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The Assessment of Cognitive Dysfunction in Major Depressive Disorder: A 16-Week Prospective Case-Control Study

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ABSTRACT

Objective: Cognitive dysfunction is one of the core components of major depressive disorder (MDD). It is estimated that two-thirds of patients diagnosed with MDD have cognitive deficits. Cognitive symptoms are pervasive and affect functioning in several domains. This 16-week prospective case-control study aimed to assess the change of mood and cognitive symptoms during treatment.

Materials and Methods: Ninety-eight patients with MDD and 113 healthy controls (HCs) participated in the study. The MDD group was evaluated 6 times (baseline, 2nd, 4th, 8th, 12th, and 16th weeks). For mood symptoms, the Montgomery-Asberg Depression Rating Scale was used, and for neurocognitive functions, the Perceived Deficits Questionnaire-Depression was used, and the Digit Symbol Substitution Test was administered to both groups.

Results: At baseline, compared with the HCs, the neurocognitive function of patients with MDD was worse. From the 8th to the 16th week assessments, in both neurocognitive tests, the cognitive functions of patients with MDD had improved. Despite this improvement and the patients achieving remission, the patients' cognitive performance did not improve to the level of the HC group at the 16th week.

Conclusion: Our longitudinal research revealed that even though mood symptoms decreased and patients with depression did achieve symptomatic remission, their cognitive deficits perpetuated.

ARTICLE HISTORY

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KEYWORDS: Cognition, cognitive dysfunction, depression, major depressive disorder, neurocognitive function

INTRODUCTION

Major depressive disorder (MDD) is a chronic disease, in which symptoms include depressed mood, loss of interest, vegetative symptoms such as disturbed sleep or appetite, and impaired cognitive function.[1] Cognitive dysfunction is acknowledged to be a salient deficiency in psychiatric disorders including, schizophrenia, bipolar disorders, anxiety disorders, and particularly, MDD.[2-5] Until now, cognitive dysfunction has received less attention in MDD relative to other major psychiatric disorders.[6] According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*),[7] cognitive dysfunction and psychomotor retardation are the criteria for a major depressive episode. Besides *DSM-5*, the National Institute of Mental Health (NIMH) identified cognition as a research priority as evidenced by the Biobehavioral matrix: the Research Domain Criteria (RDoC).[8]

Cognitive dysfunction is common in MDD. Cognitive deficits have been estimated to occur in approximately two-thirds of patients with MDD.[9-11] Based on patient self-reports and clinical ratings, the Sequenced Treatment Alternatives to Relieve Depression (STAR∗D) study revealed that approximately 90% of patients had difficulty with concentration and decision-making.[12] Furthermore, residual cognitive difficulties were found in 22% of remitters.[13] Fava et al.[14] showed that residual cognitive difficulties such as word-finding difficulty, inattentiveness, apathy, forgetfulness, and mental slowing were found in more than 30% of responders. Bhalla et al., found that more than 90% of patients who had cognitive deficits, and patients with depression continued to experience cognitive dysfunction when they reached remission.[15] Cognitive symptoms are pervasive, affecting functioning in several

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domains, including reduced executive functioning, attention, memory, learning, psychomotor speed, and verbal processing.[16-18] However, there is no firm consensus regarding which domains of cognition are selectively affected by depression.[19]

In light of these data, the purpose of this 16-week prospective case-control study was to assess the change of mood and cognitive symptoms during treatment. This study aimed to examine the oscillations in cognitive functions of the patients with MDD during a 16-week follow-up. In addition, we strived to find whether any clinical variables could affect cognitive functioning in longitudinal observation.

MATERIALS AND METHODS

Participants

The study was approved by the Scientific Research Ethics Committee of Manisa Celal Bayar University Faculty of Medicine (Date: June 13, 2019 20.478.486). All participants signed the written informed consent form.

Two groups of volunteers were included. The patient group consisted of 98 persons with a diagnosis of MDD. The patient group consisted of individuals who applied to the psychiatric outpatient unit of the 7 centers. The patients met *DSM-5* criteria for MDD and the diagnosis was confirmed with the Structured Clinical Interview for *DSM-5-Patient Edition* (SCID-5).[20] The inclusion criteria were being at the age between 18 and 65 years and willing to participate in the study. The exclusion criteria were determined as the presence of additional psychiatric illness (excluding nicotine addiction and anxiety disorders in remission), the presence of electroconvulsive therapy (ECT) in the last 6 months, the presence of neurologic diseases, presence of chronic diseases (e.g., hypertension and diabetes mellitus), mental retardation, presence of psychotic symptoms, history of (hypo) mania, pregnancy or lactation, and use of antipsychotics in last 2 months or depot antipsychotics in the last 6 months. The HCs comprised 113 volunteers who had no psychiatric diagnosis (based on clinical SCID-5 interviews conducted by an experienced psychiatrist). HCs were matched with the MDD group according to their demographic features such as age, sex, and education level.

Procedure

The study lasted 16 weeks. The MDD group was evaluated 6 times (baseline, 2nd, 4th, 8th, 12th, and 16th week) during the study. At the beginning of the study, 98 patients diagnosed as having MDD were included in the study. In the first evaluation interview, a sociodemographic data form, the Montgomery-Asberg Depression Rating Scale (MADRS), Perceived Deficits Questionnaire-Depression (PDQ-D), and Digit Symbol Substitution Test (DSST) were administered to both groups. MADRS was applied to the MDD group at each evaluation time point. The PDQ-D was used in the 8th and 16th weeks, and the DSST was administered in the 16th week to the patient group. In the 8th week, the MDD group was divided into responder and non-responder groups. The criterion of response was a decrease of MADRS score decreased by more than 50% of the baseline MADRS score at the 8th week. The non-responder participants were excluded from the study in the 8th week. A total of 48 patients with MDD completed the study, and thus achieved response or remission. The evaluation times, number of participants, and the rating scores are shown in Figure 1.

Instruments

Sociodemographic Data Form: The sociodemographic data form included gender, age, occupation, marital status, education, duration of illness, treatment selection, number of past episodes, presence of suicide attempts, age of onset, and duration of this episode.

Montgomery-Asberg Depression Rating Scale (MADRS): The MADRS, which has 10 items, was used in this study where each item is rated on a 6-point scale (0-6) with higher scores denoting more severe depression. The scale was developed by Montgomery and Asberg.[21] Özer et al., performed the Turkish reliability and validity study.[22]

Digit Symbol Substitute Test (DSST): The DSST is a component of the Wechsler Adult Intelligence Scale. The DSST provides an objective assessment of neurocognitive symptoms. The test is based on the substitution of the symbols assigned for the numbers in a given 90 seconds. The DSST is not standardized for the Turkish population. Higher scores indicate better neurocognitive function. There is no cutoff value of DSST.

Perceived Deficits Questionnaire-Depression (PDQ-D): The PDQ-D is used to make subjective assessments of neurocognition through 20 items. The domains of PDQ-D are attention/concentration, retrospective memory, prospective memory, and planning/organization. It has a 5-point scale for each item rating between 0 and 4. A higher score indicates worse functioning in neurocognition. Aydemir et al., performed the reliability and validity study for the Turkish version.[23]

Statistical Analysis

Statistical analyses were performed with a total of 211 participants. Variables were checked for the assumptions of parametric statistical testing using the Kolmogorov-Smirnov test. In the analyses of the data, descriptive statistics were used primarily. The Chi-square test was used for categorical variables to examine the relationship between the groups, and the *t*-test was used for independent variables. When the data did not have a normal distribution, the Mann Whitney-U test was performed. Cohen's *d* effect size was calculated for each

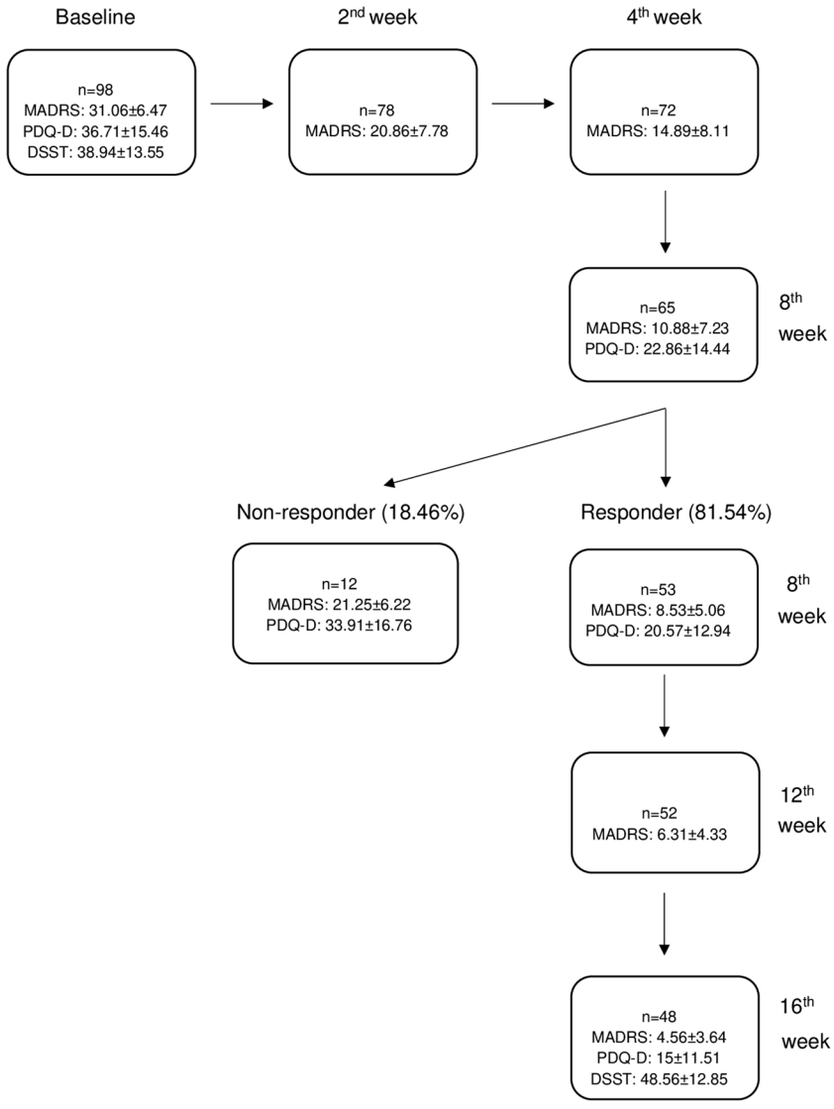

Figure 1. Evaluation times, number of participants, and the tests score of patients with MDD.

measure. Cohen suggested that $d=0.2$ be considered a 'small' effect size, 0.5 represents a 'medium' effect size, and 0.8 a 'large' effect size.[24] For dependent variables in the numeric variables, the paired samples *t*-test and repeated measures Analysis of Variance (ANOVA) were used. Pearson's correlation analysis was applied to examine the relationship between independent continuous variables. Linear regression analyses were performed to estimate the relationship between the PDQ-D and DSST as dependent variables, and the duration of this episode, number of episodes, education duration, MADRS (at the 16th week), age, duration of depression, and onset age of depression were used as independent variables. The analyses were conducted using the SPSS statistical analysis software (Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA).[25] Statistical significance (*P*) criteria were set to 0.05.

RESULTS

Sociodemographic and Clinical Variables in Both Groups

The mean ages of the MDD and HC groups were 34.93 ± 10.6 and 32.47 ± 8.39 years, respectively. The majority (70.4%) of the MDD group were female ($n=69$), as well as 65.5% of the volunteers in HC group were female ($n=74$). The mean education duration was 11.88 ± 3.57 years for MDD group and 12.27 ± 4.05 years for HCs.

There were no statistical differences between MDD and HC groups in terms of age ($t(209)=-1.879$, $P=.062$), education years ($t(209)=0.733$, $P=.465$), and gender ($x^2(1)=0.582$, $P=.446$). In the MDD group, the age of onset of depressive disorder was 30.68 ± 10.23 years. The mean

Table 1. Sociodemographic and Clinical Variables in Both Groups

	MDD $n=98$		HC $n=111$	
Age (mean ± SD)	34.93 ± 10.6		32.47 ± 8.39	
Duration of education (years) (mean ± SD)	11.88 ± 3.57		12.27 ± 4.05	
Gender	*n*	%	*n*	%
Female	69	70.4	74	65.5
Male	29	29.6	39	34.5
Age of onset (mean ± SD)	30.68 ± 10.23			
Duration of illness (years) (mean ± SD)	4.1 ± 5.28			
No. of episodes (mean ± SD)	1.87 ± 1.21			
Duration of this episode (months) (mean ± SD)	5.86 ± 6.12			

MDD: Major Depressive Disorder; HC: Healthy Control; SD: Standard Deviation.

duration of illness in the MDD group was 4.1 ± 5.28 years. The number of episodes was 1.87 ± 1.21 and the duration of this episode was 5.86 ± 6.12 months. Data are presented in Table 1. Treatment selection for the MDD groups at every assessment time are shown in Table 2. All the patient's treatment option is pharmacological. None of the MDD patient received any structured psychotherapy option.

Neurocognitive Tests

In terms of the DSST and PDQ-D, the MDD group had significantly higher scores than the HCs at baseline (PDQ-D; $t(209)=-18.338$, $P < .001$, DSST; $t(209)=8.589$, $P < .001$), the 8thweek visit (PDQ-D; $t(164)=-1.664$, $P < .001$), and the 16th week visit (PDQ-D; $t(159)=-5.072$, $P < .001$, DSST; $t(159)=2.847$, $P=.005$). In the MDD group, the DSST test score was significantly decreased in the 16th week compared with the baseline score ($t(47)=-7.337$, $P < .001$). Repeated-measures ANOVA determined that the mean PDQ-D scores differed significantly across the 3 time points (baseline, 8th week, and 16th week) ($F(2,46)=68.201$, $P < .001$). Bonferroni correction showed a decreased PDQ-D score between assessment times (36.71, 20.57,15.00, respectively), and these were statistically significant ($P < .001$). The data are presented in Table 3.

Correlations Between Clinical-Sociodemographic Variables and Cognitive Tests

The MADRS total score was positively correlated with baseline PDQ-D ($r=0.273$, $P=.007$), 8th week PDQ-D ($r=0.354$, $P=.009$), and 16th week PDQ-D ($r=0.617$, $P < .001$). Age of onset was negatively correlated with baseline PDQ-D ($r=-0.336$, $P=.001$) and DSST ($r=-0.271$, $P=.007$) tests scores. The duration of this episode was positively correlated with 16th week PDQ-D ($r=0.376$, $P=.008$) scores. Age was negatively correlated with baseline DSST ($r=-0.449$, $P <$) and 16th week DSST ($r=-0.288$, $P=.047$). Duration of education was positively correlated with baseline DSST ($r=0.511$, $P < .001$) and 16th week DSST ($r=0.464$, $P=.001$). There were no significant correlations between other clinical variables and cognitive tests scores. Data are presented in Table 4.

Effect of Treatment Selection on Neurocognitive Tests and Mood Symptoms

Between the selective serotonin reuptake inhibitor (SSRI) and selective serotonin-norepinephrine reuptake inhibitor (SNRI) groups, no significant differences were observed in age, gender, duration of education, age of onset of depression, duration of this episode, duration of depression, and the number of episodes at baseline, 8th week and 16th week.

Table 2. Use of Antidepressants at Every Assessment Time in the MDD Groups

	Baseline $n=98$		2nd week $n=78$		4th week $n=72$		8th week $n=53$		12th week $n=52$		16th week $n=48$	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
SSRIs	41	41.8	32	41	31	43.1	20	37.7	20	38.5	18	37.5
SNRIs	40	40.8	31	39.7	27	37.5	20	37.7	20	38.5	19	39.6
Vortioxetine	13	13.3	12	15.4	11	15.3	10	18.9	9	17.3	8	16.7
Others	4	4.1	3	3.8	3	4.2	3	5.7	3	5.8	3	6.3

MDD: Major Depressive Disorder; SSRIs: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors.

Table 3. Neurocognitive Tests in Both Groups

	Baseline			8th week		16th week		*P*
	HC	MDD	stats. (ES)[c]	MDD	stats. (ES)[c]	MDD	stats. (ES)[c]	
	n=113	*n*=98		*n*=53		*n*=48		
PDQ-D	8.27 ± 5.36	36.71 ± 15.46	*t*(209)=-18.338 *P* < .001* (2.46)	20.57 ± 12.94	*t*(164)=-1.664 *P* < .001* (1.25)	15 ± 11.51	*t*(159)=-5.072 *P* < .001* (0.90)	*F*(2,46)=68.201 *P* < .001**
DSST	55.24 ± 13.92	38.94 ± 13.55	*t*(209)=8.589 *P* < .001* (1.19)			48.56 ± 12.85	*t*(159)=2.847 *P*=.005* (0.50)	*t*(47)=-7.337 *P* < .001***

HC: Healthy Controls; MDD: Major Depressive Disorder; PDQ-D: Perceived Deficits Questionnaire; DSST: Digit Symbol Substitute Test; (ES)c: Cohen's *d*.
* Student's *t*-test (Comparisons between HC and MDD groups at baseline, 8th and 16th week).
** Repeated measures ANOVA test.
*** Paired samples *t*-test.

There were significant differences between the baseline MADRS scores of the two groups ($t(79)=-3.157$, $P=.002$) (SSRI < SNRI). MADRS scores significantly differed in the 8th week between groups ($t(38)=-2.357$, $P=.024$) (SSRI < SNRI). Neurocognitive tests scores did not significantly differ between the SSRI and SNRI groups at every assessment time. Data are presented in Table 5.

Linear Regression Analyses

The duration of this episode, number of episodes, duration of education, MADRS at 16th week, age, duration of depression, and age of onset were included in the final models (PDQ-D; *df*: 7.48, $F=5.440$, $P < .001$, DSST; *df*: 7.48, $F=2.490$, $P=.029$). The regression model showed considerable R^2 values (PDQ-D; 0.361, DSST; 0.159). MADRS score ($P < .001$) at 16thweek was found as a predictor for PDQ-D at the 16th week, and education duration ($P=.004$) was found as a predictor for DSST at the 16th week. The results are shown in Table 6.

DISCUSSION

The major aim of the study is to examine the changes in neurocognitive functions of the patients with MDD. Similar to the literature, despite the majority of the MDD patients achieved remission, their cognitive dysfunction was still persisted, comparable to that of the HCs.

The number of studies investigating cognitive function in depression is gradually increasing. Physicians must target treating both depressive symptoms and cognitive dysfunction because the persistence of cognitive dysfunction causes many disturbances during depression. Residual cognitive deficits may contribute to ongoing occupational and social dysfunction.[26,27] and promote suicide ideation.[28] Besides, retention of cognitive impairment may interact with existing emotional and social vulnerability, increasing the risk of recurrent depressive episodes.[29,30]

There are some factors that may influence cognitive function in patients with MDD such as age of onset,[31,32] duration

Table 4. Pearson Correlations Between Clinical-Sociodemographic Variables and Neurocognitive Tests in MDD Group.

		Baseline		8th week	16th week	
		PDQ-D	DSST	PDQ-D	PDQ-D	DSST
Age of onset	*r*	**-0.336**	**-0.271***	-0.159	-0.072	-0.139
	P	**.001**	**.007**	.254	.627	.345
Duration of illness (years)	*r*	0.074	-0.056	0.079	0.011	-0.058
	P	.47	.585	.576	.943	.694
No. of episodes	*r*	-0.012	-0.099	0.044	-0.018	-0.128
	P	.907	.33	.757	.902	0,387
Duration of this episode(months)	*r*	0.041	-0.118	0.154	**0.376***	-0.144
	P	.691	.245	.269	**.008**	.327
MADRS score	*r*	**0.273**	-0.080	**0.354**	**0.617***	-0.167
	P	**.007**	0.435	**.009**	**<.001**	.257
Age	*r*	-0.054	**-0.449**	-0.115	-0.037	**-0.288**
	P	.432	**<.001**	.412	.803	**.047**
Duration of education (years)	*r*	0.014	**0.511**	--0.001	0.070	**0,464**
	P	.837	**<.001**	.993	.637	**.001**

MDD: Major Depressive Disorder; MADRS: Montgomery-Asberg Depression Rating Scale; PDQ-D: Perceived Deficits Questionnaire; DSST: Digit Symbol Substitute Test.

Table 5. MADRS and Neurocognitive Tests Scores Comparisons Between SSRI and SNRI Groups

	Baseline			8th week			16th week		
	SSRI	SNRI	stats. (ES)[c]	SSRI	SNRI	stats. (ES)[c]	SSRI	SNRI	stats.
	n=41	*n*=40		*n*=20	*n*=20		*n*=18	*n*=19	
MADRS	29.68 ± 5.50	33.7 ± 5.95	*t*(79)=-3.157 ***P*=.002* (0.7)**	6.75 ± 4.08	10.30 ± 5.36	*t*(38)=-2.357 ***P*=.024*(1.20)**	4.33 ± 2.79	4.16 ± 3.34	*U*=-0.337 *P*=.753*
PDQ-D	36.34 ± 15.14	37.6 ± 15.28	*t*(79)=-0.372 *P*=.711*	19.40 ± 10.84	17.25 ± 9.12	*t*(38)=0.679 *P*=.502*	11.50 ± 8.55	14.79 ± 9.57	*t*(35)=-1.100 *P*=.279*
DSST	39.76 ± 16.26	37.65 ± 11.36	*t*(79)=0.674 *P*=.502*				49.11 ± 13.78	49.84 ± 12.21	*t*(35)=-0.171 *P*=.865*

SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; MADRS: Montgomery-Asberg Depression Rating Scale; PDQ-D: Perceived Deficits Questionnaire; DSST: Digit Symbol Substitute Test; ES[c]: Cohens effect size.
* Student's *t*-test.
** Mann Whitney-U test.

of illness,[33] the number of episodes, presence of psychosis,[34,35] and severity of depression.[36,37] In our study, the MADRS score was positively correlated with PDQ-D scores in every assessment time (baseline, 8th week, and 16th week). The age of onset was negatively correlated with both PDQ-D and DSST at the baseline assessment. Finally, the duration of this depressive episode time was positively correlated with the PDQ-D score in the 16th week. As the time spent with depression increases, cognitive functions are more negatively affected.

Despite its prevalence and significance, the neurobiological mechanisms underlying cognitive dysfunction in MDD remain partially undefined.[38] Neuroanatomic abnormalities,[37,39,40] neurochemical abnormalities, alterations in connectivity between networks,[41,42] inflammatory processes and immune dysfunction,[43,44] hormone imbalances,[45] and dysregulation of neurotrophins[46] have been linked with dysfunction of cognition in patients with MDD. In terms of neurochemical abnormalities, abnormalities in monoaminergic systems involving neurotransmitters (serotonin, dopamine, and norepinephrine) have been implicated as mediators of cognitive impairment in patients with MDD.[6,47] To date, there are no gold standard treatment options for cognitive dysfunction in MDD. There is evidence that antidepressants (e.g., SSRIs, SNRIs, and norepinephrine reuptake inhibitors (NRIs), vortioxetine) have shown promising results.[48] Also, other psychopharmacologic interventions such as psychostimulants,[49] ketamine,[50,51] and tumor necrosis factor (TNF)-α antagonists[52]have been investigated for improving cognitive functions. Many studies have demonstrated the procognitive effects of vortioxetine,[53-55]and it is the only United States Food and Drug Association (FDA) approved agent for the treatment of depression in the United States. Besides vortioxetine, duloxetine has been studied and the results are promising.[56,57] In our study, we cannot make any inference about the effect of vortioxetine because the sample size was small. When we compare two treatment options, SSRIs and SNRIs (venlafaxine, duloxetine), physicians tended to select SNRIs when the depression was more severe at the initial assessment. MADRS scores of the SSRI group were significantly lower than the scores of the SNRI group on the 8th week. This significance was disappeared at 16th week assessment. At the 8th week, PDQ-D scores of the SSRI group were higher than of the SNRI group, but in the 16th week, the scores of the SSRI group were lower than that of the SNRI group. We could interpret that the effect of SSRIs on mood symptoms starts earlier than on cognition, but the sample sizes were insufficient to make this assertion.

Measures commonly used to assess depressive symptoms in daily routine (e.g., MADRS, Hamilton Depression Rating Scale) are inadequate in evaluating cognitive functions. Furthermore, a study that included 61 psychiatrists from 6 different countries showed that many psychiatrists only paid attention to the subjective declaration of the patient with MDD for cognitive evaluation and mostly disregarded the cognitive assessment scales (e.g., Mini-Mental State Examination, Clock Drawing Test, and Weschler Memory Test).[58] In our study, we used one objective test (DSST) to evaluate integrated cognitive functioning, including executive function, processing speed, attention, spatial perception, and visual scanning.[59] Also, we used subjective patient-reported assessment of cognitive function (PDQ-D) to evaluate retrospective memory, prospective memory, attention/concentration, and planning/organization. At baseline, compared with HCs, the neurocognitive function of the patients MDD was worse, as expected. At the 8th and 16th week assessments, in both subjective and objective tests, cognitive functions of the MDD patients had improved. Despite this improvement and the patients achieving remission, the cognitive performance of the patients did not improve to the level that of the HC group in the 16th week. Similar to our results, evidence suggests that cognitive dysfunction persists following symptomatic remission,[13,31,60-62] highlighting the need to treat cognition separately from mood symptoms.

According to the regression analysis, at the 16th week, MADRS scores were a predictor of PDQ-D. At the 16th week, all of the patients (*n*=48) reached remission based on their MADRS scores. Despite the patients reaching remission, the residual symptoms of depression

Table 6. Logistic Regression Analysis Evaluating the Effect of Age and Clinical Variables on DSST and PDQ-D in Patients with MDD at the 16th Week

Predictors	B	SE	Beta	*t*	*P*
PDQ-D (16th week) R^2: 0.361					
Constant	2.340	9.844		0.238	.813
Duration of this episode (months)	0.400	0.233	0.191	1.713	.093
Number of episodes	1.973	2.199	0.184	0.897	0.374
Duration of education (years)	0.217	0.461	0.055	0.471	0.640
MADRS (16th week)	1.785	0.355	0.639	5.027	**<0.001**
Age	-0.512	0.499	-0.375	-1.025	0.310
Duration of depression (years)	-0.117	0.528	-0.045	-0.221	0.826
Age of onset	0.454	0.488	0.330	0.930	0.357
DSST (16th week) R^2: 0.159					
Constant	41.982	10.777		3.896	<0.001
Duration of this episode (months)	-0.217	0.255	-0.108	-0.849	0.400
Number of episodes	-1.034	2.407	-0.127	-0.542	0.591
Duration of education (years)	1.535	0.504	0.410	3.043	**0.004**
MADRS (16th week)	-0.331	0.389	-0.124	-0.852	0.398
Age	-0.265	0.546	-0.203	-0.484	0.630
Duration of depression (years)	0.284	0.578	0.115	0.490	0.626
Age of onset	0.050	0.535	0.038	0.094	0.925

MDD: Major depressive disorder; MADRS: Montgomery-Asberg Depression Rating Scale; PDQ-D: Perceived Deficits Questionnaire; DSST: Digit Symbol Substitute Test.

were perceived as cognitive deficiency by the patients. Current clinical and cognitive literature often uses the terminology of "hot" and "cold" cognition to refer to cognitive functions, which are either influenced by the emotional state (i.e., hot), or independent of emotional state (i.e., cold). In our study, our cognitive tests (PDQ-D and DSST) evaluated cold cognition.[63] It would have been good to evaluate hot cognition in our study to see how the emotional state affected them. Regression analysis showed that duration of education was a predictor of DSST in the 16th week. Based on this result, we may infer that patients experience more cognitive problems if they received less education, independent of their depressive symptomatology. Physicians who decide to use the DSST to evaluate cognition in their research must be aware that DSST test scores can be affected by duration of education.

Our study has some limitations. First, our sample size is small and our dropout rate is high at every assessment point. Second, we used the PDQ-D and DSST tests to evaluate cognitive function, but we know that these two tests cannot evaluate all cognitive domains that are affected in MDD. Finally, we are unable to comment on the effects of therapies (e.g., cognitive behavioral therapy and cognitive rehabilitation therapy) or vortioxetine on cognition because the sample treated with vortioxetine is too small and none of the patients with MDD received any structured psychotherapy.

Our longitudinal research revealed that even though mood symptoms decreased and patients with depression were able to achieve symptomatic remission, their cognitive deficits persisted. Furthermore Salik et al.[64] showed that even in the early phase of depression, cognitive functions of the patients were worse than that of the HCs. To date, there is no consensus about which domains are affected and which neuropsychological test battery should be applied in patients with MDD. With new and more comprehensive studies, we must specify which domains are affected in depression and finalize which neurocognitive tests would be more specific for patients with MDD. To sum up, in our daily routine practice, we must assess the cognitive functions of every patient with MDD and try to improve their cognitive functions even if they are in remission.

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Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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