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Is cognitive dysfunction involved in difficult-to-treat depression? Characterizing resistance from a cognitive perspective

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Research Article

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Abstract

Background. This study aimed to identify clinical and cognitive factors associated with increased risk for difficult-to-treat depression (DTD) or treatment-resistant depression (TRD).
Methods. A total of 229 adult outpatients with major depression were recruited from the mental health unit at a public hospital. Participants were subdivided into resistant and nonresistant groups according to their Maudsley Staging Model score. Sociodemographic, clinical, and cognitive (objective and subjective measures) variables were compared between groups, and a logistic regression model was used to identify the factors most associated with TRD risk.
Results. TRD group patients present higher verbal memory impairment than the nonresistant group irrespective of pharmacological treatment or depressive symptom severity. Logistic regression analysis showed that low verbal memory scores (odds ratio [OR]: 2.02; 95% confidence interval [CI]: 1.38–2.95) together with high depressive symptom severity (OR: 1.29; CI95%: 1.01–1.65) were associated with TRD risk.
Conclusions. Our findings align with neuroprogression models of depression, in which more severe patients, defined by greater verbal memory impairment and depressive symptoms, develop a more resistant profile as a result of increasingly detrimental neuronal changes. Moreover, our results support a more comprehensive approach in the evaluation and treatment of DTD in order to improve illness course. Longitudinal studies are warranted to confirm the predictive value of verbal memory and depression severity in the development of TRD.

Introduction

Major depressive disorder (MDD) is a prevalent and complex mental illness that severely impacts health and daily functioning. Despite the large number of pharmacological treatments available, around 30% of MDD patients are considered treatment-resistant. Recent conceptualizations of treatment response suggest difficult-to-treat depression (DTD) as an alternative label. This approach aims to optimize disease management by means of a more comprehensive patient evaluation. However, identification of individuals with DTD currently implies the absence of response after several treatments [1].

Since the first reports in the literature in 1970s, treatment-resistant depression (TRD) has been described as an "insufficient response to adequate antidepressant therapy" [2,3]. However, this definition is imprecise, and there is a lack of consensus regarding the operational criteria for treatment resistance [4]. In order to overcome heterogeneity in the definition of an "adequate treatment for depression" (which includes adequate pharmacological doses, duration of treatment, and a satisfactory demonstration of treatment adherence), and since the management of depression involves stepwise administration of treatments, several staging models have been developed for its treatment. These models establish several resistance levels considering response to antidepressant treatments available based on their dose and duration (see a review in Ruhé et al. [5]). In this regard, the Maudsley Staging Model (MSM) provides a comprehensive solution for establishing the treatment resistance level of a particular patient with depression, including other clinical issues such as the duration of the current depressive episode (acute, subacute, and chronic), symptom severity (subsyndromal to severe), and treatment failures with different antidepressants, augmentation drugs, and electroconvulsive therapy (ECT) [6].

Several sociodemographic, clinical, and neurobiological factors have been associated with the presence of treatment resistance in depression. A recent review by Caraci et al. [7], which includes the study performed by the European Group for the Study of Resistant Depression, reported several clinical features significantly associated with treatment resistance. These variables were comorbid psychiatric disorders, suicide risk, severity and duration of current episode, number of hospitalizations, depressive recurrences, melancholic and psychotic features, nonresponse to a first antidepressant treatment, occurrence of side effects during treatment, lower age at onset, high occupational level, and family psychiatric history.

Neurocognitive complaints have frequently been reported by patients with MDD [8]. Interestingly, previous literature on subjective and objective cognition posit that these different constructs of the disorder need to be addressed separately [9–11]. Whereas objective neurocognitive impairment has been studied in greater depth and confirmed by well-validated assessments, less is known about subjective cognitive complaints. Although an association between depression severity and subjective cognition has recently been reported [12], the effects of subjective cognition in TRD have not been studied to date.

Overall, since the first study reporting on the neurocognitive profile of TRD [13], several meta-analyses have found that patients with MDD demonstrate poor performance on a range of cognitive domains, such as executive function, attention, verbal and visual memory, and processing speed/reaction time [14–18]. Moreover, these impairments in neurocognition have been shown to be present in the disorder regardless of certain demographic and clinical mediators, such as gender, symptom severity, age at onset, and number and duration of depressive episodes [15,19–22]. Previous literature has reported that objective neurocognitive deficits may be present at different stages of the disorder, suggesting a likely role for cognition serving as a risk biomarker predating illness onset, as a marker of greater severity illness, or even as a trait marker that is present in patients with remitted depressive symptoms. This last proposal would support neuroprogression models [16], in which the presence of cognitive residual deficits in the absence of affective symptoms would be considered an indirect sign of illness persistence.

Notably, these neurocognitive alterations, present at various stages of the disease, have been significantly associated with poorer response to treatment, reduced social functioning, and impaired quality of life [15,17,20,23–25]. Regarding treatment response in particular, lower verbal memory [26] and flexibility [27], together with chronic depression and older age [22,28], have been described as predictors of poor response to both antidepressant medication and cognitive therapy [28–30]. Moreover, persistence of residual symptoms such as neurovegetative and neurocognitive symptoms, even in patients without depressive symptomatology, hinders full recovery and increases the probability of relapse [31].

Thus, neurocognitive deficits appear to be important therapeutic targets in order to improve treatment response, reduce the risk of a relapse, and lead to a full restoration of patients' everyday functioning. However, the extent to which these cognitive factors are associated with treatment resistance in depression is unknown. This study aims to identify the clinical factors, subjective cognitive complaints, and neurocognitive markers associated with an increased risk for TRD or DTD.

Methods

Participants

A total of 229 major depressive outpatients (68% women),18–65 years of age, were consecutively recruited from the adult Mental Health Unit of the Psychiatry Department at Parc Taulí Hospital over a 12-month period (February 2016 to February 2017). Patients had to meet the following criteria to be selected for the study: fulfilling criteria for a past or present diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition, Text Revision (DSM-IV TR); an IQ >85 measured by means of the Vocabulary subtest from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV) [32]; and to be able to understand and sign the informed consent. Senior psychiatrists established diagnoses. Exclusion criteria were the presence of neurological or any other somatic conditions that can affect cognitive functioning, as well as comorbidity with bipolar disorder, schizophrenia, past or present substance use disorders, or any personality disorders. The presence of dysfunctional personality traits was not an exclusion criterion, being compiled according to the clinical impression of the evaluator/research psychiatrist. The MDD sample was divided into two groups (resistant, $n = 104$, and nonresistant, $n = 125$) according to their score obtained on the MSM scale used to assess treatment resistance. This sample is part of a broader study assessing cognition and depression [12].

Assessment procedure

Clinical and sociodemographic variables

A set of prominent patients' characteristics was collected during a clinical semi-structured interview (1.5–2 h duration): age at first MDD episode, number of previous MDD episodes (including the present one), current psychopharmacological treatment doses measured following the system code proposed by Sackeim [33], comorbid conditions according to the DSM-IV TR (such as anxiety disorders and dysthymia) or dysfunctional personality traits according to clinical impressions, and the current severity of depressive symptomatology using the *Hamilton Depressive Rating Scale* (HDRS-17) [34]. Medication used at the time of evaluation was categorized as (a) monotherapy with antidepressants, (b) antidepressants in combination with benzodiazepines or with any other psychotropic medication (antipsychotics, lithium, and/or anticonvulsants), and (c) medication-free. Sociodemographic variables were also collected: age, gender, years of education, marital status, and current employment status.

Treatment resistance was assessed by means of the MSM scale ranging from 3 to 15 [6]. The MSM includes information regarding three items: (a) duration, (b) severity, and (c) treatment strategies of the current episode. (a) Duration is scored 1–3 corresponding to acute (<1 year), subacute (1 to <2 years), and chronic (>2 years); (b) severity is scored 1–5 corresponding to subsyndromal, mild, moderate, severe without psychosis, and severe with psychosis; and (c) treatment strategies are scored 1–5 with regard to antidepressants (level 1: 1–2 medications; level 2: 3–4 medications; level 3: 5–6 medications; level 4: 7–10 medications; and level 5: >10 medications), plus 0 or 1 with regard to pharmacological augmentation strategy, and plus 0 or 1 with regard to ECT. Study participants were categorized as resistant (7–15) or nonresistant (3–6) according to their total MSM score.

Self-reported cognitive measure—subjective cognitive functioning

The Perceived Deficit Questionnaire (PDQ-20) [35–37] is a 20-item self-administered questionnaire used to measure patients' perspective of their cognitive functioning. The PDQ-20 assesses three cognitive domains by asking patients about their everyday activities: attention, memory (retrospective and prospective), and

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executive functions (planning and organization). The combined subscales yield a total score ranging from 0 to 80, with higher scores indicating greater perceived cognitive impairment.

Neuropsychological battery—objective cognitive functioning

Based on prevalent neuropsychological assessment manuals [38,39], four neurocognitive domains were assessed to create composite scores including the following validated tests:

1. **Attention and working memory index**: Digit Span Forward and Backward subtests from the WAIS-IV [32].
2. **Verbal memory index**: Rey Auditory Verbal Learning Test (RAVLT), RAVLT Total Score (trials 1–5) and 30-minute delayed recall score [39].
3. **Executive functions index**: Phonetic Verbal Fluency (PMR) [40,41] set-shifting (Wisconsin Card Sorting Test, WCST, and Trail Making Test Part B, TMT-B) and abstraction (Similarities subtest, WAIS-IV). The computerized version of the WCST was administered from the Inquisit Test Library (http://www.millisecond.com/download/library/).
4. **Processing speed index**: Trail Making Test Part A (TMT-A) [40] and Digit Symbol Substitution subtest (WAIS-IV).

Statistical analyses

To study differences in demographic, clinical, and neuropsychological variables between the two study groups (resistant and nonresistant), a two-tailed equal variances *t*-test for independent samples was applied. Furthermore, a logistic regression (using the enter method) was carried out with treatment resistance as the dependent variable in order to find specific clinical and neurocognitive factors that might be associated with a higher risk of TRD. Sociodemographic, clinical, and neuropsychological variables in which the *t*-test reached statistical significance ($p \leq 0.05$), as well as clinical variables previously related with a higher risk of treatment resistance described in the literature (age, gender, age at MMD onset, and number of episodes) were entered as independent variables in the regression model. In a first step, depression severity and pharmacological treatment were not entered in the statistical model as they are considered in the MSM definition of TRD. However, since severity and pharmacological treatment may have been related to the independent variables, they were included in a second step of the logistic regression model in order to control for their effects on the results. Post-hoc analyses were conducted to further control for the influence of pharmacological treatment on the results. The *t*-tests and regression analysis were reassessed excluding patients under pharmacological treatments that showed significance in the analysis.

Data from each individual neuropsychological test were first standardized to remove the effects of age, gender, and education level. The resulting standardized scores were averaged to create objective neuropsychological composites that were normalized and transformed into *z*-scores (mean = 0 and standard deviation = 1). Scores on the HDRS-17 were transformed using 7-point intervals to aid the clinical interpretation of the results obtained from the logistic regression. All data were analyzed using the Statistical Package for the Social Sciences software version 21.0 (SPSS Inc; Chicago, IL).

Results

Sociodemographic and clinical characteristics of the study sample are described in Table 1. A total of 125 patients were classified as nonresistant since they scored 3–6 at the MSM and 104 patients reported 7 or more at the MSM and were included in the resistant group. As expected, HDRS-17 scores were significantly higher in the TRD group. The percentage of patients receiving antipsychotics, lithium, anticonvulsants (lamotrigine), or benzodiazepines was also higher in the TRD group. No differences were observed between groups regarding other clinical and sociodemographic variables, or in the use of antidepressants and psychotherapy. More extended information with a description of the mean doses of all pharmacological treatments used by each study group is provided in Supplementary Table S1.

Patients in the TRD group reported significantly higher subjective cognitive complaints according to the PDQ-20 total score, and specifically, on the memory (both retrospective and prospective) and executive functions subscale (Table 2), although these differences did not remain significant after Bonferroni correction. In the objective cognitive domains, patients with TRD presented poorer results in verbal memory, processing speed, and executive functions than their nonresistant counterparts (Table 2). Since psychopharmacological treatments and the severity of depressive symptoms may have an impact on neurocognition, we compared performance in objective and subjective cognition further, controlling for these variables. After the exclusion of patients receiving antipsychotics, benzodiazepines, lithium, or anticonvulsants and covarying for the severity of depressive symptoms, between-group cognitive differences remained significant for verbal memory. In contrast, differences in the other objective cognitive domains partially retained significance, depending on the excluded treatment. Differences in subjective cognition did not remain significant (Supplementary Tables S2 and S3).

After studying the clinical and cognitive profiles of resistant and nonresistant groups, a logistic regression analysis was used to identify the variables that might be associated with a higher risk for TRD. In the first regression model, we included treatment resistance as dependent variable and scores on objective cognitive domains assessed, scores on PDQ-20, gender, age, age at MDD onset, and number of MDD episodes as independent variables. This first model found verbal memory to be the only independent variable significantly associated with higher TRD risk (Table 3). In the second step, the variables that showed significant differences between study groups (Table 1) and that were included in the MSM definition of TRD (depression severity, independently assessed by the HDRS-17 and transformed to a 7-point interval, and pharmacological treatment) were entered in the regression model, as they are relevant factors that could potentially affect TRD. Although severity of depression and the use of antipsychotics and anticonvulsants emerged as factors that were significantly associated with a higher risk for TRD, verbal memory remained significant in the model (Table 4).

The final logistic regression model including significant variables in the second step model (Table 4) showed that low scores on verbal memory together with higher symptom severity were associated with a higher risk of treatment resistance in depression. Thus, for each extra point on the HDRS-17 scale, risk increased by 1.29 (95% confidence interval [95% CI]: 1.01–1.65) and for each *z*-score point decrease on the verbal memory score (worse memory), risk increased by 2.02 (95% CI: 1.38–2.95) (Table 5). As expected, the use of antipsychotics and anticonvulsants was also related with treatment resistance in the statistical model. To further assess the influence of pharmacological treatment on the results, the final regression model was also reassessed after the exclusion of patients under antipsychotic or anticonvulsant treatment. Verbal memory remained significantly associated with a higher risk for TRD in this model (Supplementary Table S4). To address a possible

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Table 1. Sociodemographic and clinical variables of the two study groups.

Variables	Nonresistance ($N = 125$)	Moderate–severe resistance ($N = 104$)	t test/χ^2 (df)	p value (two-tailed)
Sex[a] (female)	85 (68.0)	70 (67.3)	0.01 (1)	1.000
Age[b]	51.70 (9.88)	53.83 (7.32)	−1.87 (224)	0.062
Years of education[b]	10.80 (3.81)	9.90 (3.33)	1.90 (227)	0.059
Age of onset[b]	41.44 (12.62)	40.85 (11.32)	0.37 (227)	0.711
Number of episodes[b]	2.15 (1.32)	2.40 (1.28)	−1.46 (227)	0.147
Severity (HDRS)[b]	13.67 (8.65)	17.64 (8.57)	−3.47 (227)	0.001
Marital status[a,c]				
Married	89 (71.2)	71 (68.9)	7.32 (3)	0.062
Divorced	21 (16.8)	25 (24.3)		
Single	15 (12)	5 (4.9)		
Widowed	0 (0)	2 (1.9)		
Employment status[a,c]				
Employed[d]	33 (26.4)	13 (12.6)	20.14 (5)	0.001
Sick leave because of MDD	33 (26.4)	25 (24.3)		
Non-MDD-related leave	8 (6.4)	3 (2.9)		
Unemployment	5 (4)	1 (1)		
Pensioner[d]	24 (19.2)	45 (43.7)		
Looking for an employment	22 (17.2)	16 (15.5)		
Comorbidity[a]				
Dysthymia	24 (19.2)	26 (25.0)	1.12 (1)	0.336
Anxiety disorders	9 (7.2)	10 (9.6)	0.435 (1)	0.632
Personality traits[e]	18 (14.4)	16 (15.4)	0.044 (1)	0.854
Medication[a]				
Antidepressants	118 (94.4)	103 (99.0)	3.62 (1)	0.075
Antipsychotics	15 (12.0)	41 (39.4)	23.11 (1)	<0.001
Lithium	2 (1.6)	8 (7.7)	5.05 (1)	0.046
Anticonvulsants	16 (12.8)	28 (26.9)	7.30 (1)	0.011
Benzodiazepines	53 (42.4)	65 (62.5)	9.18 (1)	0.003
Medication free	6 (4.8)	1 (1.0)	2.83 (1)	0.243
Nonpharmacological treatment[a,c]				
Past psychotherapy	53 (44.9)	47 (54.7)	1.89 (1)	0.202
Ongoing psychotherapy	26 (22.6)	26 (29.9)	1.37 (1)	0.259

Abbreviations: HDRS, Hamilton Depressive Rating Scale; MDD, major depressive disorder; SD, standard deviation.
[a]Variable reported as n (%).
[b]Variables reported as mean (SD).
[c]Past psychotherapy and ongoing psychotherapy have missing data in 25 and 27 subjects respectively. Marital status and employment status have missing data in one subject.
[d]Significant differences were observed between both study groups in employed and pensioner ($\chi^2 = 6.66$, $p = 0.012$ and $\chi^2 = 16.05$, $p < 0.001$ respectively).
[e]Presence of dysfunctional personality traits according to the clinical impression of the evaluator.

effect of collinearity among cognitive domains in the results of the logistic regression, we repeated the analysis including only one cognitive domain at a time, and only verbal memory remained significant.

Last, we explored the risk (odds ratio [OR]) for TRD when both significant variables were present at the same time. With this aim in mind, we defined patients with higher risk (defined as those with the highest HDRS-17 score and worst verbal memory performance) and lower risk (those with the lowest HDRS-17 score and the highest verbal memory performance). Both groups represented quartiles 1 (lower risk) and 4 (higher risk) within the distribution of each variable. Patients in quartile 1 presented HDRS-17 scores of ≤7 (low severity) and a verbal memory score of ≥−0.30 (z scores), while patients in quartile 4 scored ≥22 on the HDRS-17 (moderate severity) and ≤−1.47 on verbal memory. As such, patients who presented both risk factors presented an OR of 4.04 (CI 95%: 3.02–8.43) for being treatment-resistant in comparison to MDD patients with low depressive symptoms and preserved verbal memory.

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Table 2. Subjective and objective cognitive functioning.

Variables	Nonresistance ($N = 125$)	Moderate–severe resistance ($N = 104$)	t test (df)	p Value (two-tailed)
PDQ-20[a]				
Total	33.89 (17.45)	38.73 (16.91)	−2.12 (227)	0.035
Attention	10.14 (4.96)	11.25 (4.60)	−1.75 (227)	0.082
Memory Total	14.28 (8.61)	16.67 (8.77)	−2.08 (227)	0.039
Retrospective Memory	7.47 (4.64)	10.81 (4.77)	−1.98 (227)	0.049
Prospective Memory	6.81 (4.41)	8.13 (4.60)	−2.21 (227)	0.028
Executive functions	9.47 (5.32)	8.55 (4.64)	−1.75 (227)	0.028
Verbal memory[b,c]	−0.61 (0.93)	−1.19 (0.77)	5.02 (219)	<0.001
Attention/working memory[b,c]	−0.62 (0.83)	−0.93 (0.74)	2.96 (226)	0.003
Processing speed[b,c]	−0.32 (0.97)	−0.76 (0.93)	3.52 (225)	0.001
Executive functions[b,c]	−0.59 (0.73)	−0.96 (0.79)	3.64 (225)	<0.001

Abbreviations: PDQ-20, Perceived Deficit Questionnaire; SD, standard deviation.
[a]Variables reported as mean (SD).
[b]Variables reported as Z values (SD).
[c]Missing data exist for verbal memory, attention/working memory, processing speed, and executive function in 8, 1, 2, and 2 subjects respectively.

Table 3. Results of the logistic regression analysis (excluding variables considered in the definition of resistance according to the MSM).

	B	SE	Significance (p-value)	Exp (B)
Verbal memory	−0.659	0.216	**0.002**	1.934[a]
Attention/working memory	−0.189	0.250	0.449	0.828
Executive functioning	−0.133	0.337	0.693	0.875
Processing speed	−0.008	0.257	0.975	0.992
PDQ-20 attention	−0.060	0.063	0.344	0.942
PDQ-20 memory	0.030	0.031	0.336	1.030
PDQ-20 executive functions	0.018	0.050	0.726	1.018
Gender	−0.242	0.323	0.453	0.785
Age	0.041	0.023	0.075	1.042
Age of MDD onset	−0.015	0.018	0.412	0.985
Number of MDD episodes	0.121	0.138	0.383	1.128
Constant	−2.508	1.221	0.040	0.081

Abbreviations: MDD, major depressive disorder; MSM, Maudsley Staging Model; PDQ, Perceived Deficit Questionnaire; SE, standard error.
[a]This value represents 1/0.517.
Bold values represent statistically significant results.

Discussion

To our knowledge, this is the first study to examine TRD risk associated with objective and subjective cognition. In our sample, verbal memory was found to be associated with a higher risk for TRD independently of pharmacological treatment or symptom severity. Moreover, symptom severity was also associated with a higher risk for TRD. Results showed a higher impairment in the resistant group for other subjective and objective cognitive variables, although they were not associated with a higher risk for TRD.

Clinical variables

In our study sample, 45.4% of our patients presented treatment resistance, which is somewhat higher than the rates previously reported. The difference may be due to the heterogeneity in the definition of TRD [42] and the potential bias caused by the recruitment at a specialized psychiatry service, where patients are often attended after a first treatment trial in primary care.

Patients in the resistant group showed a higher severity of depressive symptoms and a greater use of antipsychotics, lithium, anticonvulsants, and benzodiazepines. These findings are in agreement with the previous literature and clinical practice. Although studies have assessed clinical characteristics related to treatment resistance in depression, the specific role of these variables in increasing the risk of developing a TRD has received less attention. In this sense, our results showed a mild risk of TRD in patients with severe depressive symptoms, which decreases after excluding cases under antipsychotics or anticonvulsants, probably due to the reduction of the number of resistant patients included in the analysis. In line with these findings, the ORs for clinical predictors in TRD have previously been demonstrated to be low (around 1.5) [43]. Moreover, a recent study using machine learning algorithms for classifying treatment-resistant patients with clinical variables reported low accuracy for the final model (0.74), suggesting the importance of exploring other factors not considered so far in predictive models, such as cognitive variables [44].

Cognitive variables

Our results found that verbal memory was significantly associated with an increased risk for TRD above and beyond demographic and clinical characteristics and pharmacological treatment. The role of cognition in the prediction of response to pharmacological interventions (selective serotonin reuptake inhibitors (SSRI) and serotoninâ norepinephrine reuptake inhibitors (SNRI)) but also to other treatment strategies reserved for patients who did not respond to standard pharmacological treatments (ketamine, transcranial magnetic stimulation (TMS), or ECT) has received increased interest [45–48]. The first TRD study on neurocognition found that individuals with TRD displayed slightly reduced neurocognitive performance, both globally and across all domains [13]. Notably, regarding non–first line treatment strategies, a better baseline performance in episodic memory has been described as a good predictor of depression response and remission using TMS [47]. Moreover, another study performed

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Table 4. Results of the logistic regression analysis including depression severity and pharmacological treatment.

	B	SE	Significance (p-value)	Exp (*B*)
Verbal memory	−0.699	0.233	**0.003**	2.012[a]
Attention/working memory	−0.295	0.276	0.286	0.745
Executive functioning	−0.255	0.369	0.490	0.775
Processing speed	0.423	0.294	0.149	1.527
PDQ-20 attention	−0.095	−0.072	0.186	0.910
PDQ-20 memory	0.017	0.033	0.608	1.017
PDQ-20 executive functions	−0.017	0.055	0.753	0.983
Gender	−0.180	0.348	0.606	0.835
Age	0.029	0.025	0.255	1.029
Age at onset	−0.017	0.020	0.403	0.983
Number of episodes	0.051	0.152	0.736	1.052
Severity	0.452	0.187	**0.016**	1.572
Antipsychotics	1.566	0.401	**<0.001**	4.787
Lithium	1.049	0.962	0.275	2.854
Anticonvulsants	0.970	0.437	**0.026**	2.637
Benzodiazepines	0.548	0.329	0.096	1.729
Constant	−2.658	1.327	0.045	0.070

Abbreviations: MDD, major depressive disorder; MSM, Maudsley Staging Model; PDQ, Perceived Deficit Questionnaire; SE, standard error.
[a]This value represents 1/0.497.
Bold values represent statistically significant results.

Table 5. Final statistical model including the variables associated with a higher risk of treatment-resistant depression.

	B	SE	Significance (p-value)	Exp (*B*)	95% CI for Exp (*B*) Lower–upper
Verbal memory	−0.703	0.193	<0.001	2.020[a]	1.383–2.950[a]
Severity	0.255	0.125	0.042	1.290	1.009–1.649
Antipsychotics	1.367	0.367	<0.001	3.924	1.912–8.055
Anticonvulsants	0.813	0.397	0.040	2.254	1.036–4.905
Constant	−1.900	0.367	<0.001	0.150	

Abbreviations: CI, confidence interval; SE, standard error.
[a]Those values represent 1/0.495 and CI: 1/0.723–1/0.339.

in unipolar and bipolar depression showed that overgeneral memory (a lack of memory for specific events) was inversely related with time to depression recovery and the risk of a new relapse after ECT [46]. These previous results coincide with our findings, in which patients with more altered verbal memory were most associated with TRD risk.

The association between verbal memory impairment and the increased TRD risk could be linked to alterations in specific brain regions, such as the hippocampus, which has been previously associated with MDD pathophysiology [49–51] and memory [52,53]. Moreover, our findings in verbal memory suggest the existence of a specific subtype of MDD patients that is more resistant to treatment [54], a clinical condition that would imply longer disorder duration and, presumably, higher neurotoxicity. Interestingly, memory impairment is also associated with treatment resistance in other psychiatric disorders such as schizophrenia [55,56] and post-traumatic stress disorder [57–59], suggesting that memory could be considered a cognitive marker for treatment resistance across mental disorders.

Our study is not without limitations. First, the heterogeneity of the definition of TRD may make it difficult to integrate our findings to the rest of the literature. Second, since one of the predictive variables for TRD in our analysis was depression severity, which is included in the definition of treatment resistance in the MSM, results regarding this variable should be carefully considered. In this regard, it is important to note that the observed association between verbal memory and TRD remained significant independently of symptom severity. Finally, the design of this study makes it difficult to disentangle whether cognitive impairment could represent a predictor of TRD or a symptom of depression itself. Longitudinal studies are needed to confirm the predictive value of verbal memory and depression severity in the development of TRD.

In summary, our results highlight the potential role of verbal memory and depression severity as risk factors for TRD. These results support neuroprogression models, in which more severe patients (in terms of memory and depressive symptoms) present an unfavorable clinical development and a more resistant profile. A

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more comprehensive evaluation of patients with depression would aid in identifying potential cognitive and clinical risk factors involved in DTD. The chance to adapt more personalized treatment approaches would have an impact on clinical course and on the functional recovery of patients with depression.

Our findings raise the possibility that treating verbal memory impairments could be therapeutically beneficial in reducing the probability of developing TRD. In this regard, and in accordance with a recent systematic review, verbal memory and processing speed seem to be modifiable, rather than traits that remain stable over the clinical course of the disorder [60–62]. Recently, a randomized control trial using erythropoietin found memory improvement in TRD patients which was associated with increased subfield hippocampal volume, independent of mood change [63]. Finally, it would be of interest to continue investigating specific depressive symptoms, including cognition, that are prone to become treatment resistant in order to improve the definition of a more homogeneous subgroup of difficult-to-treat patients.

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Conflict of Interest. All authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. All authors contributed to and have approved the final manuscript.

Data Availability Statement. The data that support the findings of this study are available upon request from Dr. Narcís Cardoner at ncardoner@tauli.cat.

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