the two-sample z-test for comparing means. The Mann-Whitney U test and Fisher's exact test were used for subgroup analysis. Pearson's correlation analysis was performed to investigate the relationships between irritability and dimensional variables. Multivariate analysis using forward stepwise logistic regression was performed in order to control for confounding factors.

RESULTS

In all, 32.3% of the patients met the criteria for irritability (30/93). Irritable MDE patients did not differ significantly in terms of sociodemographic characteristics from those that were not irritable, but more of the irritable MDE patients had a personal and family history of bipolar disorder. There weren't any significant differences between the 2 groups regarding the use of psychotropic drugs before admission (Table 1). More of the irritable MDE patients had atypical symptoms and depressive mixed states. Among the depressive symptoms (including atypical and melancholic features), excessive guilt, weight gain, and rejection sensitivity were significantly more common in the irritable MDE group, whereas weight loss was significantly more common in the not irritable MDE group. Although hypomanic symptoms were more frequent in the irritable MDE group, only the occurrence of racing thoughts was significantly more common in the irritable MDE group (Table 2).

Table 1. Comparison of sociodemographics and psychiatric history between the MDE patients with and without irritability.

	MDE patients without irritability (63)	MDE patients with irritability (30)	P
Age (years $\pm$ SD)	44.5 $\pm$ 13.5	40.5 $\pm$ 10.3	0.2
Female (%)	66.7	70	0.7
Educational attainment index ($\pm$ SD)	3.5 $\pm$ 1.4	3.7 $\pm$ 1.4	0.5
Living with a partner (%)	58.7	63.3	0.7
Parent (%)	63.5	70	0.5
Currently employed (%)	46.0	53.3	0.5
History of manic, hypomanic, or mixed episodes (%)	39.7	63.3	0.03*
History of attempted suicide (%)	36.5	46.7	0.4
History of MDEs (%)	84.1	90	0.4
Family history of depression (%)	42.9	56.7	0.2
Family history of bipolar disorder (%)	11.1	33.3	0.04*
Family history of attempted suicide (%)	17.5	23.3	0.5
Antidepressants prescribed before admission (%)	65.1	46.7	0.09
Mood stabilizers (anticonvulsants, lithium) prescribed before admission (%)	23.8	40.0	0.12
Benzodiazepines prescribed before admission (%)	54.0	46.7	0.5
Second-generation antipsychotics prescribed before admission (%)	17.5	16.7	0.9

*P < 0.05

**P < 0.01

From a dimensional viewpoint irritability was correlated with the MADRS depression score, and MATHyS emotional reactivity and cognition subscale scores. Doubtful correlations were observed between irritability, and mania (YMRS score) and psychic anxiety (HAM-A psychic anxiety subscale score) (Table 3). In addition, analysis of the relationship between inwardly directed irritability, and depression and anxiety showed that, in contrast to outwardly directed irritability, inwardly directed irritability was correlated with both somatic anxiety and psychic anxiety. With regard to Cloninger's temperament dimensions, it was observed that irritable MDE patients had higher novelty seeking scores, and lower cooperation and

Table 2. Pairwise comparison of symptoms between the MDE patients with and without irritability.

Symptoms	MDE patients without irritability (63)	MDE patients with irritability (30)	P
Depressive mood (%)	95.2	100	0.1
Diminished interest (%)	81.0	90.0	0.2
Psychomotor agitation (%)	17.5	26.7	0.3
Loss of energy (%)	98.4	100	0.3
Worthlessness (%)	79.4	76.7	0.8
Diminished concentration (%)	85.7	90.0	0.5
Thoughts of death (%)	49.2	53.3	0.7
Leadens paralysis (%)	22.2	16.7	0.5
Weight gain (%)	12.7	40.0	0.006**
Rejection sensitivity (%)	38.1	73.3	0.001**
Weight loss (%)	63.5	40.0	0.03*
Hypersomnia (%)	17.5	23.3	0.5
Lack of reactivity to pleasurable stimuli (%)	28.6	23.3	0.6
Morning worsening (%)	41.3	33.3	0.5
Distinct quality of depressive mood (%)	14.3	13.3	0.9
Early morning awakening (%)	44.4	43.3	0.9
Excessive guilt (%)	12.7	33.3	0.03*
Index atypical features ($\pm$ SD)	22.6 $\pm$ 30.7	38.3 $\pm$ 33.9	0.03*
Index melancholic features ($\pm$ SD)	31.5 $\pm$ 26.3	32.5 $\pm$ 26.3	0.9
Increased self-esteem (%)	7.9	6.7	0.8
Distractibility (%)	11.1	26.7	0.08
Reduced need for sleep (%)	1.6	3.3	0.6
Talkativeness (%)	11.1	23.3	0.2
Racing thoughts (%)	15.9	36.6	0.04*
Increased goal-directed activity (%)	0	0	-
Increased risky activities (%)	1.6	3.3	0.6
3 symptoms (DMX3) (%)	7.9	26.7	0.03*

*P < 0.05

**P < 0.01

lower harm avoidance scores. In terms of Akiskal's temperaments irritable MDE patients had higher irritable and hyperthymic temperament scores (Table 4).

Non-parametric testing of unipolar patients was performed to ensure that some of the findings were not the result of overrepresentation of bipolar patients in the irritable MDE group, and that they remained true in non-bipolar patients; the results are shown in Table 5. Despite the low statistical power of these analyses, there remained significant differences in weight gain, atypical features, novelty seeking, irritable

Table 3. Correlations between irritability (IDA-out and IDA-in) and several dimensional variables (including depression, mania, and anxiety scores, and MATHyS scores).

	IDA-out	P
MATHyS		
Total	0.12	0.26 (NS)
Motivation and psychomotor function	0.016	0.9 (NS)
Emotion	0.246	0.02*
Sensory Perception	-0.02	0.9 (NS)
Interpersonal communication	-0.138	0.2 (NS)
Cognition	0.208	0.045*
MADRS		
Total score	0.293	0.004*
YMRS		
Total	0.305	0.003*
Total score without item n°5 'irritability'	0.16	0.1 (NS)
HAM-A		
Total	0.19	0.1 (NS)
Somatic anxiety	0.10	0.4 (NS)
Psychic anxiety	0.255	0.014*
	IDA-in	P
HAM-A		
Total	0.28	0.006**
Somatic anxiety	0.25	0.01*
Psychic anxiety	0.24	0.02*
MADRS		
Total score	0.21	0.01*

*P < 0.05

**P < 0.01

temperament, and hyperthymic temperament between the unipolar MDE patients with and without irritability. Using irritability as the dependent variable binary logistic regression was performed on variables found different between the 2 groups at the P = 0.10 level of significance (Table 6). These analyses showed that there were significant independent associations between irritable MDE, and weight gain (P = 0.001, $\chi^2=10.6$), irritable temperament traits (P = 0.002, $\chi^2=9.5$), depressive mixed states (P = 0.016, $\chi^2=5.8$), novelty seeking (P = 0.023, $\chi^2=5.2$), and MADRS score (P = 0.03, $\chi^2=4.7$).

DISCUSSION

The most important findings of the present study were the independent associations between MDE-related irritability, and clinical features thought to be linked to dopaminergic dysregulation and dimensions of personality such as novelty seeking, which may also be indicative of dopaminergic dysfunction. Some studies reported a decrease in the incidence of

Table 4. Comparison of temperament and character dimensions in Cloninger's and Akiskal's models between the MDE patients with and without irritability.

	MDE patients without irritability (63)	MDE patients with irritability (30)	P
Novelty Seeking (% $\pm$ SD)	39.4 $\pm$ 15.9	54.8 $\pm$ 18.7	0.0003**
Harm Avoidance (% $\pm$ SD)	73.1 $\pm$ 18.6	62.7 $\pm$ 24.6	0.048*
Reward Dependence (% $\pm$ SD)	59.3 $\pm$ 20.3	60.5 $\pm$ 20.6	0.99
Persistence (% $\pm$ SD)	54.9 $\pm$ 29.8	59.3 $\pm$ 34.2	0.4
Cooperativeness (% $\pm$ SD)	75.6 $\pm$ 12.5	66.3 $\pm$ 16.1	0.005**
Self-Transcendence (% $\pm$ SD)	35.6 $\pm$ 20.8	33.3 $\pm$ 18.8	0.6
Self-Directedness (% $\pm$ SD)	53.1 $\pm$ 18.4	49.3 $\pm$ 20.0	0.7
Cyclothymic Temperament (% $\pm$ SD)	59.4 $\pm$ 27.5	61.6 $\pm$ 29.6	0.5
Irritable Temperament (% $\pm$ SD)	17.9 $\pm$ 20.0	44.2 $\pm$ 27.8	<0.0001**
Dythymic Temperament (% $\pm$ SD)	57.9 $\pm$ 28.7	58.8 $\pm$ 35.8	0.9
Hyperthymic Temperament (% $\pm$ SD)	43.1 $\pm$ 28.6	64.6 $\pm$ 24.4	0.001**
Anxious Temperament (% $\pm$ SD)	71.4 $\pm$ 34.3	56.6 $\pm$ 37.3	0.06

*P < 0.05

**P < 0.01

depression-related irritability with age (Benazzi 2005), whereas in the present study only a tendency (P = 0.2) towards such a decrease was noted; however, the present findings are very comparable to those reported by Benazzi, and the lack of a significant decrease with age in the present study might have been due to the small study population. Based on the the IDA-out subscale of the IDA scale (a validated instrument), the frequency of irritability during MDEs (32.3%) in the present study was slightly lower than Benazzi's empirical evaluation (roughly 50%), but similar to Fava's estimations of the frequency of anger attacks during MDEs using the Anger Attack Questionnaire (30%-50%). According to these earlier reports and the present findings, irritability is a frequent symptom of major depression.

The present findings also highlight the strong relationship between depression-related irritability and bipolar disorder, based on the large number of bipolar patients among the irritable MDE patients and the higher frequency (though not significantly higher [P = 0.13]) of a family history of bipolar

Table 5. Comparison of scores that were significantly different between groups than in the entire sample, in unipolar MDE patients with and without irritability.

	Unipolar MDE patients without irritability (38)	Unipolar MDE patients with irritability (11)	P
Family history of bipolar disorder (%)	5.3	27.3	0.13
Symptoms			
Weight gain (%)	7.9	54.5	0.01*
Index atypical features (% $\pm$ SD)	20.4 $\pm$ 31.2	47.7 $\pm$ 37.8	0.01*
Excessive guilt (%)	13.2	36.4	0.1
Depressive mixed state (DMX3) (%)	2.7	9.1	0.4
TCI-125			
Novelty Seeking (% $\pm$ SD)	37.6 $\pm$ 11	50.4 $\pm$ 15	0.01*
Harm Avoidance (% $\pm$ SD)	74.2 $\pm$ 16.5	61.82 $\pm$ 27.1	0.2
Cooperativeness (% $\pm$ SD)	75.7 $\pm$ 11.9	69.5 $\pm$ 19	0.5
TEMPS-A			
Irritable temperament (% $\pm$ SD)	16 $\pm$ 16	36 $\pm$ 25	0.01*
Hyperthymic temperament (% $\pm$ SD)	38 $\pm$ 28	59 $\pm$ 22	0.02*
Anxious temperament (% $\pm$ SD)	75 $\pm$ 31	52 $\pm$ 40	0.06

*P < 0.05

**P < 0.01

Table 6. Forward logistic regression (dependent variable: MDE patients with irritability; independent variables: variables that were different at the P = 0.10 level of significance based on pairwise comparisons).

Independent variables	Odds ratio (95% CI)	χ^2	P
Weight gain	13.63 (2.83-65.59)	10.614	0.001**
Irritable Temperament	1.04 (1.0-1.07)	9.513	0.002**
DMX3/no	0.09 (0.01-0.64)	5.813	0.016*
NS	1.04 (1.0-1.08)	5.161	0.023*
MADRS score	1.12 (1.01-1.25)	4.718	0.030*

*P < 0.05

**P < 0.01

disorder among the irritable unipolar patients. In addition, more of the irritable MDE patients had atypical and mixed features. As atypical depression and depressive mixed states are 2 clinical forms of depression that have been explicitly related to a bipolar diathesis (Perugi et al. 2011)—perhaps due to dopaminergic dysregulation (Lara and Akiskal 2006)—these findings are noteworthy. The atypical features observed in the present study were similar to those reported by Benazzi and Akiskal (2005). Weight gain was more common in the present study's irritable MDE patients, as was

rejection sensitivity, but the frequency of leaden paralysis and hypersomnia did not differ between the irritable and not irritable MDE patients. Although atypical depression may have clinical relevance, its current criteria, combining the strange “leaden paralysis” symptom and trait “rejection sensitivity”, might need redefinition. Moreover, more of the irritable MDE patients had depressive mixed states, including 3 hypomanic symptoms, according to Benazzi’s definition of DMX3 (Benazzi 2002). Among these symptoms, none really outweighed the others when taken separately, except “racing/crowded thoughts”. Among other depressive symptoms, only inappropriate guilt was significantly more common among the irritable MDE patients, which might have been due to self-criticism following episodes of anger. Logistic regression analysis showed that only weight gain and depressive mixed states were significantly more frequent in the irritable MDE patients.

In the present study there were weak correlations between irritability and mood assessment scale scores, except for the MADRS score, and the MATHyS emotional reactivity and cognition scores. Given the small effect sizes, it is difficult to draw clear conclusions from these weak correlations, although irritability is likely to have something to do with emotional reactivity, at least to a certain extent. Several studies have reported an association between irritability and depression (Fava et al. 1996), and the positive effect of antidepressant treatment on depression-related irritability; however, the effect of such treatment on dimensions of personality—regardless of depression scores—might be confounding (Svrakic 1992). There was no longer an association between irritability and mania (evaluated via YMRS) in the present study when the irritability item was removed from the scale, but it is likely that YMRS is not a good instrument for the assessment of intradepressive hypomanic symptoms. Outward irritability was correlated with the HAM-A psychic anxiety subscale score, but not with its somatic anxiety subscale score. As many researchers have emphasized the links between irritability and somatization, it was expected that irritability would have exhibited a stronger correlation with the latter HAM-A subscale. As previously reported (Snaith 1978), in the present study there was also a slightly stronger correlation between inwardly directed irritability and somatic anxiety; however, in contrast to earlier reports, the correlation between and depression in the present study was not stronger than the correlation between outward irritability and depression. The irritable MDE patients had a limited number of specific symptoms, which were primarily related—directly or indirectly—to a bipolar diathesis.

In the present study there were some important findings regarding dimensions of personality. The irritable MDE patients had higher TCI-125 novelty seeking scores, even when the unipolar patients were analyzed separately. On the other hand, TCI-125 harm avoidance scores were slightly lower in the irritable MDE patients, but this finding should be

considered carefully, given that temperament was evaluated during MDEs and that there is evidence that harm avoidance increases as the depression score increases (Svrakic 1992). Indeed, the present study’s TCI-125 harm avoidance scores were higher than the French normative scores (0.73 and 0.62 versus 0.46) due to a current MDE and perhaps to some specific temperamental features of depressed patients. There weren’t any differences in the reward dependence, persistence, self-transcendence, or self-directedness dimensions, but the cooperativeness character dimension score was, as expected, significantly lower in the irritable MDE patients. As for Akiskal’s model, in the present study irritable MDE patients had higher irritable temperament (IT) and hyperthymic temperament (HT) scores, which is indicative of the importance of trait-irritability in irritable MDE patients. Multivariate analysis showed that there remained independent associations between MDE patients with irritability, and irritable temperament and novelty seeking; thus, regardless of unipolar/bipolar status, the temperamental features of the irritable MDE patients were associated with activation—as conceptualized by Gray (2000)—via the behavioral activation system. It has been suggested that temperamental features related to the behavioral activation system, such as novelty seeking, might be involved in the genesis of emotional reactivity (Yoshiho 2005). In contrast, these individuals may have limited inhibition ability, as suggested by low harm avoidance scores, and reduced social interaction ability, as suggested by low cooperativeness scores.

It could be argued that such distinctive clinical characteristics might be indicative of a bipolar diathesis or a trait, rather than the depressive state itself. In short, these data suggest that personality is a primary determinant of depression-related irritability, and that depressive states may have a modulating effect on these traits. Another hypothesis of particular interest is that if mixed states can be conceptualized as the result of transitory mood states conflicting with firmly grounded temperaments (Perugi et al 1997), then irritability—in the framework of depressive episodes—may be indicative of an underlying irritable or hyperthymic temperament, hypothetically via the dopaminergic mesolimbic pathway. This might explain the high novelty seeking scores and the high frequency of hyperthymic traits in patients that are depressed and irritable.

The present study has several limitations. Due to its cross-sectional design precise causal relationships cannot be identified. The small study population precluded powerful subgroup analysis. As interviews were conducted by one interviewer, the possibility of evaluation bias cannot be excluded, but the systematic use of validated instruments, questionnaires, and symptom charts based on the DSM-IV-TR make such bias unlikely. Additionally, there might have been a selection bias due to hospital selection, which may have led to overrepresentation of patients with severely depressive states, bipolar disorder, and comorbidities; however, comorbidities were

thoroughly examined and some other studies had similar proportions of bipolar patients. In addition, we performed multivariate analysis and subgroup analysis among the unipolar patients to verify that bipolar disorder did not explain the major differences between the MDE patients with and without irritability. As personality was assessed during MDEs, some of Cloninger's TCI-125 dimensions might have been affected; however, the most relevant dimensions (novelty seeking in particular) are not affected by these state-related variations. Finally, the cut-off value chosen for irritability was high, which probably resulted in selection of a sample of very irritable patients, which may not be representative of all the people that experience irritability during the course of a depressive episode.

In conclusion, the present findings indicate that depression-related irritability might be determined by both personality traits and mood states. Thus, the latter may have modulating or conflicting effects on specific traits related to activation, temperamental features, and/or a bipolar diathesis, which is indicated by the strong association observed between irritability, and atypical depressions, depressive mixed states, and the specific personality traits (high novelty seeking, irritable and hyperthymic traits) in irritable MDE patients. These findings indicate that clinicians should more often treat such patients with mood stabilizers and antipsychotics, along with selective serotonin reuptake inhibitors, and that they should avoid using antidepressants that enhance dopamine and norepinephrine reuptake, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs). Additional systematic assessment of personality traits could help us better understand how mood states and personality interact.

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