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Atypical depression and emotion dysregulation: clinical and psychopathological features

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Abstract:	Background Most atypical depression (AD) cases endorse prominent mood reactivity, anxiety, and interpersonal sensitivity, resembling some of the characteristics of emotional dysregulation (ED). The present study assesses the frequency and clinical features of different levels of ED in ADyes vs. non-AD(ADno) cases. Methods The present cross-sectional study discriminated depressed outpatients screened with the Hamilton Depression rating scale with the Atypical Depression Supplement (SIGH-ADS), Symptom Checklist-90-Revised, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire, 110-item version, 36-item Difficulties in Emotion Regulation Scale (DERS), and Young Mania Rating Scale into people with high (EDhigh) vs. low (EDlow) for a broad range of clinical and psychopathological features. Descriptive statistics were followed by random forest analysis with “out-of-bag”[OOB] computation.

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	Results We included 326 patients (MDD=204[62.60%], BD-II=105[32.20%], and BD-I=17[5.20%]). ADyesEDhigh cases had the earliest age at the onset of depression and overall clinical burden. Higher scores at interpersonal sensitivity, somatization, early age at onset of depression, anxious features, non-atypical core of depression, cyclothymic and depressive temperament, DERS total, and strategies scores predicted higher odds of atypical depression (OOB=0.25). Among other predictors, age at onset of depression somatization and cyclothymic temperament predicted EDhigh group membership (OOB=0.23). Hyperthymic temperament, the SIGH-ADS atypical balance percentage score, and somatization emerged as top predictors of treatment-resistant-depression (OOB=0.12) in contrast to the SIGH-ADS-8-item atypical balance, psychotic features, and age at onset for treatment-resistant-bipolar-depression (OOB=0.16). Limitations Cross-sectional design; treatment-seeking outpatients. Conclusions AD and ED represent intertwined clinical entities potentially relevant to enhanced treatment outcomes, warranting more accurate random-forest models.
Opposed Reviewers:	
Response to Reviewers:	

Naples, December 11th, 2024

Dear Dr. Brambilla, Dear Dr. Soares,

The co-authors and I would like to submit for consideration for publication in the Journal of Affective Disorders the present report entitled: *"Atypical depression and emotion dysregulation: clinical and psychopathological features*".

The present cross-sectional study appraises a broad range of clinical and psychopathological features across people with depression with atypical features vs. cases of depression without atypical features, with an emphasis on different levels of emotional dysregulation and treatment outcomes by implementing both descriptive statistics and machine learning algorithms.

The study included 326 patients (MDD=204[62.60%], BD-II=105[32.20%], and BD-I=17[5.20%]). Cases with atypical depression and high levels of emotion dysregulation ($AD^{yes}ED^{high}$) had the earliest age at the onset of depression and overall clinical burden. Higher scores at interpersonal sensitivity, somatization, early age at onset of depression, anxious features, non-atypical core of depression, cyclothymic and depressive temperament, DERS total, and strategies scores predicted higher odds of atypical depression in random-forest classification analyses (Out-of-bag/OOB=0.25). Among other predictors, age at onset of depression somatization and cyclothymic temperament predicted ED^{high} group membership (OOB=0.23). Hyperthymic temperament, the SIGH-ADS atypical balance percentage score, and somatization emerged as top predictors of treatment-resistant-depression (OOB=0.12) in contrast to the SIGH-ADS-8-item atypical balance, psychotic features, and age at onset for treatment-resistant-bipolar-depression (OOB=0.16).

The clinical implications (and the study limitations) have been fully acknowledged in the report, and procedures have been a-priori approved by the local Ethical Committee, as detailed in the main text.

We warrant that this work represents original material and does not infringe upon any third party's copyright. No part of the work has been published or will be submitted for publication elsewhere unless and until the Journal of Affective Disorders rejects it. To our knowledge, the present work contains no unlawful matter. All the authors have contributed substantially to the scientific process. They have all participated in drafting the manuscript and reviewing/revising it. Finally, I and the coauthors approve the submission of this work and all subsequent revisions for publication and transfers, assign, or otherwise convey all copyright ownership to the Journal of Affective Disorders in case of editorial acceptance. None of the authors has any conflict of interest in financial disclosure to declare in conjunction with the present work. Finally, we agree to indemnify the Publisher against any loss or damages arising from a breach of this agreement, and we agree that if our submission is not published, copyright ownership shall revert to us.

We are grateful for your consideration of the present submission.

Yours sincerely,

Michele Fornaro, MD, PhD, on behalf of the co-authors.

Naples, February 1st, 2025

Re: JAFD-D-24-09470 – "*Atypical depression and emotion dysregulation: clinical and psychopathological features*".

Dear Dr. Sanches, dear Reviewers,

Thank you for your revision. Please find below a point-to-point response to the raised comments. The corresponding editing has been highlighted in the main-text and its attachments for your convenience.

Reviewer 1: Dear Colleagues,

This is a timely and interesting study on the topic of emotion dysregulation, an increasingly studied transdiagnostic construct which could potentially allow for intradiagnostic stratification within categorical disorders.
Among its points of strength, this study brings a throughout symptomatic definition of the patients sample. Also, from background to conclusions, the study is presented in a clear way, with meaningful tables and images.

Thank you so much for appreciating our work.

I have some minor commentaries to propose, the first of which is more conceptual.

Q1) *Among the significant factors associated with ED, early age of first depression, female sex, bulimia comorbidity, somatic symptoms and, from a neurobiological standpoint, a clear implication of the noradrenergic system, all factors associated with ADHD comorbidity, which appears surprisingly low in the sample.
Also, the characteristics enlisted in your conclusion seem to clinically converge towards an ADHD phenotype. Could this be a kind of historical diagnosis bias in the clinical enrollment site? I believe it should be disclosed and addressed in the discussion section.

R1) Dear Reviewer, Thank you so much for your insightful remark. In the original table, n.1, we correctly reported 30 patients out of 326 cases diagnosed with ADHD, but a typo occurred in the percentage, which was listed as 0.09%. We are grateful to you for spotting this.

Besides, some of the outpatients with a potential primary diagnosis of ADHD seeking medical consultation in our tertiary unit are automatically referred to an alternative facility in our department devoted to ADHD. This may have contributed to relatively overshadowing it in favor of phenotypically-related conditions such as depression at an early age onset, especially in females or people with comorbid bulimia and somatic symptoms (which, we agree with you, may also share a common neurobiological underpinning involving noradrenaline as a core neurotransmitter). We nonetheless adopted the SCID to minimize the chance of historical diagnostic bias. (30/326). Finally, while we expected a slightly higher prevalence of ADHD among people with higher levels of emotional dysregulation, especially those with atypical features of depression, we could not detect a statistically significant difference across the subgroups, so the supplementary material n.2 does not follow up with contrasts for that specific variable.

Please refer to the edited content in Table 1 for the correct percentage of ADHD, which is 9.2%, and to the edited version of the discussion (page n.15) to fully acknowledge your clinical insight, which is highly appreciated!

Q2) Also, the sample seems a bit underpowered or, better said, on the lower end of the minimum size, but I think this can be simply clearly stated in the limitations. Ideally, a dimension reduction before the ML approach could have sorted out this issue, maintaining the more preliminary nature of the Gini approach.

R2) While the overall sample size exceeds 300 patients, allowing for the allocation of 80% of the sample to the training of the ML model, we acknowledge that the sample size of specific subsets may have resulted in the lower end (actually, a result of the study). We carefully appraised your elegant and insightful comment about dimensional reduction (e.g., PCA) to allow a more efficient and parsimonious Gini indexing in the RF.

The pros: a dimension reduction method before using the ML approach could help address issues of overfitting or noise, especially with a smaller sample size. Techniques like or even feature selection methods could focus on retaining the most essential information while simplifying the dataset. This could align well with the Gini approach by streamlining the input space while maintaining its exploratory and preliminary nature.

The cons: Decision trees inherently handle feature selection. Trees prioritize splitting on the most relevant features by their design, effectively reducing noise. Retaining essential information is effective, but “essential” information-theoretically means that even a tiny (yet not necessarily negligible or clinically irrelevant) amount of information would be left behind, which should be an undesired outcome for an explorative report. Specifically, since the goal of this analysis was exploratory, we chose to maintain the current approach. Decision trees inherently manage feature selection; by their design, trees prioritize splitting on the most relevant features, effectively reducing noise.

We are nonetheless grateful for such a skilled remark. Thus, we added this sentence to the limitations: “While the goal of the present analysis was exploratory, future studies could explore hybrid dimension reduction techniques (e.g., correlation thresholding followed by principal component analysis) to refine the feature space and improve the robustness of results) to mitigate the potential influence of dimensionality and sample size constraints.” Please refer to the edited passage on page n.17.

Q3) *the Italian-validated version of the scales used should be acknowledged.

R3) Correct; please refer to edited passages on page n.7 for the updated references.

Q4) *The abbreviations used throughout the manuscript are a bit reader-unfriendly (e.g. "ADyesEDhigh"), and maybe the authors could consider more fluent abbreviations).

R4) Thank you for your suggestion. While we understand this labeling is not the best for the final reader, it nonetheless allowed for a clear-cut report and relatively succinct labels across multiple tables, figures, and supplementary material. Therefore, we preferred to retain it even

in the main text, as we think the final reader could quickly get accustomed to it after reading the first lines of the methods onward.

Q5) *In order to improve readability, all tables and images should independently explain the abbreviations used.

R5) Thank you for this input; main tables (1-4) were further reviewed accordingly. Additional content was likewise revised, even if it was supplementary material.

Reviewer 2: The manuscript aims to evaluate the relationships between Atypical Depression (AD) and Emotional Dysregulation (ED) in a population of outpatients with MDD.
The methodology is clearly described and the results clearly reported.

Thank you so much for your positive feedback.

Q1) The results are largely expected and, at least in part, tautological. For this reason, at the end of the introduction, the authors should report the hypotheses on which the study was planned.

R1) Correct. The substantial overlap expected between depression with atypical features and prominent emotional dysregulation is part of the rationale hypothesis for the study, aimed at quantitatively testing such a premise. Therefore, we specifically appended a sentence for that in the revised version of the introduction. Please refer to page n.5, bottom lines.

Q2) The diagnosis of atypical depression includes trait mood reactivity among its criteria, therefore it is not surprising that it is associated with the presence of ED. The presence of trait ED involves the presence of cyclothymic temperament, cluster B personality disorders and resistance/non-response to antidepressant treatments. Furthermore, the study confirms the relationship with bipolar spectrum disorders and comorbidity with anxiety disorders and bulimia nervosa. The main conclusion of the study confirms that trait mood reactivity, cyclothymic temperament and emotional dysregulation are constructs that are partly superimposable on a clinical and diagnostic level. This consideration should be added to the conclusions.

R2) Once again, this is a very relevant remark. We agree that this is a significant implication of the study, so we explicitly reinforced it even at the end of the conclusions. Please see page n.18 for the edited passage.

We thank you again for your valuable revisions. I hope the present manuscript version suits publication in the Journal of Affective Disorders.

Sincerely Yours,

Michele Fornaro, MD, Ph.D., on behalf of the co-authors.

Study Highlights:

- Atypical depression (AD) is a frequent occurrence, especially in the outpatient setting.
- AD and emotion dysregulation (ED) have not previously been systematically assessed despite their psychopathological intertwined relationship and clinical implications.
- AD and ED are tightly associated against each and affect treatment outcomes of depression.

Abstract (249/250 words)

Background: Most atypical depression (AD) cases endorse prominent mood reactivity, anxiety, and interpersonal sensitivity, resembling some of the characteristics of emotional dysregulation (ED). The present study assesses the frequency and clinical features of different levels of ED in AD^{yes} vs. non-AD(AD^{no}) cases. **Methods**: The present cross-sectional study discriminated depressed outpatients screened with the Hamilton Depression rating scale with the Atypical Depression Supplement (SIGH-ADS), Symptom Checklist-90-Revised, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire, 110-item version, 36-item Difficulties in Emotion Regulation Scale (DERS), and Young Mania Rating Scale into people with high (ED^{high}) vs. low (ED^{low}) for a broad range of clinical and psychopathological features. Descriptive statistics were followed by random forest analysis with "out-of-bag"[OOB] computation. **Results**: We included 326 patients (MDD=204[62.60%], BD-II=105[32.20%], and BD-I=17[5.20%]). $AD^{yes}ED^{high}$ cases had the earliest age at the onset of depression and overall clinical burden. Higher scores at interpersonal sensitivity, somatization, early age at onset of depression, anxious features, non-atypical core of depression, cyclothymic and depressive temperament, DERS total, and strategies scores predicted higher odds of atypical depression (OOB=0.25). Among other predictors, age at onset of depression somatization and cyclothymic temperament predicted ED^{high} group membership (OOB=0.23). Hyperthymic temperament, the SIGH-ADS atypical balance percentage score, and somatization emerged as top predictors of treatment-resistant-depression (OOB=0.12) in contrast to the SIGH-ADS-8-item atypical balance, psychotic features, and age at onset for treatment-resistant-bipolar-depression (OOB=0.16). **Limitations**: Cross-sectional design; treatment-seeking outpatients. **Conclusions**: AD and ED represent intertwined clinical entities potentially relevant to enhanced treatment outcomes, warranting more accurate random-forest models.

Atypical depression and emotion dysregulation: clinical and psychopathological features

"AD-ED"

Text=4,107 words
Abstract=249 words
References=74
Figures=2
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Supplementary material=9

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Declaration of Competing Interest

EV has received grants and served as a consultant, advisor, or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbvie, Aimentia, Angelini, Biogen, Boehringer -Ingelheim, Casen-Recordati, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Janssen, Lundbeck, Organon, Otsuka, Sage, Sanofi-Aventis, Sunovion, Takeda, and Via- tris. All outside of the present work. MF received consulting fees & fees for non-CME/CE services from Angelini, AstraZeneca, Boehringer Ingelheim, Bristol Meyers Squibb, Eli Lilly, GlaxoSmithKline, Innova Pharma, Lundbeck, Pfizer, Sanofi, Servier—all outside of the present work. **MS** received honoraria/has been a consultant for Angelini, AbbVie, Boehringer Ingelheim, Lundbeck, and Otsuka. **MF** received honoraria from the American Society of Clinical Psychopharmacology (ASCP) for his speaker activities and served as a consultant for Angelini, Otsuka, Lundbeck, Sanofi-Aventis, and Boehringer Ingelheim.

Other authors have no competing interest to disclose with the present report.

Author statement, contributions

MF conceptualized the work, led patient enrollment, drafted the main document, and conducted the statistical analyses. Other authors either enrolled or assessed the patients, input the relevant data, assisted with manuscript drafting and statistical analyses, and contributed to the critical interpretation of the results.

Role of the Funding Source

There is no funding source to disclose in conjunction with the present piece of work.

Acknowledgments

None.

Revised manuscript (highlighted) Click here to view linked References

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"AD-ED"

Text=4,229 words
Abstract=249 words
References=75
Figures=2
Tables=4
Supplementary material=9

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Abstract (249/250 words)

Background: Most atypical depression (AD) cases endorse prominent mood reactivity, anxiety, and interpersonal sensitivity, resembling some of the characteristics of emotional dysregulation (ED). The present study assesses the frequency and clinical features of different levels of ED in AD^{yes} vs. non-AD(AD^{no}) cases. **Methods**: The present cross-sectional study discriminated depressed outpatients screened with the Hamilton Depression rating scale with the Atypical Depression Supplement (SIGH-ADS), Symptom Checklist-90-Revised, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire, 110-item version, 36-item Difficulties in Emotion Regulation Scale (DERS), and Young Mania Rating Scale into people with high (ED^{high}) vs. low (ED^{low}) for a broad range of clinical and psychopathological features. Descriptive statistics were followed by random forest analysis with "out-of-bag"[OOB] computation. **Results**: We included 326 patients (MDD=204[62.60%], BD-II=105[32.20%], and BD-I=17[5.20%]). $AD^{yes}ED^{high}$ cases had the earliest age at the onset of depression and overall clinical burden. Higher scores at interpersonal sensitivity, somatization, early age at onset of depression, anxious features, non-atypical core of depression, cyclothymic and depressive temperament, DERS total, and strategies scores predicted higher odds of atypical depression (OOB=0.25). Among other predictors, age at onset of depression somatization and cyclothymic temperament predicted ED^{high} group membership (OOB=0.23). Hyperthymic temperament, the SIGH-ADS atypical balance percentage score, and somatization emerged as top predictors of treatment-resistant-depression (OOB=0.12) in contrast to the SIGH-ADS-8-item atypical balance, psychotic features, and age at onset for treatment-resistant-bipolar-depression (OOB=0.16). **Limitations**: Cross-sectional design; treatment-seeking outpatients. **Conclusions**: AD and ED represent intertwined clinical entities potentially relevant to enhanced treatment outcomes, warranting more accurate random-forest models.

Keywords: Atypical depression; emotion dysregulation; bipolar disorder; major depressive disorder; treatment-resistance.

1. **Introduction**

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013) identifies atypical depression (AD) as a specifier of depressive episodes for both major depressive disorder (MDD) and bipolar disorders (BDs). The presence of mood reactivity defines AD alongside at least two additional symptoms: i) weight gain or increased appetite, ii) hypersomnia, iii) leading paralysis, or iv) a long-lasting pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment (DSM-5) (APA, 2013).

Emerging evidence suggests that AD and typical depression are not only clinically distinct but also exhibit different neurobiological underpinnings (Badini et al., 2022; Chae et al., 2023; Oliva et al., 2023b), as already historically postulated upon the observation of a preferential response of AD towards the Monoamine Oxidase Inhibitors (MAOIs) rather than the tricyclic antidepressants (TCAs) (West and Dally, 1959), long before the postulate of an 'atypical' depressive syndrome characterized by reverse neurovegetative symptoms, such as hyperphagia, increased sleep, weight gain, and increased sexual drive (Davidson et al., 1982). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and imbalances in major signaling pathways, including serotonin and dopamine, have been implicated in depression (Murck, 2003). However, noradrenaline has been postulated as the core neurotransmitter involved in the pathophysiology of AD (Asnis et al., 1995). These changes in molecular neurobiology can affect those brain regions crucial for emotional and cognitive functioning, including the prefrontal cortex (PFC), whose ventromedial portion is involved in emotion regulation and integrates emotional feedback in decision-making. In contrast, its dorsolateral portion plays a crucial role in cognitive control and regulation of emotional responses. Dysfunctional activity within the amygdala, a region critical for emotion processing and autonomic regulation, and hippocampus has been theorized to exacerbate emotional instability further and contribute to the dysregulated emotional responses seen in AD (Etkin et al., 2015).

An intriguing yet debated (Quitkin et al., 2003) model challenging the construct of AD first incorporated in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (APA, 1994) redefined the disorder as a dimensional non-melancholic syndrome in which individuals with a personality subtype of "interpersonal rejection sensitivity" are prone to develop anxiety disorders and depression, exhibiting both emotion dysregulation (ED) and self-consolatory responses (Parker and Manicavasagar, 2005; Parker and Thase, 2007), thus questioning the primacy of "mood reactivity" (the ability of one's mood to "brighten" in response to positive events or expectancy) as a core distinctive feature of AD vs. typical depression (Łojko and Rybakowski, 2017).

A central convergence point between AD and ED—a phenomenon encompassing maladaptive patterns of emotional identification and expression in intensity, duration, and response (D'Agostino et al., 2017; Gross, 2015), lies in the maladaptive cognitive and affective processing underlying both conditions. For instance, an increased emotional reactivity to environmental stimuli can drive mood shifts. In contrast, emotional reasoning distortions may underlie interpersonal rejection hypersensitivity since individuals with high ED may engage in catastrophizing, interpreting minor or ambiguous social cues as evidence of inevitable rejection or disapproval (Deperrois and Combalbert, 2022). Similarly, physical manifestations such as leaden paralysis (i.e., a sense of heaviness in the limbs) can be seen as a somatic expression of emotional overload (Parker et al., 2002), maladaptively linking physical sensations to emotional states. Hyperphagia may represent a shift from food as a basic biological necessity to a coping mechanism for regulating negative affect (Macht, 2008). Chronicity and persistence (AD tend to be more chronic compared to typical depression, thus leading to periods of emotional instability and difficulty in achieving emotional balance, fostering emotional instability) may nonetheless represent shared core features of both AD and enduring ED.

The observable affective features in AD and ED also encompass overlapping characteristics with the bipolar spectrum, especially the temperamental lability observed in cyclothymia,

suggesting that these conditions may represent different phenotypic expressions of an underlying bipolar diathesis, particularly in Type II BD (BD-II) women (Perugi et al., 2015) arguably underpinned by a common genetic and neurobiological predisposition (Akiskal and Benazzi, 2005) spanning across MDD (Visted et al., 2018) and BD (De Prisco et al., 2022) without rarity zones, instead bounding with other mental disorders, especially borderline personality disorder (De Prisco et al., 2023; Miola et al., 2022). Also, ED is significantly associated with depressive symptoms (Oliva et al., 2023a) and with rumination identified as the regulation strategy most strongly linked to symptoms overall (Oliva et al., 2024).

To the best of our knowledge, to date, no comprehensive assessment of ED in AD vs. typical depression has been carried out to date even if a substantial clinical and psychopathological overlap between atypical features of depression and prominent emotional dysregulation is expected.

The present study aims to i) explore the differences in ED along with a broad range of clinical and psychopathological features of depression between patients with DSM-IV-TR-defined AD and non-AD; ii) identify predictors of treatment resistance and evaluate the potential of ED as a clinical marker for improved stratification relevant to clinical making for AD by leveraging machine learning techniques (random forest—RF) analysis to discriminate high vs. low ED groups.

2. Methods

Outpatients referred to the "Second Polyclinic Hospital, Section of Psychiatry, of the Federico II University of Naples, Italy" (a large-scale hospital including both general psychiatry and tertiary care mood disorder facilities) were consecutively appraised between June 2023 and October 2024 to achieve a meaningful sample allowing for RF. Ethical approval for this study was obtained from the local Ethics Committee (Protocol n.:160.2023), adhering to the principles of the Declaration of Helsinki upon procedures fully explained by the appointed primary investigator (MF). All patients met the DSM-5 criteria for a current major depressive episode (MDE) in the context of MDD or BD, validated by the Structured Clinical Interview for DSM-5 Disorders—Clinician Version (SCID-5-CV) (First et al., 2015). Exclusion criteria were the presence of psychotic features of depression (either congruent or incongruent ones), marked cognitive impairment (including those associated with Parkinson's disease or other organic brain diseases), intellectual disability, inability or refusal to provide valid informed consent.

2.1 Subjects

Patients endorsing atypical features of depression (AD^{yes}) were deemed as cases. People without atypical features were deemed controls (AD^{no}). Patients were of both sexes and were aged 18-65.

2.2a Measures and Procedures: essential clinical and treatment history

The treatment history of the patients was recorded owing to the following operative definitions for treatment-resistant (unipolar) depression – TRD: "failure to respond to two adequate trials of antidepressants" (Fava, 2003) and treatment-resistant bipolar depression (TRBD): "failure to reach sustained symptomatic remission for eight consecutive weeks after two different trials with adequate monotherapies or at least one other monotherapy and combination treatment" (Hidalgo-Mazzei et al., 2019).

2.2b Measures and Procedures: comprehensive psychopathological assessment

Depressive symptoms were evaluated through the Atypical Depression Supplement (SIGH-ADS) of the Hamilton Depression (HAM-D) rating scale (Hamilton, 1960) (Williams and Terman, 2003). SIGH-ADS comprises 21 items from the HAM-D—only the first 17 items are included in the computation of the HAM-D-17 total score, and eight additional items assess the atypical features of depression. Therefore, SIGH-ADS provides a 25-item score based on the first 17 items of the original HAM-D plus eight specific atypical items. The 8-item atypical symptoms score divided by the 25-item SIGH-ADS score multiplied by 100 provides the percent "atypical balance" score. Precisely, the eight items of the atypical addendum of the SIGH-ADS assess social withdrawal, increased appetite, increased eating, weight gain, carbohydrate craving or eating, hypersomnia, fatigability, and pattern of depression symptoms being worse in the afternoon. The SIGH-ADS also includes two un-scored questions regarding difficulty awakening and temperature discomfort suggestive of AD (Williams and Terman, 2003). The Young Mania Rating Scale (YMRS) (Young et al., 1978) assessed (subclinical) manic symptoms: YMRS scores ≤2 and a score >2 and <12 were deemed suggestive of "pure" and "mixed" depression, respectively (Miller et al., 2016). The general psychopathological symptomatology was evaluated with the Symptom Checklist-90-Revised (SCL-90-R), a multi-scale measure of current psychopathological symptomatology. The SCL-90-R comprises nine subscales, namely somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism (Derogatis, 1994). The Italian validation of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire, 110-item version (TEMPS-A-110) (Pompili et al., 2008) was administered to assess the predominant affective temperament(s), producing continuous measures for five affective temperaments: cyclothymic, dysthymic, irritable, hyperthymic, and anxious. Finally, the 36-item self-report tool Difficulties in Emotion Regulation Scale (DERS) assessed emotion regulation problems (Gratz and Roemer, 2004), submitted in its Italian adaptation (Giromini et al., 2012). The DERS measures six domains of emotional dysregulation: i) lack of awareness of emotional responses, ii) lack of clarity of emotional responses, iii) nonacceptance of emotional responses, iv) limited access to emotion regulation

strategies perceived as effective, v) difficulties controlling impulses when experiencing negative emotions, and vi) and difficulties in engaging in goal-directed behaviors when experiencing negative emotions. The total score of the DERS (range 36-180) was used to stratify participants into high emotion dysregulation (ED^{high}, scores in the 100^{th}-50^{th} percentile) and low emotion dysregulation (ED^{low}, scores in the 50^{th}-0^{th} percentile).

2.3 Statistical analysis

2.3.1 Interrater variability

Cohen' and Fleiss' κ, respectively, ascertained the levels of interrater agreement head-to-head and made multiple comparisons of the SIGH-ADS rating. They also ascertained the data distribution and homogeneity of the variance using Q-Q plots/computation of skewness and kurtosis and Levene's test.

2.3.2 Descriptive statistics

Parametric analyses for the demographic and clinical characteristics of the groups were performed using either the one- or two-way analysis of variance (ANOVA) tests followed up with Tukey HSD (Honestly Significant Difference) post-hoc correction for multiple comparisons along with η^2 effect sizes interpreted as follows: 0.01=small effect, 0.06=medium effect, and 0.14=large effect. Robust methods (i.e., bootstrapping) were preferred over data transformations and non-parametric tests (Kruskal-Wallis's test, eventually followed by Dunn correction along ε^2 effect sizes: $0.06 \leq \eta^2 < 0.14$=small; $0.06 \leq \eta^2 < 0.14$=medium; $\eta 2 \geq 0.14\eta^2$=large). Categorical variables were compared using the χ^2 test with the Yates' correction as needed and Cramer's effect sizes: ≤0.2=small; 0.2≤ 0.6=medium-to-moderate; >0.6=large, or φ to measure the strength of the association: values closer to 0 indicate a weaker association, while values closer to 1 (or -1) indicate a stronger association. Pearson's correlations were performed on selected variables emerging as significantly differing across different subsets of patients (correlation coefficients, r=±0.2=weak; ±0.5=moderate; ±0.8=strong; ±1=perfect correlation). Missing data were excluded pairwise in descriptive statistics.

Conservative two-tailed tests were adopted across the analyses setting α=.05. The statistical analysis used R v.4.4.0 and RStudio v.2024.04.2 Build 764 software for Mac (R_Core_Team, 2024).

2.3.3 Machine learning

The 300+ sample size allowed for a robust RF test set without compromising model training using the "randomForest" v.4.7-1.2 and "randomForestExplainer" v.0.10.1 packages (Breiman, 2001). Regularization techniques addressed overfitting, including parameter tuning and model training on separate datasets for validation. Specifically, hyperparameter optimization was conducted to refine the number of trees and maximum depth parameters, ensuring robust performance. The training process incorporated cross-validation to evaluate model stability, prevent overfitting, and early stopping criteria when appropriate. The "caret" package v.6.0.94 allowed for training and tuning machine learning models, parameter optimization, and resampling (Kuhn, 2008). The "vip" package v.0.4.1 visualized the variable importance (Greenwell et al., 2020); "smotefamily" v.1.4.0 addressed imbalanced datasets by applying the Synthetic Minority Over-sampling Technique (SMOTE) (Siriseriwan, 2019). The "pROC" v.1.18.5 analyzed and visualized the performance of classification models, particularly the area-under-the-curve with receiving operating characteristics (AUC-ROC) (Robin et al., 2011). The Gini index/Gini impurity was computed from AUC as 2*AUC-1 allowed for the calculation of the amount of probability of a specific feature being classified incorrectly when selected randomly. In contrast, the minimal depth index computes the average distance between the root of a tree and the node/split where a given variable was used; smaller values of the minimal depth indicate an early contribution of the variable, that is, more discriminating power. Finally, we inspected missing data using the R package "skimr" (Quinn et al., 2019), and these were assumed to be missing at random. Therefore, we included only the variables presenting at least 75% of the available data in the model. For those contributing less than 25% of missing data, imputation was performed using the R package "missRanger" (Wright and Ziegler, 2015), which is based on the "missForest" algorithm (Stekhoven and Bühlmann, 2012) and uses an RF approach. The parameter "num.trees" was set at 500, and the out-of-bag (OOB) errors were calculated for each variable to

measure the accuracy according to the method outlined in previous evidence (Breiman, 2001); OOB errors ranged from 0 (better performance) to 1 (worse performance).

3. Results

Interrater variability was κ=.086 (95%Confidence Interval[C.I.]=0.61-1.00, *p*=<.001) for the SIGH-ADS was high (Gisev et al., 2013). Missing cases were about 2.84% (whole dataset).

3.1 Descriptive statistics: essential clinical and demographic features

Upon initial screening and subsequent application of inclusion and exclusion criteria, 326 patients were included in the analyses. Of those screened, 326 out of 339(97%) patients agreed to provide written informed consent; 13 did not meet the inclusion criteria (supplementary material n.1a: study flowchart and 1b: STrengthening the Reporting of OBservational studies in Epidemiology [STROBE] checklist (Cuschieri, 2019)). In our sample, 112 out of 326(34%) patients were diagnosed with AD.

The distribution of ED varied across AD and non-AD: χ^2=4.25[1], p=0.04, V=0.11, with AD^{yes} having higher odds of being ED^{high} than ED^{low} (odd ratio (OR)=1.66, 95%C.I.=1.05-2.65 (p=0.03). The median score of the DERS total was 91 (IQR=21.72, min=62, max=154), varying across different ADED patterns (figure n.1).

<Please insert figure 1 about here>

Table n.1 details the sample's essential demographic and clinical characteristics, table n.2 the essential psychometrics, and table n.3 the treatment history. The corresponding post-hoc comparisons for the variables statistically significantly differing across AD-ED configurations have been detailed in the supplementary material n.2-4.

<Please insert tables 1-3 here>

3.2 Selected comparisons and correlation measures

Among other measures, the DERS total scores varied across sexes and diagnoses (supplementary material n.5a-b). However, the DERS total score did not differ by the interaction of the two factors: F=1.04(2), p=0.35. As expected, the DERS total score differed between ED^{high} (118.02±15.50) and ED^{low} (75.30±7.75), t=31.57(324), p=<0.01. ED^{high} cases showed higher frequency of mixed features [χ^2=5.59(1), φ=0.14, p=0.02], lifetime bulimia nervosa [χ^2=18.65(1), φ=0.25, p=<0.01], borderline personality disorder [χ2=19.86(1), φ=0.26, p=<0.01] and attention-deficit-hyperactivity-disorder (ADHD) [χ^2=0.05(1), φ=0.02, p=0.82] vs. the ED^{low} group. Younger age at the onset of depression negatively correlated with the DERS total score both in the AD^{yes} [r= -0.46(95%C.I.= -0.59 to -0.30, p=<0.01)] and the AD^{no} (r= -0.41(95%C.I.= -0.52 to -0.29, p=<0.01) groups. The overall correlation measures are documented in figure n.2, along with additional essential metrics.

<Please insert figure 2 about here>

3.3 Prediction and classification of AD group membership

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the SCL-90-R interpersonal sensitivity (Gini-index=3.35) and somatization (Gini-index=3.26) scores, age at onset of depression (Gini-index=2.96), TEMPS-A-110 anxious temperament (Gini-index=2.62), HAM-D-17 (Gini-index=1.68), TEMPS-A-110 cyclothymic temperament (Gini-index=1.58), TEMPS-A-110 depressive temperament (Gini-index=1.44), DERS total score (Gini-index=1.37), SCL-90-R depressive score (Gini-index=1.24), and the DERS-strategies score (Gini-index=1.21). Supplementary material n.6 ranks the corresponding ORs.

<Please insert table 4 about here>

3.4 Prediction of ED group membership

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the age at onset of depression (Gini-index=2.95), SCL-90-R somatization (Gini-index=2.91), TEMPS-A-110 cyclothymic temperament (Gini-index=1.6), SIGH-ADS-Atypical balance percentage score (Gini-index=1.58), SCL-90-R anxiety (Gini-index=1.35), SIGH-ADS-8 atypical item score (Gini-index=1.32), TEMPS-A-110 irritable temperament (Gini-index=1.27), SIGH-ADS-25-item score (Gini-index=1.17), age (Gini-index=1.16), and the SCL-90-R depression score (Gini-index=1.06). Supplementary material n.7 ranks the corresponding ORs.

3.5 Prediction of treatment outcome: treatment-resistant depression

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the SCL-90-R anxiety (Gini-index=0.63), SCL-90-R somatization (Gini-index=0.62), SCL-90-R phobia (Gini-index=0.48) scores, DERS clarity score (Gini-index=0.48), SCL-90-R hostility (Gini-index=0.47), age (Gini-index=0.47), DERS goals (Gini-index=0.46), SCL-90-R obsessive-compulsive (Gini-index=0.46), SIGH-ADS-atypical balance percentage (Gini-index=0.45), and the TEMPS-A-110 hyperthymic temperament score (Gini-index=0.44). Supplementary material n.8 ranks the corresponding ORs.

3.6 Prediction of treatment outcome: treatment-resistant bipolar depression

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the DERS goals (Gini-index=0.39), DERS strategies (Gini-index=0.36), SCL-90-R psychotic (Gini-index=0.36), age (Gini-index=0.34), SCL-90-R anxiety (Gini-index=0.34), SIGH-ADS-25-item score (Gini-index=0.33), age at onset of depression (Gini-index=0.31), SIGH-ADS-8-item atypical item score (Gini-index=0.31), SIGH-ADS-Atypical balance percentage (Gini-index=0.31), and the SCL-90-R depressive score (Gini-index=0.30). Supplementary material n.9 ranks the corresponding ORs.

4. Discussion

This study highlights the relationship between AD and ED, emphasizing their shared clinical characteristics and implications for treatment outcomes. In our sample, approximately 34% of the patients satisfied the AD criteria, predominating among females and a significant subset meeting the requirements for BD-II. This prevalence aligns with previous studies, including STAR*D conducted on MDD patients, which reported a 15.70–36.60% prevalence of AD in both community and clinical settings (Rush et al., 1996). However, our sample's proportion of TRD cases is lower than the STAR*D one (14% vs. 33%). The rate of TRBD was nonetheless in line with that reported by lines of evidence across different operational definitions (Fornaro et al., 2020a).

Patients with high ED^{high} displayed a complex clinical profile, including earlier onset of depression, a cyclothymic temperament, and more significant psychopathological distress across the SCL-90-R interpersonal sensitivity and somatization. These findings support the hypothesis that ED severity, along with the categorical presence of AD (Cuijpers et al., 2017), may significantly influence the clinical picture and treatment outcomes since high levels of emotional dysregulation and atypical features were associated with a higher proportion of treatment-resistance, both in MDD and BD groups.

Additionally, individuals in the $AD^{yes}ED^{high}$ group exhibited significantly higher scores on the YMRS, further suggesting a connection between subtle mixed features and ED and their clinical and psychopathological proximity to the soft bipolar spectrum. This latter finding underscores the importance of considering bipolar traits in the clinical evaluation of AD patients with high ED levels, as mood dysregulation may reflect an underlying bipolar diathesis rather than purely unipolar depression.

Somatization emerged as a predictive factor for treatment resistance at the RF, which is sound considering that somatic symptoms have been associated with increased inflammatory cytokines and glutamate dysfunction (Bai et al., 2014) that may concur to explain the resistance to classical antidepressants. The SCL-90-R Anxiety subscale also demonstrated predictive potential for TRD,

consistent with literature identifying anxious distress as a subtype associated with more severe and usually treatment-resistant depression (McIntyre et al., 2023). The TEMPS-A-110 hyperthymic temperament subscale also predicted the treatment-resistance, raising the possibility of sub-threshold bipolarity or misdiagnosis, both of which may influence treatment response. Given the relevance of these findings, it is critical to thoroughly assess the presence of atypical features and ED, particularly in female patients with earlier depression onset, higher anxiety levels, and treatment resistance, since these clinical phenotypes can significantly diverge in terms of underlying neurobiology and treatment strategies. Yet, it is worth noticing that in our sample, ADHD failed to statistically significantly differ across varying ADED configurations and that its overall prevalence was relatively low despite the phenotypical and putative neurobiological common underpinnings with early-onset depression, especially among females with comorbid bulimia nervosa or somatic symptoms.

In particular, noradrenergic dysregulation has been postulated as a critical mechanism in AD (Asnis et al., 1995), potentially contributing to differential treatment response. Specifically, bupropion and MAO-I have shown greater efficacy (Thase, 2007), while TCAs usually prove ineffective. A noradrenergic dysfunction has also been theorized to underlie emotional dysregulation symptoms, including unstable emotional patterns, agitation, fear, irritability, or aggression (and also hyperarousal and insomnia), may reflect an impaired noradrenergic activity (Yamamoto et al., 2014), which is strongly associated with altered functioning of the salience network. This network, responsible for switching between the default mode network and the central executive network, plays a critical role in salience processing and emotional regulation (Jain et al., 2024). In our sample, patients with AD (particularly the ones in the $AD^{yes}ED^{high}$ subgroup) showed the highest lifetime rates of non-response to the TCAs (table n.3), consistent with the literature data. Although MAOIs may remain a viable option for severe and treatment-resistant cases, especially in AD, where TCAs are often ineffective, their prescription is limited by reduced availability in many countries and the risks associated with inexperienced clinical use (Berk et al., 2023). As a result, the

focus has shifted toward newer antidepressants with improved safety profiles (Cattaneo et al., 2020; Fornaro et al., 2021). In this regard, we were unable to enroll a meaningful sample of depressed patients with lifetime exposure to MAOIs.

Subscales of the DERS 'lack of clarity of emotional responses' and 'difficulties in engaging in goal-directed behaviors during negative emotions' emerged as significantly correlated to the treatment-resistance status in the RF model. A lack of clarity in identifying and understanding emotional experiences can lead to misinterpretation and overwhelm of internal states, exacerbating stress and vulnerability to interpersonal conflict. Similarly, the difficulty in maintaining goal-directed behaviors during emotional distress reflects an impaired capacity to regulate emotions effectively, leading to disengagement, avoidance, or impulsive actions. Psychotherapeutic approaches such as cognitive and dialectical behavioral therapies may help identify and challenge cognitive distortions, such as catastrophizing or overgeneralizing rejection, contributing to increased interpersonal sensitivity and mood reactivity (Gupta et al., 2019). Integrating these psychotherapeutic strategies with pharmacological treatments can help address cognitive and emotional factors driving the mood shifts that may be particularly useful in resistant patients to improve both emotional well-being and functional outcomes.

Finally, it is worth noticing that the RF models for ED, TRD, and TRBD group membership shared most of the top predictors, which could be perceived as an indirect confirmation of the intertwined nature of different ED-related clinical psychopathological features accounting for treatment outcomes, putatively underpinned by a common neurobiological predisposition too. Nonetheless, while the OOB errors for the RFs were reasonably low for the models, they indicate that there is still room for improvement in classification by forthcoming replication studies encompassing additional predictors.

4.1 Limitations of the study

The lack of ad-hoc measures, such as the Hypomania Checklist 32-items (HCL-32) (Fornaro et al., 2015a; Fornaro et al., 2015b), restricts our ability to fully characterize the sub-threshold bipolarity

measures that may be present in unipolar depression. No formal measure of personality traits beyond the DSM diagnosis of BPD was recorded. The negligible proportion of patients endorsing lifetime exposure to MAOIs hinders exploring their role in contemporary treatment paradigms (Giménez-Palomo et al., 2024), and the present study did not assess the eventual mediating role of specific medications on specific association measures of clinical psychopathology and outcomes. Since the data was cross-sectional, the eventual association change could not be studied over time (Vieta and De Prisco, 2024). In addition, reporting bias for social desirability or lack of self-awareness may have occurred since we employed self-reported rating scales. In contrast, Berkson's bias (Berkson, 1946) may have occurred due to the systematic exclusion of the most severe cases of depression, especially those with psychotic features (Halvorson and Humphreys, 2015). Finally, while the goal of the present analysis was exploratory, future studies could explore hybrid dimension reduction techniques (e.g., correlation thresholding followed by principal component analysis) to refine the feature space and improve the robustness of results) to mitigate the potential influence of dimensionality and sample size constraints.

4.2 Conclusions

Beyond the validity of the construct, DSM-defined "atypical" depression is very "typical", especially in the outpatient setting (Nierenberg et al., 1998), particularly among females with prominent anxiety (Halbreich and Kahn, 2007), BD-II (Benazzi, 1999), borderline personality disorder/predominant cyclothymic temperament (Perugi et al., 2011), and bulimia nervosa (Perugi et al., 2006)– being highest (21.54%) in our $AD^{yes}ED^{high}$ subset, further reinforcing the wisdom that AD and ED may represent intertwined, rather than stirred, entities. While the present study could not systematically explore the eventual mediating role of different levels of emotion regulation in relationship with, say, for example, prominent reverse neurovegetative symptoms vs. prominent mood reactivity subtypes of AD, we nonetheless hypothesize that AD may encompass different clinical and neurobiological subtypes, worth further assessment to enhance treatment outcomes of depression (Fornaro et al., 2020b) and to shed light on the controversies about the validity of the

construct of AD raised over the past decades (Łojko and Rybakowski, 2017). Also, the distribution of many clinical and psychopathological measures recorded in the present study varied according to ED grouping rather than AD grouping, further suggesting the hypothesis of heterogeneous subgroups of DSM-defined AD forms of depression.

The need for further stratification of depression to enhance treatment outcomes is particularly relevant for AD compared to melancholia (Cuijpers et al., 2017) since ad-hoc randomized clinical trials are lacking, with a few exceptions carried out in recent years (Fornaro et al., 2014) and most of the pharmacological evidence dating back to the MAOI era (Henkel et al., 2006), hindering direct or indirect comparison with the few modern medications released over recent years, instead prompting a network meta-analysis on the matter (*Fornaro M. et al., submitted for publication*). Overall, although the clinical lore has long held that those with AD represent less severe cases of depression compared to melancholia since the first would be less likely to be hospitalized, the present study shows that people with AD have often endorsed general medical comorbidities or treatment resistance in their lifetime period and associated with specific "dramatic" cluster patterns and higher scores at the cyclothymic temperaments beyond the DERS measures affecting their interpersonal and social functioning. Moreover, trait mood reactivity, cyclothymic temperament, and emotional dysregulation are partly superimposable on a clinical and diagnostic level, soliciting patient-tailored pharmacological or psychological interventions focusing on emotional regulation strategies.

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Atypical depression and emotion dysregulation: clinical and psychopathological features

"AD-ED"

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Abstract (249/250 words)

Background: Most atypical depression (AD) cases endorse prominent mood reactivity, anxiety, and interpersonal sensitivity, resembling some of the characteristics of emotional dysregulation (ED). The present study assesses the frequency and clinical features of different levels of ED in AD^{yes} vs. non-AD(AD^{no}) cases. **Methods**: The present cross-sectional study discriminated depressed outpatients screened with the Hamilton Depression rating scale with the Atypical Depression Supplement (SIGH-ADS), Symptom Checklist-90-Revised, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire, 110-item version, 36-item Difficulties in Emotion Regulation Scale (DERS), and Young Mania Rating Scale into people with high (ED^{high}) vs. low (ED^{low}) for a broad range of clinical and psychopathological features. Descriptive statistics were followed by random forest analysis with "out-of-bag"[OOB] computation. **Results**: We included 326 patients (MDD=204[62.60%], BD-II=105[32.20%], and BD-I=17[5.20%]). $AD^{yes}ED^{high}$ cases had the earliest age at the onset of depression and overall clinical burden. Higher scores at interpersonal sensitivity, somatization, early age at onset of depression, anxious features, non-atypical core of depression, cyclothymic and depressive temperament, DERS total, and strategies scores predicted higher odds of atypical depression (OOB=0.25). Among other predictors, age at onset of depression somatization and cyclothymic temperament predicted ED^{high} group membership (OOB=0.23). Hyperthymic temperament, the SIGH-ADS atypical balance percentage score, and somatization emerged as top predictors of treatment-resistant-depression (OOB=0.12) in contrast to the SIGH-ADS-8-item atypical balance, psychotic features, and age at onset for treatment-resistant-bipolar-depression (OOB=0.16). **Limitations**: Cross-sectional design; treatment-seeking outpatients. **Conclusions**: AD and ED represent intertwined clinical entities potentially relevant to enhanced treatment outcomes, warranting more accurate random-forest models.

Keywords: Atypical depression; emotion dysregulation; bipolar disorder; major depressive disorder; treatment-resistance.

1. **Introduction**

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013) identifies atypical depression (AD) as a specifier of depressive episodes for both major depressive disorder (MDD) and bipolar disorders (BDs). The presence of mood reactivity defines AD alongside at least two additional symptoms: i) weight gain or increased appetite, ii) hypersomnia, iii) leading paralysis, or iv) a long-lasting pattern of interpersonal rejection sensitivity resulting in significant social or occupational impairment (DSM-5) (APA, 2013).

Emerging evidence suggests that AD and typical depression are not only clinically distinct but also exhibit different neurobiological underpinnings (Badini et al., 2022; Chae et al., 2023; Oliva et al., 2023b), as already historically postulated upon the observation of a preferential response of AD towards the Monoamine Oxidase Inhibitors (MAOIs) rather than the tricyclic antidepressants (TCAs) (West and Dally, 1959), long before the postulate of an 'atypical' depressive syndrome characterized by reverse neurovegetative symptoms, such as hyperphagia, increased sleep, weight gain, and increased sexual drive (Davidson et al., 1982). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and imbalances in major signaling pathways, including serotonin and dopamine, have been implicated in depression (Murck, 2003). However, noradrenaline has been postulated as the core neurotransmitter involved in the pathophysiology of AD (Asnis et al., 1995). These changes in molecular neurobiology can affect those brain regions crucial for emotional and cognitive functioning, including the prefrontal cortex (PFC), whose ventromedial portion is involved in emotion regulation and integrates emotional feedback in decision-making. In contrast, its dorsolateral portion plays a crucial role in cognitive control and regulation of emotional responses. Dysfunctional activity within the amygdala, a region critical for emotion processing and autonomic regulation, and hippocampus has been theorized to exacerbate emotional instability further and contribute to the dysregulated emotional responses seen in AD (Etkin et al., 2015).

An intriguing yet debated (Quitkin et al., 2003) model challenging the construct of AD first incorporated in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (APA, 1994) redefined the disorder as a dimensional non-melancholic syndrome in which individuals with a personality subtype of "interpersonal rejection sensitivity" are prone to develop anxiety disorders and depression, exhibiting both emotion dysregulation (ED) and self-consolatory responses (Parker and Manicavasagar, 2005; Parker and Thase, 2007), thus questioning the primacy of "mood reactivity" (the ability of one's mood to "brighten" in response to positive events or expectancy) as a core distinctive feature of AD vs. typical depression (Łojko and Rybakowski, 2017).

A central convergence point between AD and ED—a phenomenon encompassing maladaptive patterns of emotional identification and expression in intensity, duration, and response (D'Agostino et al., 2017; Gross, 2015), lies in the maladaptive cognitive and affective processing underlying both conditions. For instance, an increased emotional reactivity to environmental stimuli can drive mood shifts. In contrast, emotional reasoning distortions may underlie interpersonal rejection hypersensitivity since individuals with high ED may engage in catastrophizing, interpreting minor or ambiguous social cues as evidence of inevitable rejection or disapproval (Deperrois and Combalbert, 2022). Similarly, physical manifestations such as leaden paralysis (i.e., a sense of heaviness in the limbs) can be seen as a somatic expression of emotional overload (Parker et al., 2002), maladaptively linking physical sensations to emotional states. Hyperphagia may represent a shift from food as a basic biological necessity to a coping mechanism for regulating negative affect (Macht, 2008). Chronicity and persistence (AD tend to be more chronic compared to typical depression, thus leading to periods of emotional instability and difficulty in achieving emotional balance, fostering emotional instability) may nonetheless represent shared core features of both AD and enduring ED.

The observable affective features in AD and ED also encompass overlapping characteristics with the bipolar spectrum, especially the temperamental lability observed in cyclothymia,

suggesting that these conditions may represent different phenotypic expressions of an underlying bipolar diathesis, particularly in Type II BD (BD-II) women (Perugi et al., 2015) arguably underpinned by a common genetic and neurobiological predisposition (Akiskal and Benazzi, 2005) spanning across MDD (Visted et al., 2018) and BD (De Prisco et al., 2022) without rarity zones, instead bounding with other mental disorders, especially borderline personality disorder (De Prisco et al., 2023; Miola et al., 2022). Also, ED is significantly associated with depressive symptoms (Oliva et al., 2023a) and with rumination identified as the regulation strategy most strongly linked to symptoms overall (Oliva et al., 2024).

To the best of our knowledge, to date, no comprehensive assessment of ED in AD vs. typical depression has been carried out to date even if a substantial clinical and psychopathological overlap between atypical features of depression and prominent emotional dysregulation is expected.

The present study aims to i) explore the differences in ED along with a broad range of clinical and psychopathological features of depression between patients with DSM-IV-TR-defined AD and non-AD; ii) identify predictors of treatment resistance and evaluate the potential of ED as a clinical marker for improved stratification relevant to clinical making for AD by leveraging machine learning techniques (random forest—RF) analysis to discriminate high vs. low ED groups.

2. Methods

Outpatients referred to the "Second Polyclinic Hospital, Section of Psychiatry, of the Federico II University of Naples, Italy" (a large-scale hospital including both general psychiatry and tertiary care mood disorder facilities) were consecutively appraised between June 2023 and October 2024 to achieve a meaningful sample allowing for RF. Ethical approval for this study was obtained from the local Ethics Committee (Protocol n.:160.2023), adhering to the principles of the Declaration of Helsinki upon procedures fully explained by the appointed primary investigator (MF). All patients met the DSM-5 criteria for a current major depressive episode (MDE) in the context of MDD or BD, validated by the Structured Clinical Interview for DSM-5 Disorders—Clinician Version (SCID-5-CV) (First et al., 2015). Exclusion criteria were the presence of psychotic features of depression (either congruent or incongruent ones), marked cognitive impairment (including those associated with Parkinson's disease or other organic brain diseases), intellectual disability, inability or refusal to provide valid informed consent.

2.1 Subjects

Patients endorsing atypical features of depression (AD^{yes}) were deemed as cases. People without atypical features were deemed controls (AD^{no}). Patients were of both sexes and were aged 18-65.

2.2a Measures and Procedures: essential clinical and treatment history

The treatment history of the patients was recorded owing to the following operative definitions for treatment-resistant (unipolar) depression – TRD: "failure to respond to two adequate trials of antidepressants" (Fava, 2003) and treatment-resistant bipolar depression (TRBD): "failure to reach sustained symptomatic remission for eight consecutive weeks after two different trials with adequate monotherapies or at least one other monotherapy and combination treatment" (Hidalgo-Mazzei et al., 2019).

2.2b Measures and Procedures: comprehensive psychopathological assessment

Depressive symptoms were evaluated through the Atypical Depression Supplement (SIGH-ADS) of the Hamilton Depression (HAM-D) rating scale (Hamilton, 1960) (Williams and Terman, 2003). SIGH-ADS comprises 21 items from the HAM-D—only the first 17 items are included in the computation of the HAM-D-17 total score, and eight additional items assess the atypical features of depression. Therefore, SIGH-ADS provides a 25-item score based on the first 17 items of the original HAM-D plus eight specific atypical items. The 8-item atypical symptoms score divided by the 25-item SIGH-ADS score multiplied by 100 provides the percent "atypical balance" score. Precisely, the eight items of the atypical addendum of the SIGH-ADS assess social withdrawal, increased appetite, increased eating, weight gain, carbohydrate craving or eating, hypersomnia, fatigability, and pattern of depression symptoms being worse in the afternoon. The SIGH-ADS also includes two un-scored questions regarding difficulty awakening and temperature discomfort suggestive of AD (Williams and Terman, 2003). The Young Mania Rating Scale (YMRS) (Young et al., 1978) assessed (subclinical) manic symptoms: YMRS scores ≤ 2 and a score >2 and <12 were deemed suggestive of "pure" and "mixed" depression, respectively (Miller et al., 2016). The general psychopathological symptomatology was evaluated with the Symptom Checklist-90-Revised (SCL-90-R), a multi-scale measure of current psychopathological symptomatology. The SCL-90-R comprises nine subscales, namely somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism (Derogatis, 1994). The Italian validation of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire, 110-item version (TEMPS-A-110) (Pompili et al., 2008) was administered to assess the predominant affective temperament(s), producing continuous measures for five affective temperaments: cyclothymic, dysthymic, irritable, hyperthymic, and anxious. Finally, the 36-item self-report tool Difficulties in Emotion Regulation Scale (DERS) assessed emotion regulation problems (Gratz and Roemer, 2004), submitted in its Italian adaptation (Giromini et al., 2012). The DERS measures six domains of emotional dysregulation: i) lack of awareness of emotional responses, ii) lack of clarity of emotional responses, iii) nonacceptance of emotional responses, iv) limited access to emotion regulation

strategies perceived as effective, v) difficulties controlling impulses when experiencing negative emotions, and vi) and difficulties in engaging in goal-directed behaviors when experiencing negative emotions. The total score of the DERS (range 36-180) was used to stratify participants into high emotion dysregulation (ED^{high}, scores in the 100^{th}-50^{th} percentile) and low emotion dysregulation (ED^{low}, scores in the 50^{th}-0^{th} percentile).

2.3 Statistical analysis

2.3.1 Interrater variability

Cohen' and Fleiss' κ, respectively, ascertained the levels of interrater agreement head-to-head and made multiple comparisons of the SIGH-ADS rating. They also ascertained the data distribution and homogeneity of the variance using Q-Q plots/computation of skewness and kurtosis and Levene's test.

2.3.2 Descriptive statistics

Parametric analyses for the demographic and clinical characteristics of the groups were performed using either the one- or two-way analysis of variance (ANOVA) tests followed up with Tukey HSD (Honestly Significant Difference) post-hoc correction for multiple comparisons along with η^2 effect sizes interpreted as follows: 0.01=small effect, 0.06=medium effect, and 0.14=large effect. Robust methods (i.e., bootstrapping) were preferred over data transformations and non-parametric tests (Kruskal-Wallis's test, eventually followed by Dunn correction along ε^2 effect sizes: $0.06 \leq \eta^2 < 0.14$=small; $0.06 \leq \eta^2 < 0.14$=medium; $\eta 2 \geq 0.14\eta^2$=large). Categorical variables were compared using the χ^2 test with the Yates' correction as needed and Cramer's effect sizes: ≤0.2=small; 0.2≤ 0.6=medium-to-moderate; >0.6=large, or φ to measure the strength of the association: values closer to 0 indicate a weaker association, while values closer to 1 (or -1) indicate a stronger association. Pearson's correlations were performed on selected variables emerging as significantly differing across different subsets of patients (correlation coefficients, r=±0.2=weak; ±0.5=moderate; ±0.8=strong; ±1=perfect correlation). Missing data were excluded pairwise in descriptive statistics.

Conservative two-tailed tests were adopted across the analyses setting α=.05. The statistical analysis used R v.4.4.0 and RStudio v.2024.04.2 Build 764 software for Mac (R_Core_Team, 2024).

2.3.3 Machine learning

The 300+ sample size allowed for a robust RF test set without compromising model training using the "randomForest" v.4.7-1.2 and "randomForestExplainer" v.0.10.1 packages (Breiman, 2001). Regularization techniques addressed overfitting, including parameter tuning and model training on separate datasets for validation. Specifically, hyperparameter optimization was conducted to refine the number of trees and maximum depth parameters, ensuring robust performance. The training process incorporated cross-validation to evaluate model stability, prevent overfitting, and early stopping criteria when appropriate. The "caret" package v.6.0.94 allowed for training and tuning machine learning models, parameter optimization, and resampling (Kuhn, 2008). The "vip" package v.0.4.1 visualized the variable importance (Greenwell et al., 2020); "smotefamily" v.1.4.0 addressed imbalanced datasets by applying the Synthetic Minority Over-sampling Technique (SMOTE) (Siriseriwan, 2019). The "pROC" v.1.18.5 analyzed and visualized the performance of classification models, particularly the area-under-the-curve with receiving operating characteristics (AUC-ROC) (Robin et al., 2011). The Gini index/Gini impurity was computed from AUC as 2*AUC-1 allowed for the calculation of the amount of probability of a specific feature being classified incorrectly when selected randomly. In contrast, the minimal depth index computes the average distance between the root of a tree and the node/split where a given variable was used; smaller values of the minimal depth indicate an early contribution of the variable, that is, more discriminating power. Finally, we inspected missing data using the R package "skimr" (Quinn et al., 2019), and these were assumed to be missing at random. Therefore, we included only the variables presenting at least 75% of the available data in the model. For those contributing less than 25% of missing data, imputation was performed using the R package "missRanger" (Wright and Ziegler, 2015), which is based on the "missForest" algorithm (Stekhoven and Bühlmann, 2012) and uses an RF approach. The parameter "num.trees" was set at 500, and the out-of-bag (OOB) errors were calculated for each variable to

measure the accuracy according to the method outlined in previous evidence (Breiman, 2001); OOB errors ranged from 0 (better performance) to 1 (worse performance).

3. Results

Interrater variability was κ=.086 (95%Confidence Interval[C.I.]=0.61-1.00, *p*=<.001) for the SIGH-ADS was high (Gisev et al., 2013). Missing cases were about 2.84% (whole dataset).

3.1 Descriptive statistics: essential clinical and demographic features

Upon initial screening and subsequent application of inclusion and exclusion criteria, 326 patients were included in the analyses. Of those screened, 326 out of 339(97%) patients agreed to provide written informed consent; 13 did not meet the inclusion criteria (supplementary material n.1a: study flowchart and 1b: STrengthening the Reporting of OBservational studies in Epidemiology [STROBE] checklist (Cuschieri, 2019)). In our sample, 112 out of 326(34%) patients were diagnosed with AD.

The distribution of ED varied across AD and non-AD: χ^2=4.25[1], p=0.04, V=0.11, with AD^{yes} having higher odds of being ED^{high} than ED^{low} (odd ratio (OR)=1.66, 95%C.I.=1.05-2.65 (p=0.03). The median score of the DERS total was 91 (IQR=21.72, min=62, max=154), varying across different ADED patterns (figure n.1).

<Please insert figure 1 about here>

Table n.1 details the sample's essential demographic and clinical characteristics, table n.2 the essential psychometrics, and table n.3 the treatment history. The corresponding post-hoc comparisons for the variables statistically significantly differing across AD-ED configurations have been detailed in the supplementary material n.2-4.

<Please insert tables 1-3 here>

3.2 Selected comparisons and correlation measures

Among other measures, the DERS total scores varied across sexes and diagnoses (supplementary material n.5a-b). However, the DERS total score did not differ by the interaction of the two factors: F=1.04(2), p=0.35. As expected, the DERS total score differed between ED^{high} (118.02±15.50) and ED^{low} (75.30±7.75), t=31.57(324), p=<0.01. ED^{high} cases showed higher frequency of mixed features [χ^2=5.59(1), φ=0.14, p=0.02], lifetime bulimia nervosa [χ^2=18.65(1), φ=0.25, p=<0.01], borderline personality disorder [χ2=19.86(1), φ=0.26, p=<0.01] and attention-deficit-hyperactivity-disorder (ADHD) [χ^2=0.05(1), φ=0.02, p=0.82] vs. the ED^{low} group. Younger age at the onset of depression negatively correlated with the DERS total score both in the AD^{yes} [r= -0.46(95%C.I.= -0.59 to -0.30, p=<0.01)] and the AD^{no} (r= -0.41(95%C.I.= -0.52 to -0.29, p=<0.01) groups. The overall correlation measures are documented in figure n.2, along with additional essential metrics.

<Please insert figure 2 about here>

3.3 Prediction and classification of AD group membership

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the SCL-90-R interpersonal sensitivity (Gini-index=3.35) and somatization (Gini-index=3.26) scores, age at onset of depression (Gini-index=2.96), TEMPS-A-110 anxious temperament (Gini-index=2.62), HAM-D-17 (Gini-index=1.68), TEMPS-A-110 cyclothymic temperament (Gini-index=1.58), TEMPS-A-110 depressive temperament (Gini-index=1.44), DERS total score (Gini-index=1.37), SCL-90-R depressive score (Gini-index=1.24), and the DERS-strategies score (Gini-index=1.21). Supplementary material n.6 ranks the corresponding ORs.

<Please insert table 4 about here>

3.4 Prediction of ED group membership

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the age at onset of depression (Gini-index=2.95), SCL-90-R somatization (Gini-index=2.91), TEMPS-A-110 cyclothymic temperament (Gini-index=1.6), SIGH-ADS-Atypical balance percentage score (Gini-index=1.58), SCL-90-R anxiety (Gini-index=1.35), SIGH-ADS-8 atypical item score (Gini-index=1.32), TEMPS-A-110 irritable temperament (Gini-index=1.27), SIGH-ADS-25-item score (Gini-index=1.17), age (Gini-index=1.16), and the SCL-90-R depression score (Gini-index=1.06). Supplementary material n.7 ranks the corresponding ORs.

3.5 Prediction of treatment outcome: treatment-resistant depression

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the SCL-90-R anxiety (Gini-index=0.63), SCL-90-R somatization (Gini-index=0.62), SCL-90-R phobia (Gini-index=0.48) scores, DERS clarity score (Gini-index=0.48), SCL-90-R hostility (Gini-index=0.47), age (Gini-index=0.47), DERS goals (Gini-index=0.46), SCL-90-R obsessive-compulsive (Gini-index=0.46), SIGH-ADS-atypical balance percentage (Gini-index=0.45), and the TEMPS-A-110 hyperthymic temperament score (Gini-index=0.44). Supplementary material n.8 ranks the corresponding ORs.

3.6 Prediction of treatment outcome: treatment-resistant bipolar depression

Model performances are outlined in table n.4. The top ten important variables based on the Gini's index ranking were the DERS goals (Gini-index=0.39), DERS strategies (Gini-index=0.36), SCL-90-R psychotic (Gini-index=0.36), age (Gini-index=0.34), SCL-90-R anxiety (Gini-index=0.34), SIGH-ADS-25-item score (Gini-index=0.33), age at onset of depression (Gini-index=0.31), SIGH-ADS-8-item atypical item score (Gini-index=0.31), SIGH-ADS-Atypical balance percentage (Gini-index=0.31), and the SCL-90-R depressive score (Gini-index=0.30). Supplementary material n.9 ranks the corresponding ORs.

4. Discussion

This study highlights the relationship between AD and ED, emphasizing their shared clinical characteristics and implications for treatment outcomes. In our sample, approximately 34% of the patients satisfied the AD criteria, predominating among females and a significant subset meeting the requirements for BD-II. This prevalence aligns with previous studies, including STAR*D conducted on MDD patients, which reported a 15.70–36.60% prevalence of AD in both community and clinical settings (Rush et al., 1996). However, our sample's proportion of TRD cases is lower than the STAR*D one (14% vs. 33%). The rate of TRBD was nonetheless in line with that reported by lines of evidence across different operational definitions (Fornaro et al., 2020a).

Patients with high ED^{high} displayed a complex clinical profile, including earlier onset of depression, a cyclothymic temperament, and more significant psychopathological distress across the SCL-90-R interpersonal sensitivity and somatization. These findings support the hypothesis that ED severity, along with the categorical presence of AD (Cuijpers et al., 2017), may significantly influence the clinical picture and treatment outcomes since high levels of emotional dysregulation and atypical features were associated with a higher proportion of treatment-resistance, both in MDD and BD groups.

Additionally, individuals in the $AD^{yes}ED^{high}$ group exhibited significantly higher scores on the YMRS, further suggesting a connection between subtle mixed features and ED and their clinical and psychopathological proximity to the soft bipolar spectrum. This latter finding underscores the importance of considering bipolar traits in the clinical evaluation of AD patients with high ED levels, as mood dysregulation may reflect an underlying bipolar diathesis rather than purely unipolar depression.

Somatization emerged as a predictive factor for treatment resistance at the RF, which is sound considering that somatic symptoms have been associated with increased inflammatory cytokines and glutamate dysfunction (Bai et al., 2014) that may concur to explain the resistance to classical antidepressants. The SCL-90-R Anxiety subscale also demonstrated predictive potential for TRD,

consistent with literature identifying anxious distress as a subtype associated with more severe and usually treatment-resistant depression (McIntyre et al., 2023). The TEMPS-A-110 hyperthymic temperament subscale also predicted the treatment-resistance, raising the possibility of sub-threshold bipolarity or misdiagnosis, both of which may influence treatment response. Given the relevance of these findings, it is critical to thoroughly assess the presence of atypical features and ED, particularly in female patients with earlier depression onset, higher anxiety levels, and treatment resistance, since these clinical phenotypes can significantly diverge in terms of underlying neurobiology and treatment strategies. Yet, it is worth noticing that in our sample, ADHD failed to statistically significantly differ across varying ADED configurations and that its overall prevalence was relatively low despite the phenotypical and putative neurobiological common underpinnings with early-onset depression, especially among females with comorbid bulimia nervosa or somatic symptoms.

In particular, noradrenergic dysregulation has been postulated as a critical mechanism in AD (Asnis et al., 1995), potentially contributing to differential treatment response. Specifically, bupropion and MAO-I have shown greater efficacy (Thase, 2007), while TCAs usually prove ineffective. A noradrenergic dysfunction has also been theorized to underlie emotional dysregulation symptoms, including unstable emotional patterns, agitation, fear, irritability, or aggression (and also hyperarousal and insomnia), may reflect an impaired noradrenergic activity (Yamamoto et al., 2014), which is strongly associated with altered functioning of the salience network. This network, responsible for switching between the default mode network and the central executive network, plays a critical role in salience processing and emotional regulation (Jain et al., 2024). In our sample, patients with AD (particularly the ones in the $AD^{yes}ED^{high}$ subgroup) showed the highest lifetime rates of non-response to the TCAs (table n.3), consistent with the literature data. Although MAOIs may remain a viable option for severe and treatment-resistant cases, especially in AD, where TCAs are often ineffective, their prescription is limited by reduced availability in many countries and the risks associated with inexperienced clinical use (Berk et al., 2023). As a result, the

focus has shifted toward newer antidepressants with improved safety profiles (Cattaneo et al., 2020; Fornaro et al., 2021). In this regard, we were unable to enroll a meaningful sample of depressed patients with lifetime exposure to MAOIs.

Subscales of the DERS 'lack of clarity of emotional responses' and 'difficulties in engaging in goal-directed behaviors during negative emotions' emerged as significantly correlated to the treatment-resistance status in the RF model. A lack of clarity in identifying and understanding emotional experiences can lead to misinterpretation and overwhelm of internal states, exacerbating stress and vulnerability to interpersonal conflict. Similarly, the difficulty in maintaining goal-directed behaviors during emotional distress reflects an impaired capacity to regulate emotions effectively, leading to disengagement, avoidance, or impulsive actions. Psychotherapeutic approaches such as cognitive and dialectical behavioral therapies may help identify and challenge cognitive distortions, such as catastrophizing or overgeneralizing rejection, contributing to increased interpersonal sensitivity and mood reactivity (Gupta et al., 2019). Integrating these psychotherapeutic strategies with pharmacological treatments can help address cognitive and emotional factors driving the mood shifts that may be particularly useful in resistant patients to improve both emotional well-being and functional outcomes.

Finally, it is worth noticing that the RF models for ED, TRD, and TRBD group membership shared most of the top predictors, which could be perceived as an indirect confirmation of the intertwined nature of different ED-related clinical psychopathological features accounting for treatment outcomes, putatively underpinned by a common neurobiological predisposition too. Nonetheless, while the OOB errors for the RFs were reasonably low for the models, they indicate that there is still room for improvement in classification by forthcoming replication studies encompassing additional predictors.

4.1 Limitations of the study

The lack of ad-hoc measures, such as the Hypomania Checklist 32-items (HCL-32) (Fornaro et al., 2015a; Fornaro et al., 2015b), restricts our ability to fully characterize the sub-threshold bipolarity

measures that may be present in unipolar depression. No formal measure of personality traits beyond the DSM diagnosis of BPD was recorded. The negligible proportion of patients endorsing lifetime exposure to MAOIs hinders exploring their role in contemporary treatment paradigms (Giménez-Palomo et al., 2024), and the present study did not assess the eventual mediating role of specific medications on specific association measures of clinical psychopathology and outcomes. Since the data was cross-sectional, the eventual association change could not be studied over time (Vieta and De Prisco, 2024). In addition, reporting bias for social desirability or lack of self-awareness may have occurred since we employed self-reported rating scales. In contrast, Berkson's bias (Berkson, 1946) may have occurred due to the systematic exclusion of the most severe cases of depression, especially those with psychotic features (Halvorson and Humphreys, 2015). Finally, while the goal of the present analysis was exploratory, future studies could explore hybrid dimension reduction techniques (e.g., correlation thresholding followed by principal component analysis) to refine the feature space and improve the robustness of results) to mitigate the potential influence of dimensionality and sample size constraints.

4.2 Conclusions

Beyond the validity of the construct, DSM-defined "atypical" depression is very "typical", especially in the outpatient setting (Nierenberg et al., 1998), particularly among females with prominent anxiety (Halbreich and Kahn, 2007), BD-II (Benazzi, 1999), borderline personality disorder/predominant cyclothymic temperament (Perugi et al., 2011), and bulimia nervosa (Perugi et al., 2006)– being highest (21.54%) in our $AD^{yes}ED^{high}$ subset, further reinforcing the wisdom that AD and ED may represent intertwined, rather than stirred, entities. While the present study could not systematically explore the eventual mediating role of different levels of emotion regulation in relationship with, say, for example, prominent reverse neurovegetative symptoms vs. prominent mood reactivity subtypes of AD, we nonetheless hypothesize that AD may encompass different clinical and neurobiological subtypes, worth further assessment to enhance treatment outcomes of depression (Fornaro et al., 2020b) and to shed light on the controversies about the validity of the

construct of AD raised over the past decades (Łojko and Rybakowski, 2017). Also, the distribution of many clinical and psychopathological measures recorded in the present study varied according to ED grouping rather than AD grouping, further suggesting the hypothesis of heterogeneous subgroups of DSM-defined AD forms of depression.

The need for further stratification of depression to enhance treatment outcomes is particularly relevant for AD compared to melancholia (Cuijpers et al., 2017) since ad-hoc randomized clinical trials are lacking, with a few exceptions carried out in recent years (Fornaro et al., 2014) and most of the pharmacological evidence dating back to the MAOI era (Henkel et al., 2006), hindering direct or indirect comparison with the few modern medications released over recent years, instead prompting a network meta-analysis on the matter (*Fornaro M. et al., submitted for publication*). Overall, although the clinical lore has long held that those with AD represent less severe cases of depression compared to melancholia since the first would be less likely to be hospitalized, the present study shows that people with AD have often endorsed general medical comorbidities or treatment resistance in their lifetime period and associated with specific "dramatic" cluster patterns and higher scores at the cyclothymic temperaments beyond the DERS measures affecting their interpersonal and social functioning. Moreover, trait mood reactivity, cyclothymic temperament, and emotional dysregulation are partly superimposable on a clinical and diagnostic level, soliciting patient-tailored pharmacological or psychological interventions focusing on emotional regulation strategies.

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Figure (300 dpi and editable format)
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Figure n.1: Graphical representation of the distribution of the DERS total scores across different ADED configurations.

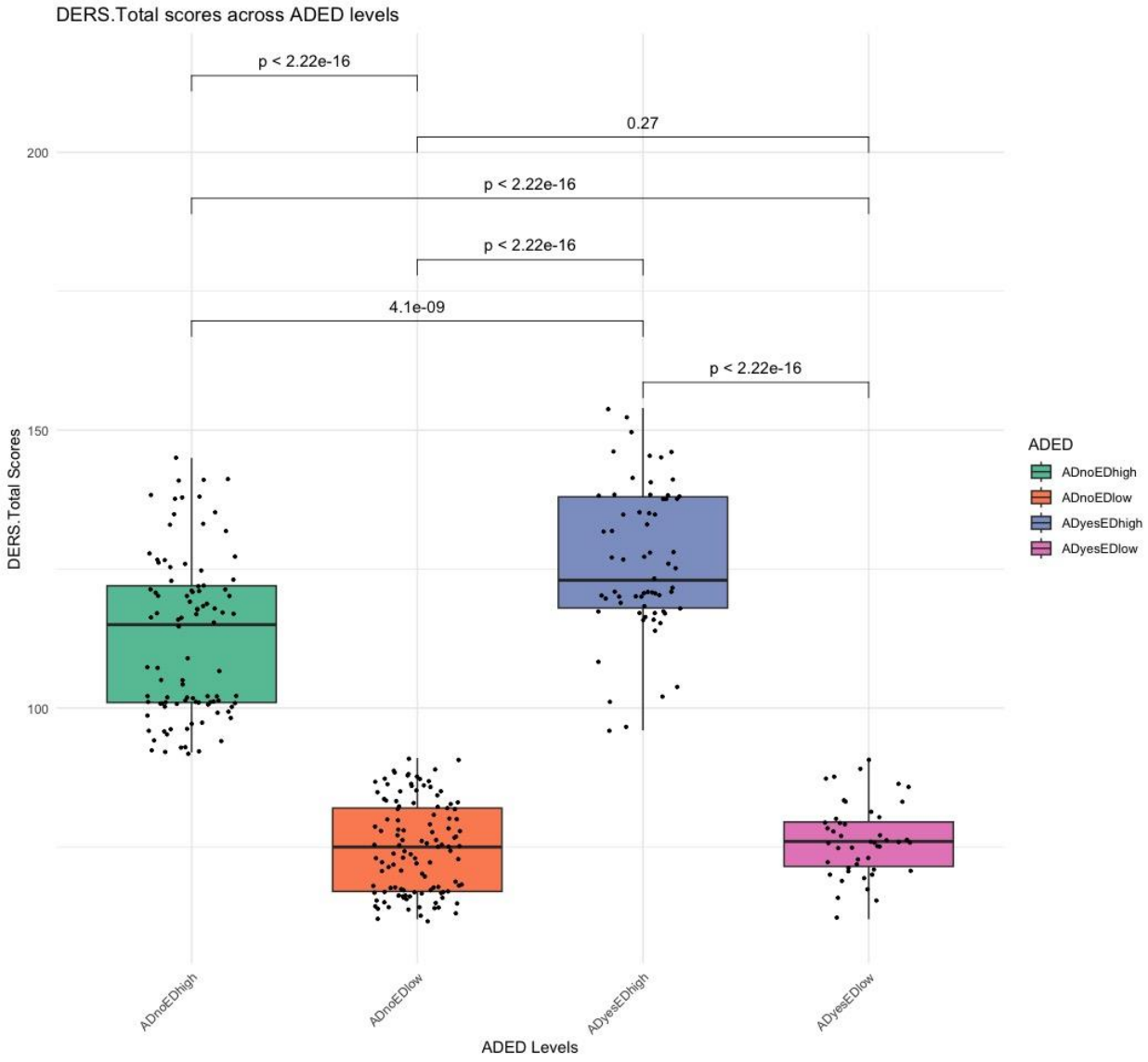

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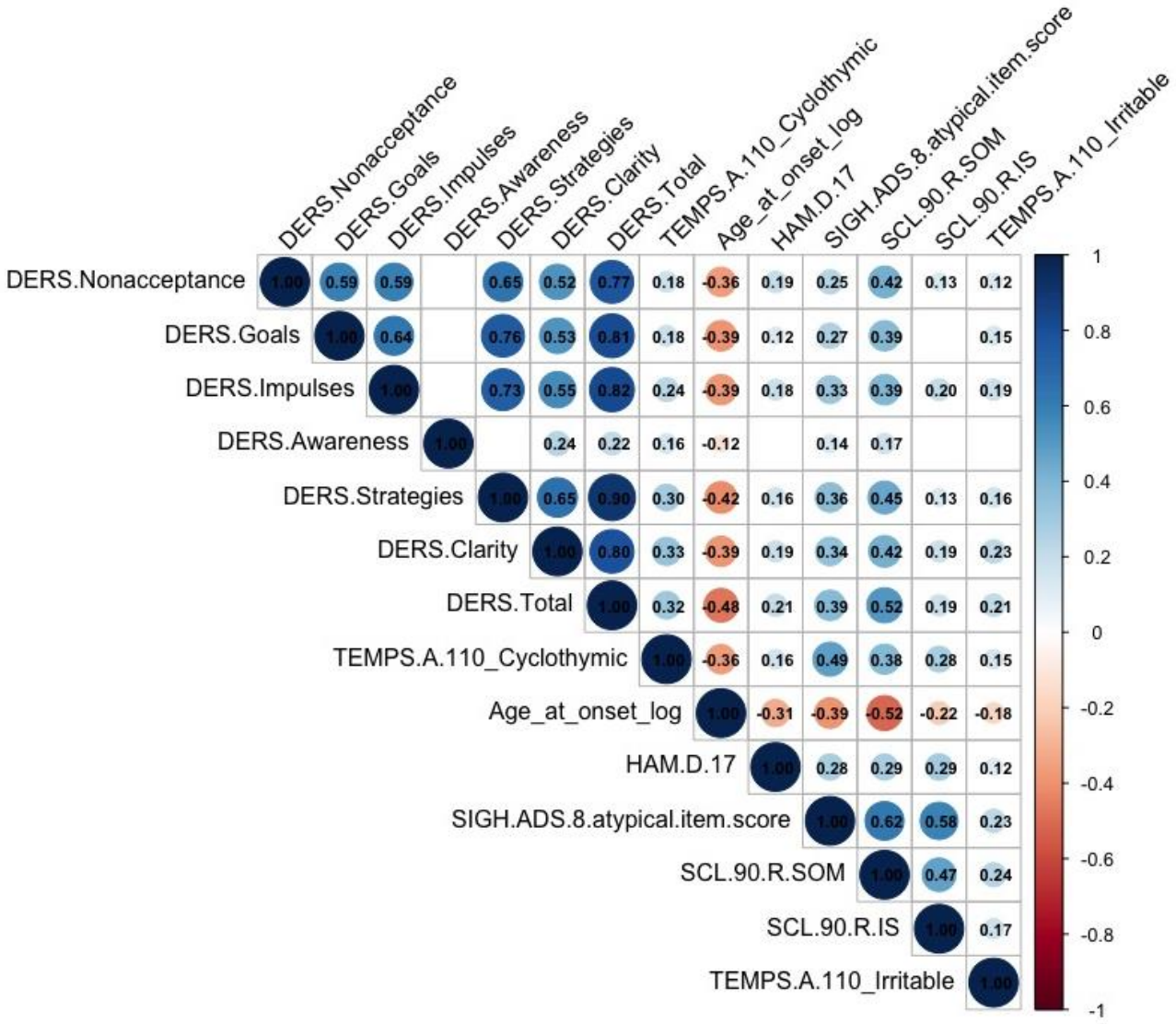
Figure n.2: Essential correlation measures in the sample. "log" denotes a transformed variable originally non-normally distributed, namely the age at the onset of depression. Specifically, the earlier the age at onset, the higher the clinical psychopathological burden. Non-significant correlations were omitted.



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Sample=326 outpatients	**AD^{yes}**, n=112(34%)		**AD^{no}**, n=214(66%)		Chi-square[χ^2](df) & Cramer's V; *F*(df) of ANOVA with eta-squared[η^2](95%C.I.); *H*(df) of Kruskal-Wallis with epsilon squared[ε^2](95%C.I.)	*p-value* (***Bold*** *denotes significant values)*
	ED^{high} N=65(58%)	**ED^{low}** N=47(42%)	**ED^{high}** N=97(45.3%)	**ED^{low}** N=117(54.7%)		
DEMOGRAPHICS						
*Age in years, mean±sd;	40.8±12.2	42.9±10.4;	43.5±10.7;	42.2±11.0;	0.84(3) η^2=7.77e-03(95%C.I.=[0.00-1.00])	0.48
Sex (Female): n=156(47.85%)	45(69.23%)	22(46.81%)	45(46.39%)	44(37.61%)	16.93(3) V=0.228	**<0.01**
Education level, n(%)						
Primary school, 2(0.6)	0	0	2(2.06%)	0	11.947(9) V=0.111	0.26
Secondary school, 25(7.7)	8(12.31%)	6(12.76%)	6(6.19%)	5(4.27%)		
High school, 224(68.7)	45(69.23%)	31(65.96%)	63(64.95%)	85(72.65%)		
College, University or higher degree, 75(23)	12(18.46%)	10(21.28%)	26(26.80%)	27(23.08%)		
Marital status, n(%)						
Unmarried, 146(44.81)	36(55.38%)	19(40.42%)	39(40.21%)	52(44.44%)	9.96(6) V=0.124	0.12
Married/cohabiting, 161(49.39)	26(40%)	23(48.94%)	56(57.73%)	56(47.86%)		
Widow/divorced, 19(5.8)	3(4.62%)	5(10.64%)	2(2.06%)	9(7.7%)		
CLINICAL features						
Diagnosis, n(%)						
MDD, 204(62.6)	32(49.23%)	31(66%)	53(54.64%)	88(75.21%)	18.908(6) V=0.17	**<0.01**
BD-II, 105(32.2)	28(43.08%)	16(34%)	38(39.18%)	23(19.66%)		
BD-I, 17(5.2)	5(7.69 %)	0	6(6.18 %)	6(5.13 %)		
Age at onset of depression in years, median[IQR]	16[3]	22[10]	20[3]	27 [13]	*H*=114.63(3) ε^2=0.346679(95%C.I.=[-0.008556314 to -0.01930759])	**<0.01**
#Cycle pattern of BD: DMI (n=34/122 BDs [27.9%]); MDI (n=11[9%]; Unclear (n=77[63.1%])	11(33.3%); 2(6.1%); 20(60.6%)	8(50%); 2(12.5%); 6(37.5%)	9(20.4%); 5(11.4%); 30(68.2%)	6(20.69%); 2(6.9%); 21(72.41%)	23.295(9) V=0.154	**<0.01**
**Melancholic features, 36(11%)	0	0	11(11.34%)	25(21.37%)	40.324(6) V=0.249	**<0.01**
**With catatonia, 22(6.75%)	0	0	10(10.3%)	12(10.26%)	20.116(6) V=0.176	**<0.01**
With anxious distress, 26(8%)	13(20%)	1(2.13%)	10(10.31%)	2(1.71%)	21.974(3) V=0.260	**<0.01**
$With peripartum onset, 11/75 (14.67%)	1(1.33%)	5(6.66%)	2(2.67%)	3(4%)	18.908(6) V=0.246	**<0.01**
With seasonal pattern n = 96(29.45%)	38(58.46%)	20(42.55%)	15(15.46%)	23(19.65%)	44.749(3) V=0.370	**<0.01**
#Rapid-cycling course, 6/122 BDs (4.91%)	2(6.1%)	0	0	4(3.6%)	8.08(3) V=0.257	**0.03**
Mixed features, 24(7.4%)	12(18.46%)	2(4.25%)	6(6.18%)	4(3.42%)	15.271(3) V=0.216	**<0.01**
Lifetime panic disorder, 19(5.8%)	5(7.69%)	1(2.13%)	8(8.25%)	5(4.27%)	3.314(3) V=0.098	0.41
Lifetime GAD, 23(7%)	7(10.77%)	3(6.38%)	6(6.18%)	7(5.98%)	1.717(3) V=0.073	0.66

Lifetime Social anxiety, 17(5.2%)	2(3.1%)	2(4.25%)	6(6.18%)	7(5.98%)	4.490(3) V=0.117	0.19
Lifetime specific phobias, 79(24.2%)	9(13.85%)	15(31.91%)	22(22.68%)	33(28.2%)	0.771(3); V=0.049	0.61
Lifetime OCD, 47(14.4%)	12(18.46%)	5(10.64%)	12(12.36%)	18(15.38%)	1.823(3) V=0.075	0.61
Lifetime ICD, 17(5.2%)	5(7.69%)	5(10.64%)	4(4.12%)	3(2.56%)	5.501(3) V=0.130	0.13
Lifetime SUD: n=24(7.4%)	4(6.15%)	6(12.76%)	9(9.28%)	5(4.27%)	4.310(3) V=0.115	0.23
Lifetime AN, 4(1.2%)	0	2(4.25%)	1(1.03%)	1(0.85%)	4.529(3) V=0.118	0.27
Lifetime BN, 32(9.8%)	14(21.54%)	1(2.13%)	14(14.43%)	3(2.56%)	22.515(3) V=0.263	**<0.01**
Lifetime BED, 43(13.19%)	17(26.15%)	7(14.89%)	12(12.36%)	7(5.98%)	15.024(3) V=0.215	**<0.01**
Lifetime ADHD, 30(9.2%)	5(7.69%)	4(8.51%)	11(11.34%)	10(8.55%)	0.795(3) V=0.049	0.891
Lifetime suicidal ideation/attempt(s), 15(4.6%)	6(9.23%)	1(2.13%)	7(7.22%)	1(0.85%)	9.082(3) V=0.167	**0.02**
Dramatic cluster "B" Personality disorders (PDs)						
Borderline PD, 36(11%)	14(21.54%)	3(6.38%)	17(17.53%)	2(1.71%)	22.853(3) V=0.265	**<0.01**
Histrionic PD, 12(3.7%)	6(9.23%)	4(8.51%)	5(5.15%)	11(9.4%)	1.534(3) V=0.069	0.66
Narcissist PD, 19(5.8%)	3(4.61%)	3(6.38%)	7(7.22%)	6(5.13%)	0.646(3) V=0.045	0.89
Antisocial SD, 7(2.1%)	0	2(4.25%)	3(3.1%)	2(1.71%)	2.94(3) V=0.095	0.3
Essential general medical comorbidities						
Lifetime liver disease, 76(23.3%)	8(12.3%)	9(19.14%)	31(31.96%)	28(12.93%)	8.94(3) V=0.166	**0.03**
***Lifetime neurological disease, 65(20%)	10(15.38%)	8(17.02%)	20(20.62%)	27(23.08%)	1.845(3) V=0.075	0.6
Lifetime endocrinological disease, 61(18.7%)	11(16.92%)	4(8.51%)	25(25.77%)	21(17.95%)	6.577(3) V=0.142	0.09
Lifetime renal disease, 92(28.2%)	20(30.77%)	10(21.28%)	22(22.68%)	40(34.19%)	4.854(3) V=0.122	0.18
Lifetime fibromyalgia, 67(20.5%)	17(26.15%)	13(27.66%)	11(11.34%)	26(22.22%)	7.944(3) V=0.156	**0.05**
$^{\$\$}$Lifetime gynecological disease, 26(16.66%)	9(20%)	6(27.27%)	4(8.89%)	7(15.9%)	9.057(6) V=0.17	0.13
Lifetime malignancy, 4(1.2%)	0	1(2.13%)	1(1.03%)	2(1.71%)	1.377(3) V=0.065	0.7
Lifetime gastroenterological disease, 11(3.3%)	3(4.61%)	1(2.13%)	6(6.18%)	1(0.85%)	5.161(3) V=0.126	0.14

Table 1: Essential clinical and demographic characteristics of study participants.

Legend: $AD^{yes/no}$=Atypical features (of depression)=”yes/no”; $ED^{high/low}$=emotion dysregulation (level)=”high/low”; MDD=Major depressive disorder; BD-II=Type-II bipolar disorder; BD-I=Type-I bipolar disorder; DMI=Depression-Mania-Interval; MDI=Mania-Depression-Interval; DSM-5-TR=Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition, Text Revision; GAD=Generalized Anxiety Disorder; OCD=Obsessive-Compulsive Disorder; ICD=Impulse Control Disorder; SUD=Substance Use Disorder; AN=Anorexia Nervosa; BN=Bulimia Nervosa; BED=Binge Eating Disorder; ADHD=Attention Deficit Hyperactivity Disorder; PD=Personality Disorder.

#The percentages in the columns refer just to the bipolar subset of the sample; thus, they do not add up to 100%. For example, 11 out of 33 BD people diagnosed as $AD^{yes}ED^{high}$ endorsed a DMI pattern of BD, encompassing 33.3% of the cases.

$The percentages in the columns refer to the female subset of the sample who reported about their pregnancy history (n=75).

$$Female subset. For example, n=45 females were labelled as $AD^{yes}ED^{high}$ out of 65 $AD^{yes}ED^{high}$ cases overall.

*The age range was 18-65, per protocol.

**Atypical depression and melancholia/catatonia are mutually exclusive diagnoses according to the DSM-5-TR.

***Dementia or other major cognitive-impairing diseases were excluded per protocol.

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Sample=326 outpatients	**AD^{yes}**, n=112(34%)		**AD^{no}**, n=214(66%)		*F*(df) of ANOVA with eta-squared[η^2](95%C.I.)	*p-value* (***Bold*** *denotes significant values))*
	ED^{high} N=65(58%)	**ED^{low}** N=47(42%)	**ED^{high}** N=97(45.3%)	**ED^{low}** N=117(54.7%)		
PSYCHOMETRICS						
*HAM-D-17 total score, mean±sd	22.8±2.57	22.3±2.10	21.3±1.74	21.2±1.84	12.46(3) 0.10(95%C.I.=[0.05-1.00])	**<0.01**
**SIGH-ADS 8-item atypical component, total, mean±sd	18.1±2.13	16.6±1.85	11.8±2.15	10.5±2.07	240.2(3) 0.69(95%C.I.=[0.65-1.00])	**<0.01**
SIGH-ADS 25-item total (non-atypical component plus atypical component), mean±sd	40.9±3.19	38.9±3.03	33.1±2.86	31.7±2.84	178(3) 0.62(95%C.I.=[0.57-1.00])	**<0.01**
SIGH-ADS atypical balance, **%**, mean±sd	43.7±4.26	42.1±3.23	35±4.65	32.6±4.69	116.3(3) 0.52(95%C.I.=[0.46-1.00])	**<0.01**
YMRS, mean±sd	8.03±2.48	7.15±2.81	6.74±2.36	7.31±2.59	3.395(3) 0.03(95%C.I.=[0.00-1.00])	**0.02**
General psychopathology						
***SCL-90-R SOM, total score mean±sd	73.1±5.79	71.2±4.3	66.6±4.56	59.4±4.92	133.3(3) 0.55(95%C.I.=[0.50-1.00])	**<0.01**
***SCL-90-R O-C, total score mean±sd	70.1±5.62	71.3±5.98	70.5±5.53	69.9±5.91	0.733(3) 6.78e-03(95%C.I.=[0.00-1.00])	0.53
***SCL-90-R I-S, total score mean±sd	68.3±5.76	68.6±4.32	59.6±4.10	59.2±3.9	101.9(3) 0.49(95%C.I.=[0.42-1.00])	**<0.01**
***SCL-90-R DEP, total score mean±sd	80.4±6.1	80.6±6.02	79.4±6.29	79.1±5.44	1.046(3) 9.65e-03(95%C.I.=[0.00-1.00])	0.37
***SCL-90-R ANX, total score mean±sd	72.1±4.82	73.4±4.79	72.5±4.98	73.1±4.7	0.981(3) 9.06e-03(95%C.I.=[0.00-1.00])	0.4
***SCL-90-R HOS, total score mean±sd	68.5±5.21	66.8±4.30	67.7±5.16	67.3±4.85	1.297(3) 0.01(95%C.I.=[0.00-1.00])	0.27
***SCL-90-R PHOB, total score mean±sd	75.8±5.53	73.9±6.26	75.7±5.95	74.9±6.53	1.243(3) 0.01(95%C.I.=[0.00-1.00])	0.29
***SCL-90-R PAR, total score mean±sd	68.8±5.87	68.7±5.34	68±6.68	69.1±7.04	0.516(3) 4.87e-03(95%C.I.=[0.00-1.00])	0.67
***SCL-90-R PSY, total score mean±sd	62.2±4.16	62.7±4.02	61.5±3.88	60.7±4.15	4.574(3) 0.03(95%C.I.=[0.00-1.00])	**0.01**
***SCL-90-R CGI, total score mean±sd	77±1.81	76.6±1.33	76.8±2.3	76.6±1.92	0.554(3) 5.14e-03(95%C.I.=[0.00-1.00])	0.6
Affective temperaments						

TEMPS Depressive, mean±sd	14.7±4	12.8±3.64	11.3±2.9	12.5±3.06	13.97(3) 0.12(95%C.I.=[0.06-1.00])	<**0.01**
TEMPS Cyclothymic, mean±sd	14.8±2.89	12.1±2.35	10.7±2.59	10.3±2.41	48.03(3) 0.31(95%C.I.=[0.24-1.00])	<**0.01**
TEMPS Hyperthymic, mean±sd	11.8±1.92	11.9±1.97	11.7±1.92	12.1±1.93	0.571(3) 5.29e-03(95%C.I.=[0.00-1.00])	0.63
TEMPS Irritable, mean±sd	8.85±3	7.6±2.68	7.35±2.56	6.65±2.56	9.426(3) 0.08(95%C.I.=[0.03-1.00])	<**0.01**
TEMPS Anxious, mean±sd	14.2±3.40	14±3.37	10.6±3.13	11.3±2.93	23.98(3) 0.18(95%C.I.=[0.12-1.00])	<**0.01**
Emotional dysregulation						
DERS-36 awareness, mean±sd	19.8±4.73	17.8±5.66	18.8±4.65	17.2±24.38	4.952(3) 0.04(95%C.I.=[0.01-1.00])	<**0.01**
DERS-36 clarity, mean±sd	18.9±3.45	11±3.53	16.1±3.77	10.4±2.96	114.2(3) 0.52(95%C.I.=[0.46-1.00])	<**0.01**
DERS-36 non-acceptance, mean±sd	21.1±4.8	12±3.56	19.8±4.86	11.7±3.39	114.3(3) 0.52(95%C.I.=[0.46-1.00])	<**0.01**
DERS-36 strategies, mean±sd	28.1±5.76	14.3±2.87	23.9±5.82	14.1±2.79	182.5(3) 0.63(95%C.I.=[0.58-1.00])	<**0.01**
DERS-36 impulses, mean±sd	19.7±4.82	10.2±2.2	16.8±4.58	10.6±2.74	113.5(3) 0.51(95%C.I.=[0.45-1.00])	<**0.01**
DERS-36 goals, mean±sd	18.7±4.55	10.9±2.67	17.1±3.59	11±2.97	104.5(3) 0.49(95%C.I.=[0.43-1.00])	<**0.01**
DERS-36 total, mean±sd	126±13.2	76.3±6.46	112±14.5	74.9±8.21	409.4(3) 0.79(95%C.I.=[0.76-1.00])	<**0.01**

Table 2: Essential psychometrics of the sample.

Legend: $AD^{yes/no}$=Atypical features (of depression)="yes/no"; $ED^{high/low}$=emotion dysregulation (level)="high/low"; MDD HAM-D-17=Hamilton rating scale for depression, first 17 items; SIGH-ADS=Hamilton Depression rating scale with Atypical Depression Supplement; SCL-90-R=Symptom-Checklist-90-Revised; SOM=Somatization; O-C=Obsessive-Compulsive; I-S=Interpersonal sensitivity; DEP=Depression; ANX=Anxiety; HOS=Hostility; PHOB=Phobic Anxiety; PAR=Paranoid ideation; PSY=Psychoticism; YMRS=Young Mania Rating Scale; TEMPS-A-110=Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire (110-item version); DERS-36=Difficulties in Emotion Regulation Scale, 36-item version.

*The minimum total score at the HAM-D-17 was 18, per protocol. The theoretical range of the total score of the first 17 items of the scale is 0-52, nonetheless. The SIGH-ADS encompasses the 21-item version of the HAM-D, which first 17 items correspond to the HAM-D-17.

**The eight starred items, namely items 1-8, have a maximum possible score of 4,2,3,3,3,4,4,3 each, yielding a theoretical score range=0-26 for that component of the SIGH-ADS.

*** T scores for standardized comparisons. The DERS measures followed a normal distribution—however, the recording of ED levels was based on the median and the interquartile range (IQR) since such an approach reflects the standard.

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Sample=326 outpatients	**AD^{yes}**, n=112(34%)		**AD^{no}**, n=214(66%)		Chi-square[χ^2](df) & Cramer's V	*p-value* (***Bold*** *denotes significant values)*
	ED^{high} N=65(58%)	**ED^{low}** N=47(42%)	**ED^{high}** N=97(45.3%)	**ED^{low}** N=117(54.7%)		
Treatment history						
TRD, n=30/204 unipolar cases (14.7%)	10(33.3)	6(20)	6(20)	8(26.67)	16.570(6) V=0.202	**<0.01**
TRBD, n=21/122 bipolar cases (17.2%)	5(23.81)	4(19.05)	6(28.57)	6(28.57)	3.773(6) V=0.124	0.66
Lifetime MAOIs exposure: response, non, response, never-exposed - n(%)	0	0	1(1.03)	0	2.368(3) V=0.085	0.64
Lifetime SSRIs or SNRIs exposure: response, non, response, never-exposed - n(%)	16(24.6), 25(38.4), 24(37)	13(27.66), 11(23.4), 23(48.94)	32(32.99), 37(38.14), 28(28.87)	31(26.49), 48(41.03), 38(32.48)	8.091(6) V=0.111	0.23
Lifetime TCAs exposure: response, non, response, never-exposed - n(%)	13(20), 6(9.23), 46(70.77)	8(17.02), 7(14.89), 32(68.09)	15(15.46), 19(19.59), 63(64.95)	26(22.22), 12(10.26), 79(67.52)	6.127(6) V=0.097	0.41
Lifetime lithium exposure: response, non, response, never-exposed - n(%)	11(16.92), 10(15.38), 44(67.69)	12(25.53), 20(42.55), 15(31.91)	23(23.71), 20(20.62), 54(55.67)	28(23.93), 19(16.24), 70(59.83)	20.529(6) V=0.177	**<0.01**
Lifetime valproate/carbamazepine exposure: response, non, response, never-exposed - n(%)	14(21.54), 5(7.69), 46(70.77)	2(4.26), 12(25.53), 33(70.21)	29(29.90), 16(16.49), 52(53.61)	24(20.51), 21(17.95), 72(61.54)	17.787(6) V=0.165	**<0.01**
Lifetime SGAs/TGAs exposure: response, non, response, never-exposed - n(%)	4(6.15), 16(24.62), 45(69.23)	8(17.02), 10(21.28), 29(61.7)	10(10.31), 14(14.43), 73(75.26)	11(9.4), 19(16.24), 87(74.36)	7.011(6) V=0.104	0.32
Lifetime CBT exposure: response, non, response, never-exposed - n(%)	17(26.15), 14(21.54), 34(52.31)	15(31.92), 7(14.89), 25(53.19)	10(10.31), 16(16.49), 71(73.20)	23(19.66), 13(11.11), 81(69.23)	16.196(6) V=0.158	**0.01**

Table 3: Essential lifetime treatment history of the sample.

Legend: AD$^{yes/no}$=Atypical features (of depression)="yes/no"; ED$^{high/low}$=emotion dysregulation (level)="high/low"; MDD TRD=Treatment-resistant depression; TRBD=Treatment-resistant bipolar depression; MAOI=monoamine oxidase inhibitor; SSRI=Selective Serotonin Reuptake Inhibitor; SNRI=Serotonin Norepinephrine Reuptake Inhibitor; TCA=Tricyclic Antidepressant; SGA=Second-Generation Antipsychotic; TGA=Third-Generation Antipsychotic; CBT=Cognitive Behavioural Therapy.

Note: Patients may have been exposed to multiple therapies over their lifetimes, meaning that the raw numbers or percentages of responders vs. non-responders documented herein may not reflect the complexity of the sample's treatment history and polypharmacy/comorbidity profiles. Moreover, the strikingly high rates of people never exposed to MAOIs during their lifetimes reflect the compounds' lack of availability despite the classical clinical wisdom of a preferential response to MAOIs compared to TCAs (possibly to newer antidepressants, too) by AD patients compared to melancholic depression.

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Data Set	*Number of trees*	*Number of features*	*OOB*	*Training subset, ratio*	*AUC-ROC*	*Accuracy, %*	*95% C.I.*	*p*	*F1-score*
AD vs. non-AD	500	72	0.25	80:20	0.6	0.72	0.6-0.83	<0.01	0.83
EDhigh vs. EDlow	500	68	0.23	80:20	0.69	0.69	0.5-0.8	<0.01	0.73
TRD vs. non-TRD	500	69	0.12	80:20	0.91	0.75	0.6-0.87	<0.01	0.86
TRBD vs. non-TRBD	500	74	0.16	80:20	0.43	0.79	0.6-0.95	<0.01	0.88

Table 4: Random forest performances output. AD=Atypical features (of depression); ED=Emotional dysregulation; TRD=Treatment-resistant depression; TRBD=Treatment-resistant bipolar disorder; OOB=out-of-bag (error); AUC-ROC=Area under the curve-receiving operating characteristics. Minimum node size=10.

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