Clinical Characteristics of Melancholic and Nonmelancholic Depressions

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Abstract: This study aimed to compare clinical-demographic features of melancholic and nonmelancholic depressions. We included 141 depressed inpatients classified as melancholic and nonmelancholic by the Sydney Melancholia Prototype Index (SMPI) and *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (*DSM-5*) criteria. Results were controlled for confounders, including severity measures. Melancholic patients by both diagnostic systems were more severely depressed and presented more psychotic symptoms, neurological soft signs, and psychomotor disturbances. Melancholic patients classified by the SMPI were also older at illness onset and had fewer suicide attempts. After controlling for confounders, although all differences remained significant for SMPI diagnosis, the *DSM-5* diagnosis of melancholia was only associated with further impaired motor sequencing. The results obtained with the SMPI support the hypothesis that melancholia has clinical features qualitatively different from those of nonmelancholic depressions. Contrarily, the *DSM-5* specifier seems to reflect the severity of depressive episodes rather than core clinical features of melancholia.

Key Words: Major depressive disorder, bipolar disorder, major depressive episode, melancholia, neurological soft signs

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Over the last century, melancholia has been nosologically positioned either as a more severe form of depression (as part of a unitary model) or as a different categorical entity based on its clinical features, its presumed biological nature, or its greater response to somatic treatments (as part of a binary model) (for a review, see Parker and Hadzi-Pavlovic, 1996).

Since the operationalization of the major depressive episode (MDE) criteria and the melancholia specifier in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (*DSM-III*), some studies using *DSM* criteria failed to find qualitative differences between melancholic and nonmelancholic MDEs, therefore supporting the unitary model (Angst et al., 2007; Melartin et al., 2004; Tondo et al., 2020). Nevertheless, the *DSM* melancholia specifier has been criticized for lacking empirical support and overlapping with MDE criteria, providing little discrimination between melancholic and nonmelancholic depression (Martino et al., 2019; Parker et al., 2010a). In fact, a recent review of studies using multivariate analyses to identify core features of melancholia found some disagreement with *DSM* criteria (Martino et al., 2019). Therefore, studies conducted with the *DSM* specifier comparing different external validators (*e.g.*, clinical features, longitudinal course, response to treatment) might lead to negative findings even if melancholia were qualitatively different from nonmelancholic depressions.

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There is a current consensus that MDE is a heterogeneous clinical construct, so identifying better-defined phenotypes has gained renewed interest (Sanacora, 2020). In this context, this study aimed to compare clinical features of patients undergoing melancholic and nonmelancholic depressive episodes by two different diagnostic systems: the *DSM-5* melancholia specifier and the Sydney Melancholia Prototype Index (SMPI) (Parker et al., 2013a, 2013b).

METHODS

Subjects

Patients hospitalized for an MDE in the Psychiatric Emergencies Hospital Torcuato de Alvear were consecutively recruited if they satisfied the following criteria: age between 18 and 65 years and diagnosis of major depressive disorder or bipolar disorder (type I, II, or other specified bipolar disorder) according to *DSM-5* criteria, confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 2016). Exclusion criteria were history of substance abuse/dependence, intellectual disability, neurological disease, or any unstable clinical condition (*e.g.*, hypothyroidism, diabetes) that could impact affective or neurological symptoms.

Patients were assessed during the first week after admission. Assignment to the melancholic or nonmelancholic group was performed through two different diagnostic systems: *DSM-5* criteria according to the MINI and the clinician-rated version of the SMPI. The SMPI is a 24-item measure weighing clinical and nonsymptom features (such as premorbid interpersonal functioning, distal and proximal stressors, or the context and impact of stressors on the depression) that has shown high discrimination between melancholic and nonmelancholic depression (Parker et al., 2013b).

Clinical Measures

Symptoms severity was evaluated with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). The presence of psychotic symptoms during the current depressive episode was assessed with the MINI. Sociodemographical and other clinical data were obtained from direct patients' interview and clinical charts. Exposure to antidepressants, mood stabilizers, antipsychotics, and benzodiazepines was assessed with the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD) (Peralta and Cuesta, 2002). This scale provides a quantitative measure of current exposure in a 0-to-5 point range. The number of depressive episodes, suicidal attempts, and hospitalizations was registered as density of events (number of total events divided by length of the illness).

Neurological and Psychomotor Measures

Neurological soft signs and psychomotor disturbances were evaluated with the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) and the CORE measure (Parker and Hadzi-Pavlovic, 1996), respectively. The NES is a 26-item battery evaluating dysfunction in three areas:

sensory integration, motor coordination, and sequencing of complex motor acts. It also includes items assessing memory, frontal release signs, and eye movement abnormalities. The CORE is an 18-item measure designed to assess signs of psychomotor disturbance in melancholia, compromising one noninteractiveness subscale capturing cognitive features and two motor subscales capturing retardation and agitation.

Data Analysis

Assumptions of normality and homoscedasticity were analyzed with the Kolmogorov-Smirnov test and the Levene test, respectively. Two different analyses were made for each variable, assigning patients to the melancholic and nonmelancholic groups by the SMPI and the *DSM-5* melancholic specifier. Diagnosis agreement was assessed with the Mcnemar test for paired proportions. Differences in percentages were tested with the chi-square test. Numerical variables were compared using *t*-test or Mann-Whitney test, as appropriate. Between-group IFD scores were also compared using Mann-Whitney test. Considering the exploratory nature of this study, no corrections for multiple comparisons were applied.

The effect of potential confounders derived from previous literature (*i.e.*, age, subtype of affective disorder [major depressive disorder versus bipolar disorder], age at illness onset, the severity of affective symptoms [MADRS and YMRS], and psychotic symptoms) was controlled using multiple linear or logistic regression models, as appropriate. Likewise, because patients with nonmelancholic depression had greater exposure to benzodiazepines in our sample, this variable was also included in the regression models. As motor retardation is a characteristic feature of melancholia that could impact neurological tasks, NES scores were additionally controlled by a retardation measure composed of the items of slowed movement and speech of the CORE scale.

Data were analyzed using SPSS v.21 for Windows (Chicago, Illinois).

RESULTS

We included 141 patients, 75 with major depressive disorder and 66 with bipolar disorder. Of these, 52.5% ($n = 74$) had a diagnosis of melancholia using *DSM-5* criteria, and 25.5% ($n = 36$) using the SMPI. Although 91.7% of SMPI melancholic patients received the same diagnosis using the *DSM-5*, only 44.6% of patients assigned to the melancholic group by the *DSM-5* were also considered melancholic by the SMPI, with a significant disagreement between both systems ($p < 0.001$).

Although patients with melancholia by the two diagnostic systems presented higher severity of depressive symptoms, those who received this diagnosis with the SMPI additionally showed lower severity of hypomanic symptoms, older age at assessment, later age at illness onset, and fewer suicide attempts (Table 1). After controlling for MADRS score and mood disorder (major depressive disorder versus bipolar disorder), SMPI diagnosis of melancholia was still associated with a lower prevalence ($\beta = -1.12$, $p = 0.01$) and a lower density ($\beta = -0.19$, $p = 0.02$) of suicide attempts. Although the prevalence of psychotic symptoms was higher among melancholic patients using both diagnostic tools (Table 1), after controlling for the MADRS score and mood disorder, differences remained significant for SMPI ($\beta = 1.79$, $p = 0.007$) but not for *DSM-5* ($\beta = 1.24$, $p = 0.14$).

Patients diagnosed with melancholia by both SMPI and *DSM-5* displayed significantly more psychomotor disturbances on all the CORE measures and were significantly more impaired on the NES total score and its subscales assessing motor coordination and sequencing of complex motor acts (Table 2). Nevertheless, after controlling for potential confounders, although all the associations between SMPI melancholic status and impairments in the CORE and the NES measures remained significant, *DSM-5* diagnosis of melancholia was only associated with further impaired motor sequencing (Table 2). Finally, when NES scores were additionally controlled by psychomotor retardation, SMPI diagnosis of melancholia was still associated with more impaired motor sequencing ($\beta = 1.38$, $p = 0.01$).

DISCUSSION

The main finding of our study was that melancholic and nonmelancholic subtypes of MDE diagnosed by the SMPI differed in relevant clinical features and that these differences were relatively independent of the severity of the depressive episode. In addition, we found important discrepancies between *DSM-5* and SMPI diagnoses of melancholia.

In line with previous literature, our study found that patients with melancholia were significantly older at the current episode and at illness onset (Dold et al., 2021; Parker et al., 2010b). Of relevance, these differences were only significant when the diagnosis was made using the SMPI. As expected, patients with melancholia also showed more severe depressive symptomatology. However, it is worth noting that both groups of patients in the present study experienced severe depressive episodes, as indicated by the need for hospitalization and the similarly high rate of suicidal ideation. In addition, we controlled for differences in MADRS and YMRS scores—along with other potential confounders—to improve the comparability of both depressive subtypes.

Previous research showed that psychotic symptoms are more frequent in melancholic than in nonmelancholic depression (Caldieraro et al., 2013; Dold et al., 2021). In the present study, although melancholia diagnosed according to the SMPI increased the odds of having psychotic symptoms by six times even after controlling for the depressive severity and the type of mood disorder, the association between psychotic symptoms and *DSM-5* diagnosis of melancholia lost significance after controlling for the same covariates. This finding is consistent with the proposal that psychotic depression would be essentially melancholic. Unfortunately, we only assessed the presence or absence of psychotic symptoms, preventing us from evaluating these symptoms' quality, which could be addressed in a future study. It is possible to hypothesize that formal psychotic symptoms would appear in melancholia, whereas psychotic-like experiences or transitory psychotic symptoms would be more prevalent in nonmelancholic depressions associated with certain personality disorders (D'Agostino et al., 2019).

On the other hand, although noticeable in both groups, patients with SMPI diagnosis of melancholia had fewer suicide attempts than those with nonmelancholic depression. This finding is consistent with some previous studies using diagnostic criteria other than the *DSM* specifier, which also reported a higher rate of suicide attempts in nonmelancholic depression (Paykel et al., 1974; Thornicroft and Sartorius, 1993). Moreover, it might be associated with the higher prevalence of personality disturbances reported in nonmelancholic depressions (Valerio et al., 2020), which could be addressed in future studies. Contrarily, we found no differences in the history of suicide attempts between patient groups when the diagnosis was made by the *DSM* specifier, which is also consistent with some previous studies using these criteria (Grunebaum et al., 2004; Tondo et al., 2020). Of note, our finding of a higher prevalence of suicide attempts in nonmelancholic depressions collides with the unitary model that postulates that melancholia is only a more severe form of MDE.

Finally, SMPI diagnosis of melancholia was associated with greater psychomotor disturbances and neurological soft signs, with a compromise of motor sequencing and coordination. Psychomotor disturbances, particularly retardation, have been reported as the most consistent clinical feature contributing to identifying melancholia (Martino et al., 2019). They have also been associated with dysfunction in fronto-subcortical pathways (Austin and Mitchell, 1995; Parker and Hadzi-Pavlovic, 1996). Regarding neurological soft signs, although classically defined as nonlocalizing abnormalities, more recently, they have been associated with a disruption of brain circuits encompassing prefrontal and subcortical areas (Zhao et al., 2014). Consistently, neurocognitive studies have

TABLE 1. Clinical and Demographic Characteristics of Patients With Diagnosis of Melancholic and Nonmelancholic MDEs

	SMPI Criteria			*DSM-5* Criteria		
	Melancholic Patients (n = 36)	Nonmelancholic Patients (n = 105)		Melancholic Patients (n = 74)	Nonmelancholic Patients (n = 67)	
Variables	**%**	**%**	**Test; p-Value**			**Test; p-Value**
Sex (female)	66.94	76.19	$\chi^2 = 0.64$; $p = 0.42$	74.32	74.63	$\chi^2 = 0.00$; $p = 0.97$
Diagnosis (bipolar disorder)	58.33	42.86	$\chi^2 = 2.58$; $p = 0.11$	51.35	41.79	$\chi^2 = 1.29$; $p = 0.26$
Psychotic symptoms	25.00	3.81	$\chi^2 = 14.38$; $p < 0.001$	14.86	2.99	$\chi^2 = 5.93$; $p = 0.02$
History of suicide attempts	61.11	80.00	$\chi^2 = 5.13$; $p = 0.02$	74.32	76.12	$\chi^2 = 0.06$; $p = 0.81$
Suicidal thoughts	75.0	87.6	$\chi^2 = 3.24$; $p = 0.07$	83.8	85.1	$\chi^2 = 0.04$; $p = 0.83$
History of previous hospitalizations	86.11	86.67	$\chi^2 = 0.01$; $p = 0.93$	86.49	86.57	$\chi^2 = 0.00$; $p = 0.99$
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	42.44 (15.56)	35.30 (12.35)	$Z = 2.35$; $p = 0.02$	38.65 (13.57)	35.43 (13.43)	$t = 1.41$; $p = 0.16$
Years of education	11.81 (3.21)	11.48 (2.33)	$t = 0.66$; $p = 0.51$	11.32 (2.74)	11.82 (2.37)	$t = -1.15$; $p = 0.25$
MADRS score	33.94 (8.09)	29.30 (6.85)	$t = 0.35$; $p = 0.001$	33.49 (6.86)	27.16 (6.65)	$Z = 5.01$; $p < 0.001$
YMRS score	0.86 (1.46)	2.34 (1.98)	$Z = -4.23$; $p < 0.001$	1.74 (1.88)	2.21 (2.04)	$t = -1.41$; $p = 0.16$
Age at illness onset	27.47 (11.89)	22.23 (12.15)	$Z = 2.96$; $p = 0.003$	24.76 (11.65)	22.25 (12.85)	$t = 1.21$; $p = 0.23$
Density of depressive episodes[a]	0.53 (0.51)	0.55 (0.39)	$Z = -0.96$; $p = 0.34$	0.55 (0.46)	0.55 (0.39)	$t = -0.04$; $p = 0.97$
Density of suicide attempts[b]	0.14 (0.21)	0.33 (0.42)	$t = -0.26$; $p = 0.79$	0.22 (0.29)	0.34 (0.46)	$t = -1.71$; $p = 0.09$
Density of hospitalizations[c]	0.31 (0.34)	0.26 (0.40)	$t = -0.83$; $p = 0.40$	0.26 (0.30)	0.28 (0.46)	$t = -0.23$; $p = 0.82$
	Mode, Mean (Range)	Mode, Mean (Range)	Test; p-Value	Mode, Mean (Range)	Mode, Mean (Range)	Test; p-Value
IFD-antidepressants	0/0 (0–5)	0/2 (0–5)	$Z = -0.97$; $p = 0.33$	0/1 (0–5)	0/0 (0–5)	$Z = -0.18$; $p = 0.85$
IFD-mood stabilizers	0/2 (0–5)	0/0 (0–5)	$Z = -1.56$; $p = 0.12$	0/0 (0–5)	0/0 (0–5)	$Z = -0.82$; $p = 0.41$
IFD-antipsychotics	2/2 (0–5)	2/2 (0–5)	$Z = -1.31$; $p = 0.19$	2/2 (0–5)	2/2 (0–4)	$Z = -0.89$; $p = 0.37$
IFD-benzodiazepines	4/4 (0–5)	4/4 (0–5)	$Z = -3.13$; $p = 0.002$	4/4 (0–5)	4/4 (0–5)	$Z = -0.28$; $p = 0.78$

[a] Total number of depressive episodes divided by length of the illness.

[b] Total number of suicide attempts divided by length of the illness.

[c] Total number of hospitalizations divided by length of the illness.

also found higher levels of cognitive dysfunction in melancholic than in nonmelancholic depressed patients, primarily affecting executive functions, which involve the same brain networks (Valerio et al., 2021). Therefore, the psychomotor and neurological disturbances associated with melancholia in this study could support the proposal of dysfunction of brain networks connecting the prefrontal cortex and basal ganglia in the physiopathology of melancholia (Austin and Mitchell, 1995; Parker and Hadzi-Pavlovic, 1996). As with the other clinical features, after controlling for confounders, the differences in soft neurological signs and psychomotor disturbances between both subtypes of depression were marked when the diagnosis was assigned with the SMPI but only marginal and limited to the sequencing of complex motor acts when using the *DSM* specifier.

Taken together, the results may contribute toward an important debate on the classification of depression that nosologically positions melancholia both as a distinct entity, as part of a binary model of depression, or as a merely more severe condition, as part of a unitary model of depression (Parker and Hadzi-Pavlovic, 1996; Shorter, 2007). Since the operationalization of MDE diagnostic criteria in the *DSM-III* (1980), the unitary model prevailed, and melancholia was relegated to a specifier. In subsequent years, some studies using *DSM* criteria failed to find differences between melancholic and nonmelancholic depression in different validators, reinforcing the unitary model (Angst et al., 2007; Melartin et al., 2004; Tondo et al., 2020). However, it has been claimed that the *DSM* specifier does not accurately distinguish between melancholic and nonmelancholic depressions, which might have contributed to explaining those negative findings (Martino et al., 2019; Parker et al., 2010a). Of note, similar to previous studies (Caldieraro et al., 2013; Parker et al., 2013b), the use of the *DSM* specifier led to an increased prevalence of melancholia in our sample, likely reflecting the overlap with MDE criteria (Martino et al., 2019; Parker et al., 2010a). Moreover, when melancholia was diagnosed using *DSM-5* criteria, most differences vanished after controlling for the severity of mood symptomatology in the present study. Overall, these findings might suggest that the *DSM-5* specifier identifies more severe depressive episodes rather than the core features of melancholia, and its use in studies comparing melancholic and nonmelancholic depressions through external validators could tautologically lead to the result that the differences are merely quantitative. Contrarily, when patients were allocated using the SMPI, melancholic and nonmelancholic depressions in both major depressive disorder and bipolar disorder differed in several clinical features regardless of the severity of the mood symptomatology. This pattern of results suggests that qualitative differences in external validators might emerge by using a diagnostic tool that "carves" more accurately between melancholic and nonmelancholic depressions. In fact, a recent study using the SMPI showed substantial differences in the clinical course of melancholic and nonmelancholic bipolar depressions (Martino et al., 2022). Therefore, further clinical research using diagnostic tools other than the *DSM* specifier might be more successful in elucidating potential qualitative differences between melancholia and nonmelancholic depressions.

Several limitations must be considered. Although patients with unipolar and bipolar depression were balanced in the melancholic and nonmelancholic groups and that diagnosis was included as a covariate in the regression analyses, future studies could replicate the present

TABLE 2. Psychomotor Disturbances and Neurological Soft Signs in Patients With Diagnosis of Melancholic and Nonmelancholic MDEs

	SMPI Criteria				*DSM-5* Criteria			
	Melancholic Patients	Nonmelancholic Patients			Melancholic Patients	Nonmelancholic Patients		
	(n = 36)	(n = 105)			(n = 74)	(n = 67)		
Variables	**Mean (SD)**	**Mean (SD)**	**Test; p-Value**	**Adjusted[a]**	**Mean (SD)**	**Mean (SD)**	**Test; p-Value**	**Adjusted[a]**
CORE-interaction	3.03 (3.38)	0.76 (0.41)	$Z = 8.21, p < 0.001$	$\beta = 1.85, p < 0.001$	1.41 (2.69)	0.19 (1.05)	$Z = 3.96, p = <0.001$	$\beta = 0.10, p = 0.76$
CORE-retardation	6.19 (4.33)	0.64 (1.45)	$Z = 7.70, p < 0.001$	$\beta = 4.13, p < 0.001$	3.34 (4.15)	0.64 (1.69)	$Z = 4.25, p < 0.001$	$\beta = 0.97, p = 0.07$
CORE-agitation	0.61 (0.96)	0.00 (0.00)	$Z = 6.16, p < 0.001$	$\beta = 0.30, p = 0.003$	0.30 (0.74)	0.00 (0.00)	$t = 3.38, p = 0.001$	$\beta = 0.03, p = 0.70$
CORE-total score	9.81 (7.83)	0.71 (1.69)	$Z = 8.15, p < 0.001$	$\beta = 6.27, p < 0.001$	5.03 (7.02)	0.84 (2.60)	$Z = 4.36, p < 0.001$	$\beta = 1.11, p = 0.19$
NES-sensory integration	3.75 (2.16)	3.43 (1.98)	$t = 0.82, p = 0.41$	$\beta = -0.02, p = 0.97$	3.81 (2.14)	3.18 (1.84)	$t = 1.89, p = 0.06$	$\beta = 0.17, p = 0.65$
NES-motor coordination	2.31 (1.77)	1.29 (1.55)	$Z = 3.30, p = 0.001$	$\beta = 0.90, p = 0.02$	1.92 (1.76)	1.13 (1.47)	$t = 2.89, p = 0.005$	$\beta = 0.51, p = 0.09$
NES-motor sequencing	3.31 (2.20)	1.83 (1.93)	$Z = 3.61, p < 0.001$	$\beta = 1.66, p < 0.001$	2.69 (2.18)	1.67 (1.88)	$t = 2.95, p = 0.004$	$\beta = 0.82, p = 0.04$
NES-total score	12.36 (6.03)	8.37 (5.25)	$Z = 3.49, p < 0.001$	$\beta = 3.47, p = 0.004$	10.91 (6.08)	7.72 (4.78)	$Z = 3.27, p = 0.001$	$\beta = 1.80, p = 0.07$

[a] Adjusted for age, diagnosis (bipolar disorder versus major depressive disorder), MADRS score, YMRS score, psychotic symptoms, suicide attempts, age at illness onset, and benzodiazepines exposure.

findings in these subsets of patients separately. In addition, the majority of women included in this study could have prevented us from finding differences in the sex distribution of melancholic and nonmelancholic depressions. Likewise, although there were only differences between groups in benzodiazepine exposure that were statistically controlled, we cannot rule out the impact of medication (*e.g.*, individual antipsychotics, mood stabilizers) on the results. Finally, nonmelancholic depressions are probably a heterogeneous clinical construct relevant for better characterization in future studies.

CONCLUSIONS

In summary, we found differences in several clinical characteristics between melancholic and nonmelancholic depressed patients, including a higher prevalence of psychotic symptoms and the presence of more psychomotor disturbances and neurological soft signs. Our results support the hypothesis that melancholia represents a distinct entity rather than a merely more severe form of MDE. In addition, we found further evidence on the usefulness of the SMPI and the limitations of the *DSM-5* specifier for studies addressing external validators of melancholia. To the best of our knowledge, this is the first study to compare the presence of neurological soft signs in a sample of melancholic and nonmelancholic acute depressed patients. Future studies might confirm and expand these findings.

DISCLOSURE

Author contributions: Dr Martino directed the project. Drs Martino and Valerio participated in the design of the study, created the database, analyzed the data, and wrote the first draft of the manuscript. Drs Martino, Valerio, Lomastro, and Igoa assessed the patients. All the authors were involved in revising the article, contributed to intellectual content, and read and provided approval of the final version to be published.

Ethical considerations: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The Hospital Ethics Committee approved the study, and all subjects gave written informed consent after receiving a complete description of the study.

The authors declare no conflict of interest.

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